PHD DAY
HEALTH

ABSTRACTS
24 JUNE 2022

AARHUS
UNIVERSITY

PHD DAY 2022 PROGRAMME

24 JUNE 2022, THE PER KIRKEBY AUDITORIUM, THE LAKESIDE LECTURE THEATRES

8.15 **Welcome by OC Chair and by the Chair of the PhD Association**
Fabio Renato Manzolli Leite, Associate professor, Department of Dentistry and Oral Health, Aarhus University and Ellen Hollands Steffensen, PhD student, Co-chair of the PhD Association at Health, Aarhus University

8.25 **Keynote lecture by Christine Parsons, Associate Professor, Interacting Minds Center, Dept. of Clinical Medicine, Aarhus University and Vice Chair of DANWISE**
Introduced Fabio Renato Manzolli Leite, Associate professor, Department of Dentistry and Oral Health, Aarhus University

9.25 **Break with coffee/tea and fruit**

9.45 **Flash talk presentations**
The Lakeside Lecture Theatres, the Bartholin Building (build. 1241), Anatomy (build. 1231) and Samfundsmedicinsk Auditorium (build. 1262/101)

11.15 **Break with lunch and networking**
The Lakeside Lecture Theatres, Anatomy (build. 1231), Samfundsmedicinsk Auditorium (build. 1262/101), and building 1264 (209 and 310)

12.00 **Poster presentations**
The Lakeside Lecture Theatres, Anatomy (build. 1231) and Samfundsmedicinsk Auditorium (build. 1262/101)

13:40 **Break with coffee/tea and cake**

14.00 **Oral sessions**
The Lakeside Lecture Theatres

15.20 **Break**

15.35 **Fogh Nielsen Competition**

16.20 **Closing remarks**
Helene Nørrelund, Head of the Graduate School of Health, Aarhus University

16.25 **The programme for the day ends**

18.30 **Dinner and award ceremonies**
Centralværkstedet, Aarhus C.
Festive speech: *Dean Anne-Mette Hvas*

Session overview

Flash talk	**Poster sessions**	**Oral sessions**
9.45-11.25	**12.10-13.40**	**14.00-15.20**

Oral session 1:	Lakeside Lecture Theatre, **Eduard Biermann Auditorium**
Oral session 2:	Lakeside Lecture Theatre, **Per Kirkeby Auditorium**
Oral session 3:	Lakeside Lecture Theatre, **Merete Barker Auditorium**

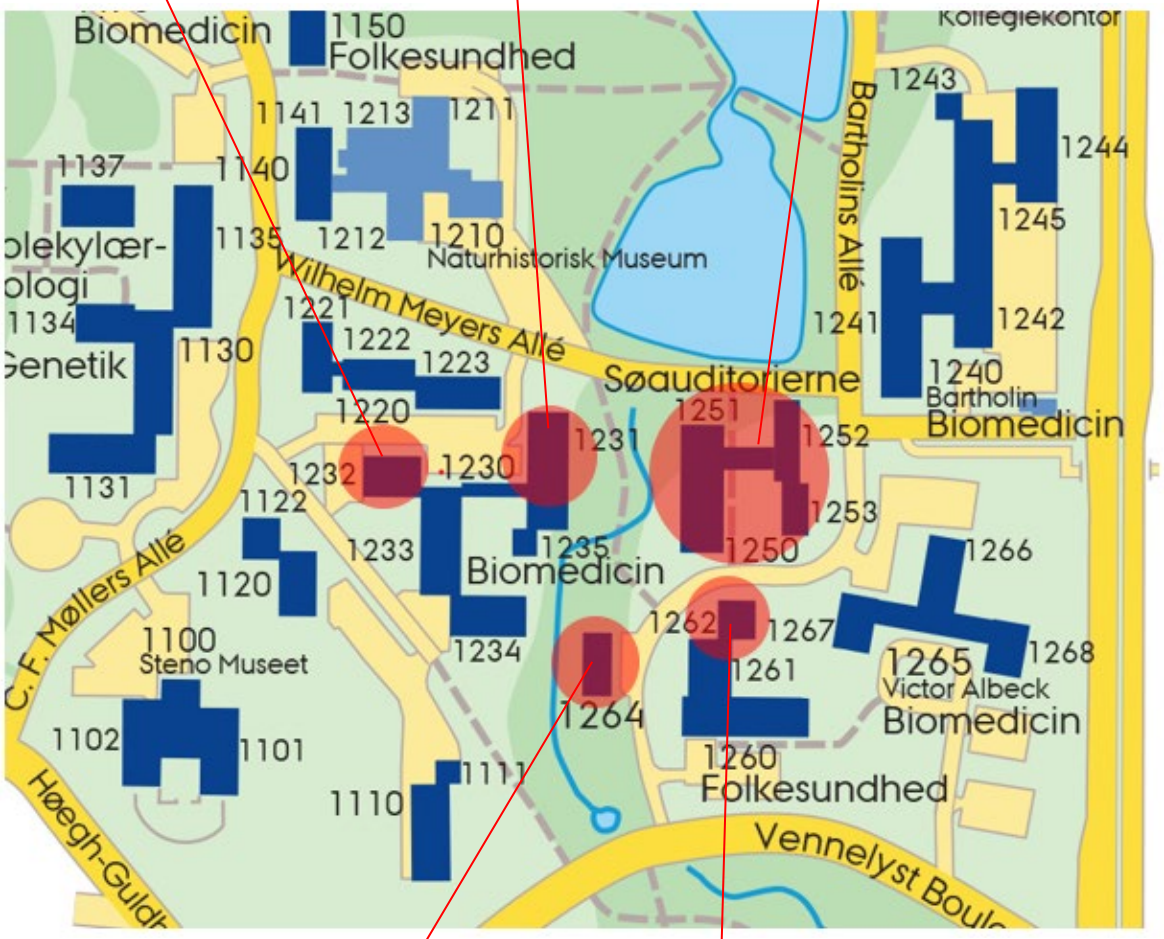
Poster session 1:	Lakeside Lecture Theatre, **William Scharf Auditorium**
Poster session 2:	Lakeside Lecture Theatre, **Eduard Biermann Auditorium**
Poster session 3:	Lakeside Lecture Theatre, **Jeppe Vontilius Auditorium**
Poster session 4:	Lakeside Lecture Theatre, **Merete Barker Auditorium**
Poster session 5:	Lakeside Lecture Theatre, **Per Kirkeby Auditorium**
Poster session 6:	Anatomy (Building 1231), 2nd floor, **Room 214**
Poster session 7:	Anatomy (Building 1231), 2nd floor, **Room 216**
Poster session 8:	Anatomy (Building 1231), 2nd floor, **Room 220**
Poster session 9:	Anatomy (Building 1231), 2nd floor, **Room 224**
Poster session 10:	Anatomy (Building 1231), 2nd floor, **Room 228**
Poster session 11:	Anatomy (Building 1231), 2nd floor, **Room 232**
Poster session 12:	Anatomy (Building 1231), 4th floor, **Small Anatomy Auditorium**
Poster session 13:	Building 1232/115, **Big Anatomy Auditorium**
Poster session 14:	Building 1264, 2nd floor, **Room 209**
Poster session 15:	Building 1264, 3rd floor, **Room 310**
Poster session 16:	Building 1262/101, **Samfundsmedicinsk Auditorium**

Flash talk session 1:	Lakeside Lecture Theatre, **William Scharf Auditorium**
Flash talk session 2:	Lakeside Lecture Theatre, **Eduard Biermann Auditorium**
Flash talk session 3:	Lakeside Lecture Theatre, **Jeppe Vontilius Auditorium**
Flash talk session 4:	Lakeside Lecture Theatre, **Merete Barker Auditorium**
Flash talk session 5:	Lakeside Lecture Theatre, **Per Kirkeby Auditorium**
Flash talk session 6:	Anatomy (Building 1231), 2nd floor, **Room 214**
Flash talk session 7:	Anatomy (Building 1231), 2nd floor, **Room 216**
Flash talk session 8:	Anatomy (Building 1231), 2nd floor, **Room 220**
Flash talk session 9:	Anatomy (Building 1231), 2nd floor, **Room 224**
Flash talk session 10:	Anatomy (Building 1231), 2nd floor, **Room 228**
Flash talk session 11:	Anatomy (Building 1231), 2nd floor, **Room 232**
Flash talk session 12:	Anatomy (Building 1231), 4th floor**, Small Anatomy Auditorium**
Flash talk session 13:	Building 1232/115, **Big Anatomy Auditorium**
Flash talk session 14:	Building 1264, 2nd floor, **Room 209**
Flash talk session 15:	Building 1264, 3rd floor, **Room 310**
Flash talk session 16:	Building 1262/101, **Samfundsmedicinsk Auditorium**

Building 1232
Poster session 13
Flash talk session 13

Anatomy Building
Poster sessions 6-12
Flash talk sessions 6-12

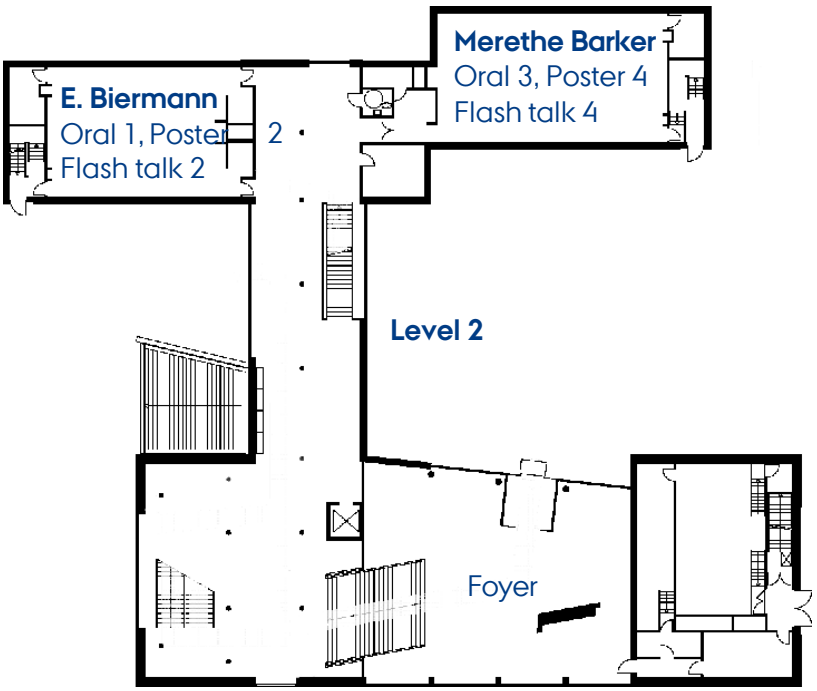
Lakeside Lecture Theatres
Oral sessions 1-3
Poster sessions 1-5
Flash talk sessions 1-5

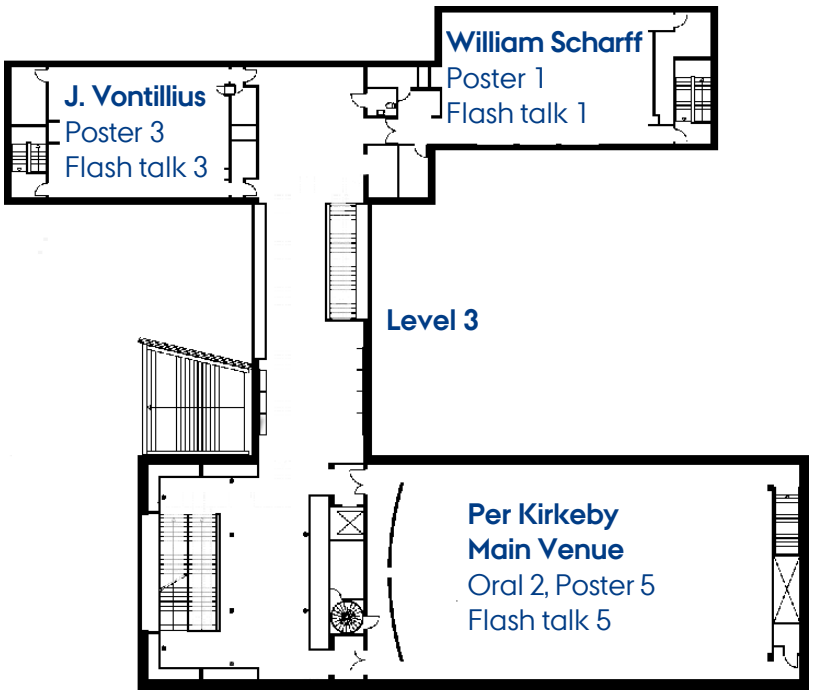


Building 1264
Poster sessions 14-15
Flash talk sessions 14-15

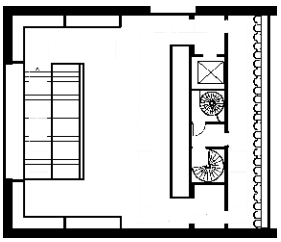
Building 1262
Poster session 16
Flash talk session 16

Lakeside Lecture Theatres





Level 4



Anatomy Building (1231, 2nd and 4th floor)
- Poster session 6-12
- Flash talk 6-12

Big Anatomy Aud. (Building 1232/115)
- Poster 13
- Flash talk 13

Building 1264 (2nd and 3rd floor)
- Poster session 14-15
- Flash talk 14-15

Samfundsmedicinsk Auditorium (1262/101)
- Poster session 16
- Flash talk 16

Session chairs

Find abstract titles and abstracts belonging to your session by searching session name

Fogh-Nielsen Competition – 15.35 – 16.20

Søren Kragh Moestrup and Charlotte Hansen Gabel (co-chair)

Oral sessions – 14.00 – 15.20

Senior chair – name	Oral session
Rikke Nørregaard	1
Gija Rackauskaite	1
Victor Pando-Naude	2
Ulf Simonsen	2
Stinne Ravn Greisen	3
Charlotte Ulrikka Rask	3

Co-chairs – name	Oral session
Peter Loof Møller	1
Mette Faurholdt Gude	2
Anne Birkeholm Jensen	3

Poster sessions – 12.00 – 13.30

Senior chairs – name	Poster session
Christoffer Laustsen	1
Ole Halfdan Larsen	2
Michael Winterdahl	3
Asami Tanimura	4
Peter Agger	5
Cecilia Ramlau-Hansen	6
Peter Nejsum	7
Renee van Der Sluis	8
Anne Hammer	9
Johan Palmfeldt	10
Tue Kragstrup	11
Vivi Schlünssen	12
Elvira Brattico	13
Bent Deleuran	14
Erling Bjerregaard Pedersen	15
David H. Christiansen	16

Co-chairs name	Poster session
Lia Valdetaro	1
Sarannya E	2
Katarzyna Grycel	3
Tobias Stærmose	4
Jacobina Kristiansen	5
Anne Høy Seemann Vestergaard	6
Johannes Enevoldsen	7
Bertram Kjerulff	8
Cecilie Siggaard Jørgensen	9
Charlotte Brinck Holt	10
TBD	11
Charlotte Gabel	12
Sanne Toft Kristiansen	13
Simon Kok Jensen	14
Jakob Wang	15
Kirsten Nordbye-Nielsen	16

Flash talk sessions – 9.45 – 11.15

Senior chairs – name	Flash talk session
Jasper Nijkamp	1
Stine Hasselholt	2
Lars Rolighed	3
Christiane Gasse	4
Ulrik Dalgas	5
Steffen Sinning	6
Iben Sundtoft	7
Simon Tilma Vistisen	8
Solmauz Eskandarion	9
Caroline Cristiano Real Gregório	10
Asif Manzoor Khan	11
Simon Eskildsen	12
Esben Søndergaard	13
Henrik A. Kolstad	14
Simon Gabriel Comerma Steffensen	15
Julian Albarran-Juarez	16

Co-chairs – name	Flash talk session
Andreas Niklassen	1
Katia Soud	2
Susanne Sandbøl	3
Mette Lauge Kristensen	4
Anna Louise Skovgaard	5
Johanne Ahrenfeldt	6

Julie Schjødtz Hansen	7
Anders Dahl Kramer	8
Luisa Schertel Cassiano	9
Sivaranjani Madhan	10
Emil Aagaard Thomsen	11
Zahra Nochi	12
Cagla Cömert	13
Buket Oztürk Esen	14
Linea Blichert-Refsgaard	15
Ankur Razdan	16

Session overview

Find abstract titles and abstracts by searching your name or session

Fogh-Nielsen Competition – 15.35 – 16.20

1. Peder Berg
2. Trine Strandgaard
3. Jacob Horsager

Oral sessions – 14.00 – 15.20

Oral session 1

1. Mikael Fink Vallentin
2. Donato Sardella
3. Alexandra Golabek Christiansen
4. Troels Græsholt Knudsen
5. Bjørn Kristensen Fabian-Jessing

Oral session 2

1. Kristoffer Højgaard
2. Tatyana Fedorova
3. Xiaoli Hu
4. Ellen Schaldemose
5. Maiken Krogsbæk Mikkelsen

Oral session 3

1. Julia Blay
2. Steen Jørgensen
3. Mateo Sokac
4. Jeppe F. Vigh-Larsen

Poster sessions – 12.00 – 13.40

Poster session 1

1. Maiken Ulhøi
2. Karen Wind
3. Louise Callesen
4. Simone Stensgaard
5. Marie Tvilum
6. Eleni Kanouta
7. Ditte Sigaard Christensen
8. Janne Møller

Poster session 2

1. Sixten Harborg
2. Julie Mondahl
3. Zixiang Wei
4. Nikola Mikic
5. Judit Kisistok
6. Søren Thorgaard Bønløkke
7. Maja Dam Andersen
8. Peter Georgi

Poster session 3

1. Lasse Stensvig Madsen
2. Mikkel Karl Emil Nygaard
3. Laura Linnea Määttä
4. Mads Ebbesen
5. Eva Bølling-Ladegaard
6. Niels Okkels
7. Lasse Knudsen

Poster session 4

1. Katia Soud
2. Hjalte Gram
3. Lucie Woloszczukova
4. Karen Marie Juul Sørensen
5. Nanna Møller Jensen
6. Mathias Kaas Ollendorff
7. Malthe Brændholt
8. Thomas Lindhardt

Poster session 5

1. Daniel Fyenbo
2. Oliver Pedersen
3. Tanja Charlotte Frederiksen
4. Nana Christensen
5. Christine Gyldenkerne
6. Bertil Ladefoged

7. Rajkumar Rajanathan
8. Kristoffer Berg-Hansen
9. Andreas Bugge Tinggaard

Poster session 6

1. Ankur Razdan
2. Helle Jørgensen
3. Cecilia Hvitfeldt Fuglsang Nielsen
4. Tine Bichel Lauritsen
5. Nicholas Papadomanolakis-Pakis
6. Martin Petri Bækby
7. Anne Wilhøft Kristensen
8. Inge Brosbøl Iversen

Poster session 7

1. Frederik Holm Rothemejer
2. Ian Møller-Nielsen
3. Nanna Steengaard Mikkelsen
4. Nikolaj Bøgh
5. Alexander Rafael Lavilla Labial
6. Peter Preben Eggertsen
7. Line Dahl Jeppesen

Poster session 8

1. Thomas Emmanuel
2. Johanna Heinz
3. Mikkel Illemann Johansen
4. Marie Pahus
5. Sofine Heilskov
6. Lea Skovmand Jensen
7. Laura Øllegaard Johnsen
8. Michael Schou Jensen
9. Morten Brok Molbech Madsen

Poster session 9

1. Stine Smedegaard
2. Lise Qvirin Krogh
3. Kathrine Dyhr Lycke
4. Anna Sofie Koefoed
5. Anna Louise Vestergaard
6. Anders Breinbjerg
7. Ellen Steffensen
8. Merete Dam
9. Britt Borg

Poster session 10

1. Anne Kathrine Nissen Pedersen

2. Mette Louise Gram Kjærulff
3. Indumathi Kumarathas
4. Kevin Marks
5. Mikkel Oxfeldt
6. Thien Vinh Luong

Poster session 11

1. Lene Ugilt Pagter Ludvigsen
2. Naziia Kurmasheva
3. Morten Horsholt Kristensen
4. Lasse Refsgaard
5. Martin Rasmussen
6. Line Raunsbæk Knudsen
7. Maithri Aspari
8. Josephine Hyldgaard
9. Frederik Prip

Poster session 12

1. Julie Suhr Villefrance
2. Tilde Kristensen
3. Emilie Hasager Bonde
4. Eeva-Liisa Røssell Johansen
5. Andreas Nielsen Hald
6. Julie Duval
7. Anders Aasted Isaksen
8. Troels Kjeldsen
9. Josephine Therkildsen

Poster session 13

1. Tina Birkeskov Axelsen
2. Erik Kaadt
3. Lotte Veddum
4. Cecilie Isaksen
5. Julie Grinderslev Donskov
6. Shokouh Arjmand
7. Rogini Balachandran
8. Aline Dragosits
9. Irina Palimaru Manhoobi

Poster session 14

1. Frederik Kraglund
2. Sham Al-Mashadi Dahl
3. Anne Karmisholt Grosen
4. Wenfeng Ma
5. Thea Vestergaard
6. Jesper Berg Nors
7. Mira Mekhael
8. Marie Bach Nielsen

Poster session 15

1. Karina Binda
2. Xiaoyu Zhou
3. Toke Alstrup
4. Lisa Carlson Hanse
5. Anne Bruun Rovsing
6. Sofie Andersen
7. Camilla G. Jensen

Poster session 16

1. Shuting Yang
2. Luisa Schertel Cassiano
3. Lisa Reimer
4. Stian Langgård
5. Anette Bach Jønsson
6. Lola Qvist Kristensen
7. Uwe M. Pommerich

Flash talk sessions – 9.45 – 11.15

Flash talk session 1

1. Ola Sobhy Ahmed
2. Lasse Hansen
3. Imaiyan Chitra Ragupathy
4. Camilla Blunk Brandt
5. Alberto Gonzalez Olmos
6. Mathis Ersted Rasmussen
7. Emma Riis Skarsø
8. Nadine Vatterodt
9. Amanda Ringmann Fagerberg

Flash talk session 2

1. Ole Ahlgreen
2. Alberte Seeberg
3. Ole Borup Svendsen
4. Mie Kristine Just Pedersen
5. Pia Boxy
6. Gemma Fernández Rubio
7. Rasmus West Knopper
8. Hani Ahmed Sheik

Flash talk session 3

1. Cecilie Boyskov
2. Josephine R. Quist
3. Tone Rubak
4. Lotte Lindgreen Eriksen
5. Mona Kristiansen

6. Andrea Lund
7. Karen Busk Hesseldal
8. Tua Gyldenholm
9. Pernille Thordal Larsen

Flash talk session 4

1. Lisbeth Mølgaard Laustsen
2. Rebecca Nyengaard
3. Marie Vadstrup Pedersen
4. Christian Jentz
5. Erik Mano Perfalk
6. Lina Münker
7. Eva Skovslund Nielsen
8. Gali Ibrahim

Flash talk session 5

1. Maja Husted Hubeishy
2. Anne Dorte Lerche Helgestad
3. Anette Bjerregaard Alrø
4. Signe Vogel
5. Tobias Gemælke
6. Laurits Taul-Madsen
7. Maiken Meldgaard
8. Karoline Kærgaard Hansen
9. Rasmus Møller Jørgensen
10. Mette Jørgensen Langergaard

Flash talk session 6

1. Christine Møberg
2. Demi van Der Horst
3. Rikke Kongsgaard Rasmussen
4. Demet Özcan
5. Theresa Jakobsen
6. Jonas Busk Holm
7. Gustav Poulsgaard
8. Maria Højen
9. Andrea René Jørgensen
10. Asta Mannstaedt Rasmussen

Flash talk session 7

1. Mathilde Kanstrup Christensen
2. Louise Krog
3. Maja Holk Vind
4. Malene Sørensen
5. Sarah Marie Bjørnholt
6. Ina Marie Dueholm Hjorth
7. Magnus Leth-Møller
8. Emma Davidsen
9. Maja Thøgersen

Flash talk session 8

1. Frederik Jensen
2. Christian Skibsted
3. Khatera Saii
4. Jacob Valentin Hansen
5. Helen Gräs Højgaard
6. Jonathan Nørtoft Dahl
7. Gregory Wood
8. Olivia Wagman
9. Judit Prat Duran
10. Dalia Karzoun

Flash talk session 9

1. Muhammed Alparslan Gøkhan
2. Anders Sørensen
3. Mathias Vestergaard
4. Simone Elmholt
5. Fernando Valentim Bitencourt
6. Ali Abood
7. Josefine Beck Larsen
8. Sarah Stammose Freund
9. Merete Nørgaard Madsen

Flash talk session 10

1. Ditte Kamille Rasmussen
2. Annita Petersen
3. Anne Sofie Frølund
4. Hakim Ben Abdallah
5. Søren Lomholt
6. Kathrine Pedersen
7. Emilie Grarup Jensen
8. Andreas Wiggers Nielsen
9. Clara Mistegaard
10. Marie Næstholt Dahl

Flash talk session 11

1. Thomas Wisbech Skov
2. Stine Sofie Frank Lende
3. Xin Lai
4. Morten Kelder Skouboe
5. Anne-Mette Iversen
6. Kristoffer Skaalum Hansen
7. Emma Faddy
8. Søren Sperling Haugen

Flash talk session 12

1. Thor Mertz Schou
2. Bjarke Søgaard
3. Victor Hvingelby
4. Peter Kolind Brask-Thomsen
5. Ida Stisen Fogh-Andersen
6. Vitalii Dashkovskyi

7. Kim Hochreuter
8. Maria Vlachou
9. Charlotte Tornøe Ekkelund Nørholm
10. Mathias Jespersen

Flash talk session 13

1. Jasper Carlsen
2. Jannick Maesen
3. Jemila Peter Gomes
4. Maya Pedersen
5. Anders Stouge
6. Ole Emil Andersen
7. Maj Bangshaab
8. Lotte Lina Kloby Nielsen
9. Mathilde Thrysøe Jespersen

Flash talk session 14

1. Jakob Kjølby Eika
2. Pernille Jul Clemmensen
3. Nadia Roldsgaard Gadgaard
4. Frederik Pagh Kristensen
5. Mette Søeby
6. Philip Munch
7. Christian S. Antoniussen
8. Martin Bernstorff
9. Stine Fjendbo Galili

Flash talk session 15

1. Tine Ginnerup Andreasen
2. Marcus Blanke
3. Sarah Kelddal
4. Layla Pohl
5. Yifan Tan
6. Aimi Hamilton
7. Lene Munk
8. Ninna Kjær Nielsen
9. Tina Lund Leunbach
10. Rikke Milling

Flash talk session 16

1. Christina Harlev
2. Helene Tallaksen
3. Sofie Fonager
4. Ida Klæstrup
5. Julie Axelsen
6. Line Mathilde Brostrup Hansen
7. Maja Fuhlendorff Jensen
8. Diana Sharysh
9. Anne Sofie Hammer

Fogh-Nielsen Competition

Brain-first versus body-first Parkinson's disease – a multimodal imaging study

Jacob Horsager, Department of Clinical Medicine

J. Horsager, Department of Clinical Medicine; K Andersen, Department of Clinical Medicine; K. Knudsen, Department of Nuclear Medicine and PET; C. Skjærbæk, Department of Nuclear Medicine and PET; TD. Fedorova, Department of Clinical Medicine; N. Okkels, Department of Clinical Medicine; E. Schaeffer, Department of Neurology, Kiel; SK. Bonkat, Department of Neurology, Kiel; J. Geday, Privat practice, Neurology; M. Otto, Department of Clinical Neurophysiology and Neurology; M. Sommerauer, Department of Neurology, University Hospital Cologne; EH. Danielsen, Department of Neurology; E. Bech, Privat practice, Neurology; J. Kraft, Privat practice, Neurology; OL. Munk, Department of Nuclear Medicine and PET; SD. Hansen, Privat practice, Neurology; N. Pavese, Department of Nuclear Medicine and PET; R. Göder, Department of Psychiatry, Kiel; DJ. Brooks, Department of Nuclear Medicine and PET; D. Berg, Department of Neurology, Kiel; P. Borghammer, Department of Nuclear Medicine and PET.

Background.
Intraneuronal accumulation of misfolded α-synuclein is the primary cause of neuronal degeneration in Parkinson's disease (PD). Compelling evidence show that α-synuclein behaves like prions – an infectious protein. That misfolded α-synuclein originate in the gut and spreads to the brain has been a leading hypothesis in nearly two decades. However, several contradicting reports have been published. To resolve this controversy, we hypothesized that PD comprise two subtypes; 1) brain-first PD, where initial α-synuclein starts in the brain, and 2) body-first PD, where the initial α-synuclein starts in the gut and spreads through the autonomic nervous system to the brain.

Methods.
We included 37 newly diagnosed PD patients. We mapped the degree of neuronal damage to different levels of the nervous system:

- Autonomic nervous system: 123I-MIBG cardiac scintigraphy and 11C-donepezil PET/CT of the colon.
- Pons: Neuromelanin-sensitive MRI of locus coeruleus and polysomnography to evaluate REM-sleep behavior disorder (RBD) status – a parasomnia caused by damage to pontine nuclei.
- Midbrain: 18F-DOPA PET of the nigrostriatal dopaminergic neurons.

Results.
Patients with RBD (body-first PD) displayed more damage to the autonomic nervous system than patients without RBD (brain-first PD).

Conclusion.
Our data strongly suggest that PD comprise a brain-first¬ PD subtype where the pathology starts in the brain, and a body-first PD subtype where the pathology start in the gut, and

spreads via the autonomic nervous system to the brain. Fundamental pathophysiological mechanism may differ between the subtypes. This is crucial when testing future neuroprotective treatments.

Keywords: Clinical neuroscience, Medical technology and diagnostic techniques, Other

Cystic fibrosis: pathophysiology beyond the airways and new clinical implications

Peder Berg, Department of Biomedicine, Physiology

Jesper Frank Andersen, Department of Biomedicine; Mads V. Sorensen, Department of Biomedicine; Tobias Wang, Department of Biology; Hans Malte, Department of Biology; and Jens Leipziger, Department of Biomedicine

Introduction: Cystic fibrosis (CF) is one of the most frequent lethal inherited diseases and is caused by dysfunction of the CFTR anion channel. In CF, the renal ability to excrete an excess amount of bicarbonate is impaired leading to an increased risk of metabolic alkalosis. The underlying cause is defective bicarbonate secretion in the β-intercalated cells of the collecting duct that requires both CFTR and pendrin for normal function. Metabolic alkalosis could cause ventilatory depression and has been proposed to contribute to acute hypercapnic respiratory failure in CF patients. However, a potential connection between impaired renal bicarbonate excretion in CF and respiratory failure has not been examined.

Methods: Using intermittent closed barometric respirometry, we studied the respiratory consequences of acute oral base-loading in wild-type, CFTR knock-out and pendrin knock-out mice. These studies were further supplemented by blood gas analysis and metabolic cage experiments.

Results: In wild-type mice, oral base-loading induced a dose-dependent metabolic alkalosis, fast urinary removal of base and a moderate base-load did not perturb respiration. In contrast, CFTR and pendrin knock-out mice, which were unable to rapidly excrete excess base into the urine, developed a marked and transient depression of respiration when subjected to the same base-load.

Discussion: Swift renal base elimination in response to an acute oral base-load is a necessary physiological function to avoid respiratory depression. In CF, metabolic alkalosis likely contributes to the commonly reduced lung function via a suppressor effect of respiration regulation.

Keywords: Nephrology, Cell biology, Respiratory system

Elevated T cell exhaustion and immune cell infiltration is associated with BCG failure in patients with non-muscle invasive bladder cancer

Trine Strandgaard, Department of Clinical Medicine, Department of Molecular Medicine

I. Nordentoft, Department of Molecular Medicine, E. Christensen, Department of Molecular Medicine, S. Lindskrog, Department of Molecular Medicine, P. Lamy, Department of Molecular Medicine, K. Birkenkamp-Demtröder, Department of Molecular Medicine, T. Steiniche, Department of Pathology, J. Bjerggaard Jensen, Department of Urology, L. Dyrskjøt, Department of Molecular Medicine

Introduction

Patients with high-risk non-muscle invasive bladder cancer (NMIBC) are treated with the immunotherapy BCG. However, 40% of the patients do not have a clinical benefit from the treatment. The composition of cells and molecular changes in the tumor, as well as levels of immune-related proteins may impact significantly on therapeutic outcome.

Materials and methods

Samples from 156 patients diagnosed with NMIBC were included in the study, including 235 tumors, 569 urine samples, and 304 biopsies from the normal appearing urothelium. Urinary levels of immune-oncology related proteins were measured before and after treatment. Whole exome and RNA sequencing data was generated from tumors, whereas DNA from adjacent normal biopsies was subjected to deep targeted sequencing.

Results

We found that treatment with BCG activated the immune system and induced cytokine release into the urine regardless of clinical outcome. However, patients with a clinical benefit of BCG had significantly higher levels of the proteins MUC-16 and CCL23 compared to clinically unresponsive patients. In total, 51% of patients had an immune infiltrated subtype after treatment compared to 14% before treatment. Clinically unresponsive patients showed signs of immune exhaustion after treatment indicated by high levels of the T cell exhaustion markers CTLA4 and LAG3. Finally, patients with multiple molecular alterations in the adjacent normal appearing tissue before treatment showed an increased clinical response.

Conclusion

BCG induces an immune response in the bladder and treatment resistance and response may be explained by exhaustion of T cell and mutations in normal appearing cells, respectively.

Keywords: Oncology, Urology, Cell biology

Oral session 1

When the heart suddenly stops: Calcium for cardiac arrest

Mikael Fink Vallentin, Department of Clinical Medicine

Granfeldt, Asger

Meilandt, Carsten

Povlsen, Amalie L

Sindberg, Birthe

Holmberg, Mathias J

Iversen, Bo N

Mærkedahl, Rikke

Mortensen, Lone R

Nyboe, Rasmus

Vandborg, Mads P

Tarpgaard, Maren

Runge, Charlotte

Christiansen, Christian F

Dissing, Thomas H

Terkelsen, Christian J

Christensen, Steffen

Kirkegaard, Hans

Andersen, Lars W

4 million times a year, a person's heart suddenly and unexpectedly stops beating. Despite advances in early help, cardiac arrest is detrimental with only one in five regaining adequate circulation and a chance at surviving. After 30 days one in six is alive, and survivors may attain mental and physical long-term functional debilitation. Recent clinical trials showed that some drugs may benefit these patients, and this increased the call for new and rigoriously tested interventions.

Calcium, an abundant mineral in the body, serves many essential functions incl. one in muscle contraction. Calcium given directly into the blood causes the heart to beat quicker and with greater force. For clinicians treating cardiac arrest, this may have introduced the idea that calcium is beneficial for regaining adequate circulation: recent

American numbers showed that 1 in 3 patients received calcium during cardiac arrest. However, this practice contrasts the lack of evidence and that international guidelines only recommend calcium in rare cases.

This randomized controlled trial compared administration of calcium vs. placebo during adult cardiac arrest.

RESULTS

At 391 included patients, the trial was stopped early due to a signal of harm. In the calcium group 19% achieved the primary outcome of regaining adequate circulation vs. 27% in the placebo group (risk ratio (RR) 0.72, 95% confidence interval (CI): 0.49, 1.03, p=0.09). The same signal was seen for 30-day survival (RR 0.57, 95%CI: 0.27-1.18, p=0.17) and 30-day survival with a favorable functional outcome (RR 0.48; 95%CI: 0.20-1.12, p=0.12).

CONCLUSION

Calcium given during cardiac arrest is not beneficial and may even cause harm.

Keywords: Cardiovascular system, Other, Other

A novel endothelial-derived cell population in the renal subcapsular space participates in dynamic renal cell remodeling after injury.

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Endothelial cells (ECs) may undergo endothelial-to-mesenchymal-transition (EndMT), an important process in development and disease processes, such as tissue fibrosis. The renal interstitial compartment is difficult to study in vivo, thus the prevalence and dynamics of EndMT are incompletely understood. Here we used serial intravital 2-photon microscopy (2PM) of transgenic mouse kidneys to track EndMT after laser-induced tissue injury.

Inducible Cdh5-Confetti mice were used to identify individual ECs through the random expression of 2 out of the 4 fluorescent proteins resulting in 1 out of 10 possible color-combinations. After implanting an abdominal imaging window, control and injured fields of view (FOV) were repeatedly scanned for 5-7 days with 2PM. Injury was achieved by laser-induced thermal ablation.

Baseline 2PM of Confetti mice, revealed a morphologically distinct Cdh5+-lineage cell population with flattened cellular body (termed flat cells) within the renal subcapsular space (SCS). Flat cells were observed isolated or in a continuum with peritubular ECs and mostly static in control FOVs. In response to injury, we frequently observed the formation of new flat cells through the transitioning of several resident ECs into a flattened phenotype followed by targeted migration towards the injury site. Strikingly, flat cells not only migrated but also engaged in the sprouting of new vascular branches at the injury sites. Immunolabelling showed that flat cells expressed the mesenchymal marker αSMA, suggestive of EndMT.

Our data identified a novel EndMT-derived endothelial lineage cell population, which engages in dynamic renal cell remodelling after acute renal injury.

Keywords: Nephrology, Animal models/disease models, Other

Sensitization and dermatitis among epoxy exposed workers producing wind turbine blades

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Introduction: Epoxy resin systems (ERS) are well-known sensitizers of the skin. A high prevalence of sensitization and dermatitis has been reported among workers exposed to ERS. Due to this, comprehensive personal protective equipment is required when working with ERS. No recent studies have evaluated the effect of the use of such safety equipment.

Objectives: The aim of this study was to estimate the occurrence of dermatitis and sensitization to ERS among epoxy-exposed workers producing wind turbine blades in Denmark while using up-to-date protective measures.

Material and Methods: A cross-sectional study was performed at two Danish factories producing rotor blades for wind turbines. A questionnaire regarding recent and former skin rashes, allergies, atopic dermatitis, and asthma was answered by 181 epoxy-exposed production workers and 41 non-exposed office workers. Physical examination of the skin was followed by testing with a tailored patch test series including epoxy resins and hardeners as well as 35 allergens from the European Standard Series (TRUE test).

Results: In total, 16 (8.7%) of the exposed workers were sensitized to one or more epoxy components, whereas none of the non-exposed workers were sensitized. A 5-fold increased odds ratio (5.10, 95% CI: 1.72-15.06) of dermatitis was observed among workers sensitized to epoxy components. 25% of the positive reactions were not found using the Standard True test only.

Conclusion: Despite up-to date skin protection sensitization to ERS remain high among epoxy- exposed lamination workers. These findings document the need for new and efficient preventive efforts.

Keywords: Dermatology, Work environment and organisation, Other

Is Parental Illness a Risk Indicator of Future Severe Physical Child Abuse?

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Child maltreatment has detrimental consequences across the lifetime. Preventive efforts are warranted, and knowledge of risk indicators is a necessity to qualify these efforts. A widely accepted theory of physical abuse is that the risk of abuse is determined by family stressors overcoming family resources. Thus, it seems reasonable that parental disease might increase the risk of physical abuse. Parental disease has been studied previously as a risk indicator, but studies are scarce and the main focus has been psychiatric diagnoses or conjugates of highly diverse disease categories.

Our current study will utilize Danish population-level data from 1997 to 2018 to create models with parental disease as the exposure and severe physical child abuse as registered in health and police data as the outcome. All children 0 through 17 years of age residing in Denmark and with Danish citizenship during the period of interest will be included. Two separate analytic strategies will be employed: a cohort study matched on exposure and covariates and analyzed using pseudovalues (this results in relative risk estimates), and a G-model allowing for treatment-confounder feedback.

Parental disease will be operationalized as severity, using a modified version of the Charlson Comorbidity Index, and as separate categories, strongly inspired by Prior et al.

We hypothesize that increased illness severity will lead to increased risk of physical child abuse and that all categories of disease will lead to increased risk. Preliminary results are expected in December 2021.

Keywords: Public health, Socio-economic conditions, Paediatrics

Increasing Protein Expression Downstream of a Double Dicer-Independent shRNA-Containing Cassette for Multi-Targeting Gene Therapy in Neovascular Age-Related Macular Degeneration

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Background
Intravitreal injections with vascular endothelial growth factor (VEGF) inhibitors constitute current standard treatment for neovascular age-related macular degeneration (nAMD). However, two thirds of patients are either partial or non-responders, and there is a need for new treatment modalities holding the potential to target multiple pathways.

We have designed multigenic vectors incorporating intron-embedded double Dicer-independent short hairpin RNA (agshRNA) with potent VEGF knockdown, followed by an antiangiogenic gene. However, analysis has revealed mis-splicing leading to low expression of the downstream gene. Accordingly, we aimed to (i) eliminate mis-splicing by designing intron-embedded agshRNAs without potential competing splice sites and to (ii) increase expression of the downstream gene.

Methods
Using the NetGene2 server for splice site prediction and mFold for RNA secondary structure prediction, we designed new constructs predicted to eliminate problematic splice sites. For easy validation, green fluorescent protein (GFP) was inserted downstream, and fluorescent microscopy, flow cytometry, and RT-PCR with sequencing of amplicons were used to investigate splicing of the agshRNA construct and GFP expression.

Results
Fluorescent microscopy and flow cytometry showed a significant increase in downstream GFP expression, and RT-PCR with sequencing of amplicons confirmed correct splicing.

Conclusion
By eliminating predicted aberrant splice sites in our agshRNA-containing cassette we corrected splicing and thereby increased downstream GFP expression, paving the way for inserting therapeutic proteins with the aim of developing efficient, persisting therapy for nAMD.

Keywords: Ophthalmology, Laboratory science, Other

Oral session 2

Novelty-induced memory enhancement

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In our daily life, we encounter many experiences, which are stored in the short-term memory and soon forgotten. However, when we experience something unexpected and new, it will create a memory lasting much longer. Short-term memories of something experienced near the novel experience will be affected too and be remembered, even if completely unrelated. This cross consolidation of memories can be explained using the 'synaptic tagging and capture' (STC) hypothesis. STC explains how early long-term potentiation (early-LTP), induced in different synapses, in the same neuron, can affect each other during the conversion into long lasting late-LTP.

Here, we use object location task (OLT) to monitor hippocampus-based spatial memory. Two identical objects placed in two corners of an arena. 24 hours later, the animal re-enter the arena, where one object has been moved to a different corner (encoding). Memory is recorded as the preference for the object in the novel location. To boost the memory consolidation, we use 'novelty exposure' 30 minutes after the encoding. For the novelty condition, a square arena containing a novel floor substrate has been used.

The behavioral task has been setup and optimized. Different contexts and encoding conditions have been tested and we found that 3 times 5 minutes encoding with the novelty-exposure produces a significant 24-hour memory compared to 'no novelty controls'.

Using the OLT we have established significant novelty-induced memory enhancement. Further research will be done using nano-string analysis of mRNA and miRNA. Moreover, studies into the brain circuits involved, will be performed using optogenetics and drug intervention.

Keywords: Basic neuroscience, Animal models/disease models, Cell biology

Parasympathetic imaging with [11C]donepezil PET in early Parkinson's disease.

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Background

Patients with PD display signs of parasympathetic denervation. We demonstrated that [11C]donepezil PET show decreased signal in the small intestine, pancreas and myocardium of moderate-stage PD patients. [11C]donepezil PET may therefore be the first successful imaging modality to visualize parasympathetic denervation. Here, we study early-stage PD patients to establish whether the parasympathetic denervation is visible already at the time of diagnosis. Patients will be compared to a group of healthy controls.

Methods

We included 19 PD patients with a mean disease duration of 1.5 years and 16 age- and sex-matched controls. Clinical stage was rated with the Hoehn and Yahr (HY) staging system. High-resolution CT-scans and PET 11C-Donepezil images of abdomen and thorax were obtained from all subjects. PMOD software was used to manually define volumes of interest based on anatomical CT scans and functional PET scans using a modified version of previously described methodology.3

Results

11C-donepezil PET signal in PD patients was decreased by 14 % (p=0.04) in the small intestine and 22 % (p=0.002) in the colon compared to healthy controls.

Conclusions

Newly diagnosed PD patients displayed lower 11C-donepezil PET signal in the small intestine and colon compared to healthy controls. In conclusion, parasympathetic denervation of the gut seems to be present already at the early stage of PD and potentially in prodromal stages of disease development.

Keywords: Clinical neuroscience, Medical technology and diagnostic techniques, Basic neuroscience

NOCICEPTIVE SCHWANN CELLS MAY BE CRITICAL FOR MAINTENANCE OF CUTANEOUS SENSORY NERVES

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Diabetic polyneuropathy (DPN) is a common disabling complication of diabetes that can either be painless or painful. Treatment of diabetic neuropathic pain is far from optimal and the mechanisms behind neuropathic pain are largely unknown. A pathological hallmark is a dramatic decrease of cutaneous nerves. In 2019, a highly specialized nociceptive Schwann cells (NSCs) were introduced for the first time, cells that are believed to protect the nerves by forming a mesh-like neural-glio networking structure. However, the NCS have not been quantified before and it is unclear whether their density differs between animals with and without pain. Here, we took hind paw biopsies from streptozocin-induced T1D mouse models and developed a set of counting rules to quantify the NSC density at early (hypersensitive to touch) and late stage (hyposensitive to touch) of type 1 diabetes. Using advanced immunohistology, we defined NSCs as being S100+/Sox10+/DAPI+ cells in close proximity with the sensory nerves, with the somas located within 25-µm depth in the subepidermis. We found that, compared with age-matched healthy mice, mice that had diabetes for a shorter duration had normal density of cutaneous nerves but decreased NSC density. In contrast, mice with a longer duration of diabetes had lower density of cutaneous nerves but normal NSC density compared with their age-matched controls. Here, we describe a novel way to define and quantify NCS, and we demonstrate that NCS density declines before the cutaneous nerves do, thereby strengthening the speculations that NSCs are crucial for maintenance of cutaneous sensory nerves and may play a vital role in sensation and nociception.

Keywords: Clinical neuroscience, Animal models/disease models, Other

Cold or warm? Paradoxical Heat Sensations in Diabetes

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Background: A paradoxical heat sensation (PHS) is the feeling of warmth when the skin is cooled. PHS is a pathological sign associated with neuropathy e.g. diabetic polyneuropathy (DPN). Characterizing patients with PHS compared to patients without PHS may improve our understanding of what leads to PHS. We hypothesized that the frequency of PHS was higher in patients with DPN and that PHS was associated with sensory loss.

Methods: Using data from a study on prevalence of neuropathy in type 2 diabetic patients (Gylfadottir and Itani et al. 2020); we analyzed the relationship between different sensory parameters, neuropathy status and PHS. We included results on quantitative sensory testing, nerve conduction and skin biopsies.

Results: 277 DPN patients, 63 patients without DPN and 97 matched non-diabetic controls were included. The frequency of PHS were higher among patients, both with and without DPN, than among controls (DPN: 31(CI:25;37)%, no DPN: 32(21;45)%, controls: 18(11;27)%, DPN: $p = 0.01$ and no DPN: $p = 0.04$, Pearson Chi2-test). There was no difference in PHS frequency between patients with or without DPN. PHS responders in the control group and patients without DPN exhibited thermal sensory loss. On the contrary, DPN patients had thermal sensory loss regardless of PHS status. Mechanical and vibration thresholds, results on nerve conduction and skin biopsies were equal among participants with or without PHS, also if subdivision into groups.

Conclusion: The frequency of PHS was larger among patients with or without DPN. PHS was related to thermal sensory loss. Further studies aiming at clarifying why some DPN patients experience PHS while others do not are needed.

Keywords: Clinical neuroscience, Basic neuroscience, Molecular metabolism and endocrinology

THE EFFECT OF OLANZAPINE TREATMENT ON THE FEEDING REGULATING REGIONS OF HYPOTHALAMUS

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Olanzapine (OLZ) is one of the most commonly used 2nd generation antipsychotic drugs for the treatment of schizophrenia. Side effects from OLZ includes increased food intake, decreased activity, obesity and metabolic dysfunction, occurring in up to 30% of treated patients. New treatment combinations of OLZ with opioid antagonists show decreased weight gain from OLZ treatment.

To understand the chronic effects of OLZ on the homeostatic hunger controlling areas and the opioid system of hypothalamus, we have treated adult female rats with long-acting injectable OLZ for 28 days. Hunger or satiety controlling neurons of hypothalamus (POMC, MCH, Orexin A and MC4R) where immunohistochemically stained for stereological counting and local neuron soma size estimation. Using RNAscope and receptor autoradiography we targeted μ, κ and δ opioid receptor (OR) RNA and active surface receptors, respectively.

OLZ lead to significant weight gain after only 48 hours of treatment and increasing throughout the study. Food intake was significantly increased after 48 hours of treatment, but returned to control levels after 14 days of treatment. In the paraventricular nucleus, κ OR RNA (Oprk1) expression was increased, and both μ OR and κ OR availability was increased after OLZ. In the arcuate nucleus, μ OR availability was increased from OLZ. Stereological estimations will be finalized soon.

Although OLZ does not bind to opioid receptors, we observe here a secondary effect on the opioid receptor system of hunger controlling regions of the hypothalamus. We believe that OLZ binding to 5-HT2A/2C receptors are part of this effect, and in future studies we will investigate this.

Keywords: Psychiatry, psychology and mental health, Clinical neuroscience, Pharmacology

Oral session 3

The glutamate-cystine antiporter SLC7A11 plays a role in anti-viral immunity

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Pathogenic viruses alter the cellular metabolism of the infected host cell to ensure sufficient levels of energy and biomolecules for de novo production of progeny viruses. Such alterations lead to virus-induced changes in the flux across central metabolic pathways and in the abundancy of distinct metabolites. If chances in metabolite abundancy is sensed by the host to induce anti-viral responses is still unclear. Here we demonstrate that glutamate is accumulated and secreted in keratinocytes upon infection with herpes simplex virus, both in vitro and in vivo. This, prompts an efficient anti-viral program that includes formation of anti-viral glutathione through a process that depends on the NRF2-induced glutamate-cysteine antiporter SLC7A11, also known as xCT. The overall expression of xCT is relatively restricted with the highest expression levels in the CNS and parts of the immune system. Moreover, elevated expression of xCT has also been reported in cancer. However, it has not previously been associated with anti-viral mechanisms. Here we demonstrate that the glutamate/cysteine anti-porter xCT is part of an anti-viral cellular program as suppression of xCT increases viral replication. In line with that, increasing the expression of xCT by CRISPR activation increases glutamate secretion, glutathione formation and impaired viral replication. In this manner, the host counters the incoming virus with metabolic changes that suppress viral replication. Finding new ways to target antiviral mechanisms can help to develop new anti-viral strategies.

Keywords: Infection, Inflammation, Cell biology

First-in-human in vivo non-invasive assessment of cardiac metabolism during adenosine stress test

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INTRODUCTION: Hyperpolarized [1-13C]pyruvate cardiac magnetic resonance imaging (HP CMR) is an emerging, non-invasive method with the ability to detect cardiac metabolism in vivo, beyond tissue glucose uptake. HP CMR visualizes the intracellular conversion of pyruvate to lactate in areas of ischemia and pyruvate to bicarbonate in areas of viable myocardium. The aim of the present study was to study feasibility of HP CMR during an adenosine stress test in the human heart.

METHODS: Healthy volunteers underwent CINE-CMR and HP CMR at rest and during an adenosine stress test. Kinetic modelling of pyruvate metabolism was used to measure rate of pyruvate conversion to lactate (kPL) and bicarbonate (kPB) at rest and during stress. Semi-quantitative assessment of first-pass myocardial [1-13C]pyruvate perfusion was used to measure time-to-peak (TTP) in the myocardium as a marker of perfusion.

RESULTS: Six healthy volunteers were recruited. No major side effects were observed. Myocardial perfusion was significantly increased during stress with reduction in TTP from 6.2 ± 2.8 sec to 2.7 ± 1.3 sec, p=0.04. The kPL increased statistically significant from 0.011 ± 0.009 sec-1 to 0.020 ± 0.010 sec-1, p=0.04. The kPB increased statistically significant from 0.004 ± 0.004 sec-1 to 0.012 ± 0.007 sec-1, p=0.008.

DISCUSSION: Our data represent the first human study of HP CMR during an adenosine stress test. We observed an increased carbohydrate oxidation during cardiac stress in the healthy human heart. The present study translates HP CMR to the clinic and forms a basis for comparisons in future studies of cardiac diseases.

Keywords: Cardiovascular system, Medical technology and diagnostic techniques, Molecular metabolism and endocrinology

Genome Mapped as Image (GMI)

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Deep learning is widely used in many applications including medical imaging, speech recognition and language processing. However, large quantities of our data come in tabular form where we do not assume spatial connectivity between observations. In multi-omics analysis all of the data is structured as a table where a single row represents a single observation. In most cases, using this type of data is computationally heavy on statistical analyses which have to be corrected for false discovery rate. Furthermore, advanced machine learning models are not popular in research because they lack interpretability as they are often described as “black box” models. Here we present a framework with multiple options for integrating multi-omics data by transforming the data into new spatially dependent space which can be utilized in deep learning models and finally used for inference.

Keywords: Oncology, Epidemiology and biostatistics, Cell biology

Cellular and Subcellular Muscle Glycogen Metabolism and High-Intensity Exercise Performance

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Muscle glycogen is the major fuel during high-intensity exercise (HIE) and large declines can occur after relatively short durations; however, the relationship between muscle glycogen and HIE performance has not been studied in a placebo-controlled design. Moreover, glycogen is stored in distinct subcellular compartments and specific depletion of these fractions may be a key aspect in any relationship between muscle glycogen and performance. PURPOSE: To investigate the effects of low muscle glycogen on repeated sprint ability (RSA) using a double-blinded design with special emphasis on subcellular glycogen. METHODS: Eighteen well-trained subjects performed glycogen-depleting cycling exercise; three periods of 10x45 s at ~110% VO2max with 135 s of passive rest between bouts and 15 min between periods. After exercise subjects were randomized to a low (LOW) or high (HIGH) carbohydrate intake for 5 hours. At baseline, after each period and following the diet intake RSA (5x6 s sprints separated by 24 s of rest) was evaluated and muscle biopsies and blood samples obtained. RESULTS: After recovery glycogen levels were 176±99 vs. 292±78 mmol·kg-1 dw in LOW and HIGH, respectively ($P<0.05$), whereas blood glucose concentrations were indifferent ($P>0.05$). This was accompanied by an impaired RSA only in LOW (8±6% reduction, $P<0.05$). Moreover, an overall moderate correlation was present between muscle glycogen content and RSA ($P<0.05$). Ongoing analyses of subcellular glycogen contents will be included in the final presentation of the data. CONCLUSIONS: Low muscle glycogen is associated with impaired RSA, which may be a result of specific depletion of subcellular glycogen fractions.

Keywords: Cell biology, Other, Other

Poster session 1

Clinical Use of Circulating Tumour DNA in Metastatic ALK-Translocated Lung Cancer

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Background

Metastatic non-small cell lung cancer (NSCLC) is a clinical challenge because of its poor prognosis. The discovery of oncogenic drivers in metastatic NSCLC has improved survival with the development of oncogene directed therapy. The ALK-translocation is an oncogenic driver found in 5% of all NSCLCs. Standard treatment for patients with incurable ALK-translocated NSCLC is ALK-inhibitors, but the clinical efficiency varies greatly. Moreover, acquired treatment resistance is inevitable and little is known about its underlying mechanisms.

Aim

To investigate if circulating tumour DNA (ctDNA) from blood samples can be used to evaluate treatment response and detect resistance mechanisms in patients with metastatic ALK-translocated NSCLC.

Methods

This is a multicenter, national PhD project. Patients with ALK-translocated metastatic NSCLC treated with ALK-inhibitors as part of routine clinical practice are included. Blood samples are collected at each routine outpatient visit. The ctDNA is extracted from plasma and analysed by next generation sequencing (NGS) analysis. NGS analysis is performed at baseline before treatment start, at 14 days after treatment start and at clinical progression or death.

Results

Preliminary results from the baseline and the first blood samples after treatment start show that the ALK translocation is cleared from the blood after initiating ALK-targeted treatment. We will continue to assess the effect of treatment and correlate it with ctDNA dynamics, and we will investigate resistance mechanisms.

Conclusions

We hope that ctDNA can be a tool for optimising future targeted treatment of ALK-translocated NSCLC.

Keywords: Oncology, Respiratory system, Other

Definitive therapy for squamous cell carcinoma of the anus with synchronous distant metastases

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Introduction: Synchronous metastatic squamous cell carcinoma of the anus (mSCCA) is rare, and little evidence exists on potential curative treatment options. The aim of this study was to present outcome of a nationwide cohort of patients with synchronous mSCCA treated with a definitive treatment strategy.

Materials and Methods: Patients with synchronous mSCCA treated with ICT and definitive RT between 2000 and 2018 were included. Pre-treatment characteristics, treatment- and outcome data were collected from medical records. The Kaplan-Meier method was used to present survival functions.

Results: Nineteen patients with synchronous mSCCA were identified. Location of distant metastases were liver (n=5), lung (n=1), bone (n=1), skin (n=3), and metastatic lymph nodes (LN) (n=9). Patients were treated with intensified ICT consisting of cisplatin, 5-flourouracil, leucovorin and ifosfamide followed by definitive RT. Prescribed RT doses to tumour and pathological LN were 50.4-64 Gy in 28-32 fractions and 49.9-51.2 Gy to the elective clinical target volume. Four patients underwent additional local treatment for distant metastases. On ICT alone, the overall objective local tumour response was 88% with 31% achieving complete local tumour response. Median follow-up time was 4.5 years (range 0.9-.17). Overall survival at 3- and 5-years was 72% and 55%, respectively, and 3- and 5-year disease-free survival was 47% and 41%, respectively.

Conclusions: Selected patients with synchronous mSCCA can be treated with a definitive strategy hereby shifting patients from a palliative to a curative treatment intent. Prospective international trials are needed to investigate this approach further.

Keywords: Oncology, Other, Other

OPTIMISE - OPTIMIzation of treatment SElection and follow up in oligometastatic colorectal cancer - a ctDNA guided phase II randomized approach

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Background: Oligometastatic colorectal cancer (CRC) can be cured from treating a single or few local metastases. Some patients obtain long-term survival, whereas others show an aggressive biological behavior with early recurrence and systemic dissemination despite the use of adjuvant chemotherapy (CT). Due to limited evidence, there is no clear consensus on the use of CT in relation to local treatment. A pilot study demonstrated, that presence of ctDNA in plasma after curative treatment for oligometastatic CRC indicates a poor prognosis. We aim to investigate the clinical utility of ctDNA-guided treatment in oligometastatic CRC.

Materials and methods: An open label 1:1 randomized phase II exploratory study investigating use of ctDNA-guided therapy compared to standard of care after local treatment for metastatic CRC. Circulating free DNA will be analyzed for CRC specific mutations by a digital droplet PCR panel and for tumor-specific hypermethylation by a methylation assay. ctDNA positivity will lead to escalation of CT. ctDNA negativity will based on shared decision making lead to de-escalation.

Results: This study will demonstrate the feasibility of patient inclusion, rate of imaging detected residual disease, rate of ctDNA positivity and shared decision making in ctDNA-guided therapy for oligometastatic CRC. It will lead to a larger multicenter randomized study, investigating the clinical utility of ctDNA-guided treatment.

Conclusion: Oligometastatic CRC can be cured, but with a high risk of recurrence. Currently, clinical indicators for optimal selection of post-treatment CT are missing. We investigate ctDNA-guided treatment to optimize use of CT and hereby outcome.

Keywords: Oncology, Other, Other

Plasma proteins as biomarkers for response to immunotherapy in non-small cell lung cancer patients

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Background: Immunotherapy development has improved survival for advanced-stage non-small cell lung cancer (NSCLC) patients. Pembrolizumab, an immune checkpoint inhibitor, targets the PD-1 signaling axis and has produced durable clinical response. Despite PD-L1 expression being used as a biomarker for treatment eligibility, its predictive value remains ambiguous. Using blood samples from NSCLC patients, we aimed to identify biomarkers with higher predictive value for therapeutic efficacy.

Materials and methods: A cohort of 42 advanced NSCLC patients receiving first- or second-line pembrolizumab treatment were included. Blood samples were collected before treatment and again three and six weeks after treatment initiation. The blood samples were analyzed using the proteomic multiplex platform Olink. We investigated the expression of 92 plasma proteins known to be associated with immuno-oncology.

Results: Patients were stratified by progression-free survival (PFS), and plasma protein expression was compared between the two groups. At all three time points (baseline, and at three and six weeks after treatment initiation) Fas ligand was associated with favorable PFS ($p=0.0003$, $p=0.0134$ and $p=0.0039$). Patients with the highest quartile Fas ligand expression at baseline had significantly longer PFS ($p=0.0077$) than patients with lower Fas ligand expression.

Conclusion: This study sheds new light on the possibilities of plasma proteins as candidates for predictive biomarkers for immunotherapy response or as indicators of resistance mechanisms.

Keywords: Oncology, Other, Other

Early response to chemotherapy as predictor of locoregional and distant failure in NSCLC

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PURPOSE/OBJECTIVES

Combined chemo-radiotherapy (cRT) is standard of care for patients with locally advanced non-small cell lung cancer (LA-NSCLC). This study evaluates the early tumour response after chemotherapy and its prognostic value in predicting pattern of failure for LA-NSCLC-patients.

MATERIAL AND METHODS

Patients with LA-NSCLC treated with curative intended cRT (2012-2019) were retrospectively reviewed (n=188). Patients had diagnostic PET/CT-(dPC) and planning PET/CT (pPC)-scans, between which they received platinum-based chemotherapy. Volume, sphericity and SUVpeak for the gross tumour volume were investigated on dPC and pPC. Failure was characterized as loco-regional (LR), distant metastasis (M) or simultaneous (LR+M). Two multivariate competing risk analyses (Fine-Gray model) were performed.

RESULTS

Median follow-up was 33 months. Median decrease in GTV-T volume and SUVpeak were 19.1% and 32.7%, respectively. In Model 1, squamous cell carcinomas (SCC) presented a significantly lower risk of M failure (SHR=0.246 [0.0887-0.684], p<0.01), and higher risk of LR failure (SHR=2.15 [1.09-4.21], p=0.026) compared to adenocarcinomas (AC). In Model 2, SUVpeak at diagnosis was the only significant predictor of LR failure (SHR=1.07 [1.02-1.13], p<0.01), while histology was still a significant predictor of M failure (SHR=0.259 [0.0970-0.694], p<0.01, SCC). Analysis on subgroups (histology, SUVpeak above and below

median) illustrated that ACs with high SUVpeak are more prone to failure than ACs with low SUVpeak.

CONCLUSION

Histology and tumour SUVpeak were significant predictors of LR failure in a multivariate model based on 188 LA-NSCLC patients treated with cRT.

Keywords: Oncology, Respiratory system, Other

Time-resolved dose rate measurements in pencil beam scanning proton FLASH therapy

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Introduction: It has been found that delivering the dose in radiotherapy with high dose rates leads to normal tissue sparring while maintaining the tumor response (FLASH therapy). To ensure that high enough dose rate is obtained, a detector system for time-resolved dose rate measurements was developed. The detector was used in pre-clinical pencil beam scanning proton FLASH studies to measure the instantaneous dose rate during mouse irradiations.

Methods: The detector system consisted of four probes and measured the dose rate every 20 us. Prior to the mice studies, the probes were cross-calibrated against an ionization chamber that was irradiated simultaneously with the probes using a range of dose rates. A calibration curve was produced linking the probe signal (in voltage) to the absolute instantaneous dose rate (in Gy/s). The calibrated probes were then used to measure the instantaneous dose rates during mouse experiments.

Results: For each probe, the instantaneous dose rate as function of measured detector signal was modelled with a third-degree polynomial function. The dose rate in the mouse irradiations was consistent with the dose rates recorded by machine log-files of the treatments with a root-mean-square difference of 13Gy/s across a wide range of instantaneous dose rates up to 1000Gy/s.

Conclusion: A detector system for direct measurements of the instantaneous dose rate was developed and calibrated in a wide range of dose rates. The calibrated system was successfully used in vivo in mouse irradiations, enabling time-resolved dose rate measurements in pre-clinical proton FLASH studies.

Keywords: Oncology, Other, Other

Deciphering metastatic cancer biology. A panel-based study

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Metastatic disease is responsible for 90% of all cancer deaths. Understanding the process of how primary tumours achieve metastatic potential is of great importance and paramount to the development of precision medicine that may limit the aggressive distant spread of metastatic cancer. We wish to investigate if potential metastatic gate-keeper mutations exist.

We analysed panel-based DNA sequencing datasets from the GENIE (Genomics Evidence Neoplasia Information Exchange) project. Analyses were performed on 174 shared genes and 37,791 patients were included. Using bioinformatic tools, we compared genomic alterations in primary versus metastatic samples.

We found a higher tumour mutation burden and increased levels of chromosomal instability for metastatic samples compared to primary. Overall, TP53, MYC and CDKN2A were the most significantly enriched genes in metastatic cancer. Notably, we also identified several genes as significantly depleted in metastatic cancer. These particularly include ARID1A and PIK3CA.

We demonstrate how the power of large datasets can be utilised to make novel inferences on cancer biology. We identified both enrichments and depletions of specific alterations in metastatic disease potentially revealing how certain driver gene combinations associate with cancer progression more commonly than others. However, no prevalent differences were identified, and considering the large number of patients included, it might suggest that the metastatic process is driven less by new acquired metastatic features, but more by a non-cancer feature such as inflammation in the surrounding tissue.

Keywords: Oncology, Cell biology, Other

Characteristics of Danish patients with pulmonary sarcoidosis

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Background and aim: Systematic data registration in sarcoidosis is warranted in order to phenotype patients with sarcoidosis and to enhance the understanding of the disease variability that differs among ethnic groups. The aim was to characterize a Danish cohort with pulmonary sarcoidosis at the time of diagnosis.

Methods: Patients diagnosed with sarcoidosis from January 2018 to August 2021 were included. Data on patient demographics, family history, symptoms, comorbidities, radiology and pathology was registered.

Results: In august 2021, 128 patients, all Caucasians (38% women) were included. Mean age at inclusion were 47 years. Five patients (4%) reported a first degree relative with sarcoidosis. Dyspnea and cough were reported in 52 (41%) and 47 (37%) of patients. Comorbidities were present in 47% with hypertension being most prevalent. Most patients never smoked (63%). In 91 patients (71%) the diagnosis was verified by biopsy. Mean BAL lymphocyte count from 81 patients was 26% and mean CD4/CD8 ratio in 70 patients was 9.3. Distribution of Scadding stages on chest x ray (n=119) were: 0: 25%, I: 48% II: 24%, III: 5%, IV: 3%. Forced vital capacity was normal in 90% (n=123), mildly impaired (FVC 70-79%) in 7% (n=9) and moderately impaired (FVC 50-69%) in 2% (n=3). Diffusion capacity (n=99) was normal in 37(55%), mildly impaired (60-79%) in 32 % (n=32) and moderate impaired (40–60%) in 5% (n=5).

Conclusions: Danish sarcoid patients are predominantly males, and older at diagnosis compared to a previous Danish cohort. The majority had mild pulmonary disease at diagnosis according to Scadding stage and pulmonary function test.

Keywords: Respiratory system, Inflammation, Other

Poster session 2

Statin use and recurrence patterns in postmenopausal breast cancer

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Background: Accumulating evidence suggests that statins have a beneficial effect on breast cancer prognosis. Previous studies have reported an association between statin use and breast cancer survival; however, the relationship between statin use and patterns of breast cancer recurrence is incompletely mapped.

Patients and Methods: We identified all Malmö Diet and Cancer Study (MDCS) participants diagnosed with incident invasive breast cancer between 2005-2014. Follow-up time began at breast cancer diagnosis and continued until the first event of invasive breast cancer recurrence, death, emigration or end of follow-up, June 8, 2020. We estimated incidence rates (IR) of recurrence and fit Cox regression models to compute crude and adjusted hazard ratios (HRs) with 95% confidence intervals (95%CI) of disease recurrence, comparing post-diagnosis statin users with non-users.

Results: We enrolled 360 eligible patients with a median follow-up of 8.6 years. Overall, there were 68 recurrences in 2,931 total person-years. According to statin use, there were 14 recurrences in 903 person-years among statin users, and 54 recurrences in 2,028 person-years in non-users (IR per 1000 person-years: 15.5 [95%CI: 9.2–26.2] and 26.6 [95% CI: 20.4–34.8], respectively). Regarding pattern of recurrence, statin use was associated with reduced risk of distant recurrence (HRadj=0.34 [95%CI: 0.14–0.86]), but not loco-regional recurrence (HRadj=0.64 [95%CI: 0.15–2.66]).

Conclusion: In the MDCS, statin use was associated with a reduced risk of distant breast cancer recurrence in postmenopausal patients, whereas no association between statin use and loco-regional breast cancer recurrence was observed.

Keywords: Oncology, Epidemiology and biostatistics, Pharmacology

Why do patients' misunderstandings of information increase inequality in cancer treatment? – An observational study

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The risk of inequality in cancer treatment increases the lower the socio-economic status of the patient. Patients with head and neck cancer thus face a higher risk of inequality in their treatment due to the lower socio-economic status among the majority.

We conducted an observational study investigating the treatment pathway of head and neck cancer patients with lower socio-economic status. Inspired by James Spradley, we observed patients' encounters with healthcare professionals throughout their treatment pathway to determine the origin and nature of any inequality in their cancer treatment pathway. In addition, we conducted formal and informal interviews with health professionals and patients.

We found that patients with lower socio-economic status are challenged during communication with health professionals, especially in the early stages of the pathway. These communication challenges may explain their sub-threshold treatment outcomes. Patients are challenged by the large amount of information they receive early in the treatment pathway, and their understanding of what is communicated is therefore limited. We find that patients make decisions crucial for the outcome of their treatment without knowing the consequence of these decisions. We also show health professionals fail to detect such misunderstandings.

In conclusion, poor communication with health professional may contribute to inequality in the treatment pathway of head and neck cancer for patients with lower socio-economic status. Patients' inability to understand what is being communicated hampers their ability to make properly informed choices, which thus affects how their treatment pathway will be.

Keywords: Oncology, Qualitative research, Socio-economic conditions

Interactive deep learning-based tumor segmentation

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Radiotherapy is one of the cornerstones in the treatment of cancer. Treatment effect is highly dependent on the definition of the target volume. In recent years, much research focuses on auto-segmentation using deep learning, as manual delineation is time-consuming. However, the inter-observer variation and the inter-patient variation will directly limit the achievable segmentation accuracy. Sub-optimal segmentations need substantial corrections from physicians and limit clinical implementation. Therefore, instead of aiming for a perfect auto-segmentation in one step, we developed an interactive tumor segmentation tool using deep learning, which limits the need for physicians' corrections by learning from them while being performed. We used multi-model medical images(CT, PET, and 2 different weighted-MR) from 153 head and neck cancer patients. The delineations of clinical tumor and pathological lymph nodes were added together as the ground truth. We first train an auto-segmentation convolutional neural network(CNN) on our data set as a baseline. Subsequently, manual correction(adaptation) was simulated on random slices, by replacing the auto-segmentation results with the ground truth. The adapted slices were then fed back to the CNN for re-training to make the CNN both patient and observer-specific. We simulated up to 5 slices adapted per patient. The average 3D Dice of the baseline neural network on our test set(24 patients included) was 0.73. After 5 slices adapted, Dice improved by 12%, reaching 0.85. With our interactive tumor segmentation tool, we can substantially improve the segmentation accuracy with limited slices adapted by the physicians.

Keywords: Oncology, Medical technology and diagnostic techniques, Other

OptimalTTF-2: Optimizing Tumor Treating Fields therapy for recurrent glioblastoma with skull remodeling surgery. A multi-center randomized phase 2 trial

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Introduction

We have initiated (October 2020) a randomized, comparative, multi-center, investigator-initiated, interventional phase 2 trial (NCT04223999) examining a potential new treatment for first recurrence glioblastoma (rGBM). The new treatment involves combining skullremodeling surgery (SR-surgery) with Tumor Treating Fields therapy and best practice oncological therapy. SR-surgery involves performing five burrholes in the skull directly above the pathological tissue during tumor resection surgery. The burrholes remove the resistance created by the bone and thus increase the electric field strength focally in the pathological tissue underneath.

We concluded (April 2019) a phase 1 safety/feasibility trial indicating improved overall survival without additional toxicity from the intervention. The following randomized, comparative phase 2 trial aims to validate superior efficacy of this new treatment.

Method

We have currently recruited 13/84 patients. After 12-months follow-up of the first 52 patients, an interim futility analysis will be performed. Patients will be 1:1 randomized to either a) TTFields, best practice oncological treatment (control arm), or b) SR-surgery, TTFields, and best practice oncology (interventional arm). Primary endpoint aims to detect a 20% increase in the overall survival rate 12 months (OS12) assuming OS12 = 40% in the control group and OS12= 60% in the intervention group.

Major eligibility criteria include age ≥ 18 years, supratentorial rGBM, Karnofsky performance score (KPS) ≥ 70, focal tumor, and lack of uncontrollable epilepsy or significant co-morbidity. Patient follow-up is until death or 36 months (trial duration).

Keywords: Oncology, Clinical neuroscience, Medical technology and diagnostic techniques

ctDNA shedding behavior suggests the existence of an aggressive disease phenotype in a lung adenocarcinoma cohort

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Circulating tumour DNA (ctDNA) is cell-free DNA (cfDNA) hypothesized to be released from cancer cells into the bloodstream through apoptosis, necrosis, and possibly active secretion. It is considered as a real-time snapshot of tumour burden, carrying both qualitative and quantitative information about the tumour it originated from. In lung cancer, different subtypes have been found to release different amounts of ctDNA. In lung squamous cell carcinoma (LUSC), ctDNA was detected in 97% of patients, compared with 19% of lung adenocarcinoma (LUAD) patients, irrespective of size. This suggests that cancer cell mass is not the sole predictor of ctDNA release, but cancer-specific biology may play a role in this process.

In this project, we utilised the TRACERx 421 lung adenocarcinoma cohort to define a ctDNA shedding phenotype by analysing transcriptomic, genomic and chromosomal instability data. Whole exome sequencing and total RNAseq was performed on multi-region tumour DNA and RNA samples obtained from 82 lung adenocarcinoma patients. ctDNA was purified from plasma samples obtained at the time of surgery and analysed using a proprietary deep sequencing multiplex PCR method.

Differential enrichment analysis uncovered significant overexpression of genes involved in cell cycle and proliferation, as well as significant enrichment of proliferative pathways in tumours shedding ctDNA, suggesting the existence of an aggressive disease phenotype conductive to ctDNA shedding. Additionally, we have noted that the ctDNA-positive subgroup tended to exhibit higher levels of chromosomal instability as measured by the weighted genomic instability index (wGII).

Keywords: Oncology, Epidemiology and biostatistics, Other

Fibrinolysis in patients with hematological malignancy

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BACKGROUND: Bleeding and thrombosis are potentially life-threatening complications in hematological malignancy. Changes to the fibrinolytic system can lead to increased risk of both bleeding and thrombosis. We recently published a systematic review of the changes in the fibrinolytic system in hematological malignancy which revealed very sparse research into this area. The available research was largely inconclusive but displayed a tendency towards hypofibrinolysis in myeloproliferative disorders while hyperfibrinolysis was observed in amyloid light-chain amyloidosis. AIM OF PRESENT STUDY: To examine changes to the fibrinolytic system in patients with hematological malignancy.

METHODS AND MATERIALS: We expect to include approximately 300 patients at the Department of Hematology, Aarhus University Hospital. Patients will be included at diagnosis, prior to any chemotherapy treatment and followed for three months. At inclusion we will obtain history of thrombosis and bleeding and clinical information regarding risk factors for thrombosis and bleeding. At inclusion and every three weeks blood will be drawn and analyzed for conventional coagulation tests, and the fibrinolytic system will be investigated in detail by an in-house dynamic clot formation and clot lysis assay and by quantification of plasminogen-activator-inhibitor 1 and plasmin-alpha-2—antiplasmin complex levels. Clinical information regarding bleeding and thrombosis will be collected at each visit.

PERSPECTIVE: Increased knowledge about changes in the fibrinolytic system in these patients, will support the treating clinicians in decisions about treatment of bleeding and need for thromboprophylaxis.

Keywords: Oncology, Laboratory science, Other

Late Relapse in Hodgkin Lymphoma – A Study from the Danish Lymphoma Registry (LYFO)

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Background: In Hodgkin lymphoma (HL), 20-30% of the patients will experience a relapse after first complete remission (CR), even after appropriate treatment. Among these (pts), most relapses will occur within the first 1-2 years, while a small subset of pts will experience a late relapse (LR), i.e. beyond the first two years of follow-up.

Aims: Characterize 1) the pattern of LR over a 35 year period, 2) the clinicopathological parameters influencing the risk of LR and 3) the outcome of pts experiencing a LR.

Methods: Data review of 3350 HL pts diagnosed in DK between 1982 and 2018 and registered in the population-based LYFO registry. LR was defined as a relapse occurring ≥5 years after initial diagnosis.

Results: LR occurred in 58 pts. The cumulative incidence of LR at 15 and 20 years was 4.0% (95%CI:3.0-5.2%) and 5.4% (95%CI:4.0-7.2%). No plateau was reached. LR was more frequently observed in pts with Nodular Lymphocyte-Predominant HL (NLPHL) (HR: 4.5;95% CI:2.4-8.4). In classical Hodgkin lymphoma (cHL), older age and lymphopenia were risk factors for LR with HRs of 1.04 (95%CI:1.04-1.07) and 5.6 (95%CI:2.7-11.5). Mixed cellularity histological subtype was a risk factor for LR only in females, HR 5.4 (95%CI:1.4-20.4). As opposed to what we observed for NLPHL, the occurrence of LR in cHL was associated with an almost 3-fold increased risk of death (HR 2.68; 95%CI:1.70-4.24) compared to patients in continuous CR.

Perspectives: Further studies looking into the biology behind LR are warranted to identify factors related to e.g. tumour cells, tumor microenvironment and host features, which may help to predict the risk of LR and improve follow-up strategies in HL.

Keywords: Oncology, Other, Epidemiology and biostatistics

Study of delivered dose (to the patient) during brachytherapy of cervical cancer

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Introduction: Brachytherapy (BT) is used for treatment of cervical cancer. In BT, the cancer is irradiated from the inside by guiding a radiation-emitting source into the tumour via hollow applicators. The applicators are inserted in the patient either surgically or via cavities. It is key that the source is placed correctly to obtain the correct dose to the tumour. In vivo dosimetry (IVD) can validate if expected and delivered dose agree.

Methods: Our department routinely performs time-resolved IVD during BT. In this study the patients received two treatment fractions of 15-17.5 Gy. The dose in each fraction was delivered in 20 hourly pulses. Before treatment, a small dosimeter was placed inside the tumour region in an unused source-channel. For each plan the dosimeter position and corresponding expected dose recording were determined. Retrospectively and for each treatment fraction, measured dose was compared to expected. Furthermore, the time-resolved data was used to investigate the pulse-to-pulse variations of the dose deviations to study the applicator stability.

Results: Data from 79 BT fractions was analysed; The mean±1SD of the deviation between the total measured and expected dose was -0.7±1.4 Gy (-5±8%). The deviation was -0.3±2.3% for the first pulse and gradually increased to -8.5±16% for the last pulse. Further investigation of 15 of the fractions showed that the primary cause of the increased dose deviation was instability of the dosimeter position.

Conclusion: IVD during BT has been performed in a large cohort, showing good agreement with expected dose. Based on the findings, an improved method of fixating the detector inside the patient has been developed.

Keywords: Oncology, Laboratory science, Medical technology and diagnostic techniques

Poster session 3

Capillary function progressively deteriorates in prodromal Alzheimer's disease: A longitudinal MRI perfusion study

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Cardiovascular risk factors are associated with the development of Alzheimer's disease (AD), and increasing evidence suggests that cerebral microvascular dysfunction plays a vital role in the disease progression. Using magnetic resonance imaging, we investigated the two-year progression of microvascular blood flow in 11 mild cognitive impairment (MCI) patients with prodromal AD compared to 12 MCI patients without evidence of AD and 10 cognitively intact age-matched controls. The pAD patients displayed widespread disturbances in cerebral perfusion associated with capillary blood flow transit times. No such changes were observed in the other two groups, suggesting that the dysfunction in capillary perfusion is linked to the AD pathophysiology. The observed capillary dysfunction may limit local oxygenation in AD leading to downstream β-amyloid aggregation, tau hyperphosphorylation, neuroinflammation and neuronal dysfunction. The findings are in agreement with the capillary dysfunction hypothesis of AD, suggesting that increasing heterogeneity of capillary blood flow is a primary pathological event in AD. Together, this might provide new insights into the pathogenesis of AD.

Keywords: Clinical neuroscience, Medical technology and diagnostic techniques, Cardiovascular system

Longitudinal gray matter changes in patients with relapse-remitting multiple sclerosis

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Introduction: Multiple sclerosis (MS) usually affects the cognitive and physical capabilities of patients diagnosed with it. These impairments has linked to the diffusion of water molecules within cortical gray matter (GM) and thalamic volume of patients with relapse-remitting MS (RRMS) estimated by magnetic resonance imaging (MRI). However, it is yet to be investigated if longitudinal changes in the diffusional properties and volume of the tissue follows changes in cognitive and physical performance.

Aims/Methods: To investigate changes in morphometry and diffusion properties of GM in patients with RRMS after 24 weeks and if potential alterations resembles changes in cognitive and physical performance. Sixty-five RRMS patients with a mean disease duration of 10.9 months along with fifty-seven RRMS patients with a mean disease duration of 10.1 years underwent structural and diffusion kurtosis imaging (DKI) MRI scans and cognitive and physical assessment at baseline and after 24 weeks.

Results: Cortical DKI and thalamic volume of patients with short disease duration did not show any correlation with cognitive and physical performance at baseline. Nor did changes in these parameters following the 24 weeks for any of the groups. However, cortical mean diffusivity (MD) and thalamic volume was highly correlated with disease duration.

Conclusion: Cortical DKI and thalamic volume does not resemble cognitive and physical impairment in the early phase of RRMS nor does changes in these parameters after 24 weeks. Cortical DKI and thalamic volume might proceed other neurodegeneration and thus only reflect cognitive and physical impairment in RRMS after a longer disease duration.

Keywords: Clinical neuroscience, Medical technology and diagnostic techniques, Other

Serum Neurofilament Light Chain Levels in Diabetic Polyneuropathy

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Background: Diabetic polyneuropathy (DPN) is one of the most common complications of diabetes, routinely diagnosed by means of clinical signs and symptoms indicative of neuropathy. As DPN often is diagnosed late, an objective tool facilitating early detection and follow-up is needed. The axonal cytoskeletal protein neurofilament light chain (NfL) is a promising biomarker for DPN as it is abundant in neurons leaking out upon neuronal decay. Recent studies have shown serum NfL (s-NfL) levels to reflect presence and severity of certain inherited and acquired neuropathies why we hypothesize that NfL is comparably associated with DPN.

Methods: Biobank serum samples from the 10-year follow-up of 178 participants of the ADDITION-Denmark cohort of people with screen-detected type 2 diabetes were analysed for NfL using the Single Molecule Array technology. DPN was defined as presence of abnormal nerve conduction studies (NCS). A continuous composite NCS z-score was calculated.

Results: S-NfL concentration was significantly higher in participants with DPN (18.2 ng/L [IQR 14.1; 29.3 ng/L], N=49) than in participants without DPN (15.4 ng/L [IQR 11.7; 19.7 ng/L], p=0.012, N=129). NCS composite z-score was associated with NfL concentration (2.96 ng/L higher s-NfL ([95% CI 1.89; 4.03 ng/L], p< 0.01) for each 1 SD increment in NCS z-score). Risk of DPN increased with higher s-NfL concentrations (OR=1.31 [95% CI 1.10; 1.60] per 5 ng/L). The models were adjusted for age.

Conclusion: Elevated NfL levels in DPN are demonstrated here for the first time and indicate potential of NfL as a biomarker for DPN. The results further suggest that higher NfL levels are associated with higher DPN severity.

Keywords: Clinical neuroscience, Molecular metabolism and endocrinology, Other

Hypertension and the risk of post-stroke epilepsy

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Purpose: Stroke is the leading cause of epilepsy in the elderly. Hypertension is very common and a well-known risk factor of both hemorrhagic (ICH) and ischemic stroke (AIS). This study aims to evaluate the effect of hypertension on the risk of epilepsy following ICH or AIS.

Method: All strokes in Denmark are registered in The Danish Stroke Registry. The registry further collects information on several risk factors for stroke, including hypertension. We identified all patients with a first stroke between April 1 2004 and December 16 2016 and no prior diagnosis of epilepsy (7 634 ICH patients and 69 899 AIS patients). The patients were followed to the first diagnosis of epilepsy, death, emigration or end of follow-up (December 31 2016). We used a cox regression to estimate the HR of post-stroke epilepsy associated with hypertension.

Result: In persons with ICH, the unadjusted HR was 0.80 (95% CI 0.69-0.92) for epilepsy after stroke in persons with hypertension compared to persons without hypertension. When adjusting for stroke severity, age and sex, the adjusted HR was 0.82 (95% CI 0.71-0.94). In persons with AIS, the unadjusted HR was 0.98 (95% CI 0.91-1.05) for epilepsy after stroke in persons with hypertension compared to the persons without hypertension. After adjusting for stroke severity, gender and age, the HR was 1.03 (95% CI 0.96-1.11).

Conclusions: There was no association between hypertension and the risk of post-stroke epilepsy in persons with AIS. However, in persons ICH, the risk of post stroke epilepsy was lower in persons with hypertension than in persons without hypertension at time of stroke.

Keywords: Clinical neuroscience, Epidemiology and biostatistics, Public health

Comparison of two comorbidity indices and mortality risk in a Danish Cohort of Epilepsy Patients

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Introduction: Adjustment for confounding from comorbid conditions is key in disease studies with mortality outcomes. We compared the association of the Charlson Comorbidity Index and the Epilepsy Specific Comorbidity Index with mortality in a cohort of epilepsy patients.

Methods: In a nation-wide register-based cohort study, we identified all individuals with a first diagnosis of epilepsy in the Danish National Patient Registry from 1 Jan 1980 to 31 Dec 2016. We obtained information on diagnoses of comorbid conditions recorded on or before date of the first epilepsy diagnosis and assigned comorbidity scores to each individual according to both indices. We followed the cohort from date of epilepsy diagnosis until death, censoring or end of follow-up, and assessed the association of the comorbidity scores with mortality by Kaplan Meier-survival curves and Cox regression analyses.

Results: In a study population of 8,741,955 individuals, we identified 143,478 with a first diagnosis of epilepsy (54% males) with a median age at diagnosis of 42 years (IQ range 17-65 years). The cohort was followed for a mean of 11.6 years (SD 9.8 years). The Charlson Comorbidity Index produced steeper Kaplan Meier curves with clearer discrimination between risk scores, compared to the Epilepsy Specific Comorbidity Index. There was a stronger mortality gradient across risk scores in the Cox model for the Charlson Comorbidity Index than for the Epilepsy Specific Comorbidity Index.

Conclusion: We found that in patients with an epilepsy diagnosis in the Danish National Patient Registry, the Charlson Comorbidity Index was closer associated with mortality than the Epilepsy Specific Comorbidity Index.

Keywords: Clinical neuroscience, Psychiatry, psychology and mental health, Epidemiology and biostatistics

Visualising cholinergic nerves in the brain and internal organs in Dementia with Lewy Bodies.

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Background

Dementia with Lewy bodies is a neurodegenerative disease with loss of cholinergic neurons. We aim to visualize important cholinergic structures in the brain and internal organs that may be important to understand how the disease affects the nervous system.

Methods

The cholinergic PET-tracer 18F-FEOBV will be injected into patients and elderly healthy controls. Uptake of tracer will be described in important areas of the central and peripheral nervous system and correlated to symptoms of autonomic dysfunction, REM-sleep, colour vision, olfaction, visual hallucinations, parkinsonism, and cognitive domains.

Preliminary results

Brain scans of 10 patients and 10 healthy controls confirm previous findings of decreased uptake of FEOBV in several cortical and subcortical structures. The standard uptake value ratios were significantly reduced in the neocortex, hippocampus, amygdala and thalamus. Analyses of additional subcortical structures are pending. In order to understand the role of cholinergic dysfunction in the pathophysiology of DLB, we will correlate the distribution of the tracer to symptom scores, motor tests and cognitive profile. For the first time, we may quantify a signal from the medulla oblongata of what likely is the dorsal vagal nucleus.

Conclusion

Visualizing cholinergic binding in the dorsal vagal nucleus could lead to important insights for at least two reasons. Firstly, the nucleus is known to be heavily affected by pathology very early in the course of the disease. Secondly, the nucleus may represent a keyhole through which pathology may spread from the central to the peripheral nervous system or vice-versa.

Keywords: Clinical neuroscience, Basic neuroscience, Psychiatry, psychology and mental health

Feasibility of 3T submillimeter layer-dependent fMRI weighted toward microvasculature

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Introduction: Functional MRI with spatial resolution in the submillimeter domain enables measurements of activation across cortical layers in humans. This is valuable as different types of cortical computations, e.g., feedforward versus feedback related activity, take place in distinct cortical divisions. Layer-dependent fMRI (L-fMRI) studies have almost exclusively employed 7T MRI systems to overcome the reduced signal (tSNR) associated with small voxels. However, such systems are relatively rare and only a subset of those are clinically approved. In the present study we aim to develop a strategy for L-fMRI that is feasible with widely available 3T scanners. Methods: 5 healthy subjects were scanned on a Siemens MAGNETOM Prisma 3T scanner. To assess across-session reliability, each subject was scanned in 4-8 sessions on 4 consecutive days. A 3D GE-EPI sequence was used for BOLD acquisitions (voxel size 0.82 mm isotopic, TR=2.2 seconds) during a block design finger tapping paradigm. A recently published denoising algorithm, called NORDIC, was applied to the magnitude and phase timeseries to overcome limitations in tSNR and the denoised phase data was then used to obtain magnitude timeseries with increased weighting towards microvasculature. Results: The datasets analyzed at this stage suggest that NORDIC denoising results in sufficient sensitivity for robust detection of laminar responses with tSNR gains larger than what would be expected by moving to 7T. Furthermore, laminar activation profiles extracted from the primary motor cortex are reminiscent of those reported in previous 7T studies for a similar task and region, and exhibit consistency within and across sessions.

Keywords: Other, Basic neuroscience, Clinical neuroscience

Poster session 4

Unraveling of mechanisms of dopaminergic memory retention by the locus coeruleus-hippocampus circuit

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Daily experiences are easily forgotten, but when we witness something new, we tend to recall the events which happened on a specific time frame from that novel incident. Such as the COVID pandemic, some of its consequences will be memorable for the generations who experienced it. For example, I go grocery shopping often and I can't recall the details of each time, but I remember vividly the experience I had the day before announcing the lockdown, when I went shopping, most of the shelves were selling out fast, and many people had big bags of stuff, I remember exactly what I bought back then.

In my project I am trying to investigate how novelty improves memory retention, allowing short term memories to be stored for longer time. Novelty has been shown to improve memory retention, plasticity, and learning in animals (Lisman & Grace, 2005; Tulving & Kroll, 1995) and humans (Ballarini, 2020). The main hypothesis of the project relies on Dopamine (DA) as the responsible neuromodulator for the memory boost. According to data, the source of this Dopamine is unexpectedly the noradrenergic center of the brain, the Locus Coeruleus (LC) (Kempadoo, Mosharov, Choi, Sulzer, & Kandel, 2016; Takeuchi et al., 2016). When novelty happens LC neurons fire and co-release DA with noradrenaline (NA) to the hippocampus (HPC). The first aim of my project is to detect this co-release using fiber-photometry combined with optogenetic and chemogenetic manipulations and ex-vivo tools. The second aim is to investigate the molecular mechanisms behind this phenomenon.

Keywords: Basic neuroscience, Other, Other

α-synuclein aggregates in PD and MSA are structurally and functionally different

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$\alpha\alpha$-synuclein is a small protein involved in synaptic transmission that also has a propensity for forming toxic aggregates, critically involved in both Parkinson's disease (PD) and Multiple System Atrophy (MSA). While formation of α-synuclein inclusions are found in both diseases, they present different symptoms and neuropathology. It is speculated that this difference in pathology is due to conformational variations in the formed α-synuclein aggregates between diseases. To test this hypothesis we set out to investigate α-synuclein aggregates derived from individual patients diagnosed with either PD or MSA.

Aggregated α-syn from the cerebrospinal fluid of PD and MSA patients was amplified using protein misfolding cyclic amplification. These aggregates where then further amplified in two cycles and conformational variation was assayed by amyloid dye binding, epitope presentation and limited proteolytic digest. The functionality of the aggregates were then tested in two models of α-synuclein aggregation; α-synuclein overexpressing OLN93 cells and organotypic hippocampal slice cultures from wild-type mice.

Our results indicates that aggregates derived from PD and MSA consistently differ in epitope presentation, amyloid dye binding and digest pattern, and that these structural variations are conserved through amplification. In our two model systems, PD and MSA derived aggregates resulted in markedly different inclusion pathology.

We show that aggregates from PD and MSA are structurally and functionally different, implicating that conformational differences in aggregate structure are involved in the pathophysiology of α-synuclein aggregate-dependent neurodegenerative diseases.

Keywords: Basic neuroscience, Cell biology, Other

SorCS3 regulates cell fate decision of dopaminergic progenitors

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SorCS3 is the member of Vacuolar Protein Sorting 10 Protein (VPS10P) receptor family, a group of proteins acting as sorting adaptors or ligand-binding receptors at the surface of the various cells. Recently, SorCS3 has been recognized as one of the top-risk genes for multiple neurodevelopmental psychiatric disorders, such as Attention deficit/hyperactivity disorder (ADHD). While the etiology of ADHD is mostly unknown, the deregulation of dopaminergic (DA) system seems to be an important factor. ADHD patients often display polymorphism in Dopamine transporter (DAT) or Dopamine receptor D4 (DRD4) genes, having a direct functional consequences on DA system. Moreover, the innervation from two major DA midbrain nuclei – Ventral tegmental area (VTA) and Substancia nigra pars compacta (SNpc), is altered in ADHD patients in compare to healthy controls, which is most likely the consequence of abnormal DA system development. Thus, it is important to explore the role of SorCS3 during DA system development. In my PhD project, I use sorcs3 deficient mice model combined with wide range of methods, such as mass spectrometry, RNA-sequencing or DA lineage tracing. Our data suggest, that SorCS3 contributes to the regulation of ventral midbrain dopaminergic neurons development. The removal of SorCS3 affects proliferation and differentiation of progenitors, thus causes imbalance in cell sub-populations in the ventral midbrain during early stages of embryonic development. Further explorations of the mechanism causing this imbalance will give us the opportunity to better understand the etiology of dopamine-related psychiatric disorders, such as ADHD.

Keywords: Basic neuroscience, Cell biology, Psychiatry, psychology and mental health

Sortilin in Excitatory and Inhibitory Neurons; Implications for Memory

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Memory is essential for defining us as individuals and determining our actions, yet the molecular underpinnings remain incompletely understood. The foundation of memory is assumed to be encoded by changes in connection strength between neurons, termed synaptic plasticity. The receptor protein Sortilin is highly expressed in neurons and is critical for synaptic plasticity, regulations of synaptic morphology, and memory formation. Sortilin is a member of the mammalian vacuolar protein sorting 10 protein (VPS10P)-domain family of type-1 transmembrane receptors. A family of multifunctional receptors with critical roles in the control of neuronal development, viability, and function. Moreover, they have been found to be implicated in several diseases characterized by memory impairment or distorted cognitive function, such as Alzheimer's disease, schizophrenia, and depression. The aim of this project is to study the role of Sortilin in different types of neurons. We show that Sortilin is expressed in both excitatory neurons and in parvalbumin positive inhibitory neurons. To investigate the role of Sortilin in the two populations, we have generated three knock out (KO) mouse lines; for global inactivation of Sortilin, and for conditional ablation in excitatory and inhibitory neurons, respectively. We find that mice lacking Sortilin in inhibitory neurons have reduced contextual fear memory. Accordingly, Sortilin KO mice display altered GABAergic transmission. Together this suggests that Sortilin has consequences for the inhibitory neuronal function. Ongoing studies aims at elucidating the molecular mechanisms underlying the observed phenotype.

Keywords: Basic neuroscience, Cell biology, Clinical neuroscience

Aggregate-specific alpha-synuclein proximity ligation assay reveals oligomeric pathology in synucleinopathy models and human brain tissue from Parkinson's disease and multiple system atrophy

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Objectives
We aimed to develop a method for the detection of early-stage alpha-synuclein (AS) pathology in Parkinson's disease (PD) and multiple system atrophy (MSA), usable in both model systems and brain tissue from patients. Furthermore, we sought to design an automated method for the analysis of stained tissue sections using machine learning, thereby facilitating large-scale studies of proximity ligation assay (PLA) pathology.

Methods
We conjugated the conformation-specific anti-AS antibody MJFR-14-6-4-2 to proximity ligation probes and tested staining for AS pathology in a range of model systems as well as patient tissue samples.

To facilitate automated quantification of PLA signal, chromogenic images were segmented into their components using Trainable Weka Segmentation (Fiji), and a macro set up to compute total, neuronal, and non-neuronal PLA signal. Moreover, each neuron was analyzed individually to define nuclear and cytoplasmic PLA signals.

Results
PLA signal directly corresponds to the generation of early-stage aggregates, as inhibition of aggregation lowers the PLA signal. AS over-expressing mice show increased pathology compared to non-transgenic littermates, and the assay also detects pathology initiated by pre-formed fibrils. The PLA detects novel pathology in PD/MSA in brain regions previously considered unaffected, while it does not label the hallmark Lewy bodies.

Conclusions
The PLA is a useful method to study early-stage pathology in PD, MSA and models thereof, especially combined with automated data analysis. With its preference for oligomeric pathology, the PLA might be particularly relevant in efforts to limit disease progression.

Keywords: Basic neuroscience, Animal models/disease models, Cell biology

From GWAS to receptor function - rare variant insight to LAR function

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Neuropsychiatric disorders are a diverse group of disorders characterized by cognitive and social disabilities and account for more than 30 % of years lived with disability worldwide. The heritability of neuropsychiatric disorders are well established, but it is not until the recent advances in genetic sequencing technology that the underlying genetic risk loci have been identified and, together with functional studies, they have implicated the synapse as a key neuronal structure relevant for development of these disorders.

The PTPRF gene, encoding the presynaptic receptor LAR, was recently discovered as a GWAS risk gene for ADHD. To investigate potential disease-associated alterations in protein function, we used whole exome sequencing data from ADHD patients and healthy controls to extract rare missense variants and mapped them onto the LAR protein using crystal structure information.

Disease-associated variants clustered in the FN1-4 domain of LAR, a domain crucial for its interaction with the postsynaptic partner NGL-3 and thus their synaptogenic effects. Assessment with thermal shift assays (TSA) revealed altered thermal stability of the disease variants which was further validated with small-angle x-ray scattering (SAXS). Microscale thermophoresis (MST) analysis showed decreased affinity of the LAR-variants to NGL-3.

Our data represents a preliminary effort to investigate the biological impact of a psychiatric GWAS risk gene using rare missense variants. Further studies will elucidate the functional impact of LAR-variants on synapse formation and identify small molecule modulators of the LAR FN1-4 domain.

Keywords: Basic neuroscience, Cell biology, Psychiatry, psychology and mental health

Please take a deep breath

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Background

The view that bodily, cognitive, and neural states are closely coupled is gaining increasing interest within the fields of cognitive neuroscience and computational psychiatry.

Respiratory-brain coupling is of particular interest as it has been studied less than other (e.g., cardiac or gastric) domains. Recent evidence suggests that the respiratory phase (e.g., whether a stimulus event or condition co-occur with inspiration or expiration) influences perceptual and emotional processing. However, the exact direction of and mechanisms underlying these effects are not well understood. A deeper understanding of respiratory-brain coupling may ultimately offer a new window into breathing-based behavioral interventions.

Methods

We probed respiratory-brain effects in healthy human participants in two perceptual domains using 1) a Visual Motion Discrimination Task and 2) a Face Affect Discrimination task.

Randomly moving dots or faces were briefly presented on a computer monitor. Participants had to decide if faces were happy or angry and if dots were primarily moving up or down. Respiratory movements were recorded using a respiration belt.

Results

Preliminary analysis using circular statistics indicates that Face Affect Discrimination but not Visual Motion Discrimination behavior is coupled to the respiratory phase.

Discussion

The coupling between the respiratory phase and behavioral performance in the Face Affect Discrimination task indicates that respiration might interact with affective processing in general. To further describe the neurophysiological mechanisms behind the observed coupling, we plan to run the tasks with magnetoencephalography recordings.

Keywords: Basic neuroscience, Clinical neuroscience, Psychiatry, psychology and mental health

Awake mouse MRI of the glymphatic system

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Neuronal and astroglial metabolic waste is actively cleared from the brain's extracellular space (ECS) by the glymphatic system. This brain waste clearance is significantly increased during sleep and anesthesia. Optical measurements suggest that sleep-induced cell shrinkage is the basis for the observed increase in waste clearance. Such measurements, however, are invasive and have a limited field of view thus raising the question of whether cell size modulation during sleep/anesthesia is a brain-wide phenomenon. Here, we propose a novel strategy to investigate the phenomenon by using awake animal, whole-brain diffusion kurtosis MRI (DKI). This method is non-invasive and has a high sensitivity to brain microstructure modulation. We compare the DKI metrics (mean diffusivity, MD; mean kurtosis, MK) of awake and anesthetized mice.

Naïve C57BL/6 mice (n=24) were fitted with a 3D printed MRI compatible head-holder, surgically affixed to the skull. After recovery, the mice underwent 14 days of MRI habituation. DKI data was acquired in the awake and anesthetized state using a Bruker Biospec 9.4T MRI system equipped with a high-sensitivity rodent brain cryo-array coil.

Our analysis revealed a significantly lower MK for the anesthetized state, indicating that the diffusion properties of brain tissue are different in the awake and anesthetized states. Specifically, anesthesia seems to cause brain tissue to have less diffusional heterogeneity and reduced microstructural complexity compared to the awake brain.

Using awake mouse DKI we find anesthesia-induced microstructural modulation in agreement with the proposed mechanism for increased glymphatic clearance during sleep.

Keywords: Basic neuroscience, Animal models/disease models, Laboratory science

Poster session 5

Right ventricular lead position is not associated with clinical outcome in cardiac resynchronization therapy

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Background: Cardiac resynchronization therapy (CRT) is a guideline-directed therapy for selected heart failure (HF) patients. However, up to 40% of patients derive no measurable clinical benefit from CRT. The optimal position of the right ventricular (RV) lead is unknown. Available studies applied fluroscopy and chest radiography to assess lead position, which is inaccurate and only modestly reproducible as compared with cardiac computed tomography (CT). The aim of this study is to evaluate the association between different RV lead positions as assessed by cardiac CT and clinical long-term outcomes in patients receiving CRT.

Methods: We reviewed patient records of 278 patients formerly included in two randomized controlled trials for the occurrence of the pre-defined primary composite endpoint of HF hospitalization or all-cause death during long-term follow-up after CRT implantation. Outcomes were compared between RV lead positions (non-apical vs. apical and free wall vs. septal) using adjusted Cox regression analysis.

Results: During median (interquartile range) follow-up of 4.7 (2.9–7.1) years, 130 (47%) patients met the primary composite endpoint. The risk of meeting the primary composite endpoint was not significantly different between patients with non-apical vs. apical RV lead position (adjusted hazard ratio [HR] 0.78, 95% confidence interval [CI] 0.54–1.12, p=0.17) and free wall vs. septal RV lead position (adjusted HR 1.03, 95% CI 0.72–1.47, p=0.86).

Conclusions: In patients receiving CRT, the risk of HF hospitalization or all-cause death during long-term follow-up is not significantly associated with certain anatomical RV lead position as assessed by cardiac CT.

Keywords: Cardiovascular system, Other, Other

MicroRNA expression and association with platelet function and cardiovascular events in patients with coronary artery disease

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Introduction: New biomarkers are warranted to identify patients with coronary artery disease (CAD) and high risk of recurrent cardiovascular events. MicroRNAs (miR) may regulate platelet function and influence the risk of recurrent events in CAD. We aimed to identify candidate miRs with association to platelet function and investigate whether the candidate miRs predict cardiovascular events in CAD patients.

Methods: We investigated the expression of candidate miRs and their relation to platelet function in 749 stable CAD patients. Platelet function was analysed by impedance and optical aggregometry. Furthermore, we investigated the association between miRs expression and cardiovascular events during a median follow up of 3 years. The primary endpoint was a composite of cardiovascular death, myocardial infarction (MI), stent thrombosis (ST) and ischaemic stroke. The secondary endpoint was a composite of MI and ST.

Results: The expression of miR-93, -126 and -150 correlated significantly with platelet function ($p<0.001$) in CAD patients. The combination of miR-223 expression, miR-150 expression and conventional clinical risk factors significantly increased the predictive value (AUC) of both the primary and secondary endpoint compared with clinical risk factors alone (0.66 (0.59-0.72) vs 0.57 (0.49-0.63), $p=0.01$ and 0.75 (0.69-0.81) vs 0.59 (0.51-0.68), $p=0.0002$, respectively).

Conclusions: The expession of specific candidate miRs may be of importance for platelet function and contribute to the risk of recurrent cardiovascular events. Adding the combination of miR-223 and miR-150 expressions to clinical cardiovascular risk factors may improve risk assessment in CAD patients.

Keywords: Cardiovascular system, Laboratory science, Other

Diagnostic yield of genetic testing in young patients with atrioventricular block of unknown etiology

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Background:
The etiology of atrioventricular block (AVB) remains unknown in approximately half of all young patients with the diagnosis. Although variants in several genes associated with cardiac conduction diseases have been identified, the contribution of genetic variants in younger patients with AVB is unknown.

Methods:
We identified all patients younger than 50 years receiving a pacemaker due to AVB in Denmark in the period from January 1st 1996 to December 31st 2015 using the Danish Pacemaker and ICD Registry. From reviews of medical records, we identified patients with unknown etiology of AVB at time of pacemaker implantation. These patients were invited to a genetic screening using a panel of 102 genes associated with inherited cardiac diseases.

Results:
We identified 471 living patients with AVB of unknown etiology of whom 226 (48%) accepted participation. Median age at time of pacemaker implantation was 39 years (interquartile age 32-45 years) and 123 (54%) were males. We found pathogenic or likely pathogenic variants in genes associated with or possibly associated with AVB in 12 patients (5%). Most variants were found in the Lamin A/C (LMNA) gene (n=5). LMNA variant carriers all had a family history of either AVB and/or sudden cardiac death (SCD).

Conclusions:
In young patients with AVB of unknown etiology, a possible genetic etiology may be identified in 1/20 patients. Variants in the LMNA gene were most common and associated with a family history of AVB and/or SCD suggesting that genetic testing should be a part of the diagnostic workup in these patients to stratify risk and screen family members.

Keywords: Cardiovascular system, Other, Other

Motion Correction in 15O-water Cardiac Positron Emission Tomography (PET) Imaging

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Introduction: Patient motion constitutes a limitation to cardiac PET imaging. Approximately 3% of 15O-water cardiac PET exams are repeated due to severe motion artefacts.

Aim: Examine the ability of image readers to visually detect and correct patient motion using data with simulated motion.

Methods: Simulated data were motion-corrected by two independent observers (Obs1, Obs2). The data set consisted of 16 motions applied to 10 motion-free scans. Obs1 assessed motion by reviewing the dynamic PET images; Obs2 reviewed the pre-motion-correction parametric images and polar maps as part of the assessment process. Motion correction was performed by manually shifting image volumes frame-by-frame with an overlay of the pre-motion-correction segmentation of the myocardial wall. Data were analyzed pre and post motion correction and myocardial blood flow (MBF) was reported.

Results: Motion correction was performed on 94% (Obs1) and 64% (Obs2) of the scans. Obs1 corrected 91% of the scans with large motion artefacts, whereas Obs2 only corrected 74%. In scans without motion, Obs1 wrongly identified motion in 8/10 scans and Obs2 in 1 scan. Motion correction reduced artefacts in MBF in 56% (Obs1) and 58% (Obs2) of the scans. In coronary territories with large motion artefacts, the deviation from the original scan was reduced in 84% (Obs1) and 87% (Obs2) of the territories (median relative reduction 46%, 95% inter-percentile range -16% to 96%).

Conclusion: Frame-by-frame motion correction after visual inspection is useful in reducing motion artefacts in cardiac 15O-water PET. Using pre-correction results to assess motion, reduced corrections in motion-free scans.

Keywords: Cardiovascular system, Medical technology and diagnostic techniques, Other

Twenty-year trends in atrial fibrillation and ischemic stroke in patients with incident type 2 diabetes: a Danish nationwide cohort study

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Background

Trends in the risk of atrial fibrillation and ischemic stroke are largely unknown in patients with incident type 2 diabetes (T2DM) without prior cardiovascular disease (CVD).

Methods

Using national health registries, we identified all Danish patients with incident T2DM without prior CVD diagnosed between 1996 and 2015. Each patient was matched by sex and age with up to 3 individuals from the general population. All were followed for 3 years. Trends in first-time atrial fibrillation and ischemic stroke were examined using Cox regression. We also examined use of prophylactic cardiovascular medications.

Results

A total of 276,320 patients with incident T2DM and 734,278 general population individuals were included. The 3-year risk of first-time atrial fibrillation did not change substantially from 1996-2000 to 2011-2015 in the T2DM cohort, whereas the 3-year risk of first-time ischemic stroke decreased by 50% (cumulative incidence proportion from 3.1% [95% CI 3.0-3.3] to 1.5% [95% CI 1.4-1.6]; sex- and age-adjusted hazard ratio 0.52 [95% CI 0.49-0.57]). Patients with T2DM were still at increased risk of both outcomes compared to matched individuals in 2011-2015, although the risk difference narrowed over time. Use of prophylactic cardiovascular medications increased markedly over time, especially use of statins and multiple antihypertensive drugs.

Conclusions

From 1996 to 2015, the 3-year risk of first-time ischemic stroke was halved in patients with incident T2DM and no prior CVD, whereas the risk of first-time atrial fibrillation did not change. This coincided with increased use of statins and use of multiple antihypertensive medications.

Keywords: Cardiovascular system, Epidemiology and biostatistics, Molecular metabolism and endocrinology

The effect of Trimetazidine on Mitochondrial Function, Myocardial Performance, and Invasive Hemodynamics in Wild-type Transthyretin Cardiac Amyloidosis.

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Background:

Wild-type transthyretin cardiac amyloidosis (ATTRwt) is an infiltrative cardiomyopathy in which fibrils of misfolded amyloid protein deposit in the myocardium leading to reduced cardiac contractility and progressive heart failure. Trimetazidine (TMZ) is an anti-ischemic agent used in stable angina pectoris which improves cardiac contractility through a respiration shift from free fatty acids to glucose. In patients with ATTRwt, TMZ could potentially improve cardiac function by increasing glucose respiration and reducing tissue damage from reactive oxygen species.

Methods:

The trial is a randomized, double-blind, placebo-controlled cross-over study in which patients with ATTRwt (n=36) will be included. Participants will be randomized to either placebo or TMZ for treatment periods of 4 weeks. After the first 4-week treatment period, participants will be examined and cross-over will occur. Treatment will continue for another 4 weeks until the second examination. The examination set-up consists of right heart catherterization, cardiopulmonary exercise test, and echocardiography. Furthermore, patients will have endomyocardial biopsies taken for high resolution respirometry (HRR) and electron microscopy (EM).

Perspectives:

In patients with early-stage ATTRwt disease, we wish to characterize the oxidative capacity of myocardial mitochondria as well as investigate the treatment effect of TMZ on cardiac function at rest and during exercise.

We wish to compare the morphology and function of myocardial mitochondria by EM and HRR in early-stage ATTRwt receiving either TMZ or placebo versus late-stage ATTRwt receiving neither.

Keywords: Cardiovascular system, Cell biology, Pharmacology

The Murine Intensive Care Unit: Integrated Cardiovascular Assessment of the Anesthetized Mouse In Vivo

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Background: Despite great progress, cardiovascular morbidity remains the leading cause of death worldwide. Hence, a continued effort in developing new methods is needed to further understand the mechanisms underlying cardiovascular morbidity. The cardiovascular system is subject to extensive regulation, but existing methods are often limited to assessment of only some cardiovascular parameters. Thus, I aimed to establish an in vivo model with pacing of the heart and simultaneous assessment of blood pressure (BP), cardiac output (CO), electrocardiogram (ECG), and total peripheral resistance (TPR).

Hypothesis: I hypothesized that i) intervention with α1-adrenoceptor agonist, phenylephrine (PE), primarily has vascular effects, and ii) electric pacing of the heart modulates cardiac function without direct vascular effects.

Methods: Anesthetized mice, randomly allocated to intraperitoneal injections of vehicle control (NaCl) or PE, were mechanically ventilated and subject to i) implantation of BP catheter at arcus aorta, ii) mounting of flow probe on aorta ascendence, iii) placement of ECG electrodes, and iv) positioning of electrode at right atrium for cardiac pacing (10-12Hz).

Results: Pacing of the heart decreased CO with increasing heart rate but did not change TPR. Following PE treatment, BP and TPR rose, and these increases were maintained during pacing in the presence of PE.

Conclusion: In conclusion, PE has primarily vascular effects while pacing successfully modulates cardiac function without direct effects on vascular function. Our in vivo mouse preparation allows for simultaneous assessment of and distinguishment between the isolated cardiac and vascular functions.

Keywords: Cardiovascular system, Animal models/disease models, Other

Myocardial External Efficiency in Patients with Different Etiologies and Stages of Heart Failure

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Background: Myocardial external efficiency (MEE) is the ratio of cardiac work in relation with energy expenditure. We studied MEE in patients with different etiologies and stages of heart failure (HF) to discover the role and causes of deranged MEE. In addition, we explored the impact of patient characteristics such as sex, body mass index (BMI), and age on myocardial energetics.

Methods: Cardiac energetic profiles were assessed with 11C-acetate positron emission tomography (PET) and left ventricular ejection fraction (LVEF) was acquired with echocardiography. MEE was studied in 121 participants: healthy controls (n=20); HF patients with reduced (HFrEF; n=25) and mildly reduced (HFmrEF; n=23) LVEF; and patients with asymptomatic (AS-asymp; n=38) and symptomatic (AS-symp; n=15) aortic stenosis (AS).

Results: Reduced MEE coincided with symptoms of HF irrespective of etiology and declined in tandem with deteriorating LVEF. Patients with AS-symp and HFmrEF had reduced MEE as compared with controls (22.2±4.9%, p=0.041 and 20.0±4.2%, p<0.001 vs. 26.1±5.8% in controls) and a further decline was observed in patients with HFrEF (14.7±6.3%, p<0.001). Disproportionate left ventricular hypertrophy was as a major cause of reduced MEE. Female sex (p<0.001), a lower BMI (p<0.001), and advanced age (p=0.01) were associated with a lower MEE.

Conclusions: MEE was reduced in patients with HFrEF, HFmrEF, and HF due to pressure overload and MEE may therefore constitute a treatment target in HF. Patients with LVH, advanced age, female sex, and low BMI had more pronounced reduction in MEE and personalized treatment within these patient subgroups could be relevant.

Keywords: Cardiovascular system, Medical technology and diagnostic techniques, Molecular metabolism and endocrinology

The pathophysiology of muscle wasting in heart failure patients

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Background

Muscle wasting is characterized by loss of skeletal muscle mass and function. In heart failure patients, muscle wasting is highly prevalent - leading to increased morbidity and mortality. In other age-related diseases, such as type 2 diabetes mellitus (T2DM), muscle wasting has been associated with fibro-fatty degeneration of skeletal muscle, resulting in loss of contractile and metabolic function. However, the underlying mechanisms of muscle degeneration in heart failure patients are poorly described.

Methods

Skeletal muscle biopsies from the vastus lateralis will be obtained from patients with heart failure and from healthy controls. Heart failure patients will be divided into the following groups: 1) non-diabetic; 2) non-insulin-dependent diabetic and 3) insulin-dependent diabetic.

Immunohistochemistry will be used to examine muscle fibers and extracellular matrix. Fluorescence-actived cell sorting (FACS) will be performed to isolate specific cell populations, of particular interest: muscle stem cells, fibro-adipogenic progenitors, monocytes, lymphocytes and endothelial cells. After FACS downstream analyses including transcriptomic profiling, western blotting, proliferation and bioenergetics analysis of pure cell populations are possible.

Mitochondrial oxygen consumption will be assessed by high-resolution respirometry.

Perspectives

We designed this study to describe the cell populations of skeletal muscle, their role in muscle degeneration in heart failure patients and to identify novel targets for preventing possible fibro-fatty degeneration.

Keywords: Cardiovascular system, Cell biology, Molecular metabolism and endocrinology

Poster session 6

Age and differences in periapical and endodontic status. A repeated cross-sectional study

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Aim To evaluate if age may explain the differences in endodontic and periapical status of two similar adult Danish populations examined 10-years apart.

Methodology Full mouth intraoral radiographs of two randomly selected study populations from Aarhus County (age: 20-64 years) were taken; 616 individuals in 1997 (C1: 16,018 teeth) and 398 individuals in 2007 (C2: 10,668 teeth). Number of teeth, presence of root fillings (RFs) and apical periodontitis (AP) were assessed. AP was assessed using the Periapical Index (PAI). T-tests and multivariable and multinomial logistic regression analyses assessed the effect of cohort and age on the prevalence and relative frequency of RFs and AP.

Results The mean age and number of teeth were higher in C2 than C1 (age: C1, 42.3 years; C2, 44.6 years; p=0.003, teeth: C1: 26.0, C2: 26.8; p<0.001). Within each cohort, the prevalence of RFs and AP increased significantly with age, whereas the mean number of teeth decreased significantly with age (p<0.0001). On individual level, prevalence of RFs was significantly lower in C2; age correction further increased this difference (OR=0.55; 95% CI: 0.41-0.74; p<0.001). The prevalence of AP was similar between C1 and C2 in all age groups. On tooth level, the relative frequency of AP in root filled teeth was similar in C1 and C2 irrespective of age. However, in non-root filled teeth the relative frequency of AP was significantly higher in C2; age correction reduced this difference (OR=1.62; 95% CI: 1.17-2.24; p=0.004).

Conclusion The increased age of persons in C2 only partly explained the differences in prevalence and relative frequency of AP in non-root filled teeth.

Keywords: Dentistry, Epidemiology and biostatistics, Medical technology and diagnostic techniques

Socioeconomic status and risk of incident venous thromboembolism

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Background: Although venous thromboembolism (VTE) is a leading cause of morbidity and mortality, and socioeconomic status (SES) affects human health and health behavior, few studies have examined the association between SES and VTE.

Aim: To investigate the association between SES, assessed individually and in a composite score by levels of education, income, and employment status, and incident VTE.

Methods: We used Danish national registries to identify 51,350 persons aged 25-65 years with incident VTE during 1995-2016. For each case we used incidence density sampling to select five age-,sex-,and index-year-matched controls from the general Danish population (n=256,750). SES indicators, including education, income, and employment status, were assessed one and five years prior to the VTE. We used conditional logistic regression to compute odds ratios (ORs) with 95% confidence intervals (CIs) for VTE according to individual SES indicators and a composite SES score in analyses adjusted for age, sex, and comorbidities.

Results: Compared to low levels, high educational level (OR 0.74; 95% CI 0.71-0.77), high income (OR 0.70; 95% CI 0.68-0.72), and high employment status (OR 0.66; 95% CI 0.64-0.68) were associated with decreased risk of VTE, even after adjusting for comorbidities. A composite SES score was superior to the individual indicators in assessing VTE risk (OR for high vs. low score: 0.61; 95% CI 0.59-0.63). In sensitivity analysis with SES indicators measured 5 years prior to the VTE, the risk estimates remaine2d essentially the same.

Conclusion: High levels of both individual SES indicators and a composite SES score were associated with decreased VTE risk.

Keywords: Epidemiology and biostatistics, Socio-economic conditions, Cardiovascular system

Migraine and sex-associated risks of premature stroke and myocardial infarction

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Aim: Migraine is associated with increased risks of myocardial infarction (MI) and stroke. We examined whether migraine and male sex interact as risk factors for premature (before age 61) stroke and MI.

Methods: Using Danish medical registries we conducted a nationwide cohort study during 1996-2016. Two migraine cohorts (women and men with migraine) were identified by prescription data. Using the Civil Registration System, we sampled five controls for each migraineur, creating two comparison cohorts (women and men without migraine). Women without migraine was reference cohort. We calculated age-, calendar period- and Charlson Comorbidity Index-standardized incidence rates (SIR) of premature stroke and MI for 20 years of follow-up with 95% confidence intervals (CI). We computed the interaction contrast based on SIRs, to assess potential additive interaction between male sex and migraine.

Results: We identified approx. 198,000 individuals with migraine (82% female). The SIR per 100.000 person years (PY) of stroke was 108 (95% CI: 106-111) for women without migraine, 135 (95% CI: 129-141) for women with migraine, 166 (95% CI: 160-173) for men without migraine, and 187 (95% CI: 172-203) for men with migraine. For MI, women without migraine had the lowest SIR (51, 95% CI: 49-52), followed by women with migraine (58, 95%CI: 54-62), men without migraine (158, 95% CI: 151-164), and men with migraine (168, 95% CI: 153-183).

The interaction contrast per 100.000 PY was -6 (95%CI: -24-12) for stroke and 2 (95% CI: -14-19) for MI.

Conclusion: Though migraine and male sex are known risk factors for premature stroke and MI, we found no substantial interaction between these factors.

Keywords: Epidemiology and biostatistics, Cardiovascular system, Clinical neuroscience

Impact of socioeconomic position on clinical outcomes in patients with myelodysplastic syndromes: A Danish nationwide population-based cohort study.

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BACKGROUND: Low socioeconomic position (SEP) is associated with adverse clinical outcomes among patients with solid tumors, lymphoma, and acute myeloid leukaemia (AML). The prognostic impact of SEP in patients with myelodysplastic syndromes (MDS) remains to be clarified.

OBJECTIVE: To examine the association between level of education, cohabitation status and income, and the risk of progression to AML and all-cause mortality among patients with MDS.

DESIGN: Nationwide, population based cohort study.

PARTICIPANTS: 2233 patients diagnosed with MDS between 2010-2018 registered in the Danish Myelodysplastic Syndromes Database.

MAIN OUTCOME MEASURES: Directed acyclic graph adjusted 1-year, 3-year, and 5-year relative risks (RRs) of progression to AML and death using the pseudovalue approach.

RESULTS: There were no clear association between level of education, cohabitation status or income and risk of progression to AML. During follow-up (median 1.9 years (IQR 1.0-3.8) 1426 patients died (64%). Patients with a short education had higher 1-year all-cause mortality (33%) compared to those with medium (22%) and longer education (21%). In adjusted models, the 1-year risk of dying was higher in patients with shorter vs. longer education [RR=1.34 (95% CI: 1.08-1.65)], in patients with lower vs. higher income [RR=1.42 (95% CI: 1.14-1.77)], and among patients who lived alone compared to those who lived with a partner [RR=1.15 (0.98-1.35)]. These associations persisted after 3-years and 5-years of follow-up.

CONCLUSION: Shorter education, living alone and lower income were associated with a lower survival but not progression to AML in Danish MDS patients.

Keywords: Epidemiology and biostatistics, Socio-economic conditions, Oncology

Prediction of chronic postsurgical pain in adults: a protocol for multivariable prediction model development

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Chronic postsurgical pain (CPSP) is a condition that affects an estimated 10-50% of adults, depending on the surgical procedure. CPSP often interferes with activities of daily living and may have a negative impact on quality of life, emotional and physical well-being. Clinical prediction models can help clinicians target preventive strategies towards patients at high-risk of CPSP, however existing models are at high-risk of bias. Therefore, the objective of this study is to develop a clinically applicable and generalizable prediction model for CPSP in adults. This research will be a prospective single-centre observational cohort study in Denmark spanning approximately one year or until a predefined number of patients are recruited (n=1453). Adult patients aged 18 years and older who undergo planned surgery will be recruited at Aarhus University Hospital. The primary outcome is CPSP 3 months after surgery defined as average pain intensity at rest or on movement ≥3 on NRS within the past week, and/or average pain interference ≥3 on NRS among any of seven short-form BPI items in the past week. Logistic regression will be used to conduct multivariate analysis. Predictive model performance will be evaluated by discrimination, calibration and model classification. A CPSP risk calculator will be developed based on predictors retained in the final model. Implementation of a high-quality prediction model could help facilitate shared decision-making, result in more efficient and effective postoperative pain management and contribute to the prevention of CPSP.

Keywords: Epidemiology and biostatistics, Other, Other

Prevalence of blood borne viruses among Danish patients with severe mental illness: A cross-sectional study.

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BACKGROUND: People with severe mental illness (PSMI) live 15-20 years shorter than the general population, with approx. 60% of the excess mortality attributable to somatic diseases. The contribution of blood borne viruses (BBVs i.e., HIV, HBV and HCV) to this issue is not well studied. Non-Danish studies find varying proportions of BBVs among PSMI. Since early BBV infections are asymptomatic, timely diagnosis/treatment rely on screening guided by local seroepidemiological data. The aim of this study is to provide data on BBV prevalence and associated risk factors among Danish PSMI.

METHODS: Cross-sectional study with consecutive enrolment from Aug. 21 to Dec. 22 of all adult outpatients suffering from psychotic disorders (PD), ADHD or dual diagnosis (by ICD-10 criteria) at the Department of Psychoses, AUH. We estimate point prevalence of HIV, HBV and HCV through universal testing. We collect data on risk factors for BBV exposure through a standardized questionnaire and linkage to national health registers. We identify independent risk factors for BBV infections by multivariable logistic regression.

RESULTS: Until now we have included 33 patients (consent rate = 81%) with the following characteristics: females 58%, mean age 27.5 years (SD 7.85), diagnosis of PD 100%, lifetime substance use 62.5%, among those 0%, 100%, 60%, reported substance intakte by injection, smoking and sniffing, respectively. HIV, HBV and HCV prevalence was 0% (95% CI: 0.00-11.35), 3.3% (0.59-16.67) and 0% (95% CI: 0.00-11.35) respectively.

CONCLUSION: Universal BBV screening of people with SMI is feasible. Given the current small sample size, no inferences on BBV prevalence can be made at this time.

Keywords: Infection, Epidemiology and biostatistics, Psychiatry, psychology and mental health

Development of a patient decision aid to reduce barriers in clinical trial participation within proton therapy among patients with head and neck cancer

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Background

As the only hospital in Denmark, Aarhus University Hospital offers proton therapy (PT) to cancer patients. The majority of patients are offered PT by participating in clinical trials (CTs).

Patients with head and neck cancer (HNC) are a heterogeneous group, but compared with the population in general they are socioeconomically disadvantaged. They report more barriers to participate in CTs, which results in lower participation.

Studies are needed to understand the factors influencing decisions concerning CT participation and thus the opportunity to receive PT.

Methods

In a cross-sectional study, the correlation between non-attendance in CTs and socioeconomic, psychosocial and geographical factors will be analysed.

A qualitative study based on Interpretive Description will be conducted to explore perceptions and barriers regarding CT participation and use of PT among patients with HNC. The methods used are participant observation in radiotherapy clinics and semi-structured interviews.

The patient decision aid will be developed within The framework of complex interventions and the International Patient Decision Aid Standards.

Patients and clinicians will be engaged throughout the research process using dialogue meetings and workshops.

Results

Data collection is in process.

Conclusion

This study investigates potential inequalities in the access to PT in Denmark and contribute with new knowledge on the barriers affecting CT participation and use of PT for patients with head and neck cancer.

Furthermore, it will lead to the development of a patient decision aid to support patients and clinicians in the shared decision concerning CT participation and thus referral to PT.

Keywords: Qualitative research, Socio-economic conditions, Oncology

Occupational dust exposures and HRCT findings of interstitial lung disease and chronic obstructive pulmonary disease

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Introduction: Occupational dust exposure is associated with interstitial lung disease and chronic obstructive pulmonary disease, but little is known about the association with more discrete lung changes detected by lung scans.

Objectives: To 1) analyze the relation between occupational dust levels and HRCT (high-resolution computed tomography) detected signs of pulmonary disease, and 2) map the prevalence of these signs in the Danish workforce.

Methods: We are carrying out a cross-sectional study of 10,000 adults who underwent HRCT scans of the lungs 2011-2019 in Denmark. We will analyze the extent of emphysema and signs of pulmonary fibrosis such as, but not limited to, reticulation with Imbio Lung Texture AnalysisTM of the scans. Annual information on occupation (ISCO-88) and industry since 1976 is available for all participants. Individual exposure levels are estimated using quantitative job exposure matrices for asbestos, crystalline silica, wood dust, and endotoxins. We will conduct adjusted analyses of exposure-response relations and tabulate distributions of emphysema and signs of pulmonary fibrosis for all occupations and industries.

Conclusion: The study will provide new knowledge on pulmonary effects of occupational dust levels. We will use a new software for objective identification and quantification of signs of pulmonary disease independent of diagnostic traditions. This sensitive and graduated measure of outcome will also enable more sensitive exposure-response analyses that include discrete signs of pulmonary disease. We expect this study to serve as a basis for targeted interventions of importance to the many that still have dusty work.

Keywords: Work environment and organisation, Epidemiology and biostatistics, Respiratory system

Poster session 7

Immunoengineering T cells to kill HIV

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HIV is a chronic infection that, despite effective antiretroviral therapy, cannot be cured due to latently infected T cells. Current efforts to cure HIV has not yet led to profound reductions in the size of the viral reservoir and there is therefor an urgent need for novel approaches to eliminate latently infected cells. Chimeric Antigen Receptor (CAR) T cells have revolutionized treatment of otherwise incurable hematological malignancies by utilizing the patient's own immune system to kill diseased cells. The CAR consists of an extracellular antigen-binding domain derived from the antigen-specific part of an antibody fused to intracellular activating signaling domains. This enables the CAR T cell to MHC-independently kill any target cell of choice and because of their autologous origin, the immunoengineered T cells can engraft in the bone marrow and potentially persist in the patient lifelong. The aim of this project is to utilize site-specific gene delivery of the CRISPR/Cas9 system to produce novel anti-HIV CAR T cells by inserting the CAR cassette into the CCR5 locus, thus knocking out the co-receptor for HIV cell entry. As the antigen-binding domain, we will use two potent broadly neutralizing antibodies shown to suppress viremia in HIV-positive individuals in clinical trials. This will create HIV-resistant anti-HIV CAR T cells which we will test in vivo in an HIV-infected humanized mouse model.

Keywords: Genetic engineering, Infection, Cell biology

DELIVERY OF ACTIVE CRISPR-CAS9/SGRNA RNPS TO PRIMARY HUMAN B CELLS USING MEASLES VIRUS-PSEUDOTYPED LENTIVIRUS-DERIVED NANOPARTICLES

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Due to their involvement in autoimmune disease and their ability to function as protein factories, primary B cells are interesting targets for genome editing. However, primary B cells are difficult to culture and hard to transduce using standard vesicular stomatitis G protein (VSV-G)-pseudotyped lentiviral vectors.

To study genome editing in primary B cells, we have engineered murine MS-5 cells expressing human CD40 ligand (CD40L). Using such MS-5(CD40L) cells as feeder cells, primary B cells proliferate and are prevented from undergoing apoptosis. Furthermore, lentiviral vectors pseudotyped with measles virus (MV) glycoproteins were shown to enable efficient gene transfer to primary B cells.

Based on these findings, we set out to explore genome editing in primary B cells using engineered lentivirus-derived nanoparticles (LVNPs). LVNPs represent a novel platform for delivery of active CRISPR-Cas9/sgRNA ribonucleoprotein (RNP) complexes without delivery of a viral genome or a transgene. Using VSV-G-pseudotyped LVNPs, we demonstrated effective gene editing in human and murine cell lines. Notably, by pseudotyping LVNPs with MV glycoproteins, targeted gene knock out in HEK293T cells was observed. Also, we generated a MV pseudotype variant, 'MV-SLAM', which specifically mediates virus uptake in cells expressing signaling lymphocyte activation molecule (SLAM). Using MV-SLAM-pseudotyped LVNPs, gene editing was achieved specifically in engineered SLAM-expressing HEK293T cells. Finally, targeted ex vivo gene knockout in primary B cells was achieved by treating B cells with MV-pseudotyped LVNPs, leading to markedly higher levels of editing than with VSV-G-pseudotyped LVNPs.

Keywords: Genetic engineering, Cell biology, Other

Enrichment of cells that carry CRISPR-mediated transgene integrations by transient CRISPRa of a silent reporter gene

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The CRISPR/Cas system has revolutionized the field of genome editing by its ability to simply and precisely edit the genomes of living organisms. Double-strand DNA breaks at specific target sites mediated by the CRISPR/Cas system can be repaired through the cellular repair mechanism homology-directed repair (HDR), which can be harnessed to introduce sequences from an exogenous homologous template. Exploiting the HDR mechanism for site-specific integration of a specific sequence has wide applications in both research and clinical gene and cellular therapies for example by integrating a therapeutic cDNA to correct disease-causing mutations in stem cells or by producing gene modified CAR T cells.

However, this approach is challenged by the relatively low HDR frequencies that can be obtained in some cell lines and primary cells, thereby impairing potential gene and cellular therapies. Cells that have undergone HDR cannot directly be distinguished and sorted from cells that have not undergone HDR unless a reporter gene has been incorporated in the HDR template. However, permanent expression of a reporter gene is not desired in most therapeutic contexts.

This project seeks to develop a novel enrichment strategy based on transient CRISPR activation of an otherwise silent and clinically relevant reporter gene co-integrated along a gene of interest. Such an enrichment strategy may be widely applicable in both research and gene and cellular therapies, where this strategy has the potential to enrich for correctly gene modified cells and thereby improve gene and cellular therapies.

Keywords: Genetic engineering, Genetic engineering, Other

Multisite repeatability of hyperpolarized 13C MRI

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Magnetic resonance imaging (MRI) with hyperpolarized [1-13C]pyruvate is an emerging technology for in vivo imaging of the balance of glycolytic to oxidative metabolism. It uniquely positioned to evaluate metabolic changes in the face of cancerous disease and its treatment, but the comparability between sites and protocols is unknown. In this study, we aimed to evaluate the agreement of hyperpolarized MRI between two sites across protocols.

We included three healthy volunteers, who underwent repeated imaging of the brain with various protocols. In total, we performed 13 scans. The common metrics of pyruvate to lactate conversion were calculated, including the model-based kPL and the model-free lactate-to-pyruvate ratio. Agreement was evaluated with intraclass correlation coefficients (ICCs), where 0 is no agreement and 1 is perfect.

The mean model-based pyruvate-to-lactate conversion (kPL) across all examinations was 0.02 ± 0.006 s-1. One of the employed protocols displayed a systematically ~40% lower kPL due to a longer echo time. Upon adjustment for this, the ICC was 0.71 (P = 0.025) between sites and 0.83 between examinations (P < 0.001). The ICCs were considerably lower for the model-free lactate-to-pyruvate ratio, as this fails to consider differences in flip-angles between protocols.

In conclusion, MRI with hyperpolarized [1-13C]pyruvate shows good agreement between sites and examinations. Some differences in protocols can and should be adjusted for when comparing data retrospectively, while care should be taken to use identical protocols when conducting prospective multi-site studies. Collectively, our results inform and support larger multicenter studies.

Keywords: Medical technology and diagnostic techniques, Clinical neuroscience, Molecular metabolism and endocrinology

Nucleic acids detection by degradation of quenched fluorescent probes by CRISPR 'collateral damage'

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The ability to rapidly and effectively detect nucleic acids with single-base specificity and high sensitivity may be of high use to clinical diagnosis and monitoring. Characterization of CRISPR/Cas12 and CRISPR/Cas13 has revealed that these proteins upon recognition of their target sequences are further activated and cleave nearby non-target DNAs and RNAs, respectively. Here we explore two nucleic acids detection platforms dubbed HOLMES and SHERLOCK to detect specific target sequences. By using PCR, or LAMP, amplification of target DNA and subsequently detection by Cas12 or Cas13, we aim to achieve fluorescent readouts in less than an hour. This readout can be quantified using classical plate readers providing an easy-to-use method for rapid quantification of nucleic acids carrying the exact target sequence.

One can envision the use of this system to detect recurrent biomarkers in cancer patients. By analyzing the blood plasma containing circulating tumor DNA (ctDNA) originating from necrotic/apoptotic tumor cells, it should be possible to detect the biomarker with high specificity and sensitivity, providing rapid molecular profiling of tumor DNA isolated from cancer patients.

Keywords: Medical technology and diagnostic techniques, Oncology, Other

A novel method for simultaneous detection of five kynurenine metabolites as blood biomarkers for post-concussion syndrome

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Introduction

At least 10.000 suffer from a concussion each year in Denmark, and 10-15% develop persisting symptoms such as headache, fatigue, and depression. This is defined as post-concussion syndrome (PCS), and the pathophysiology is unknown.

The kynurenine pathway describes the degradation of tryptophan, and its metabolites are involved in psychiatric disorders and may be important in PCS as well.

However, the metabolites are chemically diverse and difficult to detect simultaneously.

The aim of the study is to develop a method of measuring kynurenine metabolites in serum.

Methods

Metabolites from the kynurenine pathway (tryptophan, kynurenine, kynurenic acid, quinolinic acid, and 3-hydroxykynurenine) including their isotope-labelled standards, were measured in aqueous solution and in serum from four healthy persons using high-performance liquid chromatography-tandem mass spectrometry (LC-MS). Serum was prepared by precipitating proteins with either methanol, acetonitrile, acetone, or trichloroacetic acid. Several LC-MS parameters, such as columns and mobile phases, were tested.

Results

All metabolites were detectable in aqueous solution, and mass spectrometry signal intensities correlated to the concentrations linearly ($R2 \approx 0.999$).

In serum, the detection of quinolinic acid was complicated by significant matrix effects which were dependent on the method of protein precipitation and LC-MS parameters.

Limit of detection, linearity in serum, and lower limit of quantification will be presented at the PhD Day.

Perspectives

The method shows potential and will be used to measure serum concentrations of the metabolites in PCS patients and a healthy control group.

Keywords: Medical technology and diagnostic techniques, Basic neuroscience, Laboratory science

Development of noninvasive prenatal testing for monogenic disorders using circulating fetal cells in maternal blood

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Prenatal diagnosis using invasive tissue sampling involves a risk of miscarriage (<0.2 %) and is associated with severe discomfort for pregnant woman. Therefore, a long-sought goal in prenatal care is a safe and accurate noninvasive prenatal test (NIPT). NIPT for aneuploidy and copy number variants can be done using circulating trophoblast cells isolated from maternal blood samples. This study aimed to develop novel strategies for cell-based NIPT using circulating trophoblasts to test for cystic fibrosis (CF), repeat disorders and recessive disorders. Pregnant women (GA 10-14) that opted for prenatal diagnostics for disorders of interest were included. Circulating trophoblasts were enriched and isolated. Nine pregnancies were tested for CF using multiplex-PCR and fragment analysis to test for 50 disease-causing variants. The cell-based NIPT showed 4 normal, 2 carriers of Phe508del, 1 carrier of Arg334Trp and two inconclusive results. A repeat expansion in the DMPK gene, causing the development of autosomal dominant myotonic dystrophy, was detected using repeat-primed PCR and haplotyping in two pregnancies. In the first pregnancy, cell-based NIPT detected a repeat expansion >150 CTG-repeats in the fetus. In the second case, two normal alleles were detected. In a pregnancy at risk of autosomal recessive diastrophic dysplasia, Sanger sequencing of two regions in SLC26A2 detected two pathogenic variants. The results of cell-based NIPT were in concordance with those of invasive prenatal diagnostics. In conclusion, cell-based NIPT can be developed to test for various monogenic disorders in the fetus as a risk-free alternative to invasive tissue sampling.

Keywords: Medical technology and diagnostic techniques, Gynecology and obstetrics, Other

Poster session 8

The Presence of a Molecular Scar in Complete Responders of Secukinumab and Dead Sea Climatotherapy: A Comparative Immunohistochemical and Transcriptome Study.

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Psoriasis is a skin disease characterized by skin manifestations ranging from scaly plaques on the skin to isolated affection of the nails. Many highly effective biological treatment options exist for psoriasis such as the interleukin-17 inhibitor secukinumab. Dead Sea climatotherapy (DSC), which has been shown to be highly effective and clinically comparative to biologics in the short term, consist of a combination of salt and minerals and prolonged sun exposure. DSC and secukinumab results in a 100% psoriasis area and severity (PASI) reduction (PASI-100) among a sizeable portion of the patients at the end of treatment (EOT).

The aim of the study was to compare patients who obtained PASI-100 from two previous cohort studies.

Skin samples from 7 psoriasis patients treated with DSC and 8 patients treated with secukinumab were acquired before and after treatment. Immunohistochemical staining for CD3, CD4, CD8, CD11c, Ki67 and MPO was performed and quantified. The transcriptome was analyzed for differentially expressed genes (DEGs).

479 DEGs were found at EOT between the two cohorts. Among a selection of 49 psoriasis-associated genes only five (SERPINB13, IL36G, IL36RN, SERPINB4, and AKR1B10) differed significantly at EOT between the two cohorts. The epidermal thickness was significantly thicker at EOT in patients treated with DSC.

In conclusion, both treatments almost equally reduced psoriasis-associated genes to baseline levels. This suggest that the molecular scar in the two treatments is almost the same independent of the two widely different modes of actions.

Keywords: Dermatology, Inflammation, Laboratory science

Role of Autophagy in VZV CNS Infection

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Varicella Zoster Virus (VZV) is a common pathogen; its invasion into the central nervous system (CNS) however constitutes a rare, yet severe complication of VZV infection. We hypothesize, that the susceptibility to viral CNS infections is explained partly by host genetics.

Exome analysis of affected patients has revealed accumulation of possibly damaging gene variations in genes involved in the early stages of autophagy. Autophagy is a highly conserved, cellular degradation pathway which has previously been described to play a role in viral infections, both in pro- and antiviral manner. Importantly, inhibition of autophagy has been suggested to be required for neurovirulence in the closely related Herpes Simplex Virus 1.

Previously, our group was able to connect severe infection with both Herpes Simplex Virus 2 and poliovirus with defect autophagy. We hypothesize that autophagy plays an important role in the antiviral response to VZV infection as well, possibly particularly prominent in neuronal cells. We therefore aim to confirm functional impairment of the identified gene variatens. Next, we want to connect this to impaired ability to control VZV infection by testing patient and knock-out cells with immunological and viral replication assays in order to demonstrate disease causing impact of the identified genetic variants. Following, we aspire to uncover the specific interactions of VZV and autophagy in different, physiologically relevant cell types.

This project is part of our efforts to increase knowledge about the pathogenesis and complications of VZV infection, which will be valuable in the future development of improved patient diagnosis, prophylaxis, and treatment.

Keywords: Infection, Cell biology, Inflammation

Establishment of best antibiotic regime for prosthetic vascular graft infections.

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Background: Acute prosthetic vascular graft infections (PVGI) occur within the first 6 weeks after graft insertion. Current treatment is associated with high mortality, but from our experience, acute PVGI could be cured with anti-biofilm antibiotics. We want to investigate the efficacy of different anti-stapylococcal drugs against PVGI caused by methicillin resistant Staphylococcus aureus (MRSA) in an in vivo model.

Materials and methods: Rats received a pre-inoculated vascular prosthetic implant in the carotid artery. Implants were inoculated with MRSA USA300 FPR3757. 10 days following surgery rats were randomized to either 1) NaCL; 2) Daptomycin 3) Daptomycin+rifampicin 4) Tedizolid or; 5) Tedizolid+rifampicin as a seven-day treatment. Hereafter, the rats were euthanized and prosthetics and organs were harvested for CFU enumeration.

Results: Monotherapy with daptomycin was ineffective, and did not significantly reduce the bacterial load on the grafts compared to the NaCl group (p=0.0545, Mann-Whitney test). Combination therapy with daptomycin and rifampicin had a marked effect on efficacy, both when compared to the NaCl (p=0.0061) and a even more pronounced when compared to the daptomycin monotherapy group (p=0.0017). Most importantly combination therapy with daptomycin and rifampicin resulted in a cure rate of 62.5% vs. 0% in the daptomycin monotherapy group (p=0.0256, Fisher's exact test).

Conclusion: Preliminary results show that antibiotic therapy with daptomycin and rifampicin was superior to daptomycin monotherapy and this combination shows promising potential as a treatment that could be able to cure some patients with acute PVGI.

Keywords: Infection, Animal models/disease models, Laboratory science

HIV-1 diversity in recently and long-term infected HIV-1 participants

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Background

A person can be infected with HIV-1 without knowing it for many years, therefore time of infection is sometimes unknown. To date no validated test can predict time of infection. Here we compare participants self-reported time of infection with the Asanté Recency Assay and intra-participant HIV-1 diversity.

Methods

Fifty-six baseline plasma samples from the clinical study eCLEAR (NCT03041012) were analyzed. The Asanté HIV-1 Rapid Recency Assay (Sedia Biosciences Corporation) was used to categorized the participants as either recently infected (<6 months) or long-term infected (>6 months). Single genome amplification and subsequent sequencing was performed on plasma HIV-1 RNA for all participants. For each participant at least 30 HIV-1 envelopes were sequenced and as a measure of HIV-1 diversity, the median number of base pair differences in the envelope sequences were calculated.

Results

The Asanté Rapid Recency Assay has not been validated, so we correlated the results with the participants self-reported time of infection. There was 86% agreement between the Asanté Rapid Recency Assay and the participants' self-reported time of infection. Additionally, there was a significant difference between the recently and long-term infected group when analyzing the intra-participant HIV-1 diversity. Plasma virus in long-term infected participants was significantly more diverse compared to plasma virus in recently infected participants ($p<0.0001$).

Conclusion

The Asanté Recency Assay conforms with the participants' self-reported time of infection. Participants with long-term infection have more diverse plasma virus than recently infected participants.

Keywords: Infection, Laboratory science, Other

The inflammatory profile of skin changes (SCORDoK) in Severe Acute Malnutrition (SAM)

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Background: Severe acute malnutrition (SAM) is a potentially life-threatenig condition. There is a need for new research approaches to improve treatment and survival. Skin changes are connected to fatal outcome and lack validated treatment. The purpose: To identify correlates between circulating cytokines and the SAM-related inflammatory skin changes. Methods: Skin changes in 120 SAM-patients were scored with our tool for skin changes in SAM, SCORDoK. Admission serum samples and 20 healthy age-matched controls were collected. Enzyme-linked immunosorbent assay (ELISA) was performed, for analysis of circulating cytokines and chemokines: IL-1beta, -2, -4, -6 , -7 -10, -17 and -18, CCL-27, Fas Ligand and TGF-beta. Median with inter quartile range (IQR) were compared. Significance was tested with Brunner-Munzel test. Results: SAM-patients have significantly higher circulating cytokine-levels than controls on all cytokines measured ($p<0.00$), except for Fas-L wich was significantly lower ($p<0.000$) and IL-17 wich did not differ significantly from controls ($p=0.53$). Adjusting for precense of inflamatory skin changes did not change this significance. SAM-patients with and without skin changes did not differ significantly from each other, on any of the cytokines. conclusions: We confirm that SAM-patients generally are under the influence of a state of systemic inflammation. We conclude that presence of inflammatory skin changes is not connected to systemic elevation of any of the investigated circulating cytokines. Histopathological assessment of biopsies is gold-standard and the next mandatory step in the investigation of the ethiology behind the skin changes in SAM.

Keywords: Inflammation, Dermatology, Paediatrics

ROLE OF STING EXPRESSION AND ACTIVATION IN A MURINE MELANOMA MODEL

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Despite great success of immunotherapy as cancer treatment, some patients are non-responders and it remains unclear why. Myeloid immune cells are abundant non-cancerous cells embedded in the tumor microenvironment (TME), where they support T-cell driven anti-tumor immunity. As a result, cancer therapy combining immune modulators and checkpoint inhibitors is investigated for its capacity to refine existing cancer treatment. Activation of the innate immune pathway driven by the host protein STING has shown improved anti-tumor immunity. However, detailed knowhow on its role in the TME is missing and needed to truly understand its anti-tumoral potential.

This project aim to understand the role of STING activation within distinct innate immune subsets as well as cancer cells themselves, and to explore improved anti-tumor immune responses by specific STING activation.

We will investigate the role of STING activation in the clinically relevant mouse models YUMM.G1 and YUMMER.G1 of metastatic melanoma. These cell lines carries clinically relevant driver mutations, but differs in a high somatic mutation burden in YUMMER.G1 resulting in a more immunogenic and anti-PD1 sensitive melanoma model as opposed to YUMM.G1. The simultaneous use of both YUMM.G1 and YUMMER.G1 allow us to distinguish between the effect of STING activity in an antigen-independent and antigen-dependent immune response.

By elucidating STING pathway regulation within tumor cells as well as tumor-infiltrating immune cells and its effects on the TME, we will bring new knowledge to the scientific field in understanding the importance of innate immune pathway activation linked to the success of T-cell immunotherapy.

Keywords: Inflammation, Oncology, Animal models/disease models

Hemorrhage-Induced Hydrocephalus and the Role of Ncbe in Mice

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The choroid plexus (CP) is a small tissue located inside brain ventricles. It produces most of the cerebrospinal fluid (CSF); approximately 500 mL of CSF per day in the adult human. CSF production occurs as a net result of transcellular movement of salt and water, carried out by various cellular transporters. The sodium-coupled bicarbonate transporter, Ncbe, is the main sodium-loader of the cell; CSF production is highly dependent on this particular transporter.

Posthemorrhagic hydrocephalus (PHH) is a pathological state, caused by an accumulation of CSF in the ventricular system following intraventricular hemorrhage. This leads to an expansion of the brain ventricles. This buildup is either due to an obstruction of the CSF circulatory system or due to a disproportion between CSF production and reabsorption.

Intraventricular hemorrhage (IVH) is known to cause inflammation in the choroid plexus, which is coupled to an over-production of CSF.

The aim of this study is to investigate the role of Ncbe in PHH. We have established an IVH model in mice. Increased CSF formation rate has been validated with ventriculo-cisternal perfusion and expanded ventricular volume will be investigated using magnetic resonance imaging (MRI).

Our initial hypothesis was that IVH would lead to an upregulation of Ncbe, leading to increased CSF production. In contrast, preliminary data suggest that Ncbe is reduced by 24% (n=4, p=0.0329) in the initial stages of PHH.

We propose that Ncbe knock down (KD) inhibits CSF production and could potentially target inflammation-dependent hypersecretion. Following KD of Ncbe the effect on CSF production in PHH will be evaluated with the methods described above.

Keywords: Inflammation, Animal models/disease models, Basic neuroscience

Selective activation of the prostaglandin E2-EP4 receptor can slow or reverse the fibrotic process in human kidney slices

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Chronic kidney disease (CKD) affects about 10% of the population, and renal fibrosis, i.e. excessive scar formation in the kidney, is one of the major pathological processes leading to end-stage renal disease (ESRD). Despite overwhelming efforts to find therapies to reduce renal fibrosis, current treatment are ineffective at preventing disease progression in CKD patients.

Activation of the prostaglandin E2-EP4 receptor has been shown to have renoprotective effects in cell and animal studies. However, translational studies using human kidney tissue are lacking.

In this project, we studied the anti-fibrotic effect of the selective EP4 receptor agonist Rivenprost using a translational model of renal fibrosis, namely human precision-cut kidney slices (PCKS). Macroscopically healthy renal tissue was obtained from tumor nephrectomies, whereas fibrotic renal tissue was obtained from ESRD nephrectomies. Subsequently, PCKS were incubated with Rivenprost (75µM) to evaluate its anti-fibrotic effect in human tissue. Fibrogenesis was evaluated on a gene level using qPCR. Viability was assessed by ATP measurements using ELISA. Protein and histological analysis are ongoing.

The expression of the EP4 receptor in PCKS was increased twofold after 48h of incubation with the pro-fibrotic cytokine TGFβ, suggesting that the EP4 receptor might play a role in the fibrotic process. Treatment with Rivenprost mitigated TGFβ-induced fibrogenesis in healthy tissue. Moreover, Rivenprost halted disease progression in fibrotic PCKS and appeared to partly reverse fibrosis, as illustrated by a reduction in the gene expression of α-smooth muscle actin, fibronectin and collagen 1A1 by at least 50%, without affecting the viability of the human PCKS.

Activation of the PGE2-EP4 receptor can slow and reverse the process of fibrosis in human renal tissue. These findings warrant further research into the clinical application of EP4 receptor agonists, as a treatment for renal fibrosis.

Keywords: Nephrology, Inflammation, Animal models/disease models

A Comparison of Intra Ocular Pressure (IOP) Related Side-effects following Descemet's Stripping Automated Endothelial Keratoplasty (DSAEK) or Descemet's Membrane Endothelial Keratoplasty (DMEK) for Fuchs' Endothelial Dystrophy (FED).

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Background:
The corneal grafting techniques DSAEK and DMEK are effective treatments for FED. The thickness of the grafts is approximately 80 µm for DSAEK and 15 µm for DMEK. The graft must attach to the bared recipient stroma without sutures which is secured by an air bobble in the anterior chamber of the eye during the procedure. The use of an air bobble may result in increased IOP that potentially can affect other ocular tissues. For instance, increased IOP can result in pressure induced retinal nerve fibre atrophy which can be estimated by the circum-papillary retinal nerve fibre layer thickness (cpRNFLT). A randomised controlled trial has not yet compared these parameters following DSAEK and DMEK.

Purpose:
The study will compare the changes in cpRNFLT and iris function following DSAEK and DMEK.

Methods:
The study is conducted as a randomized controlled trial. Patients with FED and a requirement for corneal grafting are invited to participate in the study. Included subjects are examined preoperatively and throughout the first 12 postoperative months. The cpRNFLT is evaluated using optical coherence tomography scans. Iris function is examined using pupillometry under predefined light conditions.

Results:
The follow-up of patients is still ongoing and data analysis has not yet been conducted. Preliminary results will be presented on the PhD Day.

Perspectives:
Loss of retinal nerve fibres is irreversible and can cause visual impairment by means of scotomas in the visual field (glaucoma). Patients with reduced iris function can for instance suffer from glare and reduced contrast sensitivity. Therefore, a comparison of these parameters following DSAEK and DMEK is needed.

Keywords: Ophthalmology, Inflammation, Medical technology and diagnostic techniques

Poster session 9

Pre-meal consumption of whey in gestational diabetes mellitus

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Background:

Pre-meals of whey protein isolate (WPI) lowers postprandial glucose trajectories in healthy and type 2 diabetes patients. Whether this translates into patients with gestational diabetes mellitus (GDM) is unknown, but pre-meal WPI servings may potentially improve glucose homeostasis and reduce GDM complications such as macrosomia.

Objective:

To investigate the metabolic effects of WPI in women at risk of and with GDM.

Methods:

Trial A) Twenty women at risk of GDM (n=10) or with GDM (n=10) will undergo a randomized crossover study receiving placebo and WPI prior to an oral glucose tolerance test. For five days between visits, they will consume either placebo or WPI in various doses prior to breakfast at home and wear continuous glucose monitors (CGM).

Trial B) Fifty women will undergo a randomized parallel study and have either placebo or whey protein prior to breakfast from GDM diagnosis until delivery. They will visit the laboratory twice and wear CGM at home in the four following days. At delivery, weight and sum of skinfolds of the baby, cord blood and breast milk will be sampled.

Results:

Preliminary results of trial A shows that WPI lowers peak blood glucose levels by 1.8 mM following an OGTT in women at risk of GDM (n=8).

Conclusion:

The trials are ongoing and no conclusions can yet be drawn.

Keywords: Gynecology and obstetrics, Other, Other

The WINDOW study: When to INDduce for OverWeight in pregnancy, a randomised controlled trial

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Background: In fertile women, the prevalence of obesity (BMI ≥30 kg/m2) is 33% in the US, 20% in the UK, and 13% in Denmark. Obesity is associated with pregnancy complications including fetal macrosomia and prolonged labour, resulting in an increased risk of caesarean section. It has been suggested that early induction may reduce adverse events in obese women, but there have been no clinical trials and the impact on the rate of caesarean section remains unknown.

Objective: To assess birth outcomes in women who were obese at the time of conception when labour is induced at 39 weeks of gestation compared to expectant management.

Methods: The WINDOW study is an open label randomised controlled multicentre trial conducted at Danish delivery departments aiming to include 1900 pregnant women. Recruitment started October 2020. The women are randomly assigned in a 1:1 ratio to either labour induction at 39 weeks of gestation, or to expectant management; i.e. waiting for spontaneous labour onset or induction if medically indicated. The primary outcome is caesarean section. Secondary outcomes include maternal adverse outcomes, a composite of adverse neonatal outcomes, outcomes of maternal experience on birth and postnatal depression.

Results: A total of 189 women have been enrolled from four recruiting sites. An additional seven sites start recruitment in 2022. Besides an overview of recruitment status, preliminary results are not available.

Perspectives: The results of this trial will provide knowledge about delivery timing in obese women and will add key information to an on-going discussion of the overall effects of labour induction before term.

Keywords: Gynecology and obstetrics, Paediatrics, Public health

Active surveillance of cervical intraepithelial neoplasia grade 2 and risk of cervical cancer

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Background: Historically, cervical intraepithelial neoplasia grade 2 (CIN2) has been surgically removed to prevent progression to cervical cancer. Due to CIN2 regression rates of 50-60% and since surgical treatment is associated with preterm birth, women with childbearing desire are instead offered active surveillance with semi-annual follow-up visits for up two years. However, no study has investigated whether active surveillance is associated with increased long-term risk of cervical cancer.

Methods: We conducted a nationwide population-based cohort study of all incident CIN2 cases in Denmark from 1995 to 2013 identified through the Danish Pathology Registry. Women with no surgical treatment within 4 months after CIN2 diagnosis were considered as undergoing active surveillance, otherwise they were classified as surgical treatment. Women contributed with time at risk from CIN2 diagnosis until hysterectomy, emigration, death, or December 31, 2013, whichever occurred first.

Preliminary results: We identified 18,940 women with incident CIN2 of which 70% underwent active surveillance. The active surveillance group were younger (median age 27.6 (IQR 24.2-32.2)) than women who were treated surgically (29.2 (IQR 25.4-34.0)). Further analyses will include cumulative incidence proportions and calculation of the 5-, 10-, and 15-years risk of cervical cancer comparing women who underwent active surveillance vs. surgical treatment. The analyses will be stratified according to age and calendar year at CIN2 diagnosis.

Conclusion: Conclusion await further statistical analyses. We expect the results will provide important knowledge on risks associated with active surveillance of CIN2.

Keywords: Gynecology and obstetrics, Epidemiology and biostatistics, Other

MECHANISMS BEHIND SEVERE INSULIN RESISTANCE DURING PREGNANCY IN WOMEN WITH GLUCOSE METABOLIC DISORDERS (SIR-MET).

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Aim: The first aim of this study is to examine the association between insulin sensitivity in 3rd trimester among women with type 2 diabetes mellitus (T2DM) and structural and functional changes in the placenta. The second aim of this study is to examine the consequences of placental changes on fetal growth and development.

Method: This is a prospective observational case-control study including 24 pregnant women from the outpatient clinics at Department of Gynaecology and Obstetrics at Aarhus and Aalborg University Hospital. The study includes 8 women with T2DM with a total insulin dose > 100 units/day after gestational week 24, 8 women with T2DM with a total insulin dose < 75 units/day after gestational week 24 and 8 healthy women without pregestational or gestational diabetes. Insulin sensitivity will be estimated using the homeostasis model assessment, HOMA-IR, based on measurements of fasting C-peptide and glucose concentrations. Placental structure and function will be examined during 3rd trimester using a T2*-weighted MRI scan and a postpartum histopathological examination of the placenta. Fetal growth and development will be examined during 3rd trimester with ultrasound measuring specific biometric parameters and flow.

Results: Recruitment of participants is currently underway.

Conclusion: Maternal diabetes has been associated with specific structural placental changes, and the placental function may also be compromised. It has been suggested that these changes are closely related to the level of insulin resistance and glycemic control in pregnancy, but this has not been investigated in women with T2DM.

Keywords: Gynecology and obstetrics, Molecular metabolism and endocrinology, Other

Vitamin D deficiency in pregnancy – is increased supplementation needed?

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Background

Vitamin D deficiency is widespread among Danish pregnant women despite high adherence (90 %) to the official recommendations on supplementation in pregnancy (10 µg Vitamin D). This puts the women at risk as vitamin D deficiency is associated with increased risk of pregnancy complications related to placental function like intrauterine growth restriction, pre-eclampsia and gestational diabetes, although the underlying mechanisms are far from elucidated.

The aim of our study is to investigate if a higher dose of vitamin D in pregnancy can reduce the above mentioned complications and to explore the placental effects of a high dose of vitamin D to improve our understanding of underlying risks and disease pathology.

Methods

A double blinded randomized trial investigating two doses of vitamin D: 10 µg vs. 90 µg, combined with molecular analysis of placental tissue from selected groups (healthy and complicated pregnancies, obese, medicine users). A total of 2000 pregnant women seeking prenatal care at Randers Regional Hospital will be included in the study. Maternal blood samples, questionnaires describing life-style habits, placental tissue, umbilical cord blood and information on maternal and fetal outcomes from medical records will be collected.

Results

The study is ongoing. Since June 2020, we have included 980 women and collected 330 placentas.

Conclusion

We expect to provide new knowledge about disease mechanisms and vitamin D's effect on pregnancy- and perinatal health and provide the scientific evidence for determining if

a higher dose of vitamin D supplementation constitutes a feasible, economically sustainable way of improving public health for future generations.

Keywords: Gynecology and obstetrics, Gynecology and obstetrics, Other

Risk factors for kidney scarring and vesicoureteral reflux in 421 children after their first acute pyelonephritis, and appraisal of international guidelines

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Background: Acute pyelonephritis (AP) is a common bacterial infection in childhood. Follow-up guidelines on these children are controversial. This study aimed to identify risk factors for kidney scarring and vesicoureteral reflux (VUR). Furthermore, three international follow-up guidelines were evaluated in our cohort.

Methods: Urinary culture-confirmed first-time AP patients (aged 0-14 years) were enrolled (n = 421) from review of patient charts. All underwent kidney ultrasound (US) and kidney scintigraphy (DMSA or MAG3) at 4-6 months of follow-up. The international guidelines used for simulation were from the National Institute of Health UK (NICE), the American Association of Paediatrics (AAP) and the Swedish Paediatric Society (SPS).

Results: 17.8% presented with an abnormal DMSA/MAG3 at follow-up, 7.1% were diagnosed with VUR grades III-V and 4.7% were admitted for surgery. Non-Escherichia coli infections, abnormal kidney US, elevated creatinine and delayed response to treatment (>48 h) were risk factors for abnormal DMSA findings and VUR grades III-V. NICE and SPS guidelines showed best sensitivity in diagnosing VUR grades III-V (75%) compared with AAP (56%).

Conclusions: Risk factors are helpful in identifying children in need of further investigations and minimizing invasive work-up for the rest. International guidelines on follow-up detect a varying number of children with kidney damage and/or significant VUR. Future work must focus on identifying more specific risk factors, better imaging, or specific biomarkers, to enhance sensitivity and specificity in detecting the children at high risk for developing recurrent infections and/or nephropathy.

Keywords: Paediatrics, Nephrology, Urology

Paying extra attention: A qualitative study of parents' everyday practice in families with a child with Down syndrome

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Background: Prior studies investigating parents of children with Down syndrome have described the parenting experience as both rewarding and challenging. However, there is insufficient knowledge on how parents respond to this experience through their everyday practices – the daily actions by which they manage parenthood and everyday life.

Objective: We aimed to address this gap by exploring the experienced everyday practices of parents of children with Down syndrome.

Methods: Taking a qualitative approach, we conducted semi-structured interviews with 25 parents of children with Down syndrome aged 4-12 years. Using reflexive thematic analysis, we identified themes concerned with the parents' practice.

Results: The first theme, 'Supporting our child', describes how parents perceived their child as a valuable human being and how this perception founded parents' support of the child's development and social interactions. The second, 'Managing our family life', demonstrates how the parents acted to manage a family life that had become the 'new normal' including being alert towards the child, shaping the practical and logistical framework of daily life, and balancing between being at home and away from home. Overall, the analysis presents an everyday practice characterized by the parents paying particular attention to the various aspects of family life.

Conclusion: This study provides specific knowledge on parents' everyday practice in families where a child has Down syndrome. Our findings may inform genetic counseling about Down syndrome and are of value to service providers.

Keywords: Paediatrics, Qualitative research, Gynecology and obstetrics

Pharmacokinetics and Immunogenicity of the First Doses of PEG-Asparaginase - An ALLTogether Pilot Study

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Introduction
Acute lymphoblastic leukemia (ALL) is the most common malignant disease in childhood. Survival rates exceed 90% in children and 75% in adults (aged 18-45 years). Asparaginase is an indispensable part of the multiagent treatment, but is often associated with hypersensitivity, either with clinical allergy or silent inactivation. In both cases, asparaginase is inactivated. It is well known that truncation of asparaginase treatment reduces survival. To approach an understanding of asparaginase dynamics and hypersensitivity in ALL patients it is important to examine the pharmacokinetics.

The aim of this study is to identify serological parameters for prediction of hypersensitivity reaction after the first doses of PEG-asparaginase given intravenously on the ALLTogether protocol.

Methods:
The ALLTogether Pilot Protocol was conducted in Denmark, Norway, Sweden, Lithuania and Iceland from November 2018 – August 2021. PEG-asparaginase doses of 1500 IU/m2 <16 years, 1000 IU/m2 ≥16 years were initiated at treatment day 4 and were in most patients administered intravenously (222/252).

Therapeutic drug monitoring of asparaginase enzyme activity was used to identify patients with inactivation.

Results:
In total 252 patients (209 children/42 adults) were treated according to the ALLTogether Pilot Protocol. Inactivation of asparaginase was identified in 40/252 patient (15.9%); 5 (12.5%) with silent inactivation, 12 (30%) with mild allergy and 22 (55%) with severe allergy. Hypersensitivity mainly occurred after 4th or 5th dose (22/6).

The ability to predict patients prone to inactivate asparaginase will have great consequences for the patients and their survival.

Keywords: Paediatrics, Oncology, Pharmacology

What can we learn during a pandemic and nationwide school lockdown about childhood incontinence?

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Background: Previous questionnaire studies have reported a strong correlation between toilet avoidance behavior and symptoms of bladder and bowel dysfunction (BBD), but the knowledge is from cross-sectional studies and studies with follow up and interventions are needed. Thus we seized the opportunity to examine the effect of school lockdown during Covid-19 on BBD

Method: We examined the effect of school lockdown on BBD by sending questionnaires regarding patient reported outcomes (PRO) to a cohort from the outpatient clinic at Centre for Childhood Incontinence at Aarhus University Hospital. One parent for each child from the outpatient clinic within the six months before onset of the investigation were asked to participate.

Results: 106 parents completed the first questionnaire. 83 % of the children received remote learning via computer at home during the lockdown of January 2021, 17 % of the children were still at school. For children with daytime urinary incontinence(DUI) receiving remote learning 64,3 % reported improvement of symptoms during lockdown compared to 33,3 % of the children who were at school. The CBBD questionnaire evaluating the frequency of symptoms over time of concomitant childhood bladder and bowel dysfunctions was also significantly lower in children with DUI receiving remote learning compared to children with DUI at school, 30,9 point (29.0 ; 32.9) vs 36,1 point (30.6 ; 41.5), $p<0.05$.

Conclusion: More children with DUI receiving remote learning at home during lockdown had parent reported improvement than children still at school. They also had a lower frequency of symptoms reported on the CBBD questionnaire.

Keywords: Paediatrics, Nephrology, Psychiatry, psychology and mental health

Poster session 10

Inhibition of FAP increase the levels of intact FGF21, which is associated with improved glucose tolerance

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Background: The endocrine Fibroblast growth factor 21 (FGF21), with pleiotropic effects on glucose and lipid metabolism, has become of interest as a medical treatment of metabolic disease such as T2D. FGF21 signalling requires binding to two receptors, FGFR and to beta-klotho, on the cell surface. FGF21 has a short half-life due to cleavage by the DPP4-like protease fibroblast activation protein (FAP), resulting in inactive FGF21. Paradoxically, FGF21 levels are elevated in metabolic diseases suggesting a state of FGF21 resistance or that FGF21 is cleaved and unable to activate cells, which may result in a compensatory increased FGF21 level. Previous studies do not differentiate between total and intact FGF21 nor measure FAP activity in plasma when concluding upon FGF21 signalling.

Methods: Baseline and 12 weeks follow up plasma levels of total and intact FGF21, FAP and FAP activity from 71 AMI patients with impaired OGTT randomised to sitagliptin or placebo from the BEGAMI study. Total FGF21 and FAP levels was measured using an inhouse modified TRIFMA-assay, intact FGF21 using a commercial ELISA kit and FAP activity was measured using our newly in house developed FAP-activity assay. In vitro plasma studies with sitagliptin in varied concentrations.

Results and conclusion: Sitagliptin inhibit FAP-activity and increase levels of intact FGF21 in vivo and in vitro and increase in Intact FGF21 was associated with improved OGTT. No differences were found in circulating levels of total FGF21 or FAP. Thus, we emphasize the importance of intact FGF21 and/or FAP activity measurements rather than total levels of FGF21 and FAP when concluding upon FGF21 signalling.

Keywords: Molecular metabolism and endocrinology, Laboratory science, Other

Effect of intermittent fasting on insulin resistance and cardiac substrate metabolism: A randomized, controlled crossover study

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Background and purpose. Ketone bodies are produced in the liver as an alternative fuel when blood glucose levels are low, as can be seen with various types of diet. In a previous study, we observed that ketone bodies act as a kind of cardiac "super fuel" and improve the heart's energy utilization thereby enhancing its pump function. Individuals with insulin resistance and/or heart failure have a lower cardiac glucose uptake. A “metabolic shift” away from glucose and fatty acid oxidation towards the less oxygen-requiring ketone body oxidation may thus potentially reduce morbidity seen in myocardial ischemia in individuals with type 2 diabetes and ischemic heart disease. Therefore, our primary purpose is to investigate whether three weeks of intermittent fasting (fasting every other day) improves insulin resistance, and cardiac pump function and substrate metabolism compared with three weeks of western diet (no restrictions).

Methods. The study will be performed as a randomized, controlled crossover study of 16 individuals aged 55-70 years with insulin resistance and obesity. After each 3-week intervention period, a study day with PET scans and metabolic laboratory examinations will be conducted.

Perspectives. Based on our study, we will discuss the promising potential of intermittent fasting as an unused, non-pharmacological treatment for individuals with obesity and insulin resistance at risk for heart disease and type 2 diabetes. Furthermore, the study results may have a potential impact on future, evidence based recommendations for all people at risk for cardiovascular disease and type 2 diabetes.

Keywords: Molecular metabolism and endocrinology, Cardiovascular system, Other

Cardiac and hepatic metabolic flexibility in patients with Type 2 Diabetes with and without Non-Alcoholic Fatty Liver Disease (NAFLD)

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Background:

Patients with type 2 diabetes (T2D) have increased risk of heart disease, more severe insulin-resistant glucose and free fatty acids (FFA) metabolism, and very often, increased liver fat content (NAFLD). The latter covers a spectrum from simple reversible hepatic steatosis to inflammation and fibrosis termed steatohepatitis (NASH) and cirrhosis. Accumulating evidence indicates that NAFLD is associated with development of heart failure, abnormal ventricular fatty acid (FA) utilisation and cardiac steatosis. The mechanisms behind this are poorly understood, but includes altered cardiac and intrahepatic lipid handling and may be reflected in reduced myocardial function, increased intrahepatic triglyceride content (IHTG) and perturbed adipose tissue and skeletal muscle lipid metabolism in patients with T2D and NAFLD.

Methods:

Comprehensive kinetic studies of cardiac and hepatic FA uptake and oxidation (11C-palmitat PET/CT scans), ventricular function (cardiac MRI and echocardiography) and hepatic triglyceride (TG) secretion and clearance (isotope dilution technique) will be performed in order to assess mechanisms governing cardiac and hepatic lipid trafficking in patients with T2D with and without NAFLD. Furthermore, muscle and adipose tissue biopsies for measurement of intramuscular triacylglycerol (IMTG), lipogenic and lipolytic enzyme activities and expression of key glucose and lipid regulatory enzymes, will be investigated.

Perspectives:

The results will help identifying potential novel targets of intervention against the increased incidence of heart failure and cardiovascular disease (CVD) associated with NAFLD.

Keywords: Molecular metabolism and endocrinology, Gastroenterology and hepatology, Other

Can the Adherence in Diabetes Questionnaire and Baseline HbA1c Predict 10- Year HbA1c Trajectories in Young People with Type 1 Diabetes?

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OBJECTIVE: To determine the ability of baseline glycated hemoglobin (HbA1c) and the Adherence in Diabetes Questionnaire (ADQ) to predict the ten-year trajectories of HbA1c of children and adolescents with type 1 diabetes (T1D).

RESEARCH DESIGN AND METHODS: Using longitudinal, cohort follow-up design, data from a Danish national survey among 1028 caregivers and 766 children and adolescents (age range 2-17 years; mean age 12.3 ±3.69; 50.9% female, diabetes duration of 5.2 ±3.31years) will be analyzed using group-based trajectory modeling to predict HbA1c trajectories for participants completing both a baseline HbA1c and ADQ in 2009-2010. Confounding baseline variables were age at diabetes onset, diabetes duration, gender, pump/pen status, and caregiver/parental education level. Follow up HbA1c levels were obtained annually from the Dansk Voksen Diabetes Database (DVDD) and Danish Registry of Childhood and Adolescent Diabetes (DanDiabKids).

RESULTS: At baseline, the sample's mean HbA1c=65 mmol/mol (8.1%), SD=12 mmol/mol (1.1%), range=33 mmol/mol (5.2%) to 128 mmol/mol (13.9%). Results of group-based trajectory modeling are pending regarding the ability of the ADQ with or without baseline HbA1c, to predict future HbA1c trajectories.

CONCLUSIONS: Using a Danish national survey of children and adolescents with T1D, we hypothesize that individuals with lower/concerning baseline ADQ scores, and/or a higher baseline HbA1c will be at increased risk for unfavorable HbA1c trajectories over a ten-year period. This analysis should help to inform clinicians about the predictive value of administering the ADQ at clinic visits during childhood and adolescence.

Keywords: Paediatrics, Psychiatry, psychology and mental health, Molecular metabolism and endocrinology

Influence of 10 days of Low Energy Availability on Physical Performance in Trained women

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Background

Low energy availability, defined as <30 kcal/kg FFM/day after subtracting the energy cost from exercise from the energy intake, is a well-known problem in sports and have – in addition to menstrual disturbances - been shown to negatively impact bone health, endocrine function and mental health in the long term. However, the time course and severity of these consequences and to what extend physical performance is impacted are yet to be elucidated.

Objective

To investigate the impact of 10 days with low energy availability on physical performance and training quality in young trained women.

Methods

Thirty young trained women with regular menstruation were matched in pairs based on training history and randomized into two groups a) 10 days of energy restriction (25 kcal/kg FFM/day) + supervised training or b) 10 days of energy balance (50 kcal/kg FFM/day) + supervised training. Before the intervention period, both groups underwent a five-day energy balanced control period with supervised training. Next, the 10-day intervention period followed with either an energy-restricted diet or an energy-balanced diet. Before and after the intervention period, muscle strength, vertical jump height, repeated sprint ability, and 4 min time trial performance were evaluated. Furthermore, total training volume over the course of the intervention was assessed.

Results

At the time of writing, 15 out of 30 participants have completed the study (Preliminary data will be presented at the PhD day). However, based on the current literature on relative energy deficiency in sport, we hypothesize that 10 days of low energy availability will reduce physical performance and training quality.

Keywords: Public health, Molecular metabolism and endocrinology, Other

THE EFFECT OF A KETOGENIC DIET ON HEART METABOLISM

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Background. Ketone bodies are produced in the liver as a fuel when blood glucose levels are low, as can be seen with various types of diet or prolonged fasting. In previous studies, we observed that ketone bodies act as a kind of cardiac "super-fuel" and improved the heart's energy utilization leading to an increase in pumping function. Furthermore, ketosis promotes a metabolic shift away from glucose and fatty acid oxidation towards the less oxygen requiring ketone body oxidation. This can potentially reduce the morbidity seen in myocardial ischemia in patients with type 2 diabetes and ischemic heart disease (IHD).

Purpose. The overall purpose of the study is to investigate whether three weeks of a ketogenic diet results in a "metabolic shift" towards the use of ketone bodies compared to three weeks of western diet (no restrictions).

Methods. The study is a randomized, controlled crossover study of 12 obese individuals aged 50-70 years. After each intervention period, a study day with PET scans and metabolic laboratory examinations is performed. In addition, state-of-the-science PET techniques will be performed since we have developed a new ketone body tracer (11C-β-hydroxybutyrate) to quantify ketone body uptake.

Preliminary results. Quantification of ketone body uptake in a pig model has shown PET tracer kinetics consistent with ketone body uptake.

Perspectives. The results of our study will contribute to knowledge regarding the possible effect of a ketogenic diet on cardiac substrate metabolism. Our findings might potentially have a vital impact on future dietary recommendations to people at risk for or suffering from obesity, cardiovascular disease and diabetes.

Keywords: Molecular metabolism and endocrinology, Cardiovascular system, Medical technology and diagnostic techniques

Poster session 11

EVITA study - Epstein-Barr Virus Infection moniToring in renAl transplant recipients - Early identification of increased risk of infection and cancer for individualised immunosuppression

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Background

Epstein-Barr virus (EBV) can cause posttransplant lymphoproliferative disease (PTLD) in transplant recipients. Due to immunosuppression, PTLD may progress rapidly, but early detection of EBV replication by frequent monitoring is hypothesised to provide early diagnosis leading to treatment and improved outcome. Our aim is to estimate the incidence and consequences of EBV DNA in plasma and whole blood (EBV DNAemia) in renal transplant recipients, with focus on persistence of EBV DNAemia as a marker for excessive immunosuppression as indicated by the incidence of infections, PTLD and mortality.

Methods

Five hundred children and adult renal transplant recipients will be included from Aarhus University Hospital, Odense University Hospital and Oslo University Hospital – Rikshospitalet. All recipients will be tested for EBV DNAemia (whole blood and plasma) before transplantation, once every month until 9 months and 12 months after transplantation. Recipients at particularly high risk of developing PTLD will be tested every three months during the second year. Data on infections, graft function, PTLD and mortality will be collected until two years after transplantation.

Results

Two hundred and seventy-nine renal transplant recipients (11 children) have been enrolled in the study from January 2020 to the end of October 2021. So far, three patients have developed PTLD and analysis of EBV DNA awaits.

Conclusion

The association between EBV DNAemia and development of PTLD, infections and mortality is yet to be determined. It is likely that early detection of EBV DNAemia and prompt PTLD diagnosis may improve the overall treatment success of this serious post-transplant complication.

Keywords: Nephrology, Infection, Oncology

Itaconate derivative suppresses antiviral innate immunity and sensitizes refractory cancer cells to oncolytic virotherapy.

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Traditional cancer treatments still possess limited efficacy coupled with serious side effects that can harm patients. Hence, there is a high demand for functional alternatives outside of conventional cancer therapeutics. Oncolytic viruses (OV), on the flip side, made their way to the clinic through their unique capacity to selectively infect and lyse cancer cells priming more specific immune responses due to tumor antigen release. Our study is committed to making this therapeutic approach more potent using a combination of an oncolytic virus, Vesicular Stomatitis Virus (VSVd51M), with the endogenous cellular metabolite derivative 4-octyl-itaconate (4-OI).

Here we demonstrate that human renal 786-O and murine colorectal CT26WT cancer lines are highly resistant to VSVd51M treatment. Immunoblotting showed that these tumor cells exhibit strong antiviral responses to VSVd51M that were fully ablated following 4-OI treatment. Crucially, the immunosuppressive effect of 4-OI was not observed in non-cancer primary human cells. Flow cytometry experiments showed that 4-OI treatment prior to virus exposure enhanced VSVd51M infectivity from 2-3% to more than 60% in cancer lines, but not in primary human cells. Furthermore, 4-OI enhanced VSVdM51 infection ex vivo in mouse-derived tumor tissues showing that this approach also works in platforms that are more complex. Mechanistically, OV boosting properties elucidated by 4-OI were ablated upon Nrf2 silencing. Altogether, our work demonstrates that 4-OI benefits VSVd51M spread and oncolytic efficacy in an Nrf2-dependent manner in different tumoral lines while sparing healthy cells.

Keywords: Oncology, Infection, Inflammation

Association between recurrence and stem cell marker SLC3A2, volume and HPV/p16 in HNSCC

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Purpose:

Large tumor volume and HPV/p16- status are known to be poor prognostic factors for loco-regional failure for Head and Neck Squamous Cell Carcinoma (HNSCC) after primary curative radiotherapy (RT). However, the response to RT is heterogeneous and the objective was to identify the presence and possible impact of the stem cell marker SLC3A2.

Material/Methods:

Patients (Pts) were treated with standard chemo-RT and the hypoxic radiosensitizer nimorazole. Formalin-fixed paraffin embedded tumor tissue were collected and dissected. RNA was extracted and qPCR was applied to measure the relative gene expression of the cancer stem cell marker SLC3A2.

Volume of GTV-T and -N (GTVTot) was extracted from the original planning-CT. SLC3A2 was categorized according to expression and p16-status. Subclassification was performed according to HPV/p16-status, 50-percentile of SLC3A2 (high/low) and GTVTot (large/small) into three groups. Loco-regional failure was used as endpoint.

Results:

Full data-set were available from 143 primary tumors.

Expression of SLC3A2 was more prominent in HPV/p16 negative tumors compared to HPV/p16 positive tumors, $p<0.001$ (Fig. 1).

When dividing pts into the three predefined groups, the risk of loco-regional failure was significantly worse for patients in the high-risk group, $p<0.001$ (Fig. 2). In total, 4 % of the pts in the low risk-group (n=27) and 56 % in the high-risk group (n=26) had loco-regional failure.

Conclusion:

Presence of the stem cell marker SLC3A2 is significantly more frequent in HPV/p16 negative HNSCC and is together with tumor volume a poor prognostic factor. SLC3A2 may be a putative marker of radioresistance in primary RT of HNSCC.

Keywords: Oncology, Cell biology, Laboratory science

Impact of guidelines on nationwide breast cancer radiotherapy treatment planning practices (DBCG RT Nation study)

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Purpose

The aim of this study is to show the effect of implementation of guidelines on dosimetric parameters for heart and internal mammary nodes (IMN) over time for patients treated with radiotherapy (RT) for loco-regional (LR) breast cancer (BC).

Materials and methods

We conducted national data collection based on patients identified from the Danish Breast Cancer Group (DBCG) database with an indication for LR RT. RT data from 9861 patients treated at seven centres are being collected (ongoing). We developed and implemented automatic solutions to extract and quality assure the data.

The effect of three events (E) on the volume and dose of the heart and IMN was investigated.

E1: 2010 – 2012. DBCG organ delineation consensus workshops.

E2: 2014. Inclusion of IMN in the RT target for all LR RT irrespective of laterality of the BC.

E3: 2015. ESTRO consensus guideline for target volume delineation in BC.

Results

Data was collected for 3479 patients so far. After E2, 98% of all patients with left-sided BC had IMN delineated with a median CTV V90% of 93% (IQR 79% - 98%). After E3, the mean volume of IMN converged to an average of 7.4mL (SD=3.4). The volume of the heart stabilised after E1 and a small increase in mean heart dose (MHD) after E2 was detected associated with the increase in CTV IMN V90% for LSP.

Conclusion

Dosimetric data showed the effect of delineation consensus guidelines on the volume of the heart, and the IMN. Furthermore, an increase in coverage of the CTV IMN for LSP and a corresponding increase in MHD after E2 was shown. In conclusion, there was an evident impact of introducing DBCG and ESTRO guidelines on the clinical RT planning practice in Denmark.

Keywords: Oncology, Cardiovascular system, Other

Molecular exploration of the tumor immune microenvironment and microbiome in prostate cancer

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Prostate Cancer (PC) is the most frequently diagnosed non-skin cancer among Danish men. Limited accuracy of prognostic tools results in overtreatment of indolent PC and delayed treatment of aggressive PC. Thus, novel markers are needed for a more precise risk stratification. Consequently, we investigated the influence of the prostate tumor microenvironment (TME) and PC microbiome on PC progression to identify signatures that can improve risk stratification.

To examine the role of the TME in PC aggressiveness, we performed total RNA sequencing of 127 PC tumors from men who underwent radical prostatectomy (RP). We used non-negative matrix factorization to elucidate expression signatures from changes in 88 stroma-specific or 86 epithelium-specific genes, identifying three stromal signatures and three epithelial signatures. Signatures were able to predict PC aggressiveness, assessed using Kaplan-Meier and uni- and multivariate Cox regression analyses with biochemical recurrence (BCR) as endpoint. Results were validated in two independent RP cohorts consisting of RNAseq data from 406 tumors and microarray data from 126 tumors. To characterize the signatures, we used bioinformatic tools to estimate cell type infiltration, copy number alteration burden, and cancer Hallmark gene set enrichment across the cohorts.

Furthermore, to examine the role of prostate microbiome on PC aggressiveness, we will conduct 16s rRNA gene sequencing on DNA from PC and adjacent normal tissue samples from RP patients. We will correlate bacterial signatures the TME expression signatures and evaluate if addition of bacterial signatures can improve the prognostic potential of the TME signatures.

Keywords: Oncology, Inflammation, Urology

The effectiveness of e-learning in patient education delivered to patients with rheumatoid arthritis: The WebRA study - a pragmatic randomised controlled trial

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Background

Patient education is integral to the treatment and care of patients with rheumatoid arthritis (RA). A rising prevalence due to the demographic development places new demands on the healthcare system. This calls for alternatives to conventional models of care, e.g. by using digital technologies.

Aim

To evaluate the effectiveness of an e-learning patient education programme based on self-management targeting patients with RA.

Methods

The effectiveness is tested in a multi-centre randomised controlled trial among 190 patients with a new diagnosis (<3 months) of RA. Participants are randomised 1:1 to web-based patient education at home or standard patient education at the hospital. The primary outcome is self-efficacy. Secondary outcomes are knowledge of RA, adherence to medication, health literacy and quality of life. Measurements occur at baseline and follow-up; 1, 3, 6 and 12 months after enrolment. Data on the utilisation of healthcare and the e-learning programme is assessed at the 12-month follow-up. Statistical analysis, including differences between groups, will be evaluated using the chi-square and Kruskal–Wallis tests. Statistical analysis will follow the intention-to-treat principle, and analysis of variance will be used to evaluate the within- and between-groups differences.

Conclusion/Future perspectives

Potentially, this e-learning programme will be incorporated into existing services and may improve the self-management of patients with RA. Further, web-based patient education may impact the organisation of the health care system by offering different modes of delivering patient education based on the needs and preferences of patients.

Keywords: Rheumatology, Other, Other

Signaling Through PD-L1 Plays a Central role in Extracellular Matrix Protein secretion from cutaneous Myofibroblasts in Systemic Sclerosis

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Background: The PD-1/PD-L1 pathway has been implicated in Systemic Sclerosis (dSSc). This disease is dominated by increased extracellular matrix deposition initiated by myofibroblasts. We therefore examined the PD-1/PD-L1 pathway in dSSc myofibroblasts and its influence on fibrosis.

Methods: Dermal fibroblasts were isolated from the skin from patients with dSSc (n=9) and compared with dermal fibroblasts from healthy controls (HC)(n=4). Cells were stimulated with TGF for 48 hours and analyzed by flow cytometry for expression of the surface proteins CD45,CD90 Thy-1, PDPN,PD-L1,FAP,ICAM-1 and Alpa SMA. Supernatants were analyzed for the production of Type 1 Procollagen and IL-6. Parallel to this, dcSSc fibroblasts, were stimulated with IFN for 48 hours followed by addition of anti-PD-L1 antibody and soluble, recombinant PD-1. Supernatants were harvested after 48 hours and analyzed for production of Type 1 Procollagen and Fibronectin.

Results: CD45neg fibroblasts, from both dSSc as well as HC could be identified by their expression of Thy-1 and Podoplanin. Upon stimulation with TGF , fibroblasts from dSSc increased the percentage expression of PD-L1, - SMA, ICAM-1, FAP and Podoplanin when compared to HC fibroblasts. Analyzing this data by tSNE, we could demarcate a distinct populations of the myofibroblasts that had a high expression of PD-L1 together with ICAM-1. Parallel to this we added an anti-PD-L1 monoclonal antibody, or rPD-1 to fibroblasts. Collagen production was decreased by addition of the former and increased by the addition of the later.

Conclusion : PD-L1 plays an important role in regulating fibrosis, and inflammation in dSSc

Keywords: Rheumatology, Cell biology, Inflammation

Influence of Hormone Treatment in Bladder Cancer – Incidence and Prognosis

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Aim: To investigate the effect of hormone treatment on Bladder Cancer.

Background: Bladder cancer (BC) is one of the most commonly diagnosed cancers in the world. However, there are significant gender differences regarding incidence and prognosis, even after adjusting for smoking and environmental exposure. Males have a 4:1 higher risk of BC, whereas females often experience more advanced and progressive disease. One explanation for this may be the presence of sex hormones and their receptors in the bladder. Currently, there are drugs available, which can suppress these receptors and decrease their expression. However, it has yet to be revealed in more detail if these drugs may play a role in BC.

Methods: A prospective cohort study with data collected from the National Danish Registry Database. The case-population includes all males and females with an incident diagnosis of prostate, endometrial or breast cancer from 2002-2018, with no previous history of other cancer, matched 1:10 to a control population. The cohort is stratified according to gender and to hormone treatment or not. The primary outcome of investigation is incident urinary BC and secondary outcomes are stages of BC and prognosis.

Results: Results are currently pending. The hypothesis to be tested is a protective effect of hormonal therapy against incident bladder cancer.

Conclusion and perspectives: To our knowledge, this will be the largest cohort study on the influence of hormones in BC today. Positive results may lead to a potential new target approach in BC. Furthermore, this study might reveal new answers to the gender difference that exists in urothelial B

Keywords: Urology, Oncology, Epidemiology and biostatistics

An integrative multi-omics analysis of early stage bladder cancer to identify patients with a high risk of progression

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Approximately 10% of patients with early-stage bladder cancer will progress to the often lethal muscle-invasive bladder cancer. It is critical to identify patients with a high risk of progression to treat them early and aggressive with removal of the bladder or immunotherapy. Unfortunately, we are currently not able to predict disease aggressiveness optimally.

We hypothesize that an integrated analysis of DNA (genomic alterations) and RNA (gene expression) will lead to an improved understanding of the molecular mechanisms driving disease aggressiveness.

Our strategy is to expand a previous study of total RNA-sequencing (n=460) with additional molecular layers. We are currently performing whole-exome sequencing and low coverage whole genome sequencing on tumors with RNA-sequencing data available to call somatic mutations and copy number alteration. As of November 2021, overlapping transcriptomic and genomic data is available for 129 patients and preliminary data from this cohort will be presented at the PhD day 2022.

We will integrate the genomic- (somatic mutation and copy number alterations) and transcriptomic layers to reverse engineer the network of genomic alterations in modulator genes, regulatory proteins (transcription factors) and gene expression profiles using the Multi-omics Master Regulator Analysis (MOMA) approach. Thereby we expect to identify central regulators of tumor homeostasis and highlight important genomic alterations in upstream genes.

Successful completion of this project may lead to an improved understanding of the underlying mechanisms of disease progression and to the identifications of potential therapeutic targets.

Keywords: Oncology, Urology, Cell biology

Poster session 12

Impact of cone beam CT on diagnosis of external cervical resorption: the severity of resorption assessed in periapical radiographs and cone beam CT. A prospective clinical study

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Objectives: To compare the severity of external cervical resorption (ECR) observed in periapical (PA) radiographs and cone beam CT (CBCT) using the Heithersay classification system and pulp involvement; and to assess inter- and intra-observer reproducibility.

Methods: CBCT examination was performed of 245 teeth (190 patients, mean age 40 years, range 12-82) with ECR diagnosed in PA radiographs. Three observers diagnosed the severity of ECR using the Heithersay classification system (severity class 1-4) and pulp involvement (yes/no) in both PA radiographs and CBCT. Observer variation in PA images and CBCT was described by percentage accordance and κ-statistics.

Results: The ECR score was the same in the two imaging modalities in more than half of cases (average 59%; obs1: 54%, obs2: 63%, obs3: 61%) for all three observers. However, in 38% (obs1: 44%, obs2: 33%, obs3: 36%) of the cases, the observers diagnosed more severe ECR in CBCT than in PA images ($p < 0.001$). The ECR score changed to a less severe score in CBCT only in 3% (obs1: 1%, obs2: 4%, obs3: 4%). For pulp involvement, 14% (obs1: 7%, obs2: 20%, obs3: 15%) of the cases changed from "no" in PA images to "yes" in CBCT. Kappa values were higher for CBCT than for PA images for both the Heithersay classification score and pulp involvement. Inter and intra-observer reproducibility were most of the time higher in CBCT than PA radiographs.

Conclusions: ECR was generally diagnosed as more severe in CBCT than PA images, and more teeth had pulp involvement as seen in CBCT. The severity score is believed to influence the treatment plan and prognoses for the tooth.

Keywords: Dentistry, Medical technology and diagnostic techniques, Public health

A randomized controlled, Danish multicenter trial in minimal change nephropathy: The efficacy of high dose prednisolone vs. reduced prednisolone dose and activated vitamin D.

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Background

Minimal change nephropathy (MCN) causes 10-25% of adult nephrotic syndrome. Current treatment guidelines involve high dose of steroids. It is usually effective in inducing clinical remission, but with a relapse rate of 30-70%. Many patients require long term steroid therapy associated with significant morbidity and mortality. Nephrotic syndrome is associated with low vitamin D levels. Active vitamin D reduces proteinuria in both animal and human studies by regulating podocyte function. This trial will examine the efficacy of a reduced prednisolone dose combined with activated vitamin D in patients with MCN.

Hypotheses

Treatment with reduced prednisolone and activated vitamin D is not inferior to standard high dose prednisolone in inducing remission.

Treatment with reduced prednisolone dose and activated vitamin D has fewer side effects.

Methods

A randomized, open-labelled, multicenter trial comparing the efficacy of prednisolone 1mg/kg/d to prednisolone 0.5mg/kg/d plus activated vitamin D 0.5µg/d in patients with primary MCN using a non-inferiority design.

Primary endpoints are the frequency of remission after 16 weeks and time to remission. Secondary endpoints are the frequency of relapse and objective and subjective side effects to treatment. Blood and urine tests define remission and relapse. Clinical examination and patient questionnaire measure side effects. Follow up is 1 year from remission. Since 2018 38 out of a total of 96 patients have been included from all renal departments in Denmark.

Perspectives

If successful, the study will allow for new treatment regimens to reduce side effects and thus the disease burden for individuals and society.

Keywords: Nephrology, Pharmacology, Public health

Effectiveness of adapted Mindfulness-based Stress Reduction in private companies: preliminary qualitative results of a mixed methods study

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Background: The programme "Mindfulness-based Stress Reduction" (MBSR) has been found effective in enhancing well-being, reducing perceived stress and symptoms of depression and anxiety. Previous research indicate that mindfulness in a workplace setting has positive effects not only on individual mental well-being but also on the quality of interpersonal relationships.

Purpose: Evaluate the effectiveness of implementing a systematically adapted MBSR course in private companies on both individual competencies and interpersonal relationships.

Methods: Four companies participated in this quasi-experimental study. In total, 40% of employees in the companies enrolled in a 10-weeks MBSR course. After the course, representatives from three companies participated in a workshop on further implementation of mindfulness in their company. Qualitative data was collected at baseline and post intervention using focus group interviews with managers and employees from each company. Data was analysed using qualitative content analysis.

Results: Preliminary analyses indicate that at the individual level, participants experience themselves as less reactive under stressful situations and more likely to prioritize taking breaks during the workday. At the interpersonal level, long-standing work-related conflicts were solved following project participation.

Discussion: Implications for companies and future research will be discussed; specifically, the beneficial effects for companies of implementing mindfulness in their organisation. In conclusion, this study illuminates the potential for a systematically adapted MBSR programme to evoke personal and interpersonal change in private companies.

Keywords: Public health, Work environment and organisation, Qualitative research

Predicting difference in mean survival time from cause-specific hazard ratios for women diagnosed with breast cancer

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Background: Relative reduction in breast cancer mortality is the preferred outcome measure for evaluation of mammography screening. However, mean survival time has been advocated as a better and more intuitive outcome for risk communication. We have previously introduced a method to predict difference in mean survival time from empirical hazard ratios for all-cause mortality. In this article, we aim to investigate the association between hazard ratios for breast cancer mortality and the difference in mean survival time for women diagnosed with breast cancer.

Methods: We retrieved data on all women diagnosed with first-time invasive breast cancer in Norway from 1960 through 2004. Women were followed until emigration or end of follow-up on 31 December 2015, whichever came first. Observed differences in mean survival times and hazard ratios for both breast cancer death and death from causes other than breast cancer were obtained for neighbouring time periods defined by

women's age and year of diagnosis. Based on previously developed methods, we fitted a linear relationship between observed differences in mean survival and logarithmic hazard ratios.

Results: A linear association was found between breast cancer-specific hazard ratios and difference in mean survival time for women diagnosed with breast cancer. This association was also estimated with adjustment for other causes of death than breast cancer.

Conclusions: The change in mean survival time could be predicted from an estimated reduction in breast cancer mortality. This outcome measure can contribute to better and more understandable risk information about the effect of mammography screening programmes.

Keywords: Public health, Epidemiology and biostatistics, Other

How Context and Program Conditions (CPC) affect the success of Interprofessional Collaboration in Integrated Care: using the CPC-framework to examine the Interprofessional Collaboration in Danish Primary Care

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Introduction

Increasing demands for interprofessional collaboration in health care have increased the interest in studying how different conditions influence the success of collaborations. However, there are many different conditions; and we know little about the magnitude of interactions between conditions. Studying these interactions will enable us to identify what the most important conditions are.

Thus, the aim of this paper is to further develop the Context and Program Conditions (CPC) framework; and apply it to study home care services for elderly in two Danish Municipalities. The purpose of the CPC-framework is to conceptualise the relationships between program and context conditions at the professional and organisational level; and to measure how the different conditions influence each other and the success of the collaboration.

Methods

The study was conducted as a multilevel cross-sectional survey in November 2021 in Herning and Holstebro, Denmark. The focus of the study was the interprofessional collaboration between home care and home nursing units. The study population was all frontline staff in the units, and their respective managers. Data was examined with CB-SEM based on prior hypothesised relationships and index'.

Results

Preliminary results of the analysis shows that the CPC-framework is well-suited to examine how different types of conditions influence the success of collaborations in a Danish primary care setting.

Implications

The CPC-framework can be used as a diagnostic tool to identify what the most important conditions are for a specific collaboration; and subsequently help improve existing interprofessional collaborations.

Keywords: Public health, Work environment and organisation, Other

Digital documentation practice

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Introduction

I all Danish municipalities, a new documentation method called the "Common Language Platform" is implemented through the digital platform of the electronic health record. Sub study 1 of this PhD-project examines written implementation strategies. The study indicates that the digitalization of documentation requires standardization and transforms health care practice. The aim of sub study 2 is to investigate how the written strategies are translated into health professional practice.

Methods

Sub study 2 is designed as a qualitative single-case study with a social constructivist approach. Empirical data are collected through multiple methods:

- Documents analysis: E.g. teaching materials, instructions, and guidelines on the local documentation practice. The focus is on how the practical documents represent key ideas of digital documentation.
- Field observations: 4-6 months during the planning of services, with health professionals during visits and collaborative meetings. The focus is on actions and activities in concrete documentation practice.
- Interviews: 15 Semi-structured interviews among the health professionals. The focus is on how health professionals create meaning and maintain their documentation practice.

Theoretical framework and analysis

The study places itself in a theoretical framework of institutional theory, with emphasis on the Scandinavian perspective of translational processes. Empirical data is analyzed to explore how health professionals edit institutional ideas of digital documentation and how translations affect health professional practice in the local organizational context.

Keywords: Public health, Qualitative research, Other

Biomarker levels in migrants and native Danes with type 2 diabetes: a complete-case analysis of an entire country

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Introduction

Current knowledge: Non-western immigrants have a higher risk of type 2 diabetes (T2D) relative to individuals of native Danish origin. Studies have shown poorer glycemic control in migrants with T2D relative to native populations.

Knowledge gap: Quality of T2D care has not been examined on a population-wide level in Denmark. No studies have investigated lipid levels in migrants.

Aim: To investigate potential difference between migrants and native Danes in terms of hemoglobin-A1c (HbA1c) and low-density lipoprotein-cholesterol (LDL-C) using the entire nation as the study population.

Methods

Study Design: Cross-sectional study.

Population: All register-defined prevalent cases of T2D in Denmark age 25-99 with a diabetes duration of at least 6 months on January 1, 2018.

Variable of interest: Country of origin.

Outcomes of interest: Biomarker level at the most recent measurement before January 1, 2018.

Statistical analysis: Explore empirical cumulative distributions of biomarker levels with 95% confidence intervals computed with Smirnov-Kolmogorov's D. Model relative risk of exceeding guideline recommendations in modified Poisson regression models with increasing degrees of adjustment.

Results

Unfavourably high levels of HbA1c and LDL-C are common in the T2D population in Denmark. Most migrant groups have increased levels of HbA1c and LDL-C compared to native Danes. LDL-C levels were particularly high in migrants from Somalia, who were almost twice as likely to exceed guideline recommendations as native Danes.

Conclusion

Efforts should be made to improve HbA1c and LDL-C in T2D, and should have a special focus on migrants.

Keywords: Public health, Epidemiology and biostatistics, Cardiovascular system

Progressive resistance training compared to neuromuscular exercise in patients with hip osteoarthritis, and the additive effect of exercise booster sessions: Study protocol for a multicenter cluster-randomized controlled trial (The Hip Booster Trial)

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Purpose:

The primary purpose of this multicenter cluster-randomized controlled trial is to investigate the effectiveness of 12 weeks of progressive resistance training (PRT) compared to neuromuscular exercise (NEMEX) on functional performance in patients with hip osteoarthritis (HOA).

Methods:

This randomized controlled trial will be a multicenter trial involving hospitals and physiotherapy clinics across Denmark. A total of 160 patients with clinically diagnosed HOA will be recruited. For the initial 12-week exercise intervention, participants will be cluster-randomized into two treatment arms: NEMEX or PRT. After the initial intervention, each cluster will be randomized to booster sessions or to receive no further treatment. Booster sessions will be provided at 1, 3, 5 and 7 months after the end of the initial interventions. Outcomes, including functional performance, leg extensor muscle power, self-reported physical function, pain and quality of life, will be measured at baseline, after the initial 12 weeks of intervention, and at 6-, 9- and 12-months follow-up.

Results:

Results will be submitted for publication by November 2023.

Conclusions:

This study evaluates the effectiveness of NEMEX comparing it to another well-established modality; PRT. Additionally, it examines the cost-effectiveness of booster sessions. These findings will fill the research gaps concerning which exercise modality is most effective in HOA and the long-term effectiveness of exercise. The clinical significance of this study is

that patients may receive more effective rehabilitation leading to an increase in quality of life and potential societal cost-savings.

Keywords: Rehabilitation, Public health, Orthopedic surgery

Cardiac CT Measured Low Bone Mineral Density Is Associated with Higher Fracture Rate: A Prospective Cohort Study in Denmark

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Osteoporosis, a treatable disease associated with a high fracture risk, is highly prevalent and under-diagnosed. Routine cardiac CT could be used to measure bone mineral density (BMD) to assess fracture risk.

Aim: To measure BMD from cardiac CT and assess the association with fracture risk.

Methods: Participants were referred to Cardiac CT for assessment of coronary artery disease between 2014 and 2016. Participants were then follow-up until 2018. Thoracic BMD was measured using quantitative CT. Outcomes were incident fractures and incident osteoporosis-related fractures during follow-up reported to the National Patient Registry. BMD was grouped as very low (<80), low (80-120), and normal (>120 mg/cm3) and used to calculate hazard ratios (HR).

Results: Overall, 1487 participants were included (mean age 57 yrs ± 9, 52.5% female) and very low BMD measured in 179 (12.0%). Median follow-up was 3.1 yrs. During this period, 80 participants (5.3%) had an incident fracture and in 31, it was osteoporosis-related.

Unadjusted Cox regression analyses revealed, that very low BMD predicted a greater rate for any fracture (HR 2.6, 95% CI: 1.4-4.7, p=.002) and osteoporosis-related fractures (HR 8.1, 95% CI: 2.4-26.7, p=.001) when comparing to normal BMD. Adjusting for age and sex did not change these significant associations.

Conclusion: Thoracic BMD measured from routine cardiac CT is usable to identify individuals with a greater fracture rate. This study is published in Radiology 2020; 296:499–508.

Keywords: Rheumatology, Medical technology and diagnostic techniques, Public health

Poster session 13

Barriers and facilitators for medication coordination in psychiatric residences. A qualitative study

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Background

Medication coordination (MedCo) for patients with severe mental illness in psychiatric residences is complex. The medicine is often prescribed uncoordinated by therapists from different healthcare sectors e.g. GP's and psychiatrists, which can lead to unintentional side effects.

MedCo is practiced successfully in a psychiatric residence in the Central Denmark Region. However, transferability to other residences has proven difficult.

With focus on acceptability of systematic MedCo, the aim is to uncover barriers and facilitators for MedCo.

Method

This study is a sub-study of a PhD-project based on the Medical Research Council (MRC) guidelines for complex interventions. We want to explore different experiences with MedCo and will conduct semi-structured interviews with approx. 40 patients, employees, therapists and decision-makers from 1) the regional psychiatric residence, 2) other residences and 3) the strategic level.

The transcribed data will be analysed using a thematic analysis.

Results

So far, we have conducted 36 interviews with patients (n=6), employees (n=8), therapists (n=12), and decision makers (n=10) from 1) n=11, 2) n=15 and 3) n=10.

The preliminary findings indicate that important categories of barriers and facilitators related to MedCo seem to be time spent, systematics, self-efficacy and hidden agendas, e.g. economic.

Conclusion

Additional data collection and analysis is in progress.

Knowledge of barriers and facilitators on MedCo can be a guide in developing an acceptable and transferable model for MedCo in residences in Denmark - a model that potentially will lead to a reduction in unintentional medication side effects.

Keywords: Pharmacology, Psychiatry, psychology and mental health, Qualitative research

Identification of dysregulated micro-rnas in human brain tissue from psychiatric patients

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The diagnosis of depression is made through clinical examination and based only on symptoms. This is problematic as symptoms are partly overlapping in bipolar disorder, schizophrenia, and depression. Clinical observations have also reported gender differences in prevalence, symptoms, and responses to treatment. Although progress has been made in recent years to understand the molecular mechanisms underlying depression, the knowledge is still limited. There is thus a need for biomarkers and molecular insights into depression, which allow for a more precise diagnosis and personalized treatment.

Recently, it has been demonstrated that alterations in gene-expression profiles are associated with depression and that translation efficiencies imposed by some non-coding RNAs, such as microRNAs (miRNAs), play central roles in disease etiologies.

Here, we investigate transcriptional patterns of miRNAs in human brain tissue (FFPE blocks of polus frontalis and hippocampus) from the Danish Brain Collection (Risskov). One-hundred-and-twenty males and females diagnosed with schizophrenia, bipolar disorder, and depression were included. As an unbiased profiling strategy, we utilized the Nanostring technology to investigate miRNA expression in the brains. We have previously reported that Nanostring is more accurate and sensitive than Next-Generation-Sequencing on FFPE samples for miRNA-detection. The results demonstrated both gender- and disorder-specific differences in miRNA-exprsession.

Keywords: Psychiatry, psychology and mental health, Clinical neuroscience, Basic neuroscience

Social impairments in children at familial high risk of schizophrenia or bipolar disorder – a four-year follow-up study

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OBJECTIVE Social impairments have been suggested as possible antecedents both for schizophrenia and bipolar disorder, but the nature of this remains unclear. Therefore, we examined the development of social abilities in children born to parents with schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP) and population-based controls (PBC).

METHODS This study is part of The Danish High Risk and Resilience study, which is a longitudinal cohort study of children at FHR-SZ or FHR-BP. Social responsiveness was measured with the Social Responsiveness Scale, second edition (SRS-2), completed by teachers and primary caregivers. ToM was examined with The Animated Triangles Task. We collected data from 520 children (FHR-SZ, n=201; FHR-BP, n=119; PBC, n=200), who participated in at least one of the measures at some or both assessments. The retention rate from age 7 to 11 was 89 %.

RESULTS The developmental pattern of neither social responsiveness nor ToM differed between any groups. However, children at FHR-SZ had higher SRS-2 scores compared to PBC regardless of the informant ($p<.001$), and a higher proportion of children at FHR-SZ were rated at a clinically significant level ($p\leq.004$). Compared to PBC, children at FHR-BP were rated higher on SRS-2 by primary caregivers ($p\leq.005$), and a higher proportion of children at FHR-BP were rated at a clinically significant level ($p=.019$). The three groups did not differ in ToM abilities.

CONCLUSIONS Impairments in social responsiveness may constitute a vulnerability marker particularly in children at FHR-SZ, but also FHR-BP. Interventions targeting social impairments may be an important preventive strategy for development of severe mental disorders.

Keywords: Psychiatry, psychology and mental health, Other, Other

Metacognitive subgroups and clinical characteristics in pediatric OCD

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Obsessive-compulsive disorder (OCD) is an impairing mental disorder characterized by recurrent and persistent intrusions and/or repetitive behaviors. According to an advanced metacognitive theory, metacognitive biases (MB; e.g. positive and negative beliefs about worry, cognitive self-consciousness, and superstition, punishment, and responsibility beliefs) play a significant role in the development and maintenance of OCD. Previous studies have found MB to be associated with pediatric OCD on a group-level. However, OCD is a heterogeneous disorder and MB might be more etiologically important for some children and adolescents with OCD.

Therefore, the aims of the study are to examine whether: 1) different subgroups of OCD patients exist based on their types and degrees of MB; 2) all or just one/some subgroup(s) differ from typically developing children and adolescents regarding their MB; 3) possible subgroups differ in regard to clinical characteristics including OCD severity, OCD-symptom dimensions, obsessive beliefs, insight, and internalizing/externalizing symptoms.

A total of 117 OCD patients (7-18 years) and 57 typically developing controls will be included. All participants will complete questionnaires including measures of MB, obsessive beliefs, and internalizing/externalizing symptoms. Furthermore, the OCD patients are assessed with a clinical interview of OCD-symptoms, severity, and insight. The inclusion will be finalized in 2021 and results will be available in 2022.

The study may help us differentiate patients to guide prevention and treatment initiatives which can promote the mental health of these children and adolescents with OCD.

Keywords: Psychiatry, psychology and mental health, Paediatrics, Other

BRD1+/- MINIPIGS—A LARGE NON-PRIMATE MODEL OF HUMAN PSYCHIATRIC ILLNESS

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The development of predictive animal models of human psychiatric illness is essential for advancing our understanding of their pathoetiology and neurobiological basis. Whereas rodent models have provided ample valuable biological insight in psychiatry, their lack of similarity to human brain anatomy and neurodevelopment, -maturation, -endocrinology, and -physiology, hampers their translational value. In this study, we utilize genetically modified Göttingen minipigs to explore the pathobiological impact of genetic disruption to the schizophrenia-associated epigenetic modifier, BRD1, that acts as a co-regulator of genomic steroid signaling through nuclear receptors. Guided by ongoing behavioral and brain MRI characterization of the BRD1+/- minipigs, we will assess molecular, cellular and structural changes in selected brain tissues using RNAseq, proteomics and HPLC data, ELISA, and tissue staining coupled with stereology in cryo- and formalin-preserved brain tissues. Additionally, we will assess brain-derived cholesterol metabolites and steroids using untargeted MS-based metabolomics screenings of plasma and CSF from the BRD1+/- minipigs.

Here, I present an update on my work, including preliminary data from our minipig model that hints at behavioral changes and altered cerebral cholesterol and steroid biosynthesis. As we have recently shown that ~15% of GWAS risk loci in major psychiatric disorders harbor genes that encode nuclear receptors or their co-regulators, we argue that our BRD1+/- minipig model broadly represent psychiatric genetic risk and thus holds promising translational value to psychiatry.

Keywords: Psychiatry, psychology and mental health, Animal models/disease models, Genetic engineering

Disentangling the gender-related differences in depressive disorders: The role of estrogen

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Major depressive disorder (MDD) is the most prevalent psychiatric disorder globally, affecting almost 300 million people of different ages. Depression leads to dramatic functional impairment, disability, and low quality of life. MDD affects twice as many women as men; an epidemiological observation that points to a crucial role of hormonal disparities and the associated biological consequences in the pathophysiology of depression.

Mounting evidence has indicated that the response to ketamine can largely depend on sex, suggesting that ketamine, our only currently approved rapid-acting antidepressant, and estrogen receptors can interact. Using FSL rats, a selectively-bred animal model of depression, in a preclinical setting, molecular and behavioral consequences of this crosstalk will be investigated. The primary purposes are to explore how estrogen pulls the strings behind depression and how ketamine influences estrogen receptors. The underlying mechanisms of mood regulation by estrogens will also be explored. We will further delve into how ketamine may alter depressive-like behaviors via interacting with estrogen receptors, both the nuclear receptors and membrane estrogen receptors in silico and in vitro, to alleviate depressive symptoms swiftly. The possible interaction site of ketamine will be predicted using reverse docking and molecular dynamics simulation, and will further be confirmed by site directed mutagenesis, and alanine scanning. After being subjected to depression and anxiety-related behavioral tests, molecular correlates of this proposed interaction by use of qRT-PCR and western blotting will be identified.

Keywords: Psychiatry, psychology and mental health, Pharmacology, Animal models/disease models

Organ specific adverse effects after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy - A scoping review

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Aim: We conducted a review in order to describe type and extent of organ specific adverse effects after cytoreductive surgery (CRS) + hyperthermic intraperitoneal chemotherapy (HIPEC) for gastrointestinal (GI) cancers and pseudomyxoma peritonei (PMP).

Method: In November 2020, a systematic literature search was done using 6 databases. We categorized organ specific adverse effects into gastrointestinal dysfunction, urological dysfunction, sexual dysfunction, pain and others. We extracted data on type and extent of these over short-term (0-5 months following surgery), medium-term (6-11 months) and long-term (>=12 months).

Results: In total, we screened 2451 papers. 18 studies fulfilled the eligibility criteria and the studies reported on a total of 2081 patients. The majority of studies reported an increase in organ specific adverse effects 3-6 months after surgery. A return to preoperative level differed within the domains. Diarrhea was still worse 12 months after surgery compared to preoperatively and improved later only. For constipation, symptoms improved shortly after surgery. Sexual dysfunction did not seem to improve long-term. Only one study reported on urological and stoma-related dysfunction. In the remaining domains regarding organ specific adverse effects, a return to preoperative level happened within the first year of surgery.

Conclusion: This review showed an increase in organ specific adverse effects 3-6 months after surgery. A return to preoperative level differed within the domains. Furthermore, this review demonstrated a lack of knowledge on urological dysfunction, sexual dysfunction and stoma-related issues.

Keywords: Reviews and meta-analyses, Gastrointestinal surgery, Other

Being well? Description of existential well-being and suffering in the transition from hospital to home care in older patients and their relatives: a meta-ethnography

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Background: The transition from hospital to home care means a change in needs, health status and definition of oneself in an unfamiliar social context, especially for older patients. Their relatives play an important role during this process, as older patients often leave the hospital with ongoing care needs. Previous studies point to the fact that the transition often creates a feeling of discontinuity of care as well as being left alone. This causes suffering, which effects the well-being of the older patients and their relatives.

Objective: The aim of this meta-ethnography is to gain an in-depth understanding of older patients and their relatives' description of well-being and suffering in relation to the transition from hospital to home care.

Method: The study follows a meta-ethnographic approach, which synthesizes qualitative primary research in order to reinterpret the primary findings. A systematic literature search was conducted using Pubmed, Embase, CINAHL, APA PsycInfo and Scopus databases. Inclusion criteria were empirical phenomenological studies focusing on the hospital to home transition, published in English, Danish or German within the last ten years. Nine phenomenological studies were included.

Perspective: In order to gain an in-depth understanding of the different levels of suffering and well-being and how they are intertwined, the analysis will follow Galvin and Todres (2013) humanizing framework of care. This framework is led by an existential well-being theory, where well-being is a sense of homecoming (dwelling) as well as a possibility (mobility).

This project has received funding from the European Union's H2020-MSCA-ITN-2018 programme

Keywords: Reviews and meta-analyses, Qualitative research, Other

Diagnostic accuracy of radiography, digital breast tomosynthesis (DBT), micro-CT and ultrasound for margin assessment during breast surgery: A systematic review and meta-analysis

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Background:

Achieving adequate resection margins in breast conserving surgery is challenging and often demands more than one surgical procedure. We evaluated pooled diagnostic sensitivity, and specificity of radiological methods for intraoperative margin assessment to reduce repeat surgery rate.

Methods:

We included studies using radiography, digital breast tomosynthesis (DBT), micro-CT, and ultrasound for intraoperative margin assessment with the histological assessment as the reference method. A systematic search was performed in PubMed, Embase, Cochrane Library, Scopus, and Web of Science. Two investigators screened the studies for eligibility criteria and extracted data of the included studies independently. The quality assessment on diagnostic accuracy studies (QUADAS)-2 tool was used. A bivariate random effect model was used to calculate pooled sensitivity and specificity of the index tests in the meta-analysis.

Results:

The systematic search resulted in screening of 798 unique records. Twenty-two articles with 29 index test methods were selected for meta-analysis. Pooled sensitivity and specificity and area under the curve were calculated for each of the 4 subgroups in the meta-analysis respectively: Radiography; 52%, 77%, 60%, DBT; 67%, 76%, 76%, micro-CT; 68%, 69%, 72%, and ultrasound; 72%, 78%, 80%.

Conclusion:

Ultrasound showed the highest and radiography the lowest diagnostic performance for intraoperative margin assessment. However, the heterogeneity between studies was high

and the subgroups small. The radiological methods for margin assessment need further improvement to provide reliable guidance to prevent repeat surgeries in primary breast cancer.

Keywords: Reviews and meta-analyses, Oncology, Medical technology and diagnostic techniques

Poster session 14

Risk of infections in colorectal cancer patients with inflammatory bowel disease

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Background

Inflammatory bowel disease (IBD) is a chronic inflammation of the bowel. Both ulcerative colitis (UC) and Crohn's disease (CD) are associated with an increased risk of colorectal cancer (CRC) and are also associated with adverse prognosis in CRC patients. Infections may mediate a part of the poor prognosis. We therefor hypothesized that IBD is associated with an increased risk of infections among CRC patients.

Methods

Using data linked from Danish population-based registries from 1995-2018, we conducted a cohort study including all CRC patients with a first-time IBD diagnosis and compared them with all CRC patients without IBD (comparators). The outcome was first-recorded hospital treated (ICD-codes) or community-treated infections (prescriptions).

We expressed the absolute risk of infection by cumulative incidence proportions (CIPs) treating death as competing risk. We used stratified Cox regression analysis to calculate hazard ratios (HRs) adjusted for sex, age, co-morbidities, cancer stage and year of diagnosis.

Results

We identified 93,427 patients with CRC of whom 1,637 (1.8%) had IBD and followed them for a median of 11 months until first infection. The median ages were 68 years (95% CI 67-68) for IBD patients and 71 years (95% CI 71-72) for comparators. The 1-year and 5-year CIPs of first-recorded infections were 52.8% (95% Confidence interval (CI) 50.3-55.2) and 75.7% (95% CI 73.4-77.7) for IBD patients and 45.6% (95% CI 45.3-45.9) and 67.9 (95% CI 67.6-68.2) for comparators, respectively. IBD patients had a slightly elevated risk of infections (HR 1.18, 95% CI 1.11-1.24).

Conclusion

IBD is associated with an elevated risk of infection among CRC patients

Keywords: Gastroenterology and hepatology, Inflammation, Infection

Faecal microbiota transplantation and Helicobacter pylori: transmission from donors to recipients?

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BACKGROUND: Donor screening for faecal microbiota transplantation (FMT) ensures patient safety and should perferably avoid unnecessary screening. Helicobacter pylori may colonise the stomach of healthy faeces donors, but its potential transmission to recipients during FMT is uncertain. Some, but not all, FMT centers exclude H. pylori positive donors, and there is a need to qualify if H. pylori should lead to exclusion of faeces donors.

AIM: To determine whether H. pylori is transmitted from donors to recipients by FMT. Furthermore, to investigate whether FMT application method impacts transmission.

METHODS: The study was a cohort study with a retrospective quality assurance study on H. pylori transmission. Forty faeces donors were included in the study. Donor and recipient, pre- and post-FMT, archive faeces samples were screened for H. pylori antigen.

RESULTS: Of the 40 faeces donors screened, 13 (33%) were H. pylori positive. Samples from recipients treated with faeces from H. pylori positive donors will be analyed.

PERSPECTIVES: This is the first study to investigate H. pylori transmission from donors to recipients by FMT. If H. pylori is not transmitted by FMT, regardless of application method, a high proportion of donors can be included instead of excluded. Knowledge on H. pylori transmission, positive as well as negative results, will help optimise donor screening protocols and contribute to the establishment of evidence based faeces donor criteria.

Keywords: Gastroenterology and hepatology, Infection, Laboratory science

Study Macrophage and Monocyte Subsets in the healthy and NAFLD liver by the single-cell genomic analysis

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Background: Non-alcoholic Fatty Liver Disease (NAFLD) is a clinical challenge associated with obesity and insulin resistance and may progress to end-stage liver diseases. There is an urgent need to gain novel insights into NAFLD pathophysiology and identify new treatment targets. Hepatic macrophages are involved in disease development and progression and new knowledge on macrophage diversity is key to overcoming this disease.

Methods: We analyzed the single-cell and bulk transcriptome data of the NAFLD and healthy subjects in public databases, and collected liver biopsies from NAFLD patients. We also collected the clinical information and stored the serum and PBMC referred for further investigations. The biopsy tissues were prepared for single-cell RNA sequencing (scRNA-seq) and spatial sequencing respectively. In this study, we will include 24 NAFLD patients: 12 with simple steatosis and 12 with inflammation and fibrosis.

Results: We analyzed the scRNA-seq data (GSE136103) of CD45+ cells from 2 end-stage NAFLD and 2 healthy liver samples. We confirmed that macrophage-specific expression genes CD163, MRC1, CD5L and SDC3 are mainly expressed in the macrophage cell cluster. The gene VCAN was mostly expressed in the monocyte cell cluster, and has a lower expression in NAFLD. With these marker-genes, we will further study the recruitment of macrophages from the peripheral monocytes in liver during NAFLD progression.

Conclusion: The CD163, MRC1, CD5L, SDC3 genes are mainly expressed in the macrophage cell cluster, and the VCAN was decreased in NAFLD liver monocytes compared with the healthy. The function of these marker-genes during NAFLD progressing remains to be explored.

Keywords: Gastroenterology and hepatology, Genetic engineering, Cell biology

Predictors for adverse pregnancy outcomes in women with IBD include preconception disease activity and debuting with IBD during pregnancy – a Danish prospective cohort study

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Background and aims: Women with Inflammatory Bowel Disease (IBD) are often informed of risks of adverse pregnancy outcomes as a consequence of their disease. We investigated the pregnancy outcome in a tertiary IBD center, and aimed to identify predictors for adverse outcome.

Methods: Between 2008 and 2021, 608 pregnancies in women with IBD were enrolled in a prospective cohort. Predictors examined for increased risk of adverse pregnancy outcomes included debut of IBD during pregnancy and disease activity before or during pregnancy. All data was collected through review of medical records.

Results: 322 women remained in remission throughout pregnancy. 282 experienced disease activity in one or more trimesters. 36 women debuted with IBD during pregnancy. 167 experienced flaring within 6 months of conceiving. Sustained remission was not associated with an increased risk of preterm birth, intra uterine growth retardation (IUGR), low birth weight or still birth. Flaring or debuting with IBD during pregnancy was, however, associated with a lower birth weight when adjusting for potential confounders. Flaring within 6 months of conceiving was associated with increased risk of continuous disease activity during pregnancy (RR=2.13 [1.83-2.49]).

Conclusion: Conception while in remission increases the probability of remaining in remission throughout pregnancy. Reassuringly, sustained remission is associated with a low risk of adverse birth outcomes, comparable to that of the background population. However, experiencing disease activity in one or more trimesters or debuting with IBD was associated with IUGR, cesarean section and lower birth weight.

Keywords: Gastroenterology and hepatology, Inflammation, Gynecology and obstetrics

Fear of cancer recurrence and quality of life in a circulating tumor DNA based surveillance program following curative intended treat-ment of colorectal cancer – a substudy of IMPROVE-IT2

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INTRODUCTION: The IMPROVE-IT2 study is a randomized controlled trial investigating the benefit of ctDNA guided postoperative surveillance for colorectal cancer patients compared to the current standard-of-care CT scan surveillance. The present IMPROVE-IT2-substudy aims to assess the potential effects of intensified recurrence surveillance with regards of fear of recurrence and health related quality of life (QoL).

MATERIAL & METHODS: The aim is 1:1 randomization of 255 patients to either a ctDNA-guided sur-veillance program (experimental group) with ctDNA analysis will be performed every 4 months postoperatively (4, 8, 12, 16, 20 and 24) or standard of care surveillance according to current Danish Guidelines with CT scans at months 12 and 36 postoperatively (control group). Both groups com-plete QoL questionnaires at baseline (prior to randomization and start of surveillance), and at 12, 18, 24 and 36 months. The questionnaire includes EORTC QLQ-C30 and Fear of Cancer Recurrence Inventory (FCRI).

RESULTS: By 25th of October 2021 a total of 110 patients have been randomized with 55 in the ex-perimental group and 55 in the control group. Sixty-six patients have completed questionnaire at 12 months. No differences were found between the groups when analyzing global health status or summary score from the EORTC QLQ-C30 questionnaire at baseline and 12 months. We see a trend towards higher risks of clinical fear of cancer recurrence in the experimental group at 12 months (RR=1.58 (0.99-2.41)).

CONCLUSIONS: No significant effect of ctDNA guided surveillance were found on health related QoL or fear of cancer recurrence in this preliminary analysis of the IMPROVE-IT2 study.

Keywords: Gastrointestinal surgery, Oncology, Public health

Treatment of bowel dysfunction following pelvic organ cancer

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Introduction: As cancer survival improves so does awareness on functional outcomes and the impact of late sequelae on quality of life (QoL). This study aims to present results on treatment of bowel dysfunction from our pelvic organ cancer late sequelae clinic.

Materials and methods: Patients with bowel dysfunction following pelvic organ cancer were offered treatment in a nurse-led clinic. Patients completed validated electronic patient-reported outcome measures assessing bowel function and QoL. Data collection is ongoing and is prospectively registered in an online database.

Results: To date, 345 cancer patients (50% rectal, 14% gynaecological, 12% anal, 11% colonic, 10% prostate, 3% other cancers) have started treatment for bowel dysfunction in the late sequelae clinic. The mean age was 64 years (range; 27-93) with 54.5% women. Of the symptoms examined, the most frequent were faecal urgency (95%), fragmentation (93%), emptying difficulties (93%), incontinence (flatus 89%, liquid 60%, solid 35%) and obstructed defecation (80%). In total, 135 patients have completed treatment. At the end of treatment, 54% were treated with fibre supplement, 39% with anti-diarrheal medication, 21% with rectal emptying aids, 19% with oral laxatives and 24% with transanal irrigation. Six patients received a stoma and one sacral nerve stimulation. Significant improvements in all the examined symptoms ($p<0.001$), bowel-related QoL ($p<0.001$) and generic QoL ($p<0.001$) were observed.

Conclusions: Treatment of bowel dysfunction significantly improved the symptom burden and QoL. This encourages a systematic screening for- and treatment of late sequelae following pelvic organ cancer.

Keywords: Gastrointestinal surgery, Other, Other

A protocol for studying the pharmacokinetics and side effects for tetrahydrocannabinol and cannabidiol (Sativex) among patients with chronic kidney disease and patients on dialysis.

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Background: Chronic kidney disease (CKD) is common and severe stages may be associated with a high burden of symptoms including anorexia, nausea, anxiety, muscle cramps and sleep disorders, which are often treated insufficiently. A possible effect of cannabinoids (tetrahydrocannabinol (THC) and/or cannabidiol (CBD)) on several of these symptoms has been suggested in previous studies. Therefore, cannabinoids may be an alternative treatment option. However, pharmacokinetic studies are lacking in patients with CKD.

Aim: To compare pharmacokinetics and side effects for Sativex between patients with different stages of CKD and healthy volunteers.

Methods: We aim to investigate the pharmacokinetics for THC, CBD and metabolites among patients with CKD, patients on dialysis and healthy volunteers over 24 hours after two oromucosal sprays of Sativex corresponding to 5.4 mg THC and 5.0 mg CBD. The CKD patients will be divided in two groups with an estimated creatinine clearance <15 ml/min and between 15-30 ml/min, respectively. In addition to blood sampling, the participants will regularly complete a numeric rating scale from 0-10 for questions regarding side effects of Sativex. Finally, we will investigate whether THC, CBD and metabolites are dialyzable. In total 85 participants will be included.

Perspectives: The study will provide fundamental knowledge regarding products containing THC and CBD in patients with different stages of CKD and thereby form the basis for precautions and dose selections, which is a necessary precondition before studies can be made to clarify a possible effect on symptoms in patients with CKD.

Keywords: Pharmacology, Nephrology, Other

Poster session 15

Effects of acute deep brain stimulation on synaptic SV2A density in a porcine model of Parkinson's disease: a translational in vivo neuroimaging study.

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Background: Parkinson's disease (PD) is associated with a loss of neural connections and disruptions in vesicle transport, which modulate presynaptic function. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment for PD. It acts in part by suppressing STN hyperactivation, however, the synaptic plasticity it promotes in basal ganglia-cortical networks is unclear. [11C]UCB-J binds to synaptic vesicle glycoprotein 2A (SV2A), expressed in all synapses, and can be used for positron emission tomography (PET). Here we test the hypothesis that DBS increases synaptic SV2A density in healthy minipigs and those rendered hemi-parkinsonian with 6-hydroxydopamine (6-OHDA).

Methods: Female Göttingen minipigs were injected into the right medial forebrain bundle with 6-OHDA (n=2) or saline (n=1). [18F]FDOPA PET and behavioural assessments confirmed the lesion. Minipigs received STN-DBS implants in the right hemisphere. [11C]UCB-J PET scans were acquired prior to and 2 hours after turning on the DBS.

Results: We observed 50% reduction in ipsilateral striatal [18F]FDOPA uptake in 6-OHDA-injected minipigs, as well as reduced gait speed and increased ipsilateral rotational behavior, with no changes in the saline-injected minipig. A 15% reduction of ipsilateral striatal [11C]UCB-J was observed in 6-OHDA-injected minipigs. After acute DBS, all minipigs had around 17% of bilaterally increased [11C]UCB-J binding.

Conclusion: Acute DBS-STN enhances synaptic density in healthy and 6-OHDA-injected minipigs. Longitudinal effects of DBS-STN on [11C]UCB-J will be investigated in additional minipigs, and will be correlated with MRI connectivity and postmortem synaptic measures.

Keywords: Animal models/disease models, Basic neuroscience, Laboratory science

High-resolution RNA isoform variation analysis by combining the advantages of single-cell RNA and nanopore sequencing

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Pigs are one of the ideal models for both human diseases and xenotransplantation due to similar genetic backgrounds and organ sizes. However, with the standard single-cell RNA sequencing pipeline, it is only possible to identify the expression level of each gene. In order to analyze the isoform heterogeneity in pigs, we combined the advantages for single-cell RNA library generation from 10xGenomics and long reads sequencing from Nanopore to establish RNA isoform atlas of pigs.

The pipelines of processing Nanopore long reads, the known RNA isoforms analysis, and novel RNA isoform detection have been successfully established in our team. Nanopore libraries were constructed from amplified single-cell barcoded cDNA for pig brain were sequenced by Flongle adapter as a pilot test, 4M reads were basecalled by guppy and filtered based on QC and length. Finally, the filtered long reads were aligned with minimap2. In the pilot analysis, the 3' UTR and 5' UTR annotations were curated from Ensembl for the detection of novel RNA isoforms, and the raw barcode matrixes and bam files were generated by CellRanger. The novel RNA isoforms of pig brains are shown in IGV format.

We have detected 2,289,343 reads with Nanopore adapters at both ends using the package porechop. cDNAs with the length less than 200 bp were filtered out due to the low alignment rate (average 55.73%). The clean data will be subjected to RNA isoform quantification, as well as more novel isoforms detection.

Keywords: Animal models/disease models, Cell biology, Basic neuroscience

Allogenic Mesenchymal Stromal Cell (MSC) assisted fat grafting in a rat model: Increasing dosage of MSCs correlates with decreased fat graft retention and quality.

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BACKGROUND:

Autologous fat grafting is a relatively new, but renowned and gentle alternative in the reconstructive surgery. However, fat grafting comes with a persistent problem of low viability as well as a fat-resorption ranging from 25-80% of the graft. As a result, only a small portion of the original transplanted fat as remains as reconstructive soft tissue 3 months after transplantation.

The regenerative potential of autologous mesenchymal stromal cells (MSC) has previously been shown to increase viability and resorption of fat grafts.

METHODS:

Female Lewis rats were randomized into 4 groups with 9 rats in each group. All groups received two fat grafts, one intervention fat graft with MSCs and one control fat graft with saline injection acting individual control. The MSC dosages for intervention grafts were either 1-, 5- or 25 x106 MSC/ml fat graft. Primary output, fat graft volume retention, was measured using the liquid overflow technique. Tissue for histology, protein and gene analysis was obtained during sacrifice. Donor MSC originated from HLA miss matched male Brown Norway rats. Long term donor MSC residency was evaluated using qPCR for rat Y-chromosome.

RESULTS:

Increasing dosage to 25 x106 MSC/ml resulted in significant 50% lower fat graft retention. None of the MSC dosages significantly increased fat graft retention. Histological evaluation revealed a lower proportion of adipocytes in the highest dosage group. Gene expression analysis reflected the histological evaluation with significant lower adipogenic expression in the highest dosage group.

CONCLUSION:

Contrary to previous research we did not find an increased fat graft retention using allogenic MSCs.

Keywords: Animal models/disease models, Cell biology, Inflammation

Neo-cuspidalization for pulmonary congenital heart surgery: In vitro evaluation

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Background: Congenital abnormalities of the pulmonary valve are commonly treated surgically. Often entire valve replacement is required and can first be performed in the teenage years with a rigid stent. A new surgical technique of neo-cuspidalization has the potential to grow with the recipient. Our aim was to, in a proof-of-concept setting, evaluate the functionality of this new surgical technique of neo-cuspidalization in vitro.

Methods: Eight explanted pulmonary roots from porcine hearts were evaluated in a pulsatile flow-loop model at cardiac output of 4 L/min. After testing the native pulmonary root, the native cusps were explanted. Neo-cuspidalization, designed based on mathematical model and made from 0.6% glutaraldehyde-treated porcine pericardium, were subsequently performed. The characterization is based on echocardiographic and hydrodynamic pressure data.

Results: The neo-cuspidalization properly opened and closed in each pulsatile cycle and was sufficient on color-doppler. There was no statistical difference in pulmonary artery systolic -(6.5±1.8 mmHg vs. 7.0±1.8 mmHg; $P>0.05$) and - diastolic gradient (3.4±0.9 mmHg vs. 3.0±0.9; $P>0.05$) before and after neo-cuspidalization. The coaptation statistically increased (0.8±0.2 cm vs. 1.6±0.3 cm; $P<0.05$) and the cusps statistically billowed (0.3±0.1 cm vs. -0.4±0.3 cm; $P<0.05$) after neo-cuspidalization.

Perspective: This proof-of-concept of neo-cuspidalization warrant further in vivo studies. The increased coaptation is speculated to decrease with growth, yet remain sufficient. This technique has the potential to become part of the treatment-tool-box for children born with congenital pulmonary valve abnormalities.

Keywords: Animal models/disease models, Cardiovascular system, Paediatrics

Genome-wide CRISPR Screens in DLBCL cell lines Reveal Modulators of Doxorubicin and Vincristine Response

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Today, only around 65% of diffuse large B-cell lymphoma (DLBCL) patients are cured after treatment with the standard regimen R-CHOP. The alternative treatment options offer only small hopes of cure. For patients with refractory disease undergoing next line of therapy only 20% are alive after two years. In a search for why drug resistance emerges, we performed genome-wide CRISPR knockout screens in DLBCL cell lines. We performed these screens using two of the chemotherapeutics in the standard R-CHOP treatment, doxorubicin and vincristine, as selective pressure. We discovered pathways, gene complexes as well as novel genes, which, when damaged by gene knockout, alter the cells' response towards doxorubicin and vincristine. In validating experiments, we show that knockout of the screen-identified genes KCTD5 and TOPORS renders DLBCL cell lines more tolerant towards doxorubicin, while knockout of the genes KIF18B and USP28 renders the DLBCL cells more tolerant towards vincristine. Furthermore, we used our screen data to uncover genes, which when impaired further sensitizes the DLBCL cell lines towards doxorubicin and vincristine. We show that the PRKDC-inhibitor nedisertib, which impairs DNA damage repair, synergizes with the DNA-damaging doxorubicin. The KIF18A-inhibitor BTB-1, which induces mitotic cell arrest, shows synergistic effects together with vincristine, a mitotic spindle poison. This work has revealed several modulators of DLBCL cell lines cellular response towards the chemotherapeutics doxorubicin and vincristine.

Keywords: Cell biology, Genetic engineering, Oncology

Delivery of the CRISPR/Cas9 system in lentivirus-derived nanoparticles for in vivo genetic engineering

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Monogenic disorders are diseases arising from a single gene variant causing the phenotype. An example hereof is sickle cell disease (SCD), where a single point mutation in the beta-globin gene cause the mutated globin protein to aggregate and affects the integrity of the red blood cells (RBC). The sickle-shaped RBCs fragment easily leading to anemia, pain crises and premature death. SCD can be cured by stem cell transplantation, however identification of suitable donors remains a major challenge. Autologous gene therapy of the hematopoietic stem cells (HSCs) may in the future cure SCD.

CRISPR/Cas9 is an RNA-guided nuclease-based technology that has been adapted for gene editing purposes and exploited for therapeutic ex vivo gene editing in HSCs. However, ex vivo approaches involve cumbersome procedures for expansion and culturing of HSCs, why it is a key focus to investigate ways of editing HSCs directly in patients. For in vivo approaches to be successful, it is crucial to develop new delivery strategies. To meet this challenge of delivery, we study the packaging capabilities of lentiviruses to incorporate and deliver the CRISPR/Cas9 system.

Using lentivirus-derived nanoparticles (LVNPs) as a delivery platform, we have engineered ‘all-in-one’ particles containing all essential components for correction of genes by homology-directed repair (HDR). Effective targeted gene insertion by HDR was observed in HeLa and K562 cells demonstrating the capacity of LVNPs to co-deliver DNA-cleaving complexes (Cas9-sgRNA) and donor templates for repair. We also showed editing within the beta-globin gene and are currently studying ex vivo editing in HSCs using this approach.

Keywords: Genetic engineering, Cell biology, Other

Investigation of the cellular mechanisms in nephrogenic diabetes insipidus

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Lithium (Li) salts are widely used drugs for treating patients with bipolar disorders. Li treatment impairs the urine concentration mechanism. It has been estimated that 1 in 1.000 of the population receive Li, and as a result ~ 40% of the patients develop Nephrogenic Diabetes Insipidus (NDI) with severe polyuria and polydipsia. We have previously discovered that Li causes a cellular remodeling of the collecting duct (CD) resulting in reduced fraction of principal cells relative to intercalated cells, this is associated with downregulation of AQP2.

Therefore, the aim of this project is to investigate the cellular mechanisms that occur in the kidney CD during NDI.

The first step will be to perform proteomic analysis of urinary exosomes from rats, Li-NDi patients and from healthy voluneers. The content of exosomes reflects the intracellular composition of the origin cell and is suggested to represent the physiological/pathophysiological state of the kidney. It is hypothesized that the urinary proteome will contain proteins involved in the cellular remodeling of the kidney CD, which can provide evidence that the cellular remodeling occurs in humans.

The project will allow a better understanding of the complex mechanisms involved in the Li-induced changes in the kidney CD and thus the pathophysiology of Li-induced NDI. Moreover, the projects may be relevant for developing novel targets for therapeutic intervention.

Keywords: Nephrology, Animal models/disease models, Cell biology

Poster session 16

Mechanical sensitivity changes in pericranial muscles after local anesthesia and experimentally induced pain in the temporal tendon: Implications for headache and facial pain

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To assess, in healthy individuals, changes in mechanical sensitivity (MPS) of the pericranial muscles after a local anesthetic (LA) block of the temporal tendon and if experimental-induced temporal tendon pain can lead to an increase in MPS of the pericranial muscles and reports of headache. 40 healthy participants were recruited for this study and were randomly injected with Mepivacaine and isotonic saline (IS) into the dominant-side temporal tendon in the two different sessions, and either nerve growth factor (NGF) or IS in a 3rd session. MPS was assessed in the pericranial muscles before and 10 minutes after each injection, and in a 4th session 2 days after the 3rd session. Pain drawings and headache diaries were kept for 30 days after the final session to register any developing pain or headache. LA in the temporal tendon caused a significant decrease in MPS in the temporal tendon (54.5%) and the masseter (15.4%) muscle ($P < 0.05$) but not the temporalis and trapezius muscles ($P > 0.05$). NGF injection caused a significant increase in MPS in the tendon (13.4%) and masseter muscle (9.5%) ($P < 0.05$) but not the temporalis or trapezius muscles ($P > 0.05$). A significant difference was found for the headache frequency ($P < 0.05$) but not the intensity ($P > 0.05$) after NGF injection. Overall, these findings suggest that the therapeutic effect of temporal tendon anesthetic injections on facial pain and headaches is most likely not due to a direct effect of the local anesthetic on the temporal tendon but to a more generalized block of the nerves in the area. In addition, that the temporal tendon seems to play only a minor role in the pathophysiological process of headache.

Keywords: Dentistry, Clinical neuroscience, Other

The association between halitosis and oral health-related quality of life: a systematic review and meta-analysis.

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Objectives: This study aimed to systematically review the literature to investigate whether halitosis is associated with impaired oral health-related quality of life (OHRQoL). Material and Methods: Electronic searches in four databases were performed up to and including October of 2020. Observational studies that assessed halitosis in association with OHRQoL among adults and adolescents were included. All studies should specify how halitosis and OHRQoL were evaluated. A standardized mean difference (SMD) of the association between halitosis and OHRQoL was estimated by a meta-analysis. Critical appraisal of the studies was performed. Results: Twelve studies were included in the review, and nine studies were included in the meta-analysis, comprising 2,405 individuals. The overall meta-analysis showed an association between halitosis and impaired OHRQoL [SMD 0.56; 95%CI (0.25, 0.86)]. Subgroup analyses, however, indicated that this association was statistically significant only among adults. Neither the OHRQoL instrument nor the halitosis assessment method influenced the pooled estimates. Meta-regression analyses revealed that while the OHRQoL instrument (P = 0.840), the method for halitosis assessment (P = 0.618), and the sample composition (P = 0.701) did not explain the between-study heterogeneity, the methodological quality of the study appeared to explain 20% of the overall heterogeneity (P = 0.075), as high-risk of bias studies overestimated the magnitude of the association. Conclusion: Our findings support that oral health-related quality of life is impaired by halitosis.

Keywords: Dentistry, Reviews and meta-analyses, Inflammation

Is the Femoral-Epiphyseal Acetabular Roof (FEAR) index associated with hip pain in patients with hip dysplasia?

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Background: Patients with hip dysplasia often experience hip pain. Micro instability in the hip joint has been suggested to be a cause of pain. Recently, the Femoral-Epiphyseal Acetabular Roof (FEAR) index, has been developed as a tool to evaluate hip instability among these patients.

Purpose: To investigate associations between the FEAR index and hip pain, function, and quality of life before and six months after periacetabular osteotomy (PAO).

Material and Methods: Radiographs from patients with hip dysplasia who had undergone PAO between the 1st of January 2018 and the 31st of December 2020 were retrospectively assessed by a radiologist and an orthopedic surgeon. Radiographic measures indicative of hip instability (Shentons line, FEAR index, centre-edge angle of Wiberg, acetabular index of Tönnis and the femoral neck-shaft angle) were measured. Hip pain, function, and quality of life were obtained prospectively using the Hip dysfunction and Osteoarthritis Outcome score (HOOS).

Results: 222 patients (89% females), mean age of 28 (95% CI: 26;30) were included in the study. All radiographic measurements and patient-reported outcomes improved significantly from preoperative to 6 months postoperative ($p<0.001$). There were no differences in the change score of patient-reported outcomes between patients with a FEAR index >2 (indicative of hip instability) and patients with a FEAR index ≤2.

Conclusion: Hip instability assessed by the FEAR index is not associated with hip pain, function, and quality of life among patients with hip dysplasia. This study did not find evidence supporting that instability was a cause of pain in these patients.

Keywords: Orthopedic surgery, Rehabilitation, Other

Effects of prehabilitation training on skeletal muscle mass and strength prior to total joint replacement: A systematic review and meta-analysis.

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INTRODUCTION

Twenty percent of patients receiving total hip or knee replacement (TJR) report non-optimal postoperative outcome. Increasing preoperative lower-limb-strength prior to TJR may improve postoperative functional performance.

MATERIALS AND METHODS

Eligibility criteria: RCTs 1) comparing preoperative lower-limb-exercises before TJR with standard care 2) explicitly reporting the exercise intensity and 3) reporting functional performance were included.

Information sources: Cochrane Central, MEDLINE, EMBASE, and PEDro were searched in August 2021.

Risk of bias: Cochrane Risk of Bias tool was used to evaluate the risk of bias and conducted by to reviewers.

Synthesis of results: Functional performance knee-extensor strength 3 months postoperatively as well as 12 months postoperative.

RESULTS

Seven RCTs including 234 participants were included.

A moderate effect favoring prehabilitation training on sit-to-stand performance was observed three months postoperatively (SMD(95%CI) (0.77; 0.43 to 1.12), along with moderate-to-large effects on Timed Up&Go (-1.33; -2.55 to -0.11), walking speed (-0.78; -1.16 to -0.41) and knee extensor-strength (0.55; 0.11 to 0.99).

Small-to-moderate effects favoring prehabilitation were observed twelve months postoperatively for sit-to-stand (0.49; 0.12-0.86), walking speed (-0.37; -0.74 to -0.00), stair climbing (-0.55;-1.03 to -0.06) and knee-extensor strength (0.49; 0.16 to 0.81).

CONCLUSION

Prehabilitation prior to TJR induce long-lasting improvements in functional performance and knee extensor muscle strength that are of moderate-to-large effect size.

Keywords: Rehabilitation, Orthopedic surgery, Reviews and meta-analyses

The safety of Blood Flow Restriction Exercise in Individuals with a Spinal Cord Injury

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Introduction: Spinal cord injury (SCI) is a life-changing devastating condition. SCI implies reduced quality of life (QoL) and physical functioning (PF). Improvement of residual motor function are pivotal for a successful recovery. Low-intensity Blood Flow Restricted Exercise (BFRE) is a promising form of low-tension muscle training. Increased muscle strength, hypertrophy and improved PF have been reported with BFRE in other patient groups with motor disability. However, literature regarding SCI are sparse. Aim: To investigate the safety of BFRE on changes in blood pressure and blood markers of coagulation. Methods: Six adults with SCI<Th7 participated in four sessions of BFRE twice/week. Training sessions consisted of a five minutes warm-up followed by 30x15x15x15 repetitions of seated leg extensions and leg curl leg performed with pneumatic limb occlusion corresponding to 40 % of seated arterial occlusion pressure. Continuous blood pressure (BP) were monitored at training sessions. Blood samples were obtained pre and post (0-60 + 240 minutes) the first and last training session. Analyzed blood markers were Fibrinogen and D-dimer for coagulation and high-sensitivity C-Reactive Protein (CRP) regarding inflammation. Results: There were no severe increases in either Fibrinogen (Maximum increase at first session; 1.9 mol/l. At last session; 1.0 mol/l), D-dimer (Maximum increase at first session; 0.2mg/l. At last session; 0.2 mg/l) or CRP (< 4.0 mg/l at both timepoints). The increase in blood pressure were similar to the variability of blood pressure during free-flow resistance training. Conclusion: BFRE seems to be a safe training modality in individuals with SCI below Th7.

Keywords: Rehabilitation, Other, Other

Performance of activities of daily living after surviving a cardiac arrest

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Introduction:

Impaired cognitive functions after surviving an out-of-hospital cardiac arrest (OHCA) are related to decreased activities of daily living (ADL) performance, participation in society and quality of life. Frequently reported problems among OHCA survivors include difficulties in performing activities that are instrumental in life, carrying out family roles, and returning to work. Early assessment of both cognitive function and the ability to perform daily activities are valuable means for making rehabilitative interventions and provide the support needed for patients.

Aim:

The aim of this study is to explore how OHCA survivors manage their lives after discharge from hospital. This includes (1) exploring the experienced and observed ADL performance, (2) identify predictors in ADL performance for long-term ADL ability, cognitive function, return to work, and quality of life, (3) and finally to evaluate the costs of OHCA survivors.

Methods:

A prospective cohort study with a 6-month follow-up including 200 OHCA survivors will be conducted. Participants' ADL performance, cognitive function and quality of life will be assessed before discharge and six months after the OHCA. Data from national registers will be obtained. Furthermore, a nationwide register-based cost-of-illness study will be conducted to estimate the costs of the target group from a societal perspective.

Results:

A total of 140 patients are currently included in the study and recruitment is expected to be completed during the autumn of 2022. Results may contribute to optimize rehabilitation for OHCA survivors.

Keywords: Rehabilitation, Cardiovascular system, Other

Multivariable prognostic prediction models for functional independence at discharge from post-acute inpatient rehabilitation following acquired brain injury – a systematic review

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Introduction:

Rehabilitation aims to assist people to achieve a meaningful life following an injury. The recent shift to a value-based healthcare paradigm implies efficiency: achieving the most favourable outcome at the lowest cost. Independent functioning in daily activities is a 'favourable outcome' in neurological rehabilitation. In this context, prognosis research is particularly important as it may provide information on recovery potential and efficient resource allocation serving value-based rehabilitation. Although useful, validated prognostic models in post-acute neurological rehabilitation are sparse.

Objectives:

To identify multivariable prognostic models of the Functional Independence Measure (FIM®) at discharge from post-acute inpatient rehabilitation in adults with acquired brain injury.

Methods:

This review was registered in PROSPERO and based on the PROGRESS framework. The databases PubMed, EMBASE and Web of Science were systematically searched. Main inclusion criteria were a) people with acquired brain injury, b) internally validated multivariable prognostic model and c) predicted outcome of FIM® score at discharge from post-acute inpatient rehabilitation.

Results:

The electronic search yielded 3,168 unique articles; 239 full-text articles were retrieved. Two articles fulfilled the inclusion criteria accounting for three internally validated prognostic models, each including similar predictor variables.

Conclusion:

The sparse evidence base of appropriately conducted studies predicting functional independence in post-acute neurological rehabilitation was confirmed. Future studies need to acknowledge the importance of model internal and external validation.

Keywords: Rehabilitation, Clinical neuroscience, Reviews and meta-analyses

Flash talk session 1

A novel approach to estimate calcification in the abdominal aorta and iliac arteries

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Background

The accumulation of calcium deposits in the artery walls is strongly associated with adverse cardiovascular events. Estimating the calcification in high-risk patients provides prognostic information that may guide interventions.

Most often arterial calcification is measured using non-contrast computed tomography scans(nCTs). Contrast-enhanced CTs(CTAs) of peripheral vessels are used to assess vascular stenoses; however, the suitability of CTAs to measure vascular calcification is challenged by difficulties of distinguishing the calcium from contrast. This study tested a method of calcium quantification based on CTAs of aorta and iliac arteries.

Methods

In a single-centre, retrospective study we included 39 patients with kidney failure who underwent a concurrent abdominal CTA and nCT. Aortic and iliac calcification was evaluated using both CTAs and nCTs. In nCTs calcification was evaluated using the Agatston method, while in CTAs, the calcification was measured using the software Philips Intellispace that enabled contrast exclusion. Calcium scores were compared using correlation analyses.

Results

The mean aortic and iliac calcium scores were 3764 and 2927 respectively, using nCT and 9017 and 9845, respectively, using CTA. The calcium score estimated in CTAs correlated linearly with the calcium score based on the nCT($r=0.84, P<0.0001$). Calcium scores were higher in the CTA than in the nCT and a trend towards a greater difference was observed as the mean calcium score increased.

Conclusion

Aortic and iliac calcification may be estimated using CTA. This could allow for better estimation of cardiovascular risks in patients undergoing CTA to assess peripheral vascular stenoses.

Keywords: Medical technology and diagnostic techniques, Nephrology, Cardiovascular system

Lexical Stability of Psychiatric Clinical Notes from Electronic Health Records

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Methods from Natural Language Processing hold great promise for improving clinical prediction models by utilizing information otherwise hidden in clinical notes. This potential is likely particularly pronounced in psychiatry, as a high proportion of clinical information is kept in the form of clinical notes in this medical specialty. However, clinical practice as well as the systems and databases in which these data are recorded and stored have changed over time. This might mean that the content of clinical notes may have also changed over time, which would potentially be problematic for predictive modelling. Therefore, the aim of the present study was to investigate the lexical stability of clinical notes from the Psychiatric Services of the Central Denmark Region in the period from January 1, 2011, to October 28, 2020 (n=119,291). The stability was quantified using several methods: First, descriptive statistics such as sentence length, readability metrics, and syntactic complexity were calculated. Second, the clinical content was tracked by monitoring the use of keywords from the Schedules for Clinical Assessment in Neuropsychiatry (SCAN). Third, change-point detection models were used to assess whether the content of the clinical notes remained stable over the course of the transition from the 2nd to the 3rd version of the Danish National Patient Registry. The initial results are indicative of lexical stability of the psychiatric clinical notes over time, which bodes well for the use of Natural Language Processing for predictive modelling in clinical practice.

Keywords: Medical technology and diagnostic techniques, Psychiatry, psychology and mental health, Epidemiology and biostatistics

A Three-Dimensional Spectral microCT Imaging: An Online Tool for Tumor Surgery Evaluation

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Surgery is the essential treatment for various types of tumors around the world. A key quality indicator for tumor surgery and a prognostic factor is the status of the resection margin. The conventional way of determining the status of the surgical resection margin is by histological examination. The main drawback of this method is that the final histological margin assessment is evaluated days after the surgery and not during the surgery, where there is an opportunity to secure radicality. With the existing and upcoming imaging technologies such as Optical Coherence Tomography (OCT), hyperspectral imaging, microCT and microMR imaging, the online assessment of resection margin in 3D with sub-mm resolution in a shorter time frame have not been achieved. An ideal imaging system for online resection margin assessment must have the speed and the resolution of microCT and soft tissue contrast of microMR. Therefore, the aim of this project is to show the proof-of-concept of an imaging technique called spectral microCT that can be used to create a high resolution (55 µm voxels) 3D image of a tumor in a sample with shorter time frame of < 15 minutes with sufficient tumor (including premalignant lesions) to normal tissue contrast for fast and reliable assessment of tumor resection margin. This intraoperative online tool for surgical margin evaluation could assist surgeons in obtaining negative margins at the first attempt and hereby reducing the risk of a second surgery. Though the project is mainly focussed on breast and tongue cancer, the application area is much wider, and every type of tumor surgery challenged with obtaining clear margins may greatly benefit from such a device.

Keywords: Medical technology and diagnostic techniques, Oncology, Other

DISCOVERING EARLY BIOMARKERS IN CIRCULATING ENDOTHELIAL CELLS FOR DIABETES COMPLICATIONS BY SINGLE CELL RNA SEQUENCING

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Endothelial cell dysfunction (ECD) plays a vital role in diabetes pathogenesis and diabetes complications e.g., proliferative diabetic retinopathy (PDR). Targeting the ECD is proven a prominent approach for the prevention, diagnosis, and treatment of diabetes complications. One particular type of endothelial cells (ECs) is the circulating endothelial cells (CECs) in the blood system. The common concept of CECs only refers to mature ECs shed from the vascular wall due to impaired vascular functions caused by e.g., diabetes and hypertension. Mature CECs have been proposed as highly valuable targets for the diagnosis, treatment, and prognosis of cardiovascular diseases.

The aim of the study is to reveal the heterogeneity of CECs and develop an early CEC biomarker for early diagnosis of diabetes complications.

This study will examine blood samples from healthy individuals, diabetic patients with PDR, diabetic maculopathy, or without eye disease, and thereby characterize CECs by single-cell RNA sequencing (scRNA-seq) analysis. This project will decipher the molecular and metabolic abbreviations of CECs in patients with diabetes at single-cell levels. Currently, we have used different flow cytometry methods to investigate the CECs in blood samples from healthy individuals. We have optimised the CEC enrichment method which is compatible with scRNA-seq analysis.

Conclusion: scRNA-seq analysis of CECs from healthy individuals and patients with diabetes and different degrees of microvascular complications will provide invaluable knowledge for the development of early diagnosis, prevention, and treatment of diabetes-associated endothelial cell dysfunction.

Keywords: Medical technology and diagnostic techniques, Cell biology, Cardiovascular system

Unravelling shared microcirculatory abnormalities in hypertension and Alzheimer's disease using laser speckle contrast imaging.

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Background: Dementia is a term used to refer to a set of symptoms such as progressive impairments to memory, language, and thinking. Along with cognitive dysfunction, dementia is associated with abnormal changes in brain perfusion and microcirculation. While the exact mechanisms are still debated, it is known that hypertension predisposes an individual to early cognitive impairment and increases the risk of developing Alzheimer's Disease (AD) - the most common cause of dementia. A potential link between the diseases could be the altered functional and structural properties of resistance vessels that are associated with elevated blood pressure. Therefore, developing approaches to diagnose and treat those abnormalities at the earliest stages of hypertension might reduce the future incidence of dementia.

Aim: To develop a novel translational approach for microcirculation diagnostics based on Laser Speckle Contrast Imaging (LSCI) and apply it to study the link between hypertension and AD.

Methods: We will design and optimize LSCI for human and animal retinal imaging. We will collect a long term imaging dataset of brain and retinal blood flow in rat models in the progression of hypertension (DOCA Salt) and Alzheimer's disease (TgF344-AD). Finally, we will develop new image processing algorithms to characterize the microcirculation condition using the LSCI data.

Perspective: In the final stages of the project, we will translate the findings from rat models to characterize the microcirculation of patients with hypertension and dementia. Overall this project promises to provide a new tool for monitoring microcirculation that can impact research and diagnostics in various fields.

Keywords: Medical technology and diagnostic techniques, Cardiovascular system, Animal models/disease models

Auto-segmentation of low contrast organs at risk in head and neck improves with minimal prior delineation input.

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Jasper Albertus Nijlkamp, Danish Center for Particle Therapy; Jesper Grau Eriksen, Department of Experimental Clinical Oncology; Stine Sofia Korreman, Danish Center for Particle Therapy

Segmentation of organs-at-risk (OAR) is a crucial but time consuming step in radiotherapy. Deep learning (DL) auto-segmentation (AS) can assist clinicians in the task, however AS of OARs with low visual contrast is often inaccurate. We aim to improve performance of DL AS of low contrast OARs by including minimal manual delineations as input to DL AS models.

We have planning CTs and manual segmentations of OARs from 301 head-neck cancer patients. 30 were randomly selected for an external test set. To simulate minimal manual delineation (MMD) input, we extracted the most cranial and caudal slice of the lower, middle and upper pharyngeal constrictor muscles (PCMs), glottic larynx (GL) and parotid glands (PG) and input these along with CT in 3D full resolution nnUNets [Isensee, F et al. 2020] (CT+MMD). For reference we trained CT-only nnUNets.

We obtained Dice on the external test set. Tests for similarity between paired models were done with two-sided Wilcoxon signed-rank tests.

Dice was significantly better for all OARs with CT+MMD compared to CT-only ($p \leq 0.001$). Absolute improvements in median Dice ranged from 0.18 to 0.22 for PCMs and GL and 0.02 for PG.

By training DL AS models on CT along with just two manually delineated slices per OAR, Dice improved substantially for low contrast OARs such as PCMs and GL. For the included high contrast OAR (PG) the effect was marginal.

Our findings show that it may be beneficial for clinicians to manually segment a few selected slices low contrast OARs prior to running DL AS, as the subsequent predictions are likely to require much less revision than for predictions of fully automated models.

Keywords: Oncology, Medical technology and diagnostic techniques, Other

Parametrization of artery delineation and nationwide implementation in the DBCG RT Nation cohort

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Purpose

With automation of delineation in radiotherapy making its entry in clinical routine, it is desirable to have a framework for quality assurance (QA) of delineation of small organs of limited visibility. In this study we develop a parameterization of left anterior descending coronary artery (LADCA) delineation.

methods

We included organ delineations from 4598 danish high-risk breast cancer patients treated with adjuvant radiotherapy across the nation during 2008-2017. A national delineation guideline was published in 2013. LADCA was parameterized using metrics describing volume, cranial-caudal (CC) and cumulative length, width, anterior-posterior and lateral-medial consistency between slices, missing organ slices and number of patients with delineations. Results were stratified by year and treating center. Significance was tested with the Mann-Whitney U-test.

Results

The method was successfully used in all patients included in the Danish Breast Cancer Group (DBCG) RT Nation cohort. In the period around the implementation of national delineation guidelines (2012-2014), the differences between the centers were smallest. For mean width there was a significant difference between centers in the periods 2008-2012 and 2014-2017 ($p<0.001$). For CC length, no significant differences were found between center 2 and 3 (2011-2016), however center 4 differed significantly in the periods 2010-2011 and 2015-2017 ($p<0.001$).

Conclusion

We have developed a method for parametrization of delineations of LADCA. Our results showed significant differences in delineations of LADCA among centers and need for regularly QA regarding delineations. This method is generalizable for other organs.

Keywords: Oncology, Other, Other

Robust treatment planning for anatomical variations in proton therapy

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Proton therapy treatment plans are highly sensitive to uncertainties during the treatment course. Therefore, robust treatment planning strategies are used to mitigate simple variations, however, they cannot incorporate complex anatomical variations.

The PhD project addresses this issue for the most dominant components of anatomical variations in head and neck cancer (HNC) proton therapy. Individualized adaptive and robust treatment planning approaches will be identified, based on a quantification of anatomical variations and the respective dosimetric impact for individual patients.

The study is performed based on CT/PET and daily cone-beam CT (CBCT) scans of HNC patients, who have previously been treated with either photons or protons at AUH. A pre-existing method based on principal component analysis for modelling daily anatomical changes extracted from CBCT scans is used to identify modes of anatomical variations. A priority ranking is derived by correlating localization of anatomical variations with deteriorations of the dose distribution in the patient. Individualized robust planning and adaptation strategies will then be developed and tested. The complexity of the approaches can vary from including highly localized up to global anatomical robustness based on population and/or individually identified modes of variations. Based on plan quality and robustness, the most promising approaches will be identified for patient subgroups.

The study is expected to facilitate implementation of clinical protocols for HNC in proton therapy, including robustness towards anatomical variations. This will improve the laborious plan adaptation workflow for both personnel and patients.

Keywords: Oncology, Other, Other

The LOOP-DIY Study: The effect of LOOP-DIY in Danish children with Type 1 Diabetes Mellitus.

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J. S. Sørensen, STENO Diabetes Center Aarhus and Pediatrics Department Herning, K. Kristensen, STENO Diabetes Center Aarhus, L. Borch, Pediatrics Department Herning

Development in treatment of Type 1 Diabetes Mellitus (T1DM) have become increasingly technical, with insulin pumps and continuous blood glucose sensors replacing daily insulin injections and capillary blood glucose measures. Furthermore, integration of pumps and sensors to regulate insulin dosage are a rapidly developing field, and the company-based integrated solutions have been overtaken by patient initiated open-source solutions: LOOP Do-It-Yourself (DIY). LOOP-DIY automatically integrates values from the sensor with insulin delivery, controlling the insulin dosage through algorithms. Studies have shown increased glycemic control and better quality of life (QoL).

This cross-sectional study with current and retrospective data will be the first to assess the effect, safety and use of LOOP-DIY in Danish children aged 2-18 with T1DM.

The aim is to 1) estimate prevalence of the use of LOOP-DIY, 2) estimate the effect of LOOP-DIY on the patient's daily glycemic control measuring glycemic parameters, 3) estimate the risk of the LOOP-DIY by measuring frequency of ketoacidosis and severe hypoglycemia, 4) assess the effect of LOOP-DIY on everyday life of the children and parents, including QoL, sleep, self-efficacy, and fear of hypoglycemia (FOH).

The participants will be found nationwide through pediatric diabetes outpatient clinics. Their daily glycemic control will be assessed pre and post their transition to LOOP-DIY. Participants and their parents will be sent questionnaires regarding QoL, sleep, self-efficacy and FOH, as will a matched control group.

Keywords: Molecular metabolism and endocrinology, Paediatrics, Medical technology and diagnostic techniques

Flash talk session 2

Satellite glia cell (SGC) mechanisms contributing to chemotherapy-induced peripheral neuropathy (CIPN)

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The purpose of this project is to identify mechanisms in satellite glia cells (SGCs) which contribute to the development of CIPN. This will be done by investigating dorsal root ganglia (DRG) from chemotherapy treated mice using a single-cell RNA sequencing analysis, revealing changes in SGC caused by chemotherapy.

Chronic pain and/or sensory loss in the hands of feet of cancer patients receiving chemotherapy treatment called chemotherapy-induced peripheral neuropathy (CIPN). Often, patients cannot deal with simple day-to-day task, since the sensory loss is permanent and untreatable and because current pain medication is prone to harsh side-effects, addiction, and lack of effectivity. SGCs are glial cells supporting the somata of peripheral sensory neurons, whereas Schwann cells support the axons. The somata of peripheral sensory neurons lie within dorsal root ganglia (DRG), bilaterally on each spinal level, just outside of the spinal cord. The perhaps most intriguing aspect of SGCs is that they are believed to contribute to the development of chronic pain when they are activated, which they are by certain conditions including nerve injury or chemotherapy treatment.

Therefore, SGCs are interesting as a novel target for new pain treatments that unlike current treatments, does not target the neurons themselves. Identified changes in SGC have potential in both pain and cancer treatments, as it may lead to new, much needed pain treatments, including counteracting the development of CIPN. Such counteraction would allow the use of higher chemotherapy doses, in the cases where CIPN is the dose-limiting factor and could improve the chance for a successful cancer-treatment.

Keywords: Basic neuroscience, Animal models/disease models, Cell biology

Feel the beat: multimodal rhythm perception in cochlear implant users

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Cochlear implants (CIs) are optimized for speech perception but poor in conveying music. Rhythm, however, is repeatedly reported as the most successfully conveyed property of music, with CI users often performing on par with normal hearing (NH) controls in rhythmic tasks. These are often based on rhythmic stimuli presented in single streams, being at variance with real-world music, where multiple streams of rhythmic patterns occur simultaneously. However, being able to perceive real-world musical rhythms is important for groove, i.e. the pleasurable desire to move to music.

NH listeners prefer moving to music of medium rhythmic complexity compared to high and low complexity. This relationship follows an inverted U-shape, implying that there is a "sweet spot" at which a maximum pleasurable sensation of wanting to move is experienced. However, groove perception in CI users remains largely unexplored.

For a more complete experience of rhythm and groove, it is necessary to enhance CI users' sensory input so they can distinguish and integrate sound of rhythmic instruments occurring simultaneously. Findings suggest that electro-haptic stimulation (EHS) enhances perception of various sound properties in CI users. If optimized for rhythm perception, EHS may enhance perception of more complex rhythmic patterns in CI users.

This project studies rhythm and groove perception in CI users and the potential effect of rhythm-specific EHS. CI users' perception of rhythm and groove will be mapped out with and without EHS. This will be done through behavioral testing and using electroencephalography, enabling elucidation of the neural correlates of rhythm and groove perception in CI users.

Keywords: Basic neuroscience, Medical technology and diagnostic techniques, Ear, nose and throat (ENT)

Nano- and microstructural organization of OFC top-down connectivity and its optogenetic functional role in wild type and Slitrk5 knockout mice.

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Jens Randel Nyengaard, Department of Clinical Medicine, Core Center for Molecular Morphology, Sektion for Stereology and Microscopy

The orbitofrontal cortex (OFC) and Striatum are two intensively studied brain areas, which both play essential roles in a wide range of cognitive functions. Both brain areas have been associated with obsessive-compulsive disorder (OCD), same as an impaired cortico-striatal circuit, in which both the OFC and Striatum are included. We propose to study the functional and structural role of OFC connectivity to subcortical regions (striatum) in wild-type and transgenic mice to understand and identify molecular and circuit events leading to OCD behavior. The transgenic mice, Slitrk5 KO-/-, have already shown overactivation in the OFC, structural irregularities in the striatum, such as reduced volume of the striatum, decrease in dendritic complexity of striatal neurons, and downregulation of glutamate receptors. All these dysfunctionalities and irregularities might contribute to deficient cortico-striatal neurotransmission, which is one of the primary hypotheses in developing obsessive-compulsive disorder. It is highly challenging to identify the structure and functional role of OFC to Striatum, which is why various methods are implemented in this project. We will use optogenetics to manipulate mice pathways from OFC to striatum during behavioral assessments, to identify the functional role of this pathway during a simple decision-making. Three-dimensional electron microscopy is implemented to explore and compare the physical properties of the neural connectivity from OFC to the striatum at nanometer resolution. Lastly, tissue clearing with light sheet microscopy is incorporated to provide fine structural and molecular analysis of the OFC pathways within the whole mouse brain.

Keywords: Basic neuroscience, Animal models/disease models, Cell biology

Understanding cerebral alpha-synuclein pathology in Parkinson's Disease – Histological studies of brains from the Danish Brain Collection

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Parkinson's Disease (PD) is by definition an asymmetrical disease according to the diagnostic criteria. The most influential neuropathological staging system of PD (Braak staging) cannot explain the asymmetrical onset in many PD patients. A competing system (Unified Staging System for Lewy Body Disorders) also cannot explain the asymmetry. Both these systems are based on neuropathological examination of single hemispheres at post mortem.

We have hypothesized that Lewy pathology in PD can originate in two different locations, the enteric nervous system and the brain, leading to two distinct disease courses i.e., body-first and brain-first PD. During early disease stages patients show different clinical profiles, but all cases end up in widespread pathology and clinically similar profiles during end stages.

Here, we investigate the spreading of Lewy pathology in both hemispheres of PD and incidental Lewy Body Disease post mortem brains from the Danish Brain Collection. We expect two distinctive patterns; a symmetrical pattern compatible with gut-first PD subtype and an asymmetrical pattern compatible with brain-first PD subtype.

Tissue samples obtained from 12 bihemispheric regions are immunohistochemically stained against α-synuclein, a major component of Lewy pathology, and the pathological burden in each region will be assessed quantificationally by artificial intelligence software trained to detect Lewy pathology.

An estimated 250 brains will be screened to include cases of varying degrees of Lewy pathology to assess the temporal aspect of spreading. This may elucidate the sites of the initial pathology within the CNS supporting the body- vs. brain-first hypothesis.

Keywords: Basic neuroscience, Other, Other

The role of single-chain SorCS2 in cerebellar connectivity: implications for cerebellar dysfunction and memory impairment

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Emerging research has indicated that the cerebellum is involved in higher-order cognitive functioning including spatial learning, attention, and memory, through extensive interconnections between the deep cerebellar nuclei and several limbic structures. Furthermore, aberrant cerebellar functionality is implicated in several neurodevelopmental diseases (NDDs) such as autism spectrum disorder as well as neuropsychiatric diseases. We focus on SorCS2, a member of the sortilin receptor family, known for their involvement in sorting and signaling, which is abundantly expressed during cerebellar development as well as in the adult Purkinje neurons. Additionally, SorCS2 is involved in various types of memory and a risk factor for several NDDs, including autism. The receptor undergoes proteolytic cleavage resulting in a single-chain receptor which can be further processed into a double-chain isoform, each with distinct expression patterns and biological functions. Whilst both isoforms are highly expressed at early cerebellar postnatal stages, the expression shifts to predominantly the double-chain form from postnatal day 3 and onwards. By utilizing a transgenic mouse model which solely expresses the single-chain isoform, we wish to elucidate the role of SorCS2 in cerebellar maturation, synapse formation and circuit wiring. We hypothesize that correct expression of the different isoforms in a spatiotemporal manner is critical for proper cerebellar patterning as well as circuit assembly. And that ablation of SorCS2 contributes to cognitive and affective processing impairments as well as memory deficits.

Keywords: Basic neuroscience, Cell biology, Animal models/disease models

Learning complex music: Brain mechanisms underlying the encoding of auditory patterns

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Memory is one of the most complex and crucial cognitive processes of the human mind. Research on the neural mechanisms of memory encoding and recognition is largely based on the processing of static stimuli, such as pictures or words. However, to broaden our knowledge about memory processing and understand its fast dynamics of brain activity and connectivity, we must incorporate the temporal properties of dynamic stimuli, such as speech or music. Recently, we investigated the brain mechanisms underlying the recognition of musical patterns in 71 participants using magnetoencephalography (MEG) and magnetic resonance imaging (MRI). Results showed that music recognition was strongly supported by brain areas typically linked to memory processing, such as the hippocampus, parahippocampal cortex, and cingulate and paracingulate gyri. We aim to expand our work by studying the neural mechanisms underlying the encoding of musical patterns and explore how previously acquired information (priors) influences this process. We will investigate this in a healthy population with MEG and MRI using a wide range of musical patterns of varying complexity (i.e., tonal versus atonal music). We expect that the brain mechanisms will differ between encoded and forgotten musical patterns and that encoding will be supported by memory-related brain areas such as the hippocampus and dorsolateral prefrontal cortex, as shown in previous studies of static stimuli. Furthermore, we expect that providing cognitive priors will aid the encoding and subsequent recognition of complex musical patterns. We hope that our research will shed light on the intricate spatiotemporal dynamics underlying memory encoding.

Keywords: Basic neuroscience, Psychiatry, psychology and mental health, Other

Locus coeruleus: The master switch for brain health?

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B. Hansen, Center of Functionally Integrative Neuroscience

Locus coeruleus (LC) is a pontine nucleus consisting of noradrenaline (NA) producing neurons. NA is central for brain blood flow and capillary permeability regulation. Evidence shows dysfunctional brain microvasculature to contribute significantly to the development of neurodegenerative diseases. Furthermore, LC neurons degenerate earlier than other brain regions in the course of Alzheimer's disease (AD). LC also seems to be involved in the sleep-waking cycle through LC-NA projections to the cortex and by preventing an inhibition of wake-promoting histamine release from the hypothalamus. Sleep is thought to drive the clearance of neurotoxic proteins which are accumulated in AD. All this leads to the hypothesis that LC is a significant contributor to the development of neurodegenerative diseases and may constitute a therapeutic target. We aim to investigate LC's control over brain capillary function.

An initial pilot study will employ an alpha 2 adrenergic autoreceptor agonist, clonidine, to inhibit the release of NA. Using fluorescein labelled dextrans, the study will use two-photon microscopy line scans to visualize the effect of LC ablation on red blood cell velocity. Observed microvascular effects will then aid design of improved techniques for MRI detection of subtle alterations in capillary flow. One potential window into this is via default mode network (DMN) MRI. This has direct translational value as the human DMN is known to be altered in AD patients. The cause of this, however, is not clear but may be elucidated by our study. With refinement subtle DMN changes may be detected as an earlier marker of AD thus widening the therapeutic window of the disease.

Keywords: Basic neuroscience, Clinical neuroscience, Cardiovascular system

Is the omega-6 to omega-3 ratio associated with late-onset multiple sclerosis? – A Danish Cohort Study

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Background: Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system. The prevalence of MS in Denmark was estimated to 16,500 persons in 2020; one of the highest prevalence worldwide. The aetiology of MS is not fully understood, however, environmental factors and genetic predisposition are known risk factors. The dietary intake may have an impact on MS risk, too. Omega 3 fatty acids decrease inflammatory processes, through various mechanisms. Nonetheless, the functions of omega-3 fatty acids interact competitively with those of omega-6 fatty acids, which are known to have pro-inflammatory properties. The ratio between omega-6/omega-3 (n6:n3) intake has been shown to be associated with the incidence of other inflammatory diseases. Nevertheless, there is a scarcity in studies on the n6:n3 ratio and its association with MS. Hence, the aim of this study was to investigate the association between the n6:n3-ratio and the hazards of developing late-onset MS.

Method: The present prospective cohort study is based on participants from the Danish 'Diet, Cancer and Health'-study, including middle-aged Danes (age 50-64 years). Cox proportional hazard models were used to estimate the association between tertiles of omega-3 intake and hazards of late-onset MS diagnosis. The Danish National Patient Registry was used to extract information on the diagnosis of MS during follow-up.

Results: The cohort contained 56,867 participants. A total number of 124 persons were diagnosed with late-onset MS during the follow-up. The statistical analysis is ongoing; preliminary results will be presented at PhD day.

Keywords: Multiple Sclerosis, Omega-3, Omega-6, inflammation

Keywords: Public health, Inflammation, Epidemiology and biostatistics

Flash talk session 3

Bleeding and thrombosis in intensive care patients with liver cirrhosis

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Niels Kristian Aagaard, MD, PhD, Department of Clinical Medicine;

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Background: Patients with liver cirrhosis have a fragile and "rebalanced" coagulation system. Our conventional coagulation tests provide an incomplete picture of bleeding and thrombosis risk in these patients. Therefore, we aim to investigate the coagulation system in patients with liver cirrhosis in the intensive care unit (ICU) using new dynamic assays, and to identify new biomarkers for bleeding and thrombosis. Our hypotheses are that ICU patients with liver cirrhosis have an increased endogenous thrombin generation and a hypercoagulable profile assessed with rotational thromboelastometry (ROTEM®) when compared to critically ill patients without liver cirrhosis.

Methods: This study is a longitudinal cohort study carried out in collaboration between the Departments of Anaesthesiology and Intensive Care, Hepatology and Gastroenterology, and Clinical Biochemistry. Adult patients with liver cirrhosis admitted to the ICU will be included. ICU patients without known pre-existing liver dysfunction will serve as controls.

Clinical information regarding bleeding and thrombotic events will be retrieved for a period of 30 days after admission and graded according to the WHO Bleeding Scale. Blood samples will be taken on day 1,2,3,7, and 21 and used for multiple analyses in our lab. The analyses include impedance aggregometry (Multiplate®), thromboelastometry (ROTEM), ex vivo thrombin generation (Calibrated Automated Thrombogram®) and in-house fibrin clot lysis assay.

Results: The study is a research year project planned from Sep 1, 2021-Aug 31, 2022 and is thus in progress. We plan on including 44 patients with liver cirrhosis and 44 controls.

Keywords: Cardiovascular system, Gastroenterology and hepatology, Medical technology and diagnostic techniques

randomized crossover study

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Background:

Patients with an ileostomy often have impaired quality of life, sodium depletion, complicated fatigue, secondary hyperaldosteronism, and other organ-specific pathologies. Osmolality of oral supplements is a major determinant of ileostomy output and sodium loss. Ways to increase fluid and sodium absorption in patients with an ileostomy via adjusting oral drinks' osmolality are understudied. The aim of this study is to quantify the association between osmolality in liquid oral supplements and ileostomy output.

Methods:

Twelve patients with an ileostomy will be included in a quasi-randomized crossover intervention study. Each patient will ingest between 3-15 different supplements during separate 6-hours intervention periods, and ileostomy output and urine volume will be collected. Outcome measures include faecal wet-weight, urine volume, electrolytes, osmolality, and body composition measured with bioelectrical impedance analysis.

Results:

Statistical mixed model linear regression with cluster dependency analysis can help determine the association between osmolality of oral supplement and ileostomy output and sodium loss. Hopefully, this will demonstrate an optimal osmolality range, which we call the Goldilocks zone.

Conclusion:

In conclusion, by closely examining ileostomy and urine output, this study will improve our understanding of real-life fluid and sodium absorption in the small bowel, and shed light on fluid and sodium losses in patients with an ileostomy. The study can help identify the optimal osmolality range, a Goldilocks zone. Our results may improve the advice given to patients with an ileostomy.

Keywords: Gastroenterology and hepatology, Medical technology and diagnostic techniques, Reviews and meta-analyse

Severity of Clostridioides difficile infection among older patients: an observational pilot study

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Introduction: More than 60% of the Clostridioides difficile infection (CDI) cases are reported in patients aged 60 years and older. We aimed to describe the CDI severity and prognosis at 90 days following diagnosis in patients above 60 years affected by CDI in the Central Denmark Region (CDR).

Methods: Observational study based on all clinical records conducted among older patients in CDR in the period of January- February 2018. Inclusion criteria were: 1) age ≥ 60 years 2) index CDI defined as a positive CD toxin PCR test and no treatment for CDI within the last year. Severity of CDI was rated using the Danish national guidelines for CDI. The cohort was retrospectively frailty rated using the record-based Multidimensional Prognostic Index (rMPI).

Results: In total, 63 patients were enrolled, mean age 78 years (SD 9.7), 56% male. In 87% of the cases, the CDI was related to hospital admission. An rMPI assessment was possible in 87% of the patients; Of these, 11 (20%) were categorized as non-frail, 14 (25%) moderately frail, and 30 (55%) severely frail. The 90-day mortality was 32%. CDI was categorized as mild/moderate in 21% of the cases, severe in 42%, and fulminant in 37%. Severity of CDI increases risk of 90-day mortality (relative risk 3.64, (95% CI: 1.57-7.95), p=0.001).

Conclusion: In older adults, CDI carries a high mortality. CDI is mostly diagnosed during hospital admission. Severity of CDI increases 90-day mortality and most of the patients are frail at discharge. The poor prognosis suggests a need for preventive strategies.

Keywords: Gastroenterology and hepatology, Infection, Multimorbidity

Faecal microbiota transplantation to prevent complications, progression, and mortality of cirrhosis

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Background: Liver cirrhosis is a progressive disease with high mortality. Gut dysbiosis, increased gut permeability, bacterial translocation, and chronic inflammation are key factors for disease progression and development of complications in cirrhosis, so called episodes of decompensation. Faecal microbiota transplantation (FMT) from healthy donors can possibly revert the dysbiosis and thus improve the factors for disease progression. This will possibly improve prognosis and quality of life for the patients.

Methods: In this randomized, placebo-controlled, double-blinded study, 220 patients with acutely decompensated liver cirrhosis will be randomized (1:1) to either FMT or placebo in addition to standard of care. Patients will be followed for 1 year. During follow-up, the patients will be examined for disease progression, cognitive and liver function, and quality of life. Samples will be obtained and examined for the impact of FMT on gut barrier functions, bacterial translocation, inflammation, and immune functions.

Status: Inclusion started July 2021, still recruiting.

Keywords: Gastroenterology and hepatology, Inflammation, Other

Improved imaging of hepatocellular carcinoma with a head-to-head comparison of 18F-FDGal PET/CT and 18F-choline PET/CT

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The majority of patients who develop hepatocellular carcinoma (HCC) has cirrhosis of the liver. In these patients, the diagnosis can be made non-invasively with characteristic contrast-enhancement pattern on CT and/or MRI. Extrahepatic HCC is a contraindication of liver transplantation because of the poor prognosis in disseminated disease. Correct identification of patients with extrahepatic disease is thus crucial. A PET/CT scan with the glucose tracer 18F-FDG is an important tool in the staging of many cancer forms, but PET/CT with this tracer has a suboptimal sensitivity for HCC situated in the liver and as such is not included in the staging of HCC. Other PET tracers such as 18F-choline and 18F-FDGal have been investigated in patients with HCC with improved detection rates. The two tracers have not yet been compared in a head-to-head study. The liver specific tracer 18F-FDGal has been developed in Aarhus.

The aim of the present study is to show that 18F-FDGal PET/CT is superior to 18F-choline PET/CT in diagnosing HCC. The project is a head-to-head comparison of 18F-FDGal PET/CT and 18F-choline PET/CT. Thirty patients with known HCC will be investigated with both tracers. Images will be analysed for focal lesions and compared by an experienced specialist in PET and an experienced radiologist. The study may lead to a more precise and non-invasive diagnosis of HCC.

Keywords: Gastroenterology and hepatology, Medical technology and diagnostic techniques, Oncology

Stereological Aspects of Liver Regeneration in Rats

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Post-hepatectomy liver failure may be characterized by insufficient hepatocyte hypertrophy and proliferation as suggested recently. We aim to examine liver morphology after 90% partial hepatectomy (PH), comparing surviving and non-surviving rats in an experimental model.

Rats are randomised into five groups a) euthanized 12 hours after PH, b) euthanized 24 hours after PH, c) euthanized 48 hours after PH, d) sham (laparotomy without PH), and e) baseline (no operation). Within each group, we will compare subgroups of surviving and non-surviving rats. Rats in whom euthanization is performed as scheduled will be allocated to the "survivors"-group. The groups of non-surviving rats will consist of rats presenting with a General Distress Score ≥ 10 in the postoperative period. These rats will be euthanized before planned evaluation and allocated to the subgroup closest to the time of euthanization (12, 24, or 48 hours after PH).

Through an abdominal midline incision, the right superior, right inferior, median, and left lateral lobes are ligated and resected, leaving the caudate lobes intact. At the time of euthanization, blood samples are collected from the heart, and the remaining liver is removed and stored for analyses.

The harvested tissue is fixed in formalin, cut into 2 mm thick parallel slabs, and embedded in paraffin. 30-µm sections are cut from each of the paraffin-embedded blocks, creating a set of systematic uniform random sampling sections. All sections are immunohistochemical stained for proliferation markers (Ki-67). Unbiased stereological methods (the optical fractionator and the isotropic planar rotator) are used to evaluate hepatocyte proliferation and hypertrophy.

Keywords: Gastrointestinal surgery, Animal models/disease models, Cell biology

How a task specific surgical logbook will impact laparoscopic training of surgical trainees.

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Background Tensions between receiving efficient workplace-based training in surgery and providing high-quality patient care is often highlighted in educational literature. Hence, an immense amount of literature aims to enhance surgical training outside the operating room. However, there is a lack of consensus regarding implementing educational tools in the clinical learning environment, while taking the ever-changing nature of surgery into account.

Aim Implement and validate a task specific surgical logbook by evaluating surgical trainees' time spent to reach independency and OSATS score (Objective Structured Assessment of Technical Skills) compared to conventional trained trainees.

Methods A prospective cohort study to gather evidence on the effects of a task specific surgical logbook applied by untrained first year surgical trainees, learning to perform cholecystectomy. Four surgical departments will be divided into two groups: departments with a logbook and departments without. The logbook consists of the procedure divided into seven surgical steps. The laparoscopic operations will be recorded, and the trainees will be assessed by laparoscopic experts using OSATS.

Perspectives By investigating if the logbook enhances the trainee's level of competence and time to proficiency this study has the potential to enhance patient safety and result in increased effectiveness to the production of the department. In this way, well-structured workplace-based surgical training can potentially enhance patient safety, patient and trainee satisfaction, and the economy of the department.

Keywords: Health education and simulation-based training, Gastrointestinal surgery, Work environment and organisation

Reducing Thromboembolic Risk in Oesophageal Cancer Patients

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Thrombosis is the most common cause of death in cancer patients after the cancer itself. Cancer activates the coagulation, leading to an increased thrombotic tendency. The risk of thrombosis is further exacerbated when the patients undergo surgery.

The coagulation profile of oesophageal cancer patients is only sparsely understood. It is currently standard practice to administer thromboprophylactic doses of low molecular weight heparin for 10 days following surgery. Notably, other gastrointestinal cancer types receive treatment for 30 days. We aim to investigate whether a prolonged, 30-day treatment will offer oesophageal cancer patients a better protection from thrombosis while not increasing bleeding events.

We will include 100 patients in a randomized, controlled trial. The patients receive either standard 10-day or prolonged, 30-day treatment with 5000 IU of Fragmin® daily. Coagulation profile is examined by analysing blood samples taken before, during and after surgery. We examine global haemostasis, platelet aggregation and thrombin generation as well as other markers of coagulation and fibrinolysis. The primary endpoint is the difference in prothrombin fragment F1+2 between the control and the intervention group 30 days after surgery. The patients are examined with ultrasound of the lower extremities before and 30 days after surgery to screen for deep venous thrombosis. The study has started inclusion on 1st September 2021, and results are pending.

We hope the results from this study can be used in future clinical guidelines for thromboprophylactic treatment after surgery for oesophageal cancer, and thus in the long run improve survival for this patient group.

Keywords: Laboratory science, Gastrointestinal surgery, Medical technology and diagnostic techniques

TIMING: Timely follow-up in colorectal cancer screening

Three upcoming cohort studies

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Approximately 20.000 Danish citizens get a colonoscopy each year due to a positive faecal immunochemical test in the national colorectal cancer (CRC) screening program.

Only 6% of these are diagnosed with CRC, while the rest are recommended either surveillance, screening or quarantine from the screening program depending on severity of findings at colonoscopy. The recommendations are based on expert consensus and sparse evidence. Further, the Danish guidelines differ from several other European guidelines on time intervals for screening and surveillance.

In this Ph.D. project we will evaluate the current Danish screening- and surveillance guidelines in terms of incidence of CRC and advanced adenomas (AA).

Using the national health registers, we will follow screened citizens from screen derived colonoscopy without CRC until next surveillance, screening or CRC.

The project will consist of three nation-wide register based studies: One evaluating the recommendation of 3- and 1-year surveillance intervals for the medium- and high risk individuals; One evaluating the recommendation on 2-years screening interval for low-risk individuals; One evaluating the 8-year quarantine from the CRC screening program for the 'clean colon'-individuals. The primary outcome are incidence of CRC and AA. The high-, medium-, and low risk individuals will be followed until next surveillance- or screening round, while the 'clean colon'-individuals will be followed from colonoscopy until CRC diagnosis; death; or end of 2022.

The project can provide new evidence that can help ensure an effective screening programme with a minimum of CRCs and as few colonoscopies and screening tests as possible.

Keywords: Public health, Oncology, Epidemiology and biostatistics

Flash talk session 4

Bidirectional associations between loneliness and perceived stress: A structural equation modelling analysis

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H. T. Maindal, Department of Public Health, Aarhus University, Aarhus, Denmark & Health Promotion, Steno Diabetes Center Copenhagen, Copenhagen, Denmark;

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M. Lasgaard, DEFACTUM - Public Health and Health Service Research, Central Denmark Region, Aarhus, Denmark

Aims: Loneliness is widespread and associated with an increased mortality risk. Yet, the causes of loneliness and the mechanisms linking loneliness with diminished health are not fully elucidated. For instance, loneliness has been associated with increased perceived stress, but the direction of the association remains unclear. This study set out to investigate temporal associations between loneliness and perceived stress.

Methods: The present study is based on a cohort from a representative sample of Danish citizens aged 16-80 years who participated in two questionnaire surveys; one in 2013 and one in 2017. The response rate of the cohort was 50% resulting in an analytical sample of 10,159 individuals. Cross-lagged structural equation models were used to examine the temporal associations between perceived stress and loneliness in different age groups (i.e.., 16-29, 30-64 and 65-80 years).

Results: For all age groups, cross-lagged panel analyses indicated bidirectional associations between loneliness and perceived stress. The effects were small to medium, with no statistically significant difference in the strength of the two associations. Additionally, the results indicated strong cross-sectional associations between loneliness and perceived stress and high stability over time.

Conclusions: Loneliness and perceived stress appear to act in a bidirectional manner in which the levels of loneliness and perceived stress mutually influence each other over time. The findings of both substantial bidirectional and cross-sectional associations demonstrate an interdependence between loneliness and perceived stress that may be relevant to consider in future interventions.

Keywords: Psychiatry, psychology and mental health, Public health, Epidemiology and biostatistics

Hair cortisol and self-perceived stress – a comparison between adolescents with functional somatic disorders and adolescents from the general population

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Introduction:

Functional somatic disorders (FSDs) are characterized by persistent and disabling physical symptoms that cannot be attributed to well-defined somatic disorders. In adolescents, the prevalence is around 4-10%.

The role of physiological factors in FSDs is widely debated. Evidence from adult populations suggests that cortisol is involved in the development and perpetuation of FSDs, but little is known regarding adolescents. As cortisol accumulates in hair over time, hair cortisol concentration (HCC) is a promising new biomarker for long-term physiological stress.

Objectives:

To compare HCC levels between adolescents with severe FSDs and adolescents from the general population. Furthermore, to investigate the association between HCC and self-perceived stress.

Methods:

The data are retrieved from the AHEAD trial, including 91 15-19-year-old adolescents diagnosed with a severe FSD, and the Copenhagen Child Cohort 2000, including data on 1455 16-17-year-old adolescents. Hair samples were collected for HCC analysis, and web-based questionnaires were used to asses self-perceived stress and functional somatic symptoms.

Results:

Preliminary data will be presented.

Conclusions:

This study will contribute with knowledge about the potential role of cortisol in FSDs in adolescents, and whether self-perceived stress can be used as a marker for physiological stress measured by HCC.

As treatments for adolescents with FSDs still need to be improved, this study may lead to better patient prognoses by incorporating stress management in future treatment strategies.

Keywords: Psychiatry, psychology and mental health, Paediatrics, Molecular metabolism and endocrinology

Reduced ACTH Reactivity to Psychosocial Stress in Women using Oral Contraceptives compared to Naturally Cycling Women

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L. M. Brostrup Hansen, Department of Biomedicine; P. J. Zak, Claremont Graduate University; Michael Winterdahl, Department of Clinical Medicine

More than a third of the female Danish population of reproductive age use oral contraceptives OCs, but while primarily used to prevent pregnancy, OCs are increasingly used on other indications as well and in progressively younger women. Although the main function of OCs is assumed to be in the reproductive domain, users are known to have an increased risk of developing cardiovascular, metabolic, and mental health problems compared to naturally cycling women. In the present study, we aim to characterise the influence of OCs on stress response and behaviour in women.

In the present study, 136 women were exposed to psychosocial stress. The first blood sample was taken immediately after exposure to a new group of people and the second after 15 minutes of group confirming activities. Concentrations of sex and stress hormones were determined using commercially available ELISA kits.

Initial ACTH response and ACTH recovery were analysed according to OC use and menstrual cycle phase. We found lower initial ACTH response and ACTH recovery in OC users compared to naturally cycling women. Furthermore, we found that the initial ACTH response and ACTH recovery was dependant on menstrual cycle phase in both OC users and non-users. Finally, we report the correlation between use of OCs, the menstrual cycle phase and alcohol consumption.

Our study suggests that female stress response should be categorised according to the uterine cycle phase in naturally cycling women and the pseudo cycle in OC users. Further research examining the behavioural side effects and the generalised long-term effects of OC use is warranted.

Keywords: Psychiatry, psychology and mental health, Public health, Gynecology and obstetrics

Description of a clinical intervention among patients admitted to the specialized

forensic psychiatry service in Central Denmark Region

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Background

Patients with schizophrenia suffer from increased mortality rates equivalent to 15-20 years shorter life expectancy. Up to 60% of this excess mortality can be explained by preventable, somatic conditions like cardiovascular, metabolic and respiratory comorbidities. As forensic psychiatric (FP) patients often experience the triple stigmatization of mental illness, substance misuse and criminal conviction, the risk of suboptimal diagnosis and treatment may be high.

Although benefits from the addition of general practitioner (GP) services to non-FP wards have been shown elsewhere, this cross-sectoral approach has never been attempted in a Danish FP ward. One purpose of this project is to evaluate relations between self-reported quality of life and objective measures of somatic health.

Methods

A one-year clinical intervention in which a GP consults patients in all six specialized FP wards in the Central Denmark Region (N=72). The initial consultation includes a physical examination, medication review and evaluation of blood samples. Follow-up consultations are as deemed needed by the GP. Data is collected from the electronic patient file and questionnaires regarding quality of life (SF-12), lifestyle and attitude towards GP services.

Results

The population will be described in regards to socio-demographic, clinical and forensic characteristics. Furthermore, comparisons will be made concerning quality of life (SF-12), metabolic syndrome, blood markers and heart-SCORE risk. Risk profiles for endocrinologic and coronary illness will be examined.

Conclusion

Results may guide future health interventions and will be used as a basis for adjustments to the current project.

Keywords: Psychiatry, psychology and mental health, Multimorbidity, Rehabilitation

Predicting involuntary admission among patients with psychotic disorder

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Introduction

Involuntary admissions are increasing in numbers across Europe(1). They can be traumatic for the patients(2) and are associated with large societal costs(3). Individuals with psychotic disorder are at particularly elevated risk of involuntary admission.

Objectives

This study aims to investigate whether machine learning methods including natural language processing can predict involuntary admission among patients with psychotic disorder.

Methods

We have obtained a dataset based on electronic health records for all patients having had at least one contact with the psychiatric services in the Central Denmark Region from 2011 to 2021. This dataset covers more than 120,000 patients, of which approximately 10,000 have been diagnosed with a psychotic disorder. The dataset contains both structured data, such as diagnoses, blood tests etc., as well as unstructured data (text). We will train machine learning models, basic logistic regression-models as well as state-of-the-art neural networks, to predict involuntary admission after contacts to the psychiatric services.

Results

As the machine learning models are under development, no results are available at this time. Preliminary results are expected in spring 2022.

Conclusions

If involuntary admission can be predicted among patients with psychotic disorder based on data from electronic health records, it will pave the way for potentially preventive interventions.

Referencer:

1. Sheridans-Rains, L et al., 2019

2. Frueh, B.C et al., 2005

3. Smith,S., 2020

Keywords: Psychiatry, psychology and mental health, Medical technology and diagnostic techniques, Other

'Can the unifying diagnostic construct of bodily distress syndrome (BDS) be used to assess functional disorders in adolescence?'

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BACKGROUND: The research diagnosis 'Bodily Distress Syndrome (BDS)' can be considered as a diagnostic consolidation concept for various Functional Disorders (FD) in both healthy and clinical adult populations. However, research is lacking on BDS criteria evaluation at younger life stages. The aim of this study will be to empirically test the usefulness of the BDS diagnosis in adolescence. We will examine if suggested Functional Somatic Symptom (FSS) cluster patterns within the BDS concept (i.e. 1) cardiopulmonary, 2) gastrointestinal, 3) musculoskeletal and 4) general symptoms) are rediscovered in adolescence, and estimate FSS severity according to sex and socioeconomic status.

METHOD: We will utilize data on 2462 youths from the 16-17 year follow-up of the general population Copenhagen Child Cohort (CCC2000). Self-reported FSS (Bodily Distress Syndrome checklist) and Danish national register data on sociodemograhic variables, as well as health-related quality of life (KidScreen), emotional distress (Spence Children's anxiety Scale; The Mood and Feelings Questionnaire) and illness worry (Whiteley Index) to establish convergent validity, will be used. Using confirmatory factor analyses (CFA), we anticipate to confirm the suggested BDS symptom clusters in this adolescent sample. To examine severity of FSS, Latent Class Analysis will be performed.

EXPECTED RESULTS: We expect to recognize and define the usefulness of a unifying diagnostic FD construct in adolescents.

DISCUSSION: Suggestions for future research and clinical implications, including opportunities for preventive and interventive treatment approaches, will be discussed.

Keywords: Psychiatry, psychology and mental health, Epidemiology and biostatistics, Other

Single Case Design Study: First test of Danish versions of I-CBT programmes for children and adolescents with functional gastrointestinal disorders.

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Background

Functional gastrointestinal disorders (FGID) are common in young people, cause functional disability and high health care use. The disorders are characterized by a span of different gastrointestinal symptoms and cause a large negative impact on quality of life. Symptoms often persist into adulthood. In spite of the obvious need for treatment options, there is little access to evidence based treatment in Denmark.

Internet-based cognitive behavioural therapy (i-CBT) have shown promising effect in recent Swedish studies.

Aim of the current study is to examine the trajectory of efficacy of i-CBT with graded exposure for children and adolescents with FGID in a Danish clinical context.

Our hypothesis is that i-CBT will be superior to a no-treatment randomized baseline period.

Methods:

We will perform a single case experimental design study (SCED) with multivariate baseline of 5, 10 or 15 days. We will include 6 children and 6 adolescents diagnosed with FGID, who participate in a 10-week treatment i-CBT programme, developed specifically for children and adolescents with FGID. The treatment is therapy guided and exposure based.

Measures will be assessed daily from baseline to end of treatment using a short electronic questionnaire to report on the primary outcome (abdominal symptoms) and secondary outcomes (single items on symptom catastrophizing, avoidance and control behaviour, and symptom acceptance) with a last daily assessment over a week at 3-months follow-up

Results and conclusion

The results are expected to give a detailed description of efficacy including exact time for when during the treatment the effect is seen and further evaluation of treatment targets.

Keywords: Psychiatry, psychology and mental health, Paediatrics, Gastroenterology and hepatology

"WILL ENDS MEET THIS MONTH?" AN INTERPRETATIVE PHENOMENOLOGICAL ANALYSIS (IPA) OF FOOD INSECURITY AMONGST ETHNIC MINORITY FAMILIES LIVING IN A MARGINALIZED DANISH NEIGHBORHOOD

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1. Introduction

Food insecurity refers to the experience of not having sufficient financial means to provide healthy and nutritive foods reliably for one's household members. In other social democratic welfare countries, food insecurity has been observed in neighborhoods with low socioeconomic status. However, this has not been investigated in a Danish context. This study is examining the experience of food insecurity among ethnic minority families with young children living in a marginalized Danish neighborhood.

2. Data and methods

This study is an interpretative phenomenological analysis study and the data collection consisted primarily of semi-structured individual interviews and focus group discussions. This was to assess data on whether the families experience food insecurity and if so, how it affects their households with young children.

3. Results

There are currently not any complete results as we are amid analyzing the data. However, preliminary results point out that several families have been struggling with the experience of food insecurity, which has affected both their mental well-being and the family's physical health.

4. Discussion

Although the discussion of the results will follow once we have finished the analysis, we expect that an understanding of the extent of experience-based food insecurity among ethnic minorities may have an impact on policy strategies.

Keywords: Ethnic minorities, food insecurity, social inequality in health, IPA study, support

Keywords: Public health, Socio-economic conditions, Qualitative research

Flash talk session 5

How do we enhance evidence-based practice among physiotherapists and chiropractors in primary care? An implementation science project using a mixed-methods design.

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PhD, MHS, Physiotherapist Nanna Rolving; PhD, MsN, Nurse Camilla Blach Rossen; Professor (MSO), PhD, Chiropractor Tue Secher Jensen; Professor, PhD, Physiotherapist Thomas Maribo, Department of Public Health

Introduction: Evidence-based practice is based on 1) patient preferences, 2) clinical expertise, and 3) research-based evidence (guidelines). However, studies show that health professionals in Denmark predominantly draw on their clinical expertise and patient preferences in their treatment and to a lesser extent use the guidelines. This is problematic, as it is well documented that adherence to guidelines improves patient outcomes.

Objectives: The primary aim of the PhD-project is to generate knowledge on how to enhance evidence-based practice among physiotherapists and chiropractors in primary care.

Design and methods: The PhD project is an implementation-science study using a mixed methods explorative sequential design, including three phases:

Phase 1 is a qualitative study aiming to explore the barriers and facilitators by using the guidelines in clinical practice. Data is generated through observations and individual semi-structured interviews of 9 physiotherapists and 9 chiropractors.

Phase 2 is the development phase of the active implementation strategy. The aim is in collaboration with stakeholders to develop a contextually designed active implementation strategy that addresses the identified barriers and facilitators.

Phase 3 is a quantitative study conducted as a cluster randomized controlled pilot trial. The aim is to investigate the feasibility of a cluster RCT and evaluate the implementation of the active implementation strategy.

Findings (phase 1): This study showed that the barriers for using low back pain guidelines primarily revolve around a skepticism towards the validity of the guidelines and around a rooted biomechanical identity.

Keywords: Public health, Rehabilitation, Work environment and organisation

Research protocol: Can we kill three birds with one stone? A randomised controlled trial to increase participation in cervical and colorectal cancer screening.

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Larsen M.B., Department of Public Health Programmes and University Research Clinic in Cancer Screening, Randers Regional Hospital; Tranberg M., Department of Public Health Programmes and University Research Clinic in Cancer Screening, Randers Regional Hospital; Petersen L.K., Department of Obstetrics and Gynaecology, Odense University Hospital and OPEN, Department of Clinical Medicine, University of Southern Denmark; Njor S.H., Department of Public Health Programmes and University Research Clinic in Cancer Screening, Randers Regional Hospital, Department of Clinical Medicine, Aarhus University.; Andersen B. Department of Public Health Programmes and University Research Clinic in Cancer Screening, Randers Regional Hospital, Department of Clinical Medicine, Aarhus University and Department of Clinical Medicine, Aarhus University

Introduction

Organised, population-based screening is recommended for breast cancer, cervical cancer (CCU) and colorectal cancer (CRC). In Denmark, the participation rate in breast cancer screening exceeds both CCU and CRC screening. The aim of this study is to evaluate effectiveness of an intervention offering home-based CCU and CRC screening to women when attending breast cancer screening, if they are not up to date with CCU and/or CRC screening.

Methods

On selected days, the five breast cancer screening units in Central Denmark Region are randomised to serve as intervention unit or control units. On intervention days, women attending breast cancer screening in an intervention unit will be offered a check-up on her CCU (50-64 years) and CRC (50-69 years) screening status. If the woman is not up to date with CRC screening, she will be offered to receive a kit to obtain a Faecal Immunochemical Test (FIT). If she is not up to date with CCU screening, she will be offered to receive a home-sampling kit for Human Papillomavirus (HPV) screening. Based on power calculation with an allocation of 1:4, 7600 women must be included in the study with 1250 in the intervention group to detect an increase in participation from 60% to 65% with a power of 90%. The enrolment started September 2021 and is expected to go on for one year.

Results

Main outcome will be difference in proportion of women participating in CCU and CRC screening within three and six months after the intervention as compared to the control group.

Conclusions

The study has potential to increase participation in CCU and CRC screening and reduce morbidity and mortality by using a simple and easily scalable intervention.

Keywords: Public health, Oncology, Socio-economic conditions

Patients' experiences of cognitive impairments following critical illness in the ICU. A scoping review

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Background: Critical illness and admission to an intensive care unit (ICU) can affect patients for months or years following discharge as many suffer from cognitive impairments. Long-term cognitive impairments affect patients' quality of life and ability to adapt to everyday life. Exploring their experiences on how and which cognitive impairments are affecting their everyday lives facilitates the planning of relevant research on interventions that may serve to alleviate the burden of post-ICU cognitive impairments.

Aim: To review the literature on patients' experiences of cognitive impairments following critical illness in the ICU.

Design: We conducted the scoping review using the methodology recommended by the Joanna Briggs Institute.

Methods: A systematic search was conducted in PubMed, Cinahl, PsycInfo, and Embase. References and citations in relevant studies were explored. The tool Covidence was used by two independent researchers to select, compare and discuss relevant studies to include.

Results: The scoping review included 11 studies with qualitative and/or quantitative methods. Four themes emerged during the analysis reflecting patients' experiences of critical illness in the ICU: 'Suffering from poor memory', 'Managing everyday life', 'Unsupported by the healthcare system', and 'Strategies for support in recovery'. Patients made use of different strategies in recovery and rehabilitation to regain independence and not being a burden to others.

Conclusion: Patients experienced a variety of cognitive impairments following critical illness in the ICU affecting and challenging their quality of life and adaption to everyday life.

Keywords: Qualitative research, Rehabilitation, Reviews and meta-analyses

Deconstructing the Leaky Pipeline

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Background: The expression “The Leaky Pipeline” is used to describe the fact that a disproportionate number of female researchers never make it to the top levels of the academic hierarchy. In 2014 women comprised 60% of the PhD-students but only 13% of the professors at Department of Clinical Medicine. In 2020 these numbers were 64% and 21%. This shortage of female researchers at the higher echelons translates into a serious loss of talent and a lack of diversity when it comes to research.

Aims: In order to gain insights into some of the barriers female researchers face at Department of Clinical Medicine, this project addresses three research questions:

1) How are visibility conceptualized and perceived in relation to career advancement?

2) How do sponsorships emerge, how are they structured, and what role do they play in career advancement?

3) How are the current recruitment and hiring praxis experienced and perceived?

Methods: The project is designed as applied anthropology, as the aim is to create empirically grounded knowledge that can inform future action. The ethnographic fieldwork of the project mainly comprises of participant observation and qualitative interviewing.

Conclusion and Perspective: The perspective of the project is to provide a model for the future - a model that will ensure that less female talent is lost on the way to the top. Because of its size and internal variations in structure and culture Department of Clinical Medicine provides the ideal arena for studying the leaky pipeline.

Keywords: Qualitative research, Work environment and organisation, Other

Exercise and neuroprotection in older persons with multiple sclerosis

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Background: Over the past 2-3 decades, the prevalence of multiple sclerosis (MS) has increased, with the most prominent increase found in individuals aged ≥60 years. This poses several challenges for the individual pwMS as both aging and MS lead to neurodegeneration and disability. Interestingly, exercise studies have indicated that neurodegeneration and disability progression can be reduced, hereby providing a possible supplement to established medical treatment of MS. Resistance exercise with heavy load and rapid movements (i.e. power training) appear particularly beneficial in terms of improving healthy elderly's neuromuscular function (e.g. muscle strength) as well as physical function (e.g. walking capacity). However, these effects have not been studied in older pwMS.

Purpose: The primary aim is to investigate whether 24 weeks of power training has neuroprotective effects among older pwMS through a randomized controlled study. The secondary aims are to investigate whether power training can improve neuromuscular function and physical function as well as positively affect blood biomarkers of neurodegeneration.

Hypothesis: It is hypothesized that 24 weeks of power training can reduce whole brain atrophy, improve neuromuscular function and physical function, and positively affect blood biomarkers of neurodegeneration.

Methods: Older pwMS (≥60 years) will be randomized to either a power training group (24 weeks, 2 sessions/week) or a control group. Assessments will be carried out at baseline, after 24-week intervention, and after 24-week follow-up. Assessments includes brain and leg MRI scans, blood samples, neuromuscular testing, and physical function testing.

Keywords: Rehabilitation, Clinical neuroscience, Other

Study protocol: Randomized controlled trial investigating if exercise booster sessions can preserve exercise induced effects over time in patients with multiple sclerosis.

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H. Dawes, Faculty of Health and Life Sciences (Oxford Brookes University)

U. Dalgas, Department of Public Health,

Background: Exercise therapy has long been acknowledged as a promising supplemental treatment strategy in 26 different chronic diseases, including multiple sclerosis (MS). For exercise therapy as for medical drugs – you have to follow the prescriptions. One needs to take the right dose at the right time, and you have to take the medicine as long as it is needed, in order for the medicine to be effective. Despite the many positive effects of exercise therapy as a treatment strategy, one of the remaining challenges is, that is difficult to sustain the positive exercise induced effects over time.

Methods: This project is a national, multicenter, randomized 4-armed controlled trial. The primary purpose is to investigate the effects of exercise booster sessions (EBS) (supervised, high intense, low frequent exercise sessions) on physical function over a period of 40 weeks, in the wake of a 12-week exercise intervention being either aerobic or resistance training.

The primary outcome is a composite score including the six-minute walk test and the timed up and go. Secondary outcomes will be health economic analyses, quality of life, fatigue and physical activity level.

Hypothesis: The hypothesis is that EBS will increase the sustainability of the exercise-induced effects after follow-up compared with patients receiving usual care.

Discussion: If we find that EBS are an effective way of preserving exercise induced effects, we believe this can pave a new way forward in the field of rehabilitation that will benefit both the individual patient (i.e. better maintenance of exercise effects) and the society (i.e. reduced healthcare costs).

Keywords: Rehabilitation, Public health, Other

Health Literacy in Pregnancy; the HeLP project

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A. Peeters, Deakin University, Melbourne, Australia

Background: World Health Org. suggests addressing health literacy in preventive efforts to accommodate social inequality in health, a factor increasing among pregnant women. Health literacy is the combination of personal skills and resources in the surroundings, which determine a person's possibility to access, understand, evaluate and apply information and health services in order to make decisions about health. The HeLP project is designed to systematically investigate pregnant women's health literacy levels.

Aim: The objective of HeLP is to investigate pregnant women's health literacy levels and associations between health literacy and development of complications in pregnancy and birth (among others: Gestational Diabetes Mellitus (GDM), obesity, preeclampsia, premature birth, epidural analgesia and c-section).

Method: We recruit pregnant women attending prenatal care at Aarhus University Hospital (approx. 5000 births a year) or the Regional Hospital in Viborg (approx. 2200 births a year) for study participation. Recruitment proceeds via e-box, midwifery clinics, diabetes ambulatories, or organizations helping vulnerable pregnant women. We collect health literacy data through the questionnaire, HeLP-Q. Complication data are collected from electronic patient journals post birth. Associations are analyzed in fitted regression model.

Perspectives: The Danish Health Authority recommends a four-level division in antenatal care in order to secure the necessary support in relation to obstetric, social and psychological risk factors. Health professionals require new knowledge in order to identify vulnerable pregnant women, and differentiate antenatal care services.

Keywords: Socio-economic conditions, Health education and simulation-based training, Public health

Exposure levels and early health effects when recycling municipal waste: The RECYCLE-project

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BACKGROUND

In Denmark, more waste is produced, an increasing proportion is recycled, and the number of employed in the recycling industry has increased. International studies have documented harmful chemical and biological exposure levels, but there is limited knowledge in the Danish industry. This study aims to investigate chemical and biological work exposures during recycling of municipal waste and early health effects.

METHODS

This project investigates employees from sorting and recycling companies in Denmark. Exposure measurements include levels of inhalable dust, endotoxin, microorganisms, and microplastics in air and tar substances measured with personal samplers and metals in blood and urine. Associations with inflammatory markers in blood, lung function, and gastrointestinal, eye, and skin symptoms will be analyzed in statistical models including a non-exposed control group of administration workers of each company.

RESULTS

Data collection is just finished and includes 12 companies and 102 participating employees. Respirable dust, endotoxin, blood and urine samples, lung function, and gastrointestinal, eye, and skin symptoms were obtained from all participants. Levels of tar substances, microorganisms, and microplastics were only measured on participants working with electronic/hazardous (N=33), fractions contained with organic material (N=60), and post-treatment of plastic (N=11), respectively. Around 70 % of the participants were measured twice.

DISCUSSION

In the next step, I will analyse all data and estimate the generic differences between the exposed and the non-exposed group, waste fractions, type of company, and associations with different health outcomes.

Keywords: Work environment and organisation, Epidemiology and biostatistics, Other

Uric acid is elevated in children with obesity and decreases after weight loss

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Introduction: Childhood obesity may be associated with continuous obesity into adulthood and development of obesity-related comorbidities. In adult, studies have demonstrated an association between circulating levels of uric acid (UA), body mass index (BMI), and the development of type 2 diabetes and the metabolic syndrome. The aim of the current project was to investigate the relationship between UA in children and adolescents with obesity, involved in a municipality-based lifestyle intervention.

Methods: One hundred and seventy-one children (age 4-18), with a body mass index standard deviation score (BMI-SDS) of +2 or higher were included in a multifactorial lifestyle intervention. The intervention was a collaboration between the families, community healthcare workers and the regional hospital. The children who participated, were annually invited to the hospital for anthropometrics, blood samples and DEXA-scans for up to 3 years. In between, the children were seen up 8 times per year by a community healthcare worker. Eighty-nine children were included for follow-up analysis.

Results: After a follow-up of 20.7 ± 9.4 months a reduction in BMI-SDS of -0.34 ± 0.53 ($p < 0.01$) was observed. In parallel, UA was found to be positively associated with changes in BMI-SDS. UA levels decreased in the 76 children who lost weight during the intervention, conversely, UA increased in the 23 children who gained weight during the intervention ($p < 0.01$ between groups).

Conclusion: Interestingly, UA was found to correlate with measures of childhood obesity, and for the first time demonstrates a positive relationship between weight reduction in children with obesity and changes in UA.

Keywords: Paediatrics, Public health, Epidemiology and biostatistics

Maternal age at menarche and semen quality in young men: a nationwide cohort study

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Male reproductive health is of increasing public health concern. About 50 % of Danish men have suboptimal sperm counts, and only few risk factors are known. Age at menarche (AAM) marks the beginning of the female reproductive lifespan. Studies suggest that earlier AAM increases the blood level of estrogen throughout the fertile age. Increased in utero exposure to estrogen is hypothesized to affect the spermatogenic capacity due to estrogen-triggered downregulation of follicle-stimulation hormone causing a reduction of fetal Sertoli cell proliferation which is crucial for spermatogenesis in adulthood.

We hypothesize that earlier maternal AAM causes lower semen quality and skewed levels of reproductive hormones in adult sons.

This cohort study uses prospectively collected data from 1,058 young men in Fetal Programming of Semen Quality, which is a sub-cohort nested within the Danish National Birth Cohort.

Information on maternal AAM was collected through telephone interviews during pregnancy, and semen and blood samples were provided by sons aged 18 years or older. The association between maternal AAM and semen quality and reproductive hormones will be analyzed using a multivariable negative binomial regression model. To account for potential selection bias, selections weights will be applied in all models.

Results are pending and will be presented at the PhD Day.

Our study adds novel knowledge on the possible mechanisms underlying reproductive health across generations and contributes with insight into the potential downward trend in human reproduction.

Keywords: Public health, Epidemiology and biostatistics, Gynecology and obstetrics

Flash talk session 6

Treatment effect of immune checkpoint inhibitors and prognostic biomarkers of metastatic mucosal melanoma – a retrospective evaluation

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Mucosal melanoma patients have a poor prognosis due to late diagnosis and low treatment response. However, little is known about the efficacy of treating metastatic mucosal melanoma patients with immune checkpoint inhibitors (ICI). Moreover, knowledge on predictive and prognostic biomarkers is very limited. This study investigates the efficacy of ICI treatment and potential predictive and prognostic biomarkers of metastatic mucosal melanoma.

The study is retrospective and based on data from the Danish Metastatic Melanoma Database. 66 metastatic mucosal melanoma patients treated with ICIs in the period 2014-2021 in Denmark will be included in the study. Additionally, available diagnostic tumor tissue samples will be stained for potential biomarkers such as PD-L1 expression, neutrophil infiltration and macrophage infiltration. Data will be analyzed with survival analysis using endpoints such as overall survival (OS) and progression free survival (PFS).

The expected publication will focus on the value of ICI treatment in metastatic mucosal melanoma patients, and on the prognostic and predictive significance of tissue biomarkers. This knowledge may aid the selection of patients who respond to ICIs.

Keywords: Oncology, Inflammation, Other

Metabolic control of oncovirotherapy in Nrf2-addicted cancer cells

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Cancer is a leading cause of mortality and current therapeutic approaches are all associated with significant side effects and resistance to therapy. Nuclear factor erythroid 2-related factor 2 (Nrf2), a master regulator of redox homeostasis, is frequently activated in cancer cells giving rise to Nrf2 addiction in specific tumor subsets. Dysregulation of Nrf2 activity results in aggressive tumors and correlates with resistance to therapy. We have recently demonstrated that Nrf2 plays an important role in restricting antiviral immunity in A549 lung cancer cells, a subset of cells known to constitutively activate Nrf2. Here, we hypothesize that the modulation of host metabolism provides a selective niche for oncolytic virus replication and action in Nrf2-addicted cancer cells. Using RNA sequencing and chromatin immunoprecipitation assays in A549 cells, we uncovered novel Nrf2-regulated metabolic genes including glucose-6 phosphate dehydrogenase (G6PD), phosphogluconate dehydrogenase (PGD), and lactate dehydrogenase A (LDHA), involved in either the pentose phosphate or glycolysis pathway. Interestingly, silencing G6PD using a small interfering RNA approach influenced the replicative capacity of VSVdM51, a genetically modified oncolytic virus, in A549 cells. Following, the link between rewired metabolism and antiviral response in Nrf2-addicted cancer cells will be further investigated. Notably, deciphering the metabolic mechanisms that render Nrf2 addicted cancer cells defective in antiviral activity, hence sensitive to viral infection will significantly advance our knowledge on the biology of these hard to treat cancer cells and open new therapeutic options for patients.

Keywords: Infection, Oncology, Molecular metabolism and endocrinology

The role of resident TIM4+ tumor-associated macrophages in epithelial ovarian cancer

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Epithelial ovarian cancer (EOC) is characterized by early metastatic spread, and many cases are discovered in stages with disease progression beyond the ovary. There is desperate need for treatment options for patients with EOC and metastatic disease to improve clinical outcome. Macrophages are the most abundant non-cancerous cell type in the tumor-microenvironment (TME), and the tumor-associated macrophages (TAMs) contribute to tumor progression by promoting immunosuppression, tumor growth, angiogenesis and metastasis. The TAM population is heterogenous and single cell RNA-sequencing (scRNA-seq) of TAMs from high grade serous ovarian cancer patients revealed 7 distinct TAM phenotypes. We aim to understand the Tim4+ TAM populations, and how they contribute to progression of EOC. We hypothesize that the Tim4+ TAMs are a heterogenous population with distinct functions, that depend on location in the tumor. By using an orthotopic mouse model and patient samples, scRNA-seq will be used to establish ortholog TAM phenotypes, while also identifying markers used to separate TAM clusters. High multiplex tissue imaging proteomics will be used to analyze the spatial location of TAM populations, in relation other cells in the TME, as well as blood vessels and the invasive front. Functional analysis of the Tim4+ TAM clusters identified with scRNA-seq, will identify a TAM population relevant for depletion from the TME. Subset specific depletion will be achieved by using cytotoxic antibody-labeled lipid nano particles. Employing subset specific targeting of Tim4+ TAM populations on orthotopic murine models will help evaluate Tim4+ positive macrophages as a relevant therapeutic target.

Keywords: Oncology, Animal models/disease models, Inflammation

Association between tumor immune response and risk of recurrence in breast cancer patients treated with radiotherapy

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Background:

Radiotherapy (RT) reduces risk of loco-regional recurrence and improves overall survival (OS) in breast cancer (BC). High level of tumor infiltrating lymphocytes have been shown to be associated with an improved OS benefit after RT in BC patients. It is unclear, if the association is dependent on specific immune cells (IC). The aim of this PhD study is to investigate, if presence and/or composition of IC in treatment naïve tumor tissue is associated with risk of recurrence in BC patients treated with RT

Materials:

The study is planned as a case-control study (237 cases with recurrence: 711 controls without recurrence) based on three Danish Breast Cancer Group cohorts of patients treated with various RT regimes. Tumor tissue from primary tumor and recurrences will be collected from all 948 patients, and clinical outcome data will be obtained

Study 1: Composition of specific IC in primary tumors of various subtypes will be characterized using multiplex immunohistochemistry and digital image analysis

Study 2: In the 237 cases, differences in immune response and subtype in corresponding pairs of primary tumor and recurrences will be examined. In a subgroup of patients, gene-expression analysis of specific immunogenic pathways will be performed

Study 3: Results from the histopathological analyses will be correlated with clinical outcome data for all patients to examine associations between the immune response in primary tumor and risk of recurrence

Perspectives:

If the immune response in treatment naïve tumor can predict clinical outcome in BC patients, it may lead to more individualized treatment and possible modification of treatment guidelines.

Keywords: Oncology, Cell biology, Other

Investigation of the prognostic value and functional roles of circular RNAs in Multiple Myeloma

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Multiple Myeloma (MM) is the second most common hematological malignancy. MM is becoming increasingly more common, and while several novel therapies have resulted in an improved life expectancy of patients, MM remains an incurable disease as most patients experience relapse. Therefore, we need a better understanding of the pathophysiology behind MM relapse to identify novel molecular markers with prognostic and predictive value. Consequently, we will in this project investigate the clinical potential of a new type of non-coding RNA, namely, circular RNAs (circRNAs) in MM pathophysiology.

To examine the role of circRNAs in MM, we have first conducted RNA-Seq of rRNA depleted total RNA from 43 MM patient samples taken at diagnosis. In addition, we will perform transcriptomic analyses of paired diagnosis/relapse samples from patients enrolled in a prospective collection initiated as part of this project. Relevant circRNAs will be further studied in cell culture using gain- and loss-of-function assays and visualized using circRNA-specific in situ assays, and epigenetic modifications in enhancer and promoter regions of circRNA host genes will be studied to investigate driver events behind aberrant circRNA expression.

Through these data, we expect to identify individual or panels of circRNAs with prognostic or predictive value in MM as we will correlate the expression of circRNAs with overall survival and time to relapse. We will evaluate if expression profiles of circRNAs can improve the treatment guidelines currently used in the clinic. Preliminary data will be presented at the conference.

Keywords: Oncology, Cell biology, Genetic engineering

Obesity, type 2 diabetes, and breast cancer prognosis

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Introduction: The prevalences of obesity, type 2 diabetes (T2D), and breast cancer (BC) are on the rise. Obesity and T2D are associated with an impaired prognosis in BC patients. However, the associations, including biological explanations, are incompletely mapped. This study aims to advance knowledge regarding the interplay between obesity, T2D, and BC investigating baseline circulating levels of obesity- and T2D-related biomarkers (e.g. IL6, MCP1, and TNFα). Methods: All female BC patients (stage I-III) seen at the Dept. of Plastic and Breast Surgery, Aarhus University Hospital between Mar 1st, 2010 and Aug 31st, 2020 were invited (N=4,190). Blood samples were ascertained at diagnosis and stored at the regional biobank. We have retrieved all samples for analysis of levels of the biomarkers. Baseline and prospectively collected follow-up data are ascertained from medical records and the Danish Breast Cancer Group (DBCG) database. We will examine the association of baseline levels of each biomarker with disease-free and overall survival. Results: After enrolment, 851 patients were excluded. Four patients withdrew their consent, 194 are not registered in DBCG, 283 presented with carcinoma in situ only, 90 had a previous cancer history/co-existing cancer, and 280 were registered in DBCG before Mar 1st, 2010. In total, 3,339 patients constitute the final study cohort. Further preliminary results will be presented at the PhD Day. Conclusions: This study will enhance the knowledge of the association between obesity, T2D, and BC. The study is expected to promote identification of the patients likely to have an inferior prognosis, who may benefit from heightened clinical care.

Keywords: Oncology, Epidemiology and biostatistics, Other

Future perspectives: molecular insights on the adverse effects of genotoxic chemotherapy in healthy and cancer genomes.

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Genotoxic chemotherapy induces mutations, stalls replication, and causes death in cancer cells. However, the systemic treatment also affects healthy tissues, specifically hematopoietic stem cells (HSCs) appear vulnerable, as cytopenia is a common adverse effect. The surviving HSC populations will likely accumulate additional mutations after each round of therapy. Consequently, systemic genotoxic chemotherapy may accelerate somatic evolution and, eventually, secondary cancer development. Despite their broad use as anticancer drugs, little is known about their mutagenic effects in healthy cells.

Here, we propose to evaluate the burden of mutations induced by 5-fluorouracil and oxaliplatin in HSCs from colorectal cancer patients. As we are still early in the process, we currently plan to address this in three datasets from two separate settings: (1-2) longitudinal blood samples from patients before, during, and after genotoxic chemotherapy; and (3) blood and tumor samples from patients with secondary hematological cancers. Our initial analysis will rely on detecting therapy-induced mutations in whole-genome sequenced circulating free DNA from the longitudinal blood samples. Specifically, we will quantify mismatches at expected sites of therapy-induced damage to evaluate the total therapy-induced mutation burden. We will exploit

information of therapy-dosis to establish a dose-response relationship that may predict the mutation burden in healthy cells. Better knowledge of the risk of genotoxic chemotherapy may affect cancer care, especially concerning the younger age segments (<50 years), where somatic mutations are expected to have the highest impact on future cancer risk.

Keywords: Oncology, Cell biology, Pharmacology

E-learning in cross-sectorial cancer rehabilitation

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Background: More people survive cancer and have a special need for rehabilitation, which should be managed across sectors in the healthcare system. Using an e-learning programme, information is available to patients whenever they have the need for it or feel motivated to explore and learn. If relatives use the same platform, e-learning becomes a valuable and shared source of knowledge. However, the experience and knowledge outcome of using e-learning rehabilitation programmes in people with cancer and their relatives have only been scarcely studied.

Purpose: Using the existing e-learning programme 'Life with and after cancer' as a case, the purpose is to explore if and how an e-learning platform can strengthen cross-sectorial rehabilitation and support patients' and relatives' management of daily life challenges during and after cancer treatment.

Method: The project employs mixed qualitative methods: initial interviews combined with ethnographic observation while patients and relatives navigate the e-learning programme and individual in-depth research interviews. Moreover, focus group interviews with healthcare professionals from hospital and municipalities will gain insight into their use of and referral to the e-learning programme.

Results: Knowledge from the project will support development and organization of future cancer rehabilitation initiatives in an internet-based context, elucidating the experience of use and potential barriers to e-learning. Given the cross-sectorial anchoring of the project, the project aspires to develop new models and strategies for e-learning in cancer rehabilitation that may be implemented broadly across the Danish Regions.

Keywords: Oncology, Rehabilitation, Qualitative research

Assessment of local toxicity and doxorubicin and doxorubicinol concentrations in various tissues after local and systemic administration

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Doxorubicin is a chemotherapeutic agent used to treat a wide range of cancers, here amongst osteosarcoma. In vivo experimental studies have shown a dose-response relationship between chemotherapeutic dose and tumor control, suggesting that optimal effect is attained at certain intratumorally chemotherapeutic concentrations. However, the dosage of doxorubicin is calculated based on patient body surface area and adjusted after toxicity, and very little is known about local tissue concentrations. A major dose limiting factor is cardiotoxicity, which is ascribed to the metabolite doxorubicinol. Of utmost interest is also the possibility of local treatment, which potentially can increase local treatment effect and lower systemic toxicity.

The aim of this PhD is to measure the concentrations of doxorubicin and doxorubicinol in orthopaedic relevant and toxicity-related tissues (plasma, subcutaneous tissue, muscle, bone and heart tissue) by the use of microdialysis after both systemic and local administration, as well as to explore the potential of local treatment. Microdialysis allows for a dynamic extraction of molecules providing tissue specific pharmacokinetic profiles. Furthermore, biopsies and cardiac biomarkers will be taken in order to evaluate toxicity. Measurements will be done in both a porcine model and in a clinical setting.

The concentration of doxorubicin and doxorubicinol in dialysates and plasma samples will be estimated by the use of ultra-high-performance liquid chromatography (UHPLC).

The ambition is that the data will give ground for an evaluation of the current treatment regimens in order to optimize treatment effect and lower systemic side effects.

Keywords: Oncology, Orthopedic surgery, Pharmacology

Identification and Characterization of Circular Stable Intronic RNAs in Bladder Cancer

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The majority of transcriptional output in humans is intronic. Its functional role is increasingly appreciated as more intron-derived noncoding RNAs continue to be discovered. Circular stable intronic sequence RNA (circular sisRNA) is a lowly expressed subgroup derived from excised lariats and have been shown in some instances to regulate host-gene transcription level. However, broad identification and characterization of circular sisRNAs are still lacking. Here, we analyze circular sisRNAs in comprehensive total RNAseq data sets and evaluate their biomarker potential in cancer.

We identified 9,132 circular sisRNAs in a local cohort of 457 non-muscle invasive bladder cancer samples. Intriguingly, they could be divided into two distinct groups; intronic circles spanning from the 3' splice site to the 5' splice site (27%) and stable lariats spanning from the branch point to the 5' splice site (73 %). Overall, they are lowly expressed (96% supported by four or less junction reads), with a median length of 983 bp for the intronic circles and 662 bp for the stable lariats. The circular sisRNAs are further found to be expressed in a tissue specific manner, and to be present in both nuclear and cytoplasmic cell fractions.

Clinically, we found that circular sisRNAs generally were upregulated in a risk class with good prognosis compared to one with poor prognosis. We found that progression-free survival rate significantly associated with the expression level from the most abundant circular sisRNA expressed by HNRNPK. Interestingly, the mRNA expression level of HNRNPK itself did not correlate with survival.

Keywords: Other, Oncology, Public health

Flash talk session 7

Investigation of the Association Between Maternal Obesity, the Expression of Low Density Receptor-Related Protein 1 (LRP1) in Placental Villi, Maternal Serum Levels of Pro-Inflammatory Cytokines and Vitamin D

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Obese women have an increased risk of pregnancy complications, like pre-eclampsia, when compared to normal weight women. Many pregnancy complications have been suggested to relate to a dysfunctional placenta, but the underlying biological mechanism is not fully understood. Data from our research group demonstrate increased expression of Low Density Receptor-Related Protein 1 (LRP1) in first trimester placentas from obese women. Importantly, LRP1 expression is also significantly increased in placentas from women that later had pre-eclampsia. In vitro experiments further show that LRP1 expression is upregulated by stimulation with proinflammatory cytokines. This also connects to maternal weight since other studies have established a link between obesity and increased levels of pro-inflammatory cytokines. This project investigates if placental LRP1 expression from obese women remains increased at term and examines the relation with serum levels of pro-inflammatory cytokines.

Vitamin D deficiency is a well-described risk factor for pre-eclampsia. Therefore, as part of a clinical trial investigating the possible benefits of increased vitamin D supplementation in pregnancy, this project also investigates the potential effects of vitamin D on placental biology. Specifically, investigating if vitamin D supplementation can reduce pro-inflammatory signals and affect LRP1 expression.

Patients were recruited at Randers Regional Hospital at approximately 12 weeks of pregnancy and blood samples were taken at time of inclusion. Placental samples were collected within 5 hours after birth and placental gene and protein expression of LRP1 are analysed through RT-qPCR and immunoblotting.

Keywords: Gynecology and obstetrics, Laboratory science, Inflammation

Risk of progression of cervical intraepithelial neoplasia grade 2 (CIN2) by human papillomavirus (HPV) vaccination status

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Background: Persistent infection with human papillomavirus (HPV) can lead to cervical precancer (cervical intraepithelial neoplasia, CIN) and cervical cancer. CIN is graded as CIN1 (mild), CIN2 (moderate), and CIN3 (severe). In most countries CIN2 is treated with a cone biopsy, but in Denmark women of reproductive age are recommended semi-annual follow-ups since a cone biopsy is associated with increased risk of preterm birth. Yet, some women with CIN2 will progress to CIN3 or cancer (CIN3+) and the challenge is to identify these women. HPV-vaccinated women are less likely to develop cervical cancer due to prevention of infection with the most oncogenic HPV types. Hence, we hypothesize a lower risk of progression of CIN2 among HPV-vaccinated women since they are infected with less risky HPV types (which are not included in the vaccines). To our knowledge, the effect of HPV vaccination on risk of progression of CIN2 has not yet been investigated.

Aim: To investigate whether HPV-vaccinated women diagnosed with CIN2 are less likely to progress to CIN3+ compared to unvaccinated women.

Methods: By using several health registers, we will conduct a nationwide population-based cohort study in Denmark of all women diagnosed with CIN2 between 2010-2020. We will retrieve information on HPV vaccination, socioeconomic status, and other important covariates. To estimate the rate of progression to CIN3+ by vaccination status, we will collect information on all subsequent cervical samples.

Perspectives: Our study will provide clinicians with important information that may be useful in clinical counselling. Moreover, the study will contribute with further knowledge about HPV vaccination.

Keywords: Gynecology and obstetrics, Oncology, Infection

Generation of in vitro-grown human eggs

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Approx. 10% of Danish children are born after assisted fertility treatment. Most of these treatments use hormones to increase the number of follicles to enhance the success rate. The challenge is that the hormones only act on ovarian follicles already started to mature. For many infertile women, the cause is at an earlier follicle developmental stage (the dormant follicles), and the pool of dormant follicles does not respond to the hormones. Thus, more information about the mechanisms supporting the growth of these dormant follicles could improve fertility treatment. Previously, dormant follicles from human ovarian tissue have been grown to obtain mature eggs in the laboratory (in vitro), but more information about the quality of these eggs is needed. This project aims to accomplish the growth of dormant human follicles to obtain mature eggs in vitro and compare the quality of these eggs with hormone-treated eggs.

Ovarian tissue is obtained during operative laparoscopy and cultured using a recently described multi-step culture system. The in vitro growth of dormant follicles to get mature eggs is currently ongoing. We also collect eggs from women receiving hormone-based fertility treatment. Finally, we aim to perform RNA-sequencing to compare these collected eggs with the laboratory-grown eggs.

Accomplishing in vitro growth of human follicles may be beneficial for women who cannot receive autotransplantation of cryopreserved ovarian tissue due to the risk of reintroducing malignancies. It could also serve as a model to investigate the effect of potentially harmful treatments or the mechanisms underlying the activation of dormant follicles and the development of mature eggs.

Keywords: Laboratory science, Gynecology and obstetrics, Cell biology

Altruistic surrogacy and involuntarily childlessness in Denmark - is it time for rethinking?

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The aim of this study is to form an interdisciplinary, systematic, in-depth basis of a near-future revision of the existing Danish surrogacy law from 1980s, as it has been shown to create social inequalities for the permanently involuntarily childless (PIC), who despite assisted reproductive technology do not obtain a child.

There is little knowledge regarding the annually 2-3000 Danish permanently involuntarily childless (PIC). This mixed-methods study using in-depth interviews and questionnaires will elucidate possible social and psychological implications of childlessness, experiences and attitudes towards surrogacy, and the impact of social inequality among PIC in relation to using alternative reproductive strategies.

The results from the study of the Danish PIC combined with a transnational comparison of the management of altruistic surrogacy in two European countries, are likely to be used in drafting of the new fertility legislation. This legislation is intended to reflect the societal and technological developments through the last 30 years ensuring a higher degree of social equality.

Keywords: Gynecology and obstetrics, Qualitative research, Socio-economic conditions

Sentinel lymph node mapping with robotic assisted near infra-red fluorescent imaging in women with endometrial cancer (SENTIREC)

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Introduction: Sentinel node (SN) mapping has proved efficient for early stage low-risk endometrial cancer (EC), with increased sensitivity to detect lymph node metastases (LNM). However, implementation of SN mapping to this group will lead to extended surgery, and limited evidence exists on how this will affect lymphoedema and survival. For women with early stage high-risk EC, the implementation of SN mapping remains controversial.

Aim:

For women with low-risk EC, to asses:

I. The SN detection rate and the incidence of LNM, besides the long-term effect on recurrence and survival.
II. The effect of SN mapping on the incidence and grade of lymphoedema.

For women with high-risk EC, to asses:

III. The accuracy of SN mapping alone and combined with F-18-FDG-PET/CT imaging.
IV. The effect of SN mapping combined with pelvic and para-aortic lymphadenectomy on the incidence and grade of lymphoedema.

Materials and methods:

Both studies are national prospective studies.

I. Women with low-risk EC

SN mapping is performed following a surgical algorithm. All women complete validated questionnaires on lymphoedema and quality of life before surgery and 3, 12, 24 and 36 months post-surgery.

II. Women with high-risk EC

All women undergo FDG-PET/CT before surgery. SN mapping is followed by removal of FDG positive lymph nodes and standard surgery with radical lymphadenectomy.

Results: Four gynaecological cancer centres participate. In study I 288 of 350 women are included. In study II 157 of 250 women are included, 25.10.21.

Conclusion: We expect this project to provide high quality data with substantial significance in future shared decision making for the surgical treatment of early stage EC.

Keywords: Gynecology and obstetrics, Other, Other

Improved diagnosis of ovarian cancer

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Background:

Preoperative differentiation between benign and malignant ovarian masses is a clinical challenge. Correct treatment-choice depends on optimal use of available imaging modalities in combination with the tumour marker CA 125. Ovarian masses are primally diagnosed by non-expert ultrasonography. The accuracy of the currently used diagnostic model Risk of Malignancy Index (RMI) is insufficient. New models by use of International Ovarian Tumour Analysis (IOTA) terms at ultrasonography and/or ADNEX-MRI at MRI may improve the diagnostic efficiency, but the methods need validation. Magnetic Resonance Imaging (MRI) or expert ultrasonography can be used as a second-line tool for improved characterization.

Methods:

We will compare and validate methods for discrimination between benign and malignant ovarian masses by ultrasonography and MRI in a diagnostic cohort study. Gynecologists and radiologists in Central Denmark Region are introduced to IOTA terms for evaluation of ovarian masses. Findings at ultrasonography and MRI are recorded systematically according to IOTA terms. RMI and IOTA risk estimates are calculated and compared. A systematic ultrasonography in women with suspected malignancy is evaluated by experienced ultrasonographers, and this expert-ultrasonography is compared to MRI. Reference standard is histopathological diagnosis.

Results:

The area under the ROC curves, sensitivities and specificities, positive and negative predictive values will be compared. Observer variation is calculated.

Conclusions:

We aim to rapport a realistic optimal use of available imaging methods for diagnosis of ovarian cancer in the hands of clinicians in Central Denmark Region.

Keywords: Gynecology and obstetrics, Medical technology and diagnostic techniques, Oncology

The vicious cycle of obesity – association between maternal weight and health, fetal growth and childhood overweight

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Background and aim

The prevalence of childhood obesity is increasing in Denmark and world-wide. Many overweight children and adolescents remain overweight their entire life, putting them at increased risk of morbidity.

Genetics and maternal health before and during pregnancy, fetal growth, nutrition and family socioeconomics all have an impact on the risk of childhood overweight but the interaction and timing of growth and overweight remain largely unexploited.

We aim to investigate these causes of childhood overweight and their relation to later risk of overweight or obesity in the child and explore the importance of timing of overweight.

Material and methods

By a unique combination of data on maternal health and fetal ultrasound scans collected during pregnancy and data collected on children by specialty child health nurses during home-visits in Aarhus, we have information on 40.000 children and their families. We will explore the effects of fetal growth, maternal diabetes, pre-pregnancy weight, gestational weight gain and breastfeeding on childhood overweight and explore the importance of interplay and timing of these predictors.

Results

First results expected in spring 2022.

Conclusions and discussion

We expect to gain new knowledge on the early life predictors and causes of childhood overweight. This will in the future help targeting interventions both during pregnancy and in young children to prevent the development of overweight.

Keywords: Gynecology and obstetrics, Epidemiology and biostatistics, Paediatrics

Stigma among women diagnosed with gestational diabetes mellitus – Experienced discrimination, self-blame and health consequences

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Background: Gestational diabetes mellitus (GDM) affects almost 5% of pregnant women in Denmark today. Studies suggest that women with GDM may experience stigma related to their condition in terms of discrimination and self-blame. Yet, GDM-specific stigma research is scarce and the scope, role and influence of GDM stigma remain unknown.

Aim: This PhD-project aims to study GDM-specific stigma. Specifically, to; 1) investigate women with GDM's experience with GDM-specific stigma 2) validate a measurement of internalised GDM-specific stigma 3) describe the extent and determinants of internalised GDM-specific stigma and 4) examine potential associations between internalised GDM-specific stigma and indicators of adverse health outcomes.

Methods: Semi-structured interviews with women with GDM (aim 1) will be recruited and interviewed from Danish hospital departments specialised in GDM care. The women will be included based on purposive sampling and will be of different sociodemographic backgrounds and treatment regimes. Questionnaire validation methods and regression modelling (aims 2-4) will be applied on data from the ongoing Face-it project. The analyses will be based on approximately 225 women's health and questionnaire data.

Impact: By investigating GDM stigma, this project will provide knowledge needed to improve quality of care for women with GDM and offer novel insights for developing future interventions. Investigating determinants associated with stigma as well as associations between GDM-specific stigma and adverse health outcomes, will also help us to improve prevention of GDM-specific stigma and optimise treatment of adverse health outcomes associated with stigma.

Keywords: Public health, Qualitative research, Epidemiology and biostatistics

Early prevention and predictors of obesity in children exposed to gestational diabetes during pregnancy

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K.K. Nielsen, Department of Health Promotion Research, Steno Diabetes Center Copenhagen;

H.T. Maindal, Department of Public Health, Aarhus University and Department of Health Promotion Research, Steno Diabetes Center Copenhagen

Background:

Children exposed to gestational diabetes (GDM) during pregnancy are at high risk of developing obesity and a dysmetabolic profile throughout life. Early life is a window of opportunity for obesity prevention, but so far, pre- and postnatal interventions have shown disappointing long-term results. Moreover, existing knowledge on heterogeneity in growth patterns, the complexity of predictors and strategies on obesity prevention is limited. Therefore, this PhD aims to investigate risk- and protective factors of obesity development in children exposed to GDM during pregnancy to identify potential avenues for early prevention.

Methods:

The project includes three sub-studies: 1) A systematic review of pre- and postnatal interventions measuring childhood obesity in GDM exposed offspring, 2) A nationwide register-based study of data from the Children's Database investigating early childhood BMI growth trajectories and associated maternal and offspring predictors, and 3) A secondary effect evaluation of a health promotion intervention to women with prior GDM and their families (the Face-it study) on the child's obesity risk in the first year of life.

Impact:

This project will help to identify the existing literature and knowledge gaps needed to be examined by future research on obesity prevention in this high-risk group. It will provide insights into how BMI trajectories may differ, in order to reach those at certain high risk. Finally, the project will explore whether a family-based health-promoting intervention may affect the infant's growth. In a public health perspective, the project can potentially identify new approaches to prevent obesity in GDM exposed offspring.

Keywords: Public health, Epidemiology and biostatistics, Other

Flash talk session 8

Validity and reliability of VO2-max measurements in persons with Parkinson's disease

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Introduction: Direct whole body measurement of maximal oxygen consumption (VO2-max test) is the golden standard when assessing cardiorespiratory fitness (VO2-max) in healthy people. VO2-max is considered a good health indicator for persons with Parkinson's disease (pwPD). The VO2-max test is an effective tool to evaluate exercise interventions thereby supporting prescription of training recommendations. However, no study has examined the validity of the VO2-max test in pwPD and only one study has examined the reliability (in the ON medication state).

Purpose: To investigate the validity and reliability of the VO2-max test in pwPD both ON and OFF medication.

Methods: Twenty pwPD will complete four VO2-max tests (two ON and two OFF medication), in a randomized order, on a bicycle ergometer. Each test day is separated by seven to ten days. The first tests in the ON and OFF medication states are used to assess the validity of the test based on achievement of the following criteria: VO2 plateau (primary criterion), blood lactate level ≥8 mmol/L, rating of perceived exertion ≥17 on the 6-20 Borg scale, ≥90% of predicted maximal heart rate (HRmax) (HRmax = 208 - 0.7 x age) and a respiratory exchange ratio ≥1.15. Reliability is examined by comparing the day-to-day variation of the two ON and OFF medication tests, respectively.

Results: The ethical committee has accepted the study protocol and 15 pwPD have currently been recruited. The first participants have been invited to their first test.

Keywords: Cardiovascular system, Basic neuroscience, Other

Long-term risk of atrial fibrillation after transcatheter patent foramen ovale closure in patients with cryptogenic stroke: A nationwide population-based cohort study.

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M. Schmidt, Department of Clinical Medicine; J.E. Nielsen-Kudsk, Department of Clinical Medicine; K. Korsholm, Department of Clinical Medicine; L. Pedersen, Department of Clinical Medicine.

Introduction:

Patent foramen ovale (PFO) is an interatrial communication, meant to close after birth. It is prevalent in patients <60 years with stroke without an apparent cause and may act as a right-to-left shunt for paradox embolisms. Transcatheter closure of PFO is the recommended treatment and reduces the risk of recurrent stroke and major bleeding compared with antithrombotic therapy alone.

Postprocedural atrial fibrillation (AF) is a well-known adverse effect of PFO closure. However, little is known about the long-term risk of AF. This study sets out to examine whether PFO closure increases long-term risk of AF.

Methods:

We identified all Danish patients diagnosed with stroke/transient ischemic attack and a PFO during 1977-2017. Patients <18 years or with a prior diagnosis of AF were excluded. Follow-up started at PFO diagnosis. Exposure was defined as PFO closure and assessed in a time varying manner. Outcome was defined as a diagnosis of AF.

Using the Kaplan Meier estimator, we will compute risk estimates for study outcomes. Using Cox proportional-hazards regression, we will compute hazard ratios and 95% confidence intervals. We will stratify analyses by age, sex and calendar period.

Results:

Analyses are ongoing.

Conclusion:

This will be the first population-based study on long-term AF risk after PFO closure. Through improved knowledge of potential complications to PFO closure, this study will help improve clinical decision making for patients with cryptogenic stroke and PFO.

Keywords: Cardiovascular system, Epidemiology and biostatistics, Other

Project TG2: the role of TG2 in restoring vasodilation in resistance arteries in young and old patients with and without diabetes

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Professor Ulf Simonsen, Department of Biomedicine, Aarhus University

Professor Niels Henrik Buus, Aarhus University Hospital

Postdoc Estefano Pinilla Perez, Department of Biomedicine, Aarhus University

Background: Overactivation of the enzyme transglutaminase 2 (TG2) is involved in the development of endothelial dysfunction and vascular stiffness leading to vascular complications. However, the association between TG2-activity and age-related vascular dysfunction amongst diabetic and non-diabetic patients is unknown.

Aim: To investigate whether promotion of the closed conformation of TG2 restores endothelium-dependent vasodilatation in human resistance arteries, and if the expression and activity of TG2 is linked to ageing and diabetes.

Methods: We include patients undergoing surgery at the Department of Abdominal Surgery, Aarhus University Hospital. The patients will be stratified in adults (25-45 years) and elderlies (60-80 years), and then divided in diabetic and non-diabetic patients aiming for 25 patients in each group. The subcutaneous arteries from patients are mounted in wire myography, in order to assess the contractility of vascular smooth muscles. Comparison of the expression of TG2 in the patients will be studied with immunostaining and qPCR. The incorporation of a transglutaminase substrate, 5-(biotinamido)pentylamine to measure the transamidase activity will be determined with a dot blot assay.

Results: The study is ongoing, but preliminary results will be presented.

Conclusion: This study will generate new knowledge on the TG2 enzyme and its relation to vascular dysfunction in ageing and diabetes. Furthermore, the research results are hoped to contribute to improved treatment of diabetics, hypertensive and elderly patients by pharmacological modulation of the TG2 enzyme.

Keywords: Transglutaminase 2, Diabetes, Endothelial Function, Resistance Arteries, Ageing

Keywords: Pharmacology, Cardiovascular system, Other

Lung perfusion changes in patients with chronic thromboembolic pulmonary hypertension after balloon pulmonary angioplasty.

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Background:

Around 5% of pulmonary embolism survivors develop chronic thromboembolic pulmonary hypertension (CTEPH). It is an overlooked and serious disease with a 5-year survival rate of 10% if left untreated. CTEPH patients can be treated with balloon pulmonary angioplasty (BPA). This increases pulmonary perfusion in previously occluded areas of the lung instantly, unloading the right ventricle, but further changes over time have never been investigated. We aim to evaluate early and late changes in pulmonary perfusion after the BPA procedure using Dual Energy CT (DECT).

Methods:

This is a prospective clinical study with repeated measurements. Patients (n=17) will undergo 4 DECT scans. The 1st scan is done before the 1st BPA procedure. The 2nd DECT scan is done the day after, and the 3rd scan is performed 2 – 4 weeks later. The final scan is performed 3 months after the last BPA.

The primary endpoint is total, lung, and lobar blood volumes, automatically calculated from PBV maps using software.

Secondary endpoints are correlation between total, lung, and lobar blood volumes and invasive hemodynamics, biomarkers, and clinical parameters.

Perspectives:

If we gain a greater understanding of lung perfusion changes over time after BPA, it may be possible to reduce the number of procedures needed, reducing both peri- and post-procedural risks and complications.

Further investigating the feasibility of dual-energy CT in pulmonary vascular diseases may lead to better and faster diagnostics, better monitoring of treatment response, greater understanding of the diseases, and may reduce the need for specialist assessment.

Keywords: Cardiovascular system, Medical technology and diagnostic techniques, Other

Citizens' perspective on preventive medicine for cardiovascular disease: a qualitative study of follow-up phone calls

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Introduction

Cardiovascular disease (CVD) is the second highest cause of death in Denmark. Screening for CVD followed by initiation of preventive medicine clearly improves chances of survival. A better adherence of preventive medicine may further reduce the number of CVD events among those with screen-detected CVD. We need to know how to increase medical adherence to preventive medicine for CVD. Therefore, the aim is to examine if follow-up phone calls after one, three and six months after recommendation of preventive medicine increase medical adherence.

Methods

This study is nested in the VISP cohort (VIborg Screening Program, DK). VISP is offered to all 67-year-old citizens, and screens for CVD. Data was obtained through semi-structured interviews (follow-up phone calls) with 20 VISP participants with screen-detected CVD followed by recommendation of preventive medicine. Follow-up phone calls were made one, three and six months after VISP-participation. Ian Dey´s method for qualitative data analysis was applied.

Results

Participants' non-adherence to preventive medicine are affected by decisional ambivalence, difficulties in seeing personal benefit of the medicine, and the fear of getting severe side effects. Particularly the follow-up phone calls after one and three months provide the necessary support by giving the citizens the opportunity to answer questions of doubt and discuss any concerns regarding preventive medicine.

Conclusion

This project shows that follow-up phone calls after one and three mouths may increase medical adherence to preventive medicine for CVD. Follow-up phone calls after six months sparingly changes the citizen's decision and non-adherence.

Keywords: Cardiovascular system, Qualitative research, Public health

Prognostic value of fractional flow reserve using computed tomography for predicting major adverse cardiac events and mortality in kidney transplant candidates

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Background

In kidney transplant candidates cardiac screening using coronary computed tomography angiography (CCTA) yields both diagnostic and prognostic information. Whether additional CT-derived fractional flow reserve (FFRCT) analysis improves prognostic information is unknown. In the general population low FFRCT values are associated with ischemia.

Aims

To assess whether supplementary FFRCT can predict major adverse cardiac events (MACE) and all-cause mortality in kidney transplant candidates.

Methods

CCTA scans from 340 kidney transplant candidates were evaluated with FFRCT analysis. Patients were categorized into groups based on lowest distal FFRCT; normal >0.80, intermediate 0.80-0.76, and low ≤0.75. In patients with ≥50% stenosis on CCTA, a lesion-specific FFRCT was defined as; normal >0.80 and abnormal ≤0.80.

The primary endpoint was MACE (cardiac death, resuscitated cardiac arrest, myocardial infarction or revascularization). The secondary endpoint was all-cause mortality.

Results

Median follow-up time was 3.3 years [2.0-5.1]. MACE occurred in 28 patients (8.2%), 29 patients (8.5%) died.

In patients with distal FFRCT ≤0.75 MACE occurred more frequently compared to patients with distal FFRCT >0.80: Hazard Ratio (HR): 3.8 (1.5-9.7), p<0.01.

In the lesion-specific analysis with no stenosis as reference, patients with stenosis and FFRCT >0.80 had no increase in MACE, while patients with lesion-specific FFRCT ≤0.80 had a HR of 6.0 (2.5-14.4), p<0.01.

Abnormal FFRCT values were not associated with increased mortality.

Conclusion

In kidney transplant candidates FFRCT provides prognostic information, as abnormal values were associated with increased MACE but not mortality.

Keywords: Cardiovascular system, Nephrology, Medical technology and diagnostic techniques

PhD Protocol: Coronary Artery Stenosis Identification with Super-Resolution Magnetic Resonance Imaging

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Cardiac Magnetic Resonance Angiography (CMRA) has long shown promise as a safe, non-invasive and non-ionising radiation technique to assess coronary arterial disease (CAD), however it has been limited in its clinical use by poor spatial resolution and long scan times, as compared to other modalities.

A Super-Resolution-CMRA (SR-CMRA) protocol, utilising machine learning to enhance low quality scans to high quality images, has been developed, that allows a CMRA scan to be performed within 1 minute. However, it has yet to be trialled within patients or at more than a single study site. As such, questions remain regarding the diagnostic accuracy and generalisability of this SR-CMRA protocol.

The efficacy of this protocol will be assessed in patients under investigation for CAD. Following optimisation in a healthy study group, 160 patients across 5 sites will undergo both Coronary CT Angiography (CCTA), the current non-invasive gold standard investigation, and SR-CMRA. The primary outcome will be the presence of coronary artery stenosis of >50%. The 2 modalities will be compared to determine the efficacy of SR-CMRA. Subsequently, SR-CMRA images from each site will be distributed to another study site, where a different investigator will analyse the images. The results will be compared to calculate inter-observer variability.

This project aims to determine whether SR-CMRA offers a clinically viable alternative to CCTA and whether the results are reproducible across multiple centres. If successful, this could reduce the reliance on CCTA, thereby limiting patients' exposure to radiation, and potentially allowing for more regular monitoring, and therefore better treatment, of CAD.

Keywords: Cardiovascular system, Medical technology and diagnostic techniques, Other

The effect of STING signaling activation on endothelial cell biology and function.

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J. Kalucka, Department of Biomedicine

P. Carmeliet, Department of Biomedicine

Background: Endothelial cells (ECs) are the key component of the blood vessel wall. Several growth factors, including Vascular Endothelial Growth Factor (VEGF), can stimulate ECs to proliferate and to form new vessel sprouts in a process called angiogenesis, which is important for the expansion of the vascular network in physiological and pathological conditions. The endothelium (and additionally the tumor vasculature) is prone for activation by different, pro-inflammatory factors, including type I interferons.

Aim: To investigate the role of the cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway during tumor angiogenesis, and to elucidate the potential molecular mechanism that may improve anti-cancer therapies.

Results: I could demonstrate that the STING signaling could be induced in ECs and that activation of the pathway affects proliferation and migration of ECs (using sprouting and scratch assays respectively). Knocking out of STING in ECs by CRISPR/Cas9 approach, restored the changes in proliferation and migration upon pathway activation. Furthermore, qPCR and multiplex assays indicated that the mRNA expression and production of cytokines by ECs was induced after activation of the STING pathway. Currently, different downstream proteins of STING such as IRF3 (Interferon Regulatory Factor 3) are being investigated, in order to describe the molecular mechanism that is responsible for the functional changes that were observed.

Keywords: Cardiovascular system, Inflammation, Cell biology

Transglutaminase 2 inhibition as therapeutic target in chronic kidney disease and diabetic vascular disease

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Background and hypothesis: Progressive fibrosis development is the histological hallmark of all forms of chronic kidney disease including diabetic, hypertensive, and ischemic nephropathy. Currently available treatments delay its progression but do not prevent the development of end-stage kidney disease. The enzyme transglutaminase 2 (TG2) is involved in the development of both fibrosis and vascular dysfunction through enhanced cross-linking of matrix proteins and endothelial dysfunction, related to the open conformation of the enzyme. We hypothesize that inhibition of TG2 with the specific, reversible, and cell-permeable TG2 inhibitor LDN27219 improves renal fibrosis and diabetes-related vascular disease.

Objectives: Three objectives and sub-studies have been established: (1) investigate whether high glucose concentrations, upregulate TG2 activity in endothelial and epithelial kidney cells and whether inhibition of TG2 can prevent this, (2) investigate whether LDN27219 treatment in isolated human precision-cut kidney slices reduces the expression of fibrosis biomarkers and (3) investigate whether treatment with LDN27219 improves vascular dysfunction and reduces renal fibrosis in mice exposed to unilateral ureter obstruction (UUO).

Preliminary results: LDN27219 promotes the closed conformation of TG2 exerting a direct vasorelaxant, a blood pressure-lowering effect and an increased nitric oxide sensitivity of the vascular smooth muscle caused by the opening of potassium channels, which potentiates endothelium-dependent vasorelaxation. LDN27219 prevented TG2 upregulation in preliminary results on the UUO model.

Keywords: Pharmacology, Cardiovascular system, Nephrology

Congenital Pulmonary Malformation, pre- and postnatal diagnosis and management

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Puk Sandager, Co-supervisor, MD, Associate professor, Consultant, PhD, Department of Obstetrics and Gynecology & Center for Fetal Diagnostics, Aarhus University Hospital/Aarhus University, Denmark.

Anne Kirkeby Hansen, Co-supervisor, MD, Senior specialist registrar, PhD, Neonatology/Neonatal Intensive Care Unit, Department of Pediatrics and Adolescent Medicine, Aarhus University Hospital, Denmark.

BACKGROUND Congenital pulmonary malformations (CPMs) are a group of rare developmental abnormalities in the lungs and respiratory tree. The diagnosis of CPM is now often made prenatally, due to the growing use and sensitivity of prenatal ultrasonography. In most cases, the prognosis of prenatally detected CPM is favorable, but in rare cases severe prenatal complications, and intrauterine death can occur. Some neonates with CPM will have respiratory symptoms at birth and need surgical removal of the lesion. However, most neonates with CPM have no symptoms and will remain asymptomatic beyond the neonatal period.

Surgical removal of the lung lesion is the standard of care for symptomatic children with CPM. However, the management of asymptomatic children remains controversial.

AIMS We aim to investigate the incidence of CPM in Denmark and evaluate associations between prenatal findings and pre- and postnatal outcomes. Further, to evaluate clinical outcomes after surgical excision of symptomatic CPM, and the clinical outcomes of asymptomatic CPM managed conservatively versus surgically.

METHODS National prospective cohort studies including pre- and postnatally diagnosed CPM from 2000 to 2022 and follow-up data from the highly specialized Danish centers managing CPM.

PERSPECTIVES The project will help identify potential prenatal predictors of respiratory impact among neonates with CPM. Furthermore, the study will provide national results regarding the management of children with CPM, with follow-up of several years, which may lead to an optimization of the current management of children born with CPM in Denmark.

Keywords: Paediatrics, Respiratory system, Other

Flash talk session 9

DARE - DAiry pain RElief: Role of dairy proteins in the reduction of oral burn

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L. Baad-Hansen, Department of Dentistry and Oral Health, Section for Orofacial Pain and Jaw function; ES. Sørensen, Department of Molecular Biology and Genetics.

Background: Burning mouth syndrome (BMS) is a condition with chronic burning sensation in the oral mucosa. Milk is known for reducing oral burning pain caused by the consumption of capsaicin. A recent study has shown no difference between milk with high and low-fat content in reducing capsaicin-induced oral burn.

Aim: Assess the role of milk proteins in reducing capsaicin-induced oral burn.

Methods: The study is a double-blinded placebo-controlled cross-over study consisting of two parts. In part one, 24 healthy participants will be recruited. Each will attend four experimental sessions in randomized order. In each session, mucosal pain will be evoked by having the participants dip their tongues in a cup containing 0,1% capsaicin crème for five minutes. The level of unpleasantness will be scored continuously on a numerical rating scale. After five minutes the participant rinses the mouth for 30 s with a solution containing different milk proteins. One session will be a placebo session. During and after rinsing, scoring of unpleasantness will continue until it is 0. To assess the surface temperature, a thermographic image of the tongue will be taken before, right after and 10 minutes after application of capsaicin. Using semi-quantitative sensory testing, mechanical and thermal sensitivity of the tongue will be measured at the same time points.

Depending on the results from part one, three specific proteins will be selected for further investigation in part two.

Results: The study is ongoing. No results will be presented.

Conclusion: This paper will clarify the potential role of milk proteins in reducing capsaicin-induced oral burn with potential clinical applications for BMS.

Keywords: Dentistry, Clinical neuroscience, Other

Do students assessing approximal dental caries improve their diagnostics skills by the use of artificial intelligence software?

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APS Sørensen , L Schropp1, H Devlin2, LH Matzen1

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2 Division of Dentistry, School of Medical Sciences, United Kingdom

Background: Early detection of approximal dental caries can ensure that carious lesions remain superficial if managed with preventive care. Standard tools for caries diagnostics are clinical inspection and bitewing images (BWs). Diagnosing approximal caries is a challenging task and automated systems applying artificial intelligence (AI) have been introduced to assist in this respect.

Material and method: The study included 74 dental students randomly allocated to either a test or control group. At two sessions, both groups assessed approximal caries in in 25 BWs. At the first session, the test group registered caries using AI software (AssistDent®) and the controls without using AI. One month later, both groups of students detected caries in another 25 BWs without using the software. The student's registrations were compared with a reference standard. Sensitivity and specificity were calculated, and T-tests were applied to assess if the tests and controls performed differently.

Results: At the first and second session, 291 and 315 tooth surfaces were detected with caries according to the reference standard. At session 1, the controls obtained higher sensitivity (p=0.03) than the test group (58% vs 51%), whereas the specificity was higher for the test group (86% vs 80%; p=0.02). At session 2, there was no difference between the groups. The test group improved their sensitivity from session 1 to 2 (p=0.03), while the controls improved their specificity (p=0.001).

Conclusions: The interaction between clinicians and AI is not clearly understood. The previous training, knowledge and confidence of participants can greatly affect their responses.

Keywords: Dentistry, Other, Other

3D-design and chemical functionalization of Percutaneous Implants for improved soft tissue healing and sealing properties

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David Christian Evar Kraft, Department of Dentistry and Oral Health

Morten Foss, Senior Researcher, Interdisciplinary Nanoscience Center

Ole Zoffmann Andersen, ELOS Medtech

Background

Tooth loss affect both aesthetic and masticatory function, but can be restored with an implant. We will investigate methods for improved integrations of percutaneous implants. Most implants are lost due to a secondary infection. Therefore, improved soft tissue to implant sealing is important for implant longevity.

Aim

The aim of the project is exploring soft tissue integration of coated polydimethylsiloxan (PDMS) percutaneous implants in a sheep model.

Method

Six sheep were included, with three implants in each femur bone. The PDMS implants were functionalized by either a TiO2 Molecular Layer Deposition or polydopamine coating. Titanium implants, the golden standard, will serve as a positive control and pure non-coated PDMS as a negative control. The implants have been sectioned, stained and digitalized. Histological examination will evaluate soft tissue integration i.e.by determination of type of connective tissue, inflammation, epithelial sealing and epithelial down growth.

Expectations

We expect the functionalized PDMS implants will enhance the epithelium/implant sealing property, as well as an improved integration of the implant into the collagen connective tissue compared to non-coated PDMS implant as well as the pure titanium implant.

Keywords: percutaneous implant, polydimethylsiloxane, titanium oxide, polydopamine.

Keywords: Dentistry, Animal models/disease models, Other

Treatment results after Anterior Cruciate Ligament (ACL) reconstruction with adjustable graft implants - Results from the Danish Anterior Cruciate Ligament Reconstruction register

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Background: There are numerous ways to fixate the graft during ACL reconstruction. Newly developed button implants with an adjustable-loop are used more frequently, but clinical outcome regarding failure rates, knee function and -stability is poorly investigated.

Purpose: We want to investigate if adjustable-loop button implants for femoral fixations leads to a lower graft failure rate as well as an improvement in patient reported knee functions and objective knee stability, compared to femoral fixation with fixed-loop button implants for ACL reconstruction.

Study design: Register based controlled cohort study.

Methods: Data is obtained from the nationwide Danish Knee Ligament Reconstruction Registry (DKRR). We have included a total of 14,866 patients: 10,894 in the fixed-loop group and 3,972 in the adjustable-loop group, between July 2005 and December 2020. The primary outcome is revision ACL reconstruction. Secondary outcomes will include patient reported outcomes (KOOS scores) and objective knee stability measures (KT-1000 and Pivot Shift).

Results: The revision rates will be compared with Kaplan-Meyer survival analysis with Hazard Ratios, and will be adjusted for meniscus and cartilage injury, type of ACL injury, sex and age. Mean values of KOOS scores will be compared using a student t-test, if data is normally distributed based on QQ-plots, otherwise with the Wilcoxon ran-sum test. Data from Pivot shift will be compared using Qui2 test.

Conclusion: This study will bring important knowledge about the results of the adjustable-loop button implants to help surgeons choose the best type of femoral fixation during ACL reconstruction.

Keywords: Orthopedic surgery, Other, Other

The interplay between periodontitis and diabetes

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Non-communicable diseases, including diabetes and periodontitis, share an inflammatory background that resembles a dysfunctional immune response. Given the various common facets of diabetes and periodontitis, including biological, behavioural and psychosocial, using the Danish registries in partnership with Steno Diabetes Center Aarhus, this PhD project aims to: I – evaluate whether lipid profiles interact with the effect of diabetes (exposure) on the occurrence and severity of periodontitis (outcome). A statistical model will be determined with a set of covariates identified in a direct acyclic graph, including sociodemographic, behaviour, systemic condition, and lipid profile; II - estimate the effects of lifestyle interventions on the risk of diabetes and periodontitis severity. We will simulate hypothetical interventions, such as diet, smoking, alcohol intake, and others, and verify their impact on diabetes and periodontitis in people living with diabetes. This project can promote the reduction of the global burden of diabetes and periodontitis and implement strategies for tackling other common non-communicable diseases via the common risk factor approach. We expect to contribute to the discussions on the impact of modifying common risk factors to cause notable reductions in the population burden of diabetes and periodontitis that are considered global public health priorities.

Keywords: Dentistry, Inflammation, Molecular metabolism and endocrinology

Prevention of postoperative hypoparathyroidism following thyroid surgery by using intraoperative autofluorescence

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Introduction: Postoperative hypoparathyroidism (HPT) is a frequent and serious complication to thyroid surgery on a global scale. The HPT is a result of intraoperative damage to the parathyroid glands. The challenge in preventing intraoperative parathyroid damage is partly due to difficulties in intraoperative visualization and identification of parathyroid glands. The need for intraoperative tools that are able to help visualize and identify parathyroid glands is thus urgent and needed. Novel studies have shown, that application of near-infrared autofluorescence (NIRAF) during thyroid surgery can help visualizing the parathyroid glands and enhance their preservation. However, no studies have shown that NIRAF is able to reduce permanent HPT following thyroid surgery. This might be due to the fact, that all studies report results from thyroid AND parathyroid centers. Results from such centers does not reflect outcome in centers that only perform thyroid surgery. NIRAF might therefore be able to reduce the rate of permanent HPT in non-parathyroid centers. We propose three studies aiming to highlight the role of parathyroid damage during thyroid surgery, improve parathyroid preservation and ultimately reduce postoperative HPT in non-parathyroid centers.

Methods: Study 1 is a retrospective cohort study evaluating the rate of HPT following total thyroidectomy in non-parathyroid centers. Study 2 is a prospective cohort study evaluating the rate of HPT following total thyroidectomy after the introduction of NIRAF. Study 3 is a randomized controlled trial comparing NIRAF-assisted thyroid lobectomy to conventional thyroid lobectomy in terms of parathyroid management.

Keywords: Ear, nose and throat (ENT), Medical technology and diagnostic techniques, Other

Are progressive shoulder exercises feasible in patients with glenohumeral osteoarthritis or rotator cuff arthropathy tear eligible for shoulder arthroplasty?

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Background: Only few studies have investigated the outcome of physiotherapist-led exercises in patients with glenohumeral osteoarthritis (GOA) or rotator cuff tear arthropathy (CTA). Several studies have suggested the need for trials comparing shoulder arthroplasty to non-surgical treatments. Before initiation such a trial, the feasibility of progressive shoulder exercises (PSE) in patients, who are eligible for shoulder arthroplasty should be investigated. The aim was to investigate whether 12 weeks of PSE is feasible in patients with GOA or CTA eligible for shoulder arthroplasty. Moreover, to report changes in shoulder function and range of motion (ROM) following the exercise program.

Methods: 18 patients (11 women, 14 GOA) aged 70 (57-80) years performed 12 weeks of PSE with 1 weekly physiotherapist-led and 2 weekly home-based sessions. Feasibility was measured by drop-out rate, adverse events, pain exacerbation (VAS) and adherence to PSE. At baseline and end of treatment, patients completed the Western Ontario Osteoarthritis of the Shoulder (WOOS) score, and Disabilities of the Arm, Shoulder and Hand (DASH).

Results: Two patients dropped out. No adverse events were observed. 89% (16/18) of patients had high adherence to PSE and acceptable pain levels were reported during the intervention. WOOS improved 23 (95% CI 13; 33) points, and DASH improved 13 (95% CI 6; 19) points.

Conclusion: PSE is feasible, safe and may improve pain, shoulder function and ROM in patients with GOA or CTA eligible for shoulder arthroplasty. A randomised controlled trial comparing shoulder arthroplasty to PSE is feasible.

Keywords: Orthopedic surgery, Rehabilitation, Other

Tumor megaprostheses – evaluation of serum metal ion concentrations.

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Introduction: Metal surfaces in tumor megaprostheses (TMP) are significantly increased compared to standard total hip arthroplasty (THA) or total knee arthroplasty (TKA). One study found an increased serum ion level of cobalt and chromium, 25 and 9 times respectively, in TMP compared to patients treated with standard rotating-hinge knee arthroplasty. Metal-on-metal (MoM) THA has shown to increase serum cobalt levels resulting in severe adverse effects. Two case reports describe multiple organ failure due to elevated serum cobalt after operation with MoM THA. One study describes death due to cobalt toxicity induced heart failure and recent retrospective cohort study describes an association between hospital admissions due to heart failure in patients previously operated with MoM THA.

Aim: To evaluate the serum metal ion concentration in groups of patients treated with TMP.

Hypothesis: TMP will have increased serum ion levels compared to standard THA and TKA, respectively.

Methods and Materials: A minimum of 25 patients receiving TMP of the knee or hip will be included. Blood sample results for chromium and cobalt collected pre-operatively and at 4, 8 and 12 months follow-ups, will be evaluated and compared to serum metal ion levels in standard THA and TKA patients. All patients will be asked to fill out a questionnaire regarding possible chromium and cobalt exposures.

Perspectives: The demand for long prosthetic survival and good functional outcome after major tumor surgery has increased due to increased survival in patients. Studies of the serum metal ion level in patients treated with TMP are pivotal in order to ascertain the patient safety of the treatment.

Keywords: Orthopedic surgery, Oncology, Laboratory science

Is physical rehabilitation exercise superior to no physical rehabilitation exercise following total hip arthroplasty? – Preliminary results of a systematic review

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Background

Physical rehabilitation exercises (PRE) are prescribed immediately after total hip arthroplasty (THA), but evidence for this is sparse. A systematic review indicates effect of PRE, but in all trials included, PRE was initiated at a later stage after surgery not reflecting clinical practice.

Objective

To investigate whether early initiated PRE following THA is superior to no PRE in terms of improving function, reducing pain and increasing quality of life at end of intervention and 12 months.

Methods

A systematic review with meta-analysis is being conducted. In October 2020, five databases (MEDLINE, Embase, Cinahl, Cochrane, Pedro) were searched for published articles, while Scopus, Web of Science, Clinical Trials.gov and WHO International Clinical Trials Registry Platform were searched for conference papers and pre-registered trials. Eligibility criteria: Randomized controlled trials comparing PRE initiated within 3 months after THA with no PRE. Study methodology is assessed by Cochrane Risk of Bias 2 tool and overall quality of evidence by Grading of Recommendations Assessment, Development and Evaluation approach. An update of search is planned.

Preliminary results: Of 6823 references identified, only one trial is eligible for inclusion, hence, meta-analysis is precluded. The study reports a significant improvement in favor of the PRE-group in patient-reported function and walking speed. Overall quality of evidence was low.

Preliminary conclusion

So far, no conclusions on superiority of PRE to no PRE can be drawn. Further randomized controlled trials are needed to investigate effectiveness of current clinical practice.

PROSPERO registration number: CRD42020203574

Keywords: Rehabilitation, Reviews and meta-analyses, Orthopedic surgery

Flash talk session 10

Megalin ablation in the healthy retina may cause a dedifferentiation of the tissue

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Megalin is a receptor located to absorptive epithelia such as the proximal tubule and the retinal pigment epithelia (RPE). In kidney, megalin holds an endocytic function, but our previous research suggests a different function in the RPE. Here, megalin ablation results in retinal thinning, which we hypothesized to be due to dedifferentiation.

We established an inducible, megalin knockout murine model which allowed us to study megalin deficiency in the healthy retina. Adult mice were induced by i.p. tamoxifen and left for 31 days, 100 days or 6 months before euthanasia. One eye was embedded in paraffin and used for hematoxylin/eosin staining, the other was used for q-RT-PCR of the differentiation marker RPE-65. HPLC to determine retinoid distribution (ratio between retinol, retinal and retinyl ester) was performed on eyecup homogenate by dissection under red light and extracting retinoids to a hexane phase. HPLC was performed by resuspending retinoids in ethanol and separating them on a normal phase column.

Most retinas had not yet undergone thinning at 1 month, 100 days and 6 months. Q-RT-PCR showed a reduction in RPE65 in the megalin-KO mice in all groups, but only statistically significant after 6 months ($p=0.003$). RPE65 is involved in the conversion of retinyl ester to retinol, and an analysis of the relative abundance of the different forms by HPLC showed an accumulation of retinyl-ester compared to retinol and retinal ($p=0.005$).

Our findings indicate that megalin ablation causes a thinning of the retina as well as a reduction in RPE65 mRNA and a disruption of the visual cycle. More experiments are needed to clarify if this is part of a dedifferentiation process.

Keywords: Cell biology, Ophthalmology, Other

Investigating the role of IκBζ in the pathogenesis of atopic dermatitis

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Atopic dermatitis (AD) is a chronic, itching, eczematous disease that affects up to 20% of children and 5% of adults. The pathogenesis is multifactorial and the inflammation in the skin during AD is dominated by a Th2/Th17/Th22 response. The intracellular molecules involved in the inflammatory processes in AD are less understood, although the signaling pathways of NF-κB and JAK/STAT have been suggested to play a role. As available biological treatments need to be injected into the patients new oral or topical treatments, such as small molecule inhibitors are needed. IκBζ is a potential intracellular target and is a nuclear transcriptional co-activator involved in inflammatory processes mainly by regulating specific NF-κB target genes. IκBζ has emerged as a novel regulator in the pathogenesis of psoriasis, however the role of IκBζ in AD is unknown. Thus, we aim to investigate the role of IκBζ in AD.

The expression and localization of IκBζ will be investigated in biopsies from patients with AD through RT-qPCR and immunohistochemistry. Additionally, the role of IκBζ in an AD-like setting in vitro in cultured primary human keratinocytes will be investigated. Through RT-qPCR and western blotting we aim to investigate the effect of inflammatory AD-associated cytokines on the expression level of IκBζ, as well as the underlying molecular mechanism by which IκBζ is regulated. Also, the role of IκBζ as a transcriptional regulator of AD-related inflammatory markers will be characterized through siRNA transfection before the gene expression of an immunology panel consisting of 579 genes is investigated. Depending on these findings, IκBζ could emerge as a novel treatment target in AD.

Keywords: Dermatology, Inflammation, Cell biology

Dermatological diseases in general practice in Denmark

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Introduction: Atopic dermatitis (AD) is one of the most frequent dermatological diseases with a prevalence of 20% in the childhood population and 5% in the adult population in affluent countries. Most patients with mild and moderate AD are managed in general practice and only a small proportion are referred to a dermatologist in countries where the general practitioner (GP) functions as a "gatekeeper". Overall, most skin diseases are managed by GPs, but GPs often find diagnosis and treatment approaches for skin diseases challenging.

In Denmark, we have no knowledge about frequency or challenges of skin diseases in general practice or knowledge on GPs' potential unmet needs regarding dermatology.

Methods: This is a questionnaire study developed in collaboration between specialists in dermatology and family medicine. The questionnaire has been developed specifically for this study and tested and validated on three separate populations of GPs. The questionnaire will be distributed to all GPs in the North Region of Jutland, and later to other regions in Denmark.

Results/hypotheses: We hypothesize that: 1) there is a high proportion of consultations concerning dermatology in general practice, 2) GPs find management of AD challenging and 3) there is a large dispersion in management of AD in general practice.

Discussion/perspectives: This study will provide essential knowledge about prevalence of dermatological diseases in general practice in Denmark and identify potential unmet needs in regard of dermatology for GPs. We expect that our data will provide basis for a need-oriented curriculum in dermatological education for GPs and for further studies in this area.

Keywords: Dermatology, Health education and simulation-based training, Other

The role of heat shock protein 90 in inflammation

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The heat shock protein (HSP) 90 is a molecular chaperone that folds and stabilizes client proteins, and thereby supports the activity of a wide range of proteins including transcription factors and kinases involved in inflammation. Therefore, we hypothesize that HSP90 is a key immunoregulatory protein, and inhibition of HSP90 should lead to an alleviation of inflammation and reduction of inflammatory markers.

In vitro studies were conducted with primary human keratinocytes preincubated with and without an HSP90 inhibitor (RGRN-305) and stimulated with 12-O-tetradecanoylphorbol-13-acetate (TPA), an inducer of inflammation. The mRNA expression of proinflammatory cytokines including TNFα, IL-1β, IL-6 and IL-8 measured by RT-qPCR were significantly reduced by RGRN-305, demonstrating an anti-inflammatory effect. To gain insights into the intracellular mechanisms, multiplex antibody arrays and western blotting are planned to detect the phosphorylation and activation of kinases and transcription factors involved in inflammation.

Additionally, in vitro studies using a SARS-CoV-2-like model were conducted with U937 (human monocyte cell line) by stimulation with SARS-CoV-2 spike protein. When preincubated with RGRN-305, the mRNA expression of TNFα, IL-1β and IL-6 were significantly reduced.

In summary, inhibition of HSP90 mediates a robust anti-inflammatory effect in cell cultures, providing a potential therapeutic strategy for the management of inflammatory diseases. To further examine the potential anti-inflammatory effects of HSP90 inhibition, in vivo studies in mice subjected to TPA-induced skin inflammation and SARS-CoV-2-induced lung inflammation are planned to be conducted.

Keywords: Inflammation, Dermatology, Animal models/disease models

Developing a flow cytometric analysis for characterizing pathologic fibroblast subsets in rheumatoid arthritis

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Introduction

Local pathological fibroblasts have recently been implicated with immune mediated inflammatory diseases such as rheumatoid arthritis. Here specific fibroblast subsets have been linked to specific disease traits, such as joint inflammation and joint destruction.

To elucidate these links, we aim to develop a flow cytometry analysis for characterizing the cellular composition of fibroblast subsets in synovial fluid and the synovial membrane of patients with rheumatoid arthritis.

Methods

The flow cytometry analysis will include known markers of pathological fibroblast subsets and will serve as the primary tool for characterization. When panel development is completed, we will start analyzing patient samples and compile these into a cellular atlas. Afterwards fibroblast subsets will be isolated with flow cytometry assisted sorting and tested functionally in vitro.

Results

We have recently finished optimization of individual core fibroblast subset markers and exclusion markers targeting hematopoietic cell linages. With initial optimization completed, we have begun compiling the flow cytometric analysis markers into a multi-color panel. Here we will address issues regarding data acquisition and data interpretation before transitioning to final testing on patient samples.

Discussion

A cellular atlas of synovial fluid and synovial membrane fibroblast subsets may bridge the current evidence-gap between these two adjacent compartments. It may also be the first step towards a more personalized treatment approach where our characterization of synovial fibroblast subsets compared with clinical data, may help anticipate the clinical course or treatment failure.

Keywords: Inflammation, Rheumatology, Laboratory science

Patterns of CD40L for stimulating B cells and patterns of inhibitors of CD40L for treating autoimmunity

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Central aspects in autoimmune diseases such as Systemic Lupus Erythematosus are a break of tolerance and production of antibodies with affinity towards self-components by autoreactive B cells. Activation of B cells occurs through the immunological synapse that mediates interaction between B cells and follicular helper T cells. This interaction will take place in germinal centers (GCs). The synapse involves, e.g., antigen recognition by the specific antibodies on the B cell surface, but another important factor is costimulatory signaling through the interaction between CD40 and the CD40 ligand, CD40L. CD40L presents as a trimer in the membrane, whereas CD40 undergoes ligand-induced trimerization.

Because of the central importance of CD40-CD40L in the immunological synapse, we hypothesize that successful treatment of some autoimmune diseases should consist of a drug that targets the interaction between T and B cells. We suggest that this could be achieved by inhibiting the CD40/CD40L axis.

We aim to investigate this by:

- Mimicking the immunological synapse in vitro by creating trimers of CD40 and CD40L and test for binding to cells.

- Generation of nanobodies, which are heavy-chain-only antibodies from Llamas, targeting CD40L. I shall characterize their binding to human and murine CD40L and their ability to block CD40-CD40L interaction, in vitro and in vivo.

- Examining the natural distribution of CD40 and CD40L on B and T cells, respectively.

- Testing the nanobodies in two different murine lupus models. The murine lupus models present with GCs in peripheral lymphoid tissues. The ability of the nanobodies to ablate GCs by inhibiting CD40-CD40L interaction will be investigated.

Keywords: Inflammation, Rheumatology, Animal models/disease models

Development of efficient complement inhibitors for the treatment of Age-related Macular Degeneration

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Age-related macular degeneration (AMD) is an eye disease that has been associated with an overactive complement system (CS). Treatment options, however, are limited for these patients. Thus, our research group has designed a combinatorial gene therapeutic strategy in which a complement inhibitor may be an efficient component. The size of the inhibitor should be small, as the capacity of viral vectors used in gene therapy is limited, and as the inhibitor should be able to cross several cell layers of the retina. Thus, single-domain antibodies derived from alpacas, called Nanobodies (Nbs), are explored to inhibit the CS. Firstly, Nbs were fused to different tags to enable easy detection, and the hemagglutinin (HA)-tag was found superior. In recombinant vectors, these HA-tagged Nbs were encoded downstream of a signal sequence to ensure secretion, and after transfection of HEK293 cells, the Nbs were highly expressed as detected in both media and lysates. The post-transfection media samples were also used in assays examining the complement system, which showed specific inhibitory functions of different Nbs on both the classical and the alternative pathway of the CS. As the expression and efficiency of the Nbs are confirmed, viral vectors have been produced and validated, allowing the next part of this project to be initiated; in vivo studies that will evaluate the local expression of Nbs in the eye of mice.

Keywords: Ophthalmology, Genetic engineering, Inflammation

The point-prevalence of coexistence polymyalgia rheumatica and giant cell arteritis – a systematic review and meta-analysis

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Introduction:

Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are concurrent diseases. We aimed to estimate the point-prevalence of coexisting GCA and PMR at diagnosis. Additionally, an incidence rate (IR) of late-onset GCA in patients with solely PMR was estimated.

Methods:

Two authors performed a systematic literature search, data extraction and risk of bias assessment independently. Studies assessing both GCA and PMR patients were included. The outcomes were point-prevalence of coexisting GCA and PMR and IR for development of late-onset GCA in PMR. A meta-analysis was performed to calculate a pooled prevalence of coexisting PMR and GCA.

Results:

We identified 27 studies investigating coexistence of GCA and PMR. Only two studies applied imaging systematically to diagnose GCA. Late-onset GCA in patients with solely PMR at diagnosis was assessed in 12 studies but imaging was not applied systematically. The point-prevalence of coexisting GCA in patients with PMR at diagnosis ranged from 6% to 66%. The pooled estimate of the point-prevalence from the meta-analysis was 24%. The point-prevalence of PMR in patients with GCA at diagnosis ranged from 16% to 65%. The pooled estimate of the point-prevalence from the meta-analysis was 44%. The IR ranged between 2-78 cases of late-onset GCA per 1000 person-years.

Conclusion:

This review and meta-analysis demonstrate that GCA and PMR frequently coexist at the time of diagnosis. Additionally, we present the current evidence of late-onset GCA occurring during the PMR disease course. These results emphasized the need for studies applying imaging modalities to diagnose GCA.

Keywords: Rheumatology, Reviews and meta-analyses, Inflammation

Diagnosing axial spondyloarthritis by multidisciplinary team conference in a cohort of patients with disease features according to the ASAS criteria.

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**Rosa Kiil and Clara Mistegaard contributed equally and share first authorship.*

Background:

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease characterized by inflammation in the axial skeleton; the sacroiliac joints (SIJs) and the spine. In 2009 MRI was included in the Assessment of SpondyloArthrtitis Society (ASAS) classification criteria and have often been used clinically resulting in a risk of overdiagnosis. The aim of the study was to estimate the prevalence of axSpA in a cohort of clinical patients with low back pain and imaging or biochemical findings suggestive of axSpA using multidisciplinary team (MDT) conferences.

Methods:

In 84 patients fulfilling or nearly fulfilling the ASAS criteria, clinical information regarding SpA features, biochemical tests including CRP and HLA-B27, and MRI findings at baseline and after 3.5 years of follow-up were evaluated retrospectively at MDT conferences attended by both radiologists and rheumatologists, and MDT consensus diagnoses regarding axSpA were established.

Results:

According to the MDT consensus, 25 patients (30%) had axSpA at follow-up (fig. 1); 40% of the individuals who fulfilled the ASAS 2009 criteria at baseline had axSpA and 37% at follow-up. 96% of the patients with axSpA according to MDT consensus met the ASAS criteria at baseline and 92% at follow-up.

Conclusions:

Approximately one-third of the included patients had axSpA when evaluated at a MDT conference after 3.5 years of follow-up. The ASAS 2009 criteria had a low predictive value,

but high sensitivity for axSpA, both at baseline and at follow-up. The results emphasize the importance of not using classification criteria as diagnostic criteria.

Keywords: Rheumatology, Inflammation, Other

Anti-Ro52 antibodies and autoimmune disease

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Background: Autoimmunity is on the rise and the prevalence of antinuclear antibodies (ANA) associated with autoimmune disease is rapidly increasing. One of these antibodies is anti-SSA, which is frequently present in patients with Sjögrens syndrome, rheumatoid arthritis, systemic lupus erythematosus and scleroderma. Anti-SSA is associated with a variety of disease manifestations such as dryness of the mouth and eyes (sicca symptoms), arthralgia, fatigue, interstitial lung disease, interstitial kidney disease, vasculitis of the skin, spontaneous abortions and congenital heart malformations. Anti-SSA consists of anti-Ro52 antibody (AB) and anti-Ro60 AB. Anti-Ro52 AB is targeted against the intracellular receptor TRIM21 which is crucial in our defense against viral infection.

Aim: With this PhD we aim to understand the role of anti-Ro52 ABs in both the development of Sjögrens syndrome, other autoimmune disease, pregnancy loss and congenital malformations.

Methods: We will create a biobank of lymphocytes, serum and nasal stem cells from anti-SSA positive patients. The serum will be run through column purification to extract human anti-Ro52 ABs. The stem cells will be cultured to airway epithelium. The effect of the antibodies on the epithelium is measured by the change in mucus production and the goblet cell characteristics. Furthermore, we will functionally test the antibody effects on type I interferon production as a marker of inflammation.

Perspectives: By understanding the role of anti-Ro52 ABs in the development of Sjögrens syndrome and other autoimmune disease, we can alter not only how we think about these diseases but the way we treat them.

Keywords: Rheumatology, Inflammation, Laboratory science

Flash talk session 11

Restoration of GATA2-regulated gene expression by ex vivo CRISPR-mediated allele-specific GATA2 gene correction in GATA2 deficiency

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GATA2 deficiency is an autosomal dominant disorder caused by loss of function mutations in the gene encoding the transcription factor GATA2. The main symptoms seen in GATA2 deficiency patients are immune cell cytopenia and a markedly increased risk of developing leukemia, which both can be attributed to dysfunction of hematopoietic stem cells (HSCs). Here, we describe both an allele-specific and a more generalized strategy for correction of GATA2 deficiency by genome editing based on ex vivo delivery of Cas9/sgRNA ribonucleoprotein (RNP) complexes and rAAV6-mediated DNA donor delivery to hematopoietic cell lines and stem cells. Using an allele-specific strategy, we effectively targeted a mutation giving rise to GATA2 deficiency in cell line models and heterozygous patient-derived PBMCs with no detectable activity against the normal allele. We also showed that the same locus targeted by the allele-specific strategy is readily targeted in HSCs from healthy donors, whereas the allele-specific sgRNAs showed no activity towards the normal allele. Furthermore, we used RNA sequencing of engineered GATA2 deficiency cell line models to identify transcripts with functions in hematopoietic development that were dysregulated due to knockout of GATA2. Based on the sequencing data, a panel of genes was created. To demonstrate that GATA2 function is restored upon genetic correction of the GATA2 gene, expression of the gene panel will be assessed before and after correction of the gene variant causing GATA2 deficiency. In summary, we expect to be providing proof-of-concept for a genome editing-based therapy against GATA2 deficiency.

Keywords: Genetic engineering, Cell biology, Infection

SARS-CoV-2 elicits robust adaptive immune responses regardless of disease severity

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The SARS-CoV-2 pandemic currently prevails worldwide. To understand the immunological signature of SARS-CoV-2 infections and aid the search and evaluation of new treatment modalities and vaccines, comprehensive characterization of adaptive immune responses towards SARS-CoV-2 is needed. We included 203 recovered SARS-CoV-2 infected patients in Denmark between April 3rd and July 9th 2020, at least 14 days after COVID-19 symptom recovery. The participants had experienced a range of disease severities from asymptomatic to severe. We collected plasma, serum and PBMC's for analysis of SARS-CoV-2 specific antibody response by Meso Scale serology analysis, ACE2 competition, IgA ELISA, pseudovirus neutralization capacity, and dextramer flow cytometry analysis of CD8+ T cells. The immunological outcomes were compared amongst severity groups within the cohort, and 10 pre-pandemic SARS-CoV-2 negative controls. We report broad serological profiles within the cohort, detecting antibody binding to other human coronaviruses. 202(>99%) participants had SARS-CoV-2 specific antibodies, with SARS-CoV-2 neutralization and spike-ACE2 receptor interaction blocking observed in 193(95%) individuals. A significant positive correlation (r=0.7804) between spike-ACE2 blocking antibody titers and neutralization potency was observed. Further, SARS-CoV-2 specific CD8+ T-cell responses were clear and quantifiable in 95 of 106(90%) HLA-A2+ individuals. The viral surface spike protein was identified as the dominant target for both neutralizing antibodies and CD8+ T-cell responses. Overall, the majority of patients had robust adaptive immune responses, regardless of their disease severity.

Keywords: Infection, Inflammation, Respiratory system

The Functions of RNA sensors in Herpes Simplex Encephalitis

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Herpes simplex encephalitis (HSE) is the most common form of acute viral encephalitis in industrialized countries, which is mainly caused by HSV-1 infection. TLR3 and RIG-I/MDA5 are both RNA sensors, but located in endosomes and the cytoplasm, respectively. The receptors recognize double-stranded RNA (dsRNA) intermediates or by-products generated during HSV-1 infection, triggering the production of inflammatory cytokines, including type I interferon (IFN), for the control of HSV-1 replication. In the case of TLR3, this is dependent on the adaptor protein TRIF, and in the case of RIG-I/MDA5, it depends on MAVS. One central unresolved question in innate immunology is whether and how pattern recognition receptors cross-talk, and how this impacts on host defense.

In my project, I will establish murine ocular HSV-1 infection model to mimic the natural way of HSV-1 invasion on TLR3-/- and MAVS-/- mice for studying the roles and mode of action of TLR3 and RIG-I/MDA5 in the pathogenesis of HSE. Our aim is to decipher the function of RNA sensors in vivo in HSV-1 infection, and to pave the way for improved HSE treatment.

Keywords: Infection, Animal models/disease models, Cell biology

A novel missense variant resulting in autosomal recessive IFNAR2 deficiency in a patient with disseminated disease after measles-mumps-rubella vaccination

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Type I interferons (IFN) play a critical role in innate immunity, as demonstrated by exceptionally rare inborn errors of the subunits of the IFN-α/β receptor, IFNAR1 and IFNAR2, respectively. We investigated a 3-year-old male from Greenland who presented

with viral illness following live-attenuated viral vaccination. Whole-exome sequencing revealed an IFNAR2 c.157 T>C missense variant in homozygosity, leading to a p.S53P substitution. Although absent from reference databases, p.S53P occurred at a frequency of 2.5% in the Inuit population. The substitution of serine by proline yielded expression of a less abundant, aberrantly N-glycosylated IFNAR2 protein that was not expressed at the cell-surface. Patient cells lacked responses to type I IFN and displayed abolished phosphorylation of JAK1/STAT1 proteins, reduced expression of IFN stimulated genes, together with heightened vulnerability to a panel of viruses, including measles, mumps, HSV-1, and VZV – a phenotype rescued by wild-type IFNAR2 complementation. This novel cause of autosomal recessive IFNAR2 deficiency reinforces the essential role of IFN-I in control of live-attenuated vaccines and has potential public health significance for the Inuit population.

Keywords: Infection, Paediatrics, Inflammation

Hand hygiene among healthcare workers – the effect of light-guided nudging

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Introduction:

Hospital-acquired infections continue to burden 7-10% of all patients but can be reduced by improving hand hygiene compliance (HHC). We aimed to investigate the effect of two different types of light-guided nudging on healthcare workers' HHC.

Method:
A 7-month, prospective, interventional study was conducted at four wards at a Danish university hospital. An electronic monitoring system was used to collect the data. HHC was measured in patient rooms. Data were provided as HHC rates. We compared baseline HHC across two intervention-periods with light-guided nudges displayed on the alcohol-based hand rub dispensers.

Intervention period 1: The four wards were randomly divided in two groups to start receiving either Reminder-nudges or Feedback-nudges

Intervention period 2: All four wards received both reminder-nudge and feedback-nudge simultaneously.

Results:
In total, 152.128 hygiene opportunities were collected from doctors (n=88), nurses (n=125) and cleaning assistants (n=14).

The Reminder-nudge-group increased their HHC from baseline to the first intervention period (16% vs 23%, P=0.001) and stayed at this level when they subsequently received both reminder- and feedback-nudges simultaneously.

The Feedback-nudge-group increased their HHC from baseline to the first intervention period (19% vs 29%, P=0.0001) and increased further when they subsequently received both reminder- and feedback-nudges simultaneously (29% vs 34%, P=0.008).

Conclusion:
Both groups increased HHC from baseline to intervention period 1. In intervention period 2 the Reminder-nudge-group remained at the higher level and the Feedback-nudge-group increased HHC further.

Keywords: Infection, Medical technology and diagnostic techniques, Other

Coenzyme Q10 as treatment for Long Term COVID-19

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Background

Long Term COVID-19 (LTC) is defined by persisting symptoms for more than 12 weeks after initial infection. The symptomatology is diffuse. No medical treatment is available.

In patients with the condition Myalgic Encephalomyelitis (ME), a similar symptomatology as in LTC is reported. The etiology of ME is unknown, but altered mitochondrial function and prior viral infection found in several studies. It is plausible that LTC is associated with compromised cellular metabolism resulting in decreased energy production and increased oxidative stress. Coenzym Q10 is part of the electron transport chain and has capability of restoring oxidative balance and improve mitochondrial function.

Aim: To investigate if high-dose CoQ10 can reduce the number and severity of symptoms related to LTC.

Hypothesis: LTC-related symptoms are caused by reduced capacity for cellular OXPHOS and high-dose CoQ10 supplements will decrease number and severity of symptoms in LTC patients.

Design: Investigator-initiated, randomized, placebo-controlled, double-blinded, 2x2 crossover interventional trial to evaluate the effect of CoQ10 in LTC patients.

Method:

Participants will be randomized 1:1 to receive CoQ10 in a dose of 500mg/day or placebo for 6 weeks. After a 4 weeks washout period, crossover is effectuated. Two questionnaires are completed at all visits. 120 participants have been enrolled via the LTC Clinic, AUH.

Primary endpoint analysis will be performed based on the intent-to-treat population as change in LTC symptoms score from baseline to after 6 weeks of treatment compared to placebo. Secondary endpoints are duration of potential effect and safety of CoQ10 measured by adverse events.

Keywords: Infection, Inflammation, Cell biology

RAGIPET – Rat arterial graft infection diagnosed with PET-MRI

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Background:
Prosthetic vascular grafts are prone to infections caused by biofilm-forming bacteria. Prosthetic vascular graft infections (PVGI) are life-threatening and acute infections occurring within the first 30 post-operative days are especially challenging to diagnose and thus treat correctly.

Fluorodeoxyglucose positron emission tomography (FDG-PET) imaging is a promising diagnostic tool, but its clinical application is hindered by difficulties distinguishing between PVGI and physiological uptake following surgery in sterile grafts.

The aim of this study is to investigate differences in FDG uptake patterns in rats with surgically inserted sterile and infected vascular grafts and to investigate if treatment effect correlates with reduced FDG uptake in infected grafts.

Methods:
Rats are randomized to receive a sterile PTFE graft, or a PTFE graft infected with S. aureus. The graft is surgically inserted in the common carotid artery to mimic a PVGI.

Rats are initially scanned in a rodent PET-MRI scanner to establish baseline. Then a study with rats in 3 arms is conducted: sterile, infected with no treatment and infected with 14 days antibiotic treatment.

Rats are scanned serially at day 10, 20, 31, 37 and 48 post-OP. After the last scan, rats are euthanized. The graft is removed for further analysis and quantification of bacterial load.

Site of infection is localized using PET-MRI images. FDG uptake is measured as maximum standard uptake value (SUVmax) in vivo, and further measured as counts per second (CPS) ex vivo.

Primary outcome is difference in SUVmax between groups. Secondary outcome is difference in CPS.

Results:
Pilot studies will commence in November.

Keywords: Infection, Animal models/disease models, Medical technology and diagnostic techniques

LOTUS - Long-term pulmonary outcomes after infection with SARS-CoV-2: Dyspnea is poorly explained by reduced lung function

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Background: Reports of long-lasting pulmonary sequelae after Covid-19 has raised serious concern. Still, little is known about the interplay of lasting lung function (LF) affection and patient-reported dyspnea.

Aims and objectives: To investigate the incidence of decreased LF after hospitalization for Covid-19, and to compare LF measures to patient-reported outcome measures (PROMs).

Methods: Patients hospitalized for PCR confirmed Covid-19 in the Central Denmark Region were invited for follow-up visits 3 and 12 months after discharge including LF tests, six-minute walk test, high-resolution CT scan, and selected PROMs (Medical Research Council for dyspnea (MRC), SF-36, Hospital Anxiety and Depression Score (HADS), Fatigue Assessment Score (FAS), Montreal Cognitive Assessment (MoCA)).

We present an interim analysis of LF and dyspnea score for the first 80 patients at 3 months follow-up.

Results: We included 80 patients, 44 men (55%), median age 59.3 years (range: 19-88). Mean diffusion capacity (DLCO) was 81.6% (SD: 19.9). In total, 36 (45.6%) and 15 (19.0%) patients had a DLCO below 80% and 60%, respectively. Median MRC was 2 (range 1-4). There was a weak correlation between MRC and DLCO (Spearman's r= -0.28, p=0.014). Notably, of 42 patients with normal DLCO, 21 (50%) had MRC score ≥ 2 indicating significant dyspnea.

Conclusions: Considerable patient-reported dyspnea is a common problem 3 months after hospitalization for Covid-19 but is poorly explained by reduced LF measured by DLCO. Though pre-morbid LF among these patients is unknown, our results indicate that post-Covid-19 dyspnea is complex and involves respiratory as well as non-respiratory mechanisms.

Keywords: Respiratory system, Infection, Inflammation

Flash talk session 12

COVID-19 causes psychiatric after-effects

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Background: Everyone is affected by COVID-19. Some experience the acute effects, others protracted illness; Sequalae. This phenomenon has been explored by scholars such as Taquet et al., finding increased risk of psychiatric illness. However, these articles have not adequately addressed the mechanism.

Introduction: COVID-19 increases risk of long-term psychiatric illness. No animal studies explore this.

Purpose: To assess long-term behavioral changes in mice after COVID-19.

Materials and methods: 12 transgenic K18-hACE2 mice, behavioral test-battery and state-of-the art translational laboratory. Pilot-data shows correlation between inflammatory markers and monoamines.

Results – preliminary: K18-hACE2 mice exposed to COVID-19 exhibit disease that mirrors humans; The K18-promoter increases expression of H-ACE2 in mice, which results in aggravated and dose-dependent neuroinflammation. We hypothesize that the synergistic or additive effects of high viral loads in susceptible individuals may explain the pathogenesis and temporal characteristics of psychiatric illness after COVID-19. We identified a relationship between IL-1β and noradrenaline and implicated both in the pathogenesis of psychiatric illness post-COVID-19.

Discussion: This paper discusses the implications of neuroinflammation for psychiatric illness after COVID-19 and the benefits of various pharmacological interventions in mice.

Conclusion: In conclusion, by closely examining behavior and tissue from infected mice, this study sheds new light on the neglected issue of psychiatric illness after COVID-19. The implications for neuroinflammation for psychiatric illness are, that novel treatment options exist.

Keywords: Animal models/disease models, Basic neuroscience, Inflammation

The Neuroanatomy of the Olfactory Bulb and Rhinencephalon in the Göttingen Mini-pig

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Introduction

The Göttingen minipig (GM) is emerging as a non-primate translational large animal. The smelling sense is the primary sense in pigs. However, the neuroanatomy of the olfactory bulb (OB), the olfactory cortex (OC), and their projections remains to be characterized.

Aim

The aims of this study is first to make a detailed anatomical description of the OB in the GM including a description of the OB and OC neural connectivity. Secondly, we will investigate the role of stem cells, and their migration in the porcine rostral pathways.

Methods

We will describe the OB and OC using; immunohistochemical staining-, high tesla magnetic resonance imaging (hMRI)- and neuronal tracing-methods.

Furthermore, antibodies targeting neural stem cell markers, will be used to describe the migration of basic cells in the OB.

The neural connectivity is investigated; using neuronal tracing and hMRI. Neural tracers will be stereotactically microinjected in the OB to label the olfactory tract and fibers.

Perspectives

Olfaction is affected in many diseases, including Alzheimers disease, depression and Parkinson's disease. A detailed neuroanatomical knowledge of the minipig OB and OC, and their connectivity, may refine the use of a porcine translational model.

Furthermore, this study may facilitate the development of a translational model of "major depression", as loss of primary sense may facilitate depression.

In addition, future treatment research in both neurodegenerative and psychiatric diseases, will benefit of more knowledge on nasal administrations forms.

Keywords: Animal models/disease models, Basic neuroscience, Clinical neuroscience

Spinal cord sTimulation thEraPy for Parkinson's Disease patients with gait problems

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Gait difficulties are common in Parkinson's disease (PD) and cause significant disability. No treatment is available for these symptoms. Spinal Cord Stimulation (SCS) has been found to improve gait, including freezing of gait, in a small number of PD patients. The mechanism of action is unclear and some patients are nonresponders. With this double-blind sham-controlled proof of concept and feasibility imaging study, we aim to shed light on the mechanism of action of SCS and collect data to inform development of a scientifically sound clinical trial protocol. We also hope to identify imaging biomarkers at baseline that could be predictive of a favourable or a negative outcome of SCS and improve patient selection. Patients will be assessed with clinical rating scales and gait evaluations at baseline and 6 and 12 months after SCS. They will also receive serial 18F-FDG and ([18F]FEOBV) PET scans to assess the effects of SCS on cortical/subcortical activity and brain cholinergic function.

Keywords: Clinical neuroscience, Medical technology and diagnostic techniques, Basic neuroscience

Natural history of painful and non-painful diabetic polyneuropathy

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Background: Diabetic polyneuropathy (DPN) is a common complication of type 2 diabetes (T2D). Up to 50 % of patients with DPN suffer from neuropathic pain (P-DPN). The relationship between severity in sensory symptoms, signs and the development of pain in DPN is relatively unstudied. Neuroinflammation is thought to contribute to the development of DPN and P-DPN. There is a lack of prospective studies on DPN and P-DPN.

Aim: To study the development of DPN and pain in patients with T2D over time, identify risk factors and describe the natural history of nerve changes that occur during the course of the disease.

Methods: Originally, 389 patients with newly diagnosed T2D and a likelihood of DPN as assessed by questionnaire and 97 healthy controls were recruited to establish the diagnosis of DPN. All participants from the baseline study will be invited for a 5 year follow up examination

Studies:

- In study 1 we plan to describe the development of DPN over time. We hypothesize that DPN presence and severity will increase over time causing a diagnostic shift in the overall DPN group towards more diagnostic certainty.
- In study 2 we plan to describe the development of dysesthesia and pain over time. We hypothesize that patients with P-DPN will have more pronounced sensory loss compared to baseline, and that non-painful dysesthesia predicts the development of P-DPN.
- In study 3 we plan to characterize morphological changes in intraepidermal nerve fibers and to identify markers that are increased in patients with P-DPN compared to DPN.

Perspectives: With the lack of prospective studies in DPN, this study will provide a unique insight into the natural history of DPN and P-DPN.

Keywords: Clinical neuroscience, Inflammation, Molecular metabolism and endocrinology

The HortONS study: Treatment of chronic cluster headache (Horton's headache) with transcutaneous electrical nerve stimulation and occipital nerve stimulation

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Background

Chronic cluster headache (CCH) is a rare but debilitating primary headache disorder characterized by attacks of one-sided severe pain with no attack-free periods lasting longer than three months. CCH is often medically refractory, leaving the patients with no sufficient treatment options. Occipital nerve stimulation (ONS) has been suggested as a possible treatment for CCH where all conventional treatment options seem exhausted. Conventional ONS results in perceptible paraesthesias, however newer stimulation paradigms offer paraesthesia-free stimulation enabling conduction of a blinded study, as patients do not percieve any sensation of stimulation.

Methods

The study is a blinded, randomized, placebo-controlled trial overall consisting of three phases:

1. TENS study: Treatment with transcutaneous electrical nerve stimulation (TENS), placing the electrodes over the greater occipital nerves.

2. Placebo vs. paraesthesia-free ONS study: Participants will have an ONS system implanted and will be randomized 1:1 to either placeboor paraesthesia-free stimulation.

3. Conventional ONS study: All ONS systems will be adjusted to conventional paraesthesia-inducing stimulation.

Results

The aim of the study is to evaluate:

1. The efficacy of TENS as a treatment for CCH

2. Paraesthesia-free ONS compared with placebo

3. Paraesthesia-free ONS in a head-to-head setting with coventional ONS

4. TENS as a screening tool for the outcome of ONS treatment

Conclusion

We wish to validate the the effect of ONS as treatment for medically refractory CCH and to demonstrate that TENS of the occipital nerves can be used to predict which patients who will benefit from the ONS treatment.

Keywords: Clinical neuroscience, Other, Other

Non-classical GABAergic cortical neurons and neurovascular coupling in healthy and Alzheimer's Disease model mice

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Marco Capogna, Department of Biomedicine, DANDRITE and PROMEMO; Leif Østergaard, CFIN, Institute for Clinical Medicine; Eugenio Jimenez Gutierrez, CFIN, Institute for Clinical Medicine.

Neurovascular coupling (NVC) mechanisms adjust cerebral blood flow to provide energy substrates delivery to support brain functions. Excitatory neuronal activity modulates the release of vasoactive molecules that target the neurovascular unit, regulating the capillary and arteriole blood flows. "Non-classical" inhibitory gamma-aminobutyric acid (GABA)ergic interneurons (INs) are also enriched with vasoactive substances. INs have close associations with cerebral capillaries, yet their role in regulating capillary flows remains poorly understood. In this study, we focus on the role of a recently described neocortical layer-1 population of INs (NDNF-INs) in regulating capillary flows. We will evaluate capillary hemodynamics during activation of INs using optogenetic stimulation and two-photon microscopy in awake transgenic mice. Our preliminary results show that optical stimulation of NDNF-INs at physiological theta frequency (4 Hz, 2 sec) evoke transient changes in capillary consisting of a transient increase in red blood cells velocity (RBCv) consistent with a vasodilator effect. The response was delayed as compared to the typical vascular response evoked by whiskers' air puffs. Our study supports the role of INs during NVC. The robust and delayed response to functional activation suggests that this group of INs is likely to be implicated in the post-stimulus undershoot observed in the blood-oxygen-level-dependent imaging (BOLD) used in functional magnetic resonance imaging (fMRI).

Keywords: Clinical neuroscience, Basic neuroscience, Animal models/disease models

Combined Deep Learning and Advanced Imaging for Improved Individualized Radiotherapy Target Definition in Glioblastoma Patients.

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Slávka Lukacova, Department of Oncology;

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Glioblastoma is the most aggressive type of cancer that has origin in the brain. Patients with this diagnosis has a median life expectancy of 14 months, with treatment. The treatment is radiotherapy(RT), and the radiation target is the visible part of the tumor. To account for microscopic disease, a 2 cm margin is added around the visible tumor. This results in a large volume with treatment related toxicity and consequently, a lot of healthy brain tissue get damaged in the process. The hypothesis is that using an individualized RT target that acknowledges anatomical boundaries and preferred tumor growth along white matter tracts, i.e. the highways of the brain, is superior. This project aims to improve the target definition by using a combination of deep learning(DL) and mathematical modelling(MM).

To improve the target definition we need knowledge of how the tumors tend to evolve in the brain. We know that there are anatomical boundaries, that the tumor will not cross, e.g. cerebellum and falx. The first part of the project is to automate the process of delineation using a convolutional neural network on MRI and CT images. Preliminary results show that we have satisfactory auto-segmentations of cerebellum. Further development for the falx is necessary.

In the second part we employ a MM, the Fisher-Kolmogorov growth model, to estimate the growth of the tumor using biological information. The model will use the automatically generated information on the anatomical boundaries from the first stage. The resulting DL MM-based target will be compared to the standard target for tumor coverage and unnecessary inclusion of healthy brain in a prospective cohort of 300 GBM patients.

Keywords: Oncology, Medical technology and diagnostic techniques, Other

Evaluation of electro-clinical findings using standardized feature extraction and machine learning

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My abstract is the description of my project, thus co-authors not relevant. The abstract is approved by the main supervisor:

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Epileptic seizures are classified as generalized and focal. Although the two seizure types have different electroclinical manifestations, those may be challenging to distinguish, as overlap exists. Long-term video EEG recording has paramount importance in the accurate diagnosis, treatment choice and pre-surgical evaluation of epilepsy patients. However, free-text EEG reports entail a high inter-rater variability, thus a standardized reporting is needed. Additionally, the clinical relevance of the electroclinical signs is not yet fully elucidated, with previous studies exhibiting conflicting results.

We aim to investigate the electroclinical features of drug-treated patients with idiopathic generalized epilepsy (IGE), and patients with focal epilepsy (FE) with a favorable outcome after epilepsy surgery. For this purpose, a retrospective analysis of video-EEG recordings from a large database from Danish Epilepsy Hospital is performed. The patients´ electroclinical features are extracted by using a standardized computer- based software in order to reduce the inter-observer variability. After data extraction, machine learning will be applied to test whether any features are classifiers predicting the IGE patients´ outcome, or correlate with the FE patients´ epileptogenic focus.

Our overall objective is to improve the clinical interpretation of video EEG recordings and to determine the electro-clinical correlations with the patients' focus localization and therapeutic outcome. This will improve diagnosis, classification and presurgical evaluation of patients with epilepsy.

Keywords: Other, Other, Other

Navigating Chronic Uncertainty: A mixed methods study on test practices and decision-making during COVID-19

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Background:

The SARS-CoV-2 has surpassed 244.5 million confirmed cases globally and challenged national healthcare systems worldwide. Testing is a vital weapon in the battle against COVID-19, because it provides a window into the pandemic that allows us to identify infected individuals, track chains of transmission, allocate medical resources, and assess interventions to reduce infection rates. However, we have yet to understand how people use tests for COVID-19, and how they manage the dilemmas that emerge from the decision to test or avoid testing. It is important that we understand these dilemmas and decision-making practices, as they may have significant impact on the spread of infection and the ability to identify chains of infection.

Aim:

The study explores how and why people use tests for COVID-19 to navigate uncertainty and make decisions in everyday life, and how they manage the dilemmas that emerge from the decision to test or avoid testing.

Methods:

The first phase of the study consists of an ethnographic field study to develop an in-depth understanding of test practices through participant observation and interviews with citizens and testing personnel. The second phase utilizes the findings from the first phase to develop a survey with relevant questions and variables to be tested in a larger sample.

Perspectives:

The findings are used to develop policy recommendations for the health authorities that address the multitude of dilemmas that emerge from test practices and the decision to test. These recommendations can be used to communicate proper test practices and guide public behaviour now and in future societal health crises.

Keywords: Qualitative research, Public health, Medical technology and diagnostic techniques

Prevalence and prognosis of epileptic seizures in children with brain tumors - a national retrospective study

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Approximately 40 children are diagnosed with a brain tumor each year in Denmark. Epileptic seizures are one of the most common symptoms associated with this diagnosis (~20%). It is seen both as a presenting symptom and as sequelae to the oncological treatment. This study aims to identify risk factors for developing seizures in children with brain tumors.

Journals from children treated for brain cancer in Denmark at either of the four university hospitals from 2011-2020 are being reviewed. An estimate of 400 children will be included in the study population with app. 80 of those expected to have experienced epileptic seizures.

We wish to describe both frequency and semiology of seizures and examine whether there is an association to different aspects of the brain tumor incl. location, histology, treatment, etc.

Furthermore, we wish to investigate whether the seizures can lead to delay in the oncological treatment or a reduction in the chemotherapy dose. If this delay can lead to a recurrence of the tumor or a reduced effectivity of the treatment, it is something that is important to elucidate.

The prognosis is variable for epileptic seizures that occur due to a brain tumor or as a toxicity to the treatment. It is a poor prognostic sign if there are tumor remnants left after surgery and if the seizures are a symptom of recurrence of the cancer. Further research is needed to find more prognostic signs, both positive and negative to make the best treatment regimens possible.

Keywords: Paediatrics, Oncology, Basic neuroscience

Flash talk session 13

Preclinical trials of novel treatments of Ethylmalonic Enchephalopathy

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Sulfur-containing compounds play essential roles in human biology. The gasotransmitter, hydrogen sulfide (H2S / sulfide), is one example which despite its chemical simplicity plays a complex role in our organism and has attracted huge attention in recent research.

At Research Unit for Molecular Medicine, we have utilized state of the art image cytometry and mass spectrometry to phenotypically characterize cells from patients with a fatal, currently incurable, monogenic disorder of sulfur metabolism. The disease, Ethylmalonic Enchephalopathy (EE) is named after two of the cardinal symptoms: Early onset encephalopathy and ethylmalonic aciduria. Patients with this rare disease, fail to fully oxidize sulfide and live short lives with severe morbidity affecting the muscle, kidneys, liver, and the entire cerebral, cardiovascular and gastrointestinal systems.

Our research has proven patient dermal fibroblasts to be a useful model for the disease. Our proteomics and metabolomics analyses have shown wide-ranging dysregulation of central metabolites and proteins. We have now proposed several novel treatment strategies to cure the altered cellular biology. Knowing the dysregulated panel of proteins and metabolites, we will apply the same methods, while testing these novel treatments' efficacy in our model and verify the efficacy anf hypothesized modes of action.

Our preliminary data suggests that at least one treatment can significantly improve upon the EE phenotype, and a mouse trial in an established knockout model is being designed.

Keywords: Animal models/disease models, Laboratory science, Molecular metabolism and endocrinology

Therapeutic Targets in Depression and Pain: Modulation of Function and Pharmacology by Lipids

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S. Sinning, Department of Forensic Medicine, Bioanalytical Unit

A majority of small molecule therapeutics target transmembrane receptors and transporters. This highlights the immense importance of membrane proteins and their functions.

Membrane proteins are embedded in the plasma membrane, an ordered bilayer consisting of different types of phospholipids and cholesterol, and as such, they interact with and are affected by both the aqueous intra- and extracellular environments and the lipids of the membrane. So far, the contribution of the lipid environment towards membrane protein function has been largely neglected due to the daunting complexity of the membrane environment.

However, recent research shows that membrane proteins seek out distinct membrane microdomains and concentrate specific lipids in their surroundings as well as bind certain lipids to specific binding sites. This interplay can have profound ramifications for both the function and pharmacology of membrane proteins. Lipids may exert their effect on membrane protein function by either binding directly to the protein or by changing local biophysical characteristics (thickness, curvature, lateral pressure, fluid/liquid states, viscosity etc.). Both contributions are important, but both have also been widely ignored.

Using a novel approach combining gentle detergent free solubilization of the cell membrane by nitrogen cavitation, which preserves the native lipid environment, followed by affinity purification and native mass spectrometry, we aim to identify and characterize the functional role of key lipids interacting with two membrane proteins, the human seronin transporter (hSERT) and the cannabinoid receptor 1 (CB1R), which are important in a number of diesase states.

Keywords: Basic neuroscience, Pharmacology, Cell biology

Post-translational modification derived from acetoacetyl-CoA

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Background:

Ketone bodies are mainly produced by the liver and used as an alternative energy source when glucose is not available. Increasing data suggest that elevated ketone bodies may improve several age-related diseases. Animals with an elevation of ketone bodies showed that the onset of age-related diseases was delayed and the overall longevity was prolonged in monkeys. Acetoacetate, one of the ketone bodies, is metabolized to acetoacetyl-CoA (AcAcSCoA) that consists of a thioester which chemically can undergo several types of reactions.

Aim:

The aim is to identify possible protein targets modified by AcAcSCoA in HEK293 cells and look into how these may affect the functionality of the protein. Our hypothesis is that the thioester on AcAcSCoA is reactive towards nucleophilic and electrophilic amino acids on proteins.

Methods:

Possible protein targets are identified by a chemical probe resembling the structure of AcAcSCoA. Proteins susceptible to react with AcAcSCoA are identified by applying proteomics.

Results:

We have succeeded in elucidating 129 proteins reactive towards our probe. These modifications were identified mainly on serine and lysine residues but also cysteine and threonine residues were identified as potential sites. Furthermore, the modifications have also been identified on single amino acids and on model peptides. All these data might indicate that serine modification is driven by a cysteine residue close to the modification site.

Future perspective:

Based on the results obtained so far, we will do some follow-up studies looking into how these identified modifications will affect the protein by performing functional studies.

Keywords: Cell biology, Molecular metabolism and endocrinology, Other

Chimeric antigen receptor T-cells targeting acute myeloid leukemia

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Background

The approval of anti-CD19 chimeric antigen receptor (CAR) T-cell therapy for B-cell non-Hodgkin lymphoma has validated CAR T-cell therapy as a new treatment approach. Acute myeloid leukemia (AML) is an aggressive hematological malignancy with high relapse rate and poor treatment options leading to a high mortality rate. Severe AML is associated with upregulation of FLT3 expression making it an ideal target for CAR T-cell therapy. Therefore, the goal of the current project is to construct a CAR T-cell that targets the surface extracellular domain of the FMS-like tyrosine kinase 3 (FLT3) on AML.

Approach

Preparation of CAR T-cell constructs will rely on elements previously documented to work such as the anti-FLT3 scFv with a 4-1BB intracellular signaling domain. We are exploring a CRISPR/Cas-mediated delivery mode for genomic integration of the gene encoding the CAR and will be comparing this to standard lentiviral vector delivery. We will use the clinically approved anti-CD19 CAR construct as a positive control. T-cells will be isolated using a pan T isolation kit and CAR T-cells will be generated with the two manufacturing techniques and compared in vitro on FLT3-positive target cells in terms of CAR integration efficacy and cellular viability. The potency of the CAR T-cells will be tested on cell lines inherently expressing the antigen as well as cell lines with induced expression of the target antigen evaluating both the on target and off target cytotoxicity of the CAR T-cells. We anticipate to identify optimal CAR T-cells and validate them in an in vivo mouse model utilizing target cell lines and patient-derived malignant cells.

Keywords: Cell biology, Genetic engineering, Oncology

Understanding Biomechanical Deficits of Diabetic Myopathy

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Prof. Henning Andersen, Dept. of Neurology, AUH, Denmark (Main supervisor),

Prof. Jens Meldgaard Bruun, Steno Diabetes Center, AUH, Denmark (Co-supervisor),

Postdoc Michael Væggemose, The MR Research Centre, AUH, Denmark (Co-supervisor)

Background: There is an unmet understanding of muscle dysfunction in diabetes, which is increasingly considered an important contributor to biomechanical and metabolic muscle deficits. It is known that diabetic neuropathy (DPN) results in atrophy and muscle weakness. Still, the effects of diabetes and obesity on biomechanical muscle function, unrelated to DPN, are largely unknown. Regrettably, this results in how muscle impairment in diabetes goes unnoticed, leading to dysregulation of diabetes with increased risk of complications, morbidity and mortality.

Aim: We aim to assess if diabetes and obesity are independently related to biomechanical muscle deficits, and how biomechanical changes relate to metabolic properties of diabetes and obesity.

Methods: We propose a project aiming to isolate and assess the effects of obesity and hyperglycemia on biomechanical muscle function. The effects of prolonged hyperglycemia will be assessed in participants with dysregulated type 1 and 2 diabetes prior to and 6 months following glycemic control. The effects of obesity will be assessed in obese subjects with and without type 2 diabetes prior to and following bariatric surgery. Muscle evaluation includes muscle strength and power examinations, functional tests, and dedicated MR imaging and spectroscopy techniques.

Implications: We propose a highly interdisciplinary 'close to the clinic'-approach to improve our understanding of diabetic myopathy, ultimately to improve patient care. We hope the proposed project could prove to be a steppingstone to define diabetic myopathy, and possibly change future guidelines for management and intervention in patients with diabetes and obesity.

Keywords: Molecular metabolism and endocrinology, Medical technology and diagnostic techniques, Other

Metabolism of working skeletal muscle with ageing during ketosis

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K. Overgaard, Department of Public Health

Background: During ageing skeletal muscle function decreases. Also, muscle metabolism is changed which increases the risk of type 2-diabetes. Ketone bodies, namely β-hydroxybutyrate (3-OHB), may change skeletal muscle substrate preferences during muscle work and in heart muscle, 3-OHB increases the pumping capacity proposedly due to improved metabolic efficiency. However, the effects of 3-OHB on skeletal muscle efficiency and metabolism during ageing are not known. Aim: The current study aims to investigate 1) how ketone bodies affect muscle efficiency and fatiguability during ageing, and 2) the effects of age and 3-OHB on muscular and whole-body metabolism during muscle work. Methods: Two groups of healthy participants will enrol in a cross-over study: a young group aged 20-25 years and an older group aged 65+ years. Participants will take part in two study days in randomized order: One day with 3-OHB infusion, another day with saline infusion. We will evaluate muscle efficiency of the tibialis anterior muscle during fatiguing ankle flexion/extension-exercise with a controllable, MR-compatible dynamometer. Simultaneously, ATP turnover will be measured by 31P-MR spectroscopy. We will assess muscle and whole-body metabolism over 1 hour of constant load cycle ergometer exercise by 3H-labelled palmitate tracer infusion, blood samples, indirect calorimetry, and muscle biopsies. Lastly, whole body fatiguability will be assessed based on an all-out cycle test. Perspectives: Understanding how muscle function and metabolism changes during ketone-body infusion in young and old subjects may result in novel prevention strategies of age-related muscle weakness and type 2 diabetes.

Keywords: Molecular metabolism and endocrinology, Multimorbidity, Medical technology and diagnostic techniques

Metabolic effects of the ketone body, 3-hydroxybutyrate, in patients with type 1 diabetes and healthy controls

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Background and aim:

The ketone body, 3-hydroxybutrate (3-OHB), is an alternative energy substrate and signaling metabolite produced from free fatty acids (FFA) in the liver. 3-OHB inhibits lipolysis in adipocytes and decreases FFA release, creating a negative feedback loop that controls further 3-OHB production.

In patients with type 1 diabetes (DM1) extremely high plasma levels of 3-OHB is observed in the severe condition, diabetic ketoacidosis. This may possibly be explained by an impaired 3-OHB mediated regulation of lipolysis. The aim of this study is to examine the metabolic effects and interactions of 3-OHB in patients with DM1 and healthy controls.

Materials and methods:

10 patients with DM1 and 10 healthy controls will be included in a randomized, crossover trial with two interventions: 1) 3-OHB infusion, 2) Saline infusion (control).

We will use palmitate tracer flux, circulating FFA concentrations and adipose tissue biopsies to asses lipolysis and signaling pathways involved in 3-OHB mediated regulation. With glucose and amino acid tracers we will quantify glucose and protein turnover, and skeletal muscle biopsies will be obtained to explore signaling pathways and measure mitochondrial function during 3-OHB infusion. Moreover, echocardiography will be performed to examine possible cardiac effects.

Perspectives: This study may reveal novel information about 3-OHB effects and regulation, including regulatory targets related to diabetic ketoacidosis, in patients with DM1 as well as in healthy subjects.

Keywords: Molecular metabolism and endocrinology, Laboratory science, Pharmacology

The effect of a new plant-based supplement on recovery and subsequent athletic performance

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Background

Post-exercise carbohydrate and protein (CHO-PRO) intake has been proposed to improve subsequent endurance performance by increasing the rate of muscle glycogen re-synthesis. Our aim: to compare the effect of a new plant-based supplement (VEG) to an isocaloric CHO-only control (CON) on recovery and subsequent athletic performance. The VEG supplement contains CHO-PRO encapsulated in an alginate hydrogel structure, which is thought to slow down digestion in the proximal gastrointestinal tract, resulting in a prolonged release of CHOs after intake compared to CON

Method

In a randomized, cross-over, clinical trial 14 men completed a preliminary test and 2 experimental days separated by ~6 days. An experimental day consisted of an exhaustive exercise bout followed by 5 hours of recovery and subsequent time-to-exhaustion (TTE) performance test. Subjects ingested either VEG or CON during the first 2 hours of recovery. Blood samples were measured at baseline, during the recovery period and post TTE

Results

During recovery a significantly higher plasma insulin and glucose response was found after intake of CON compared to VEG ($p<0.05$). Intake of VEG increased plasma glucagon, free fatty acids (FFA) and glycerol significantly compared to CON ($p<0.05$). No differences were found in TTE between treatments ($p=0.12$)

Conclusion

No significant differences in TTE performance between treatments were found. The increased glucagon, FFA and glycerol responses during recovery from exhaustive exercise combined with a well-maintained performance following recovery suggest that the slowed CHO release from the VEG supplement is compensated for metabolically by increased lipid turnover.

Keywords: Public health, Molecular metabolism and endocrinology, Other

ASSOCIATION BETWEEN B12 DEFICIENCY AND NEUROFILAMENT LIGHT CHAIN AND NEUROPATHY IN ADOLESCENTS WITH TYPE 1 DIABETES

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Background: Neuropathy is a well-known complication to diabetes. However, still little is known about biochemical factors to detect early signs of neuropathy in younger patients. The aim of this study is to investigate the association between neuropathy and vitamin B12 (B12) deficiency and the nerve damage biomarker, Neurofilament light chain (NfL), in adolescents with type 1 diabetes (T1D).

Methods: Blood samples from 60 adolescents (15-18 yrs) with T1D and 20 healthy controls will be analyzed as part of the clinical research study "Early detection of neuropathy in adolescents with type 1 diabetes". Serum levels of vitamin B12, vitamin B12-TC-bound and NfL will be determined by immunoassays, while methylmalonate will be determined by mass spectrometry. Analyzes will take place at Department of Clinical Biochemistry, Aarhus University Hospital. The biochemical markers will be compared to the results from neurological tests, testing for both large fiber, small fiber and autonomic neuropathy.

Results: In the group of adolescents with T1D, associations between levels of B12 and NfL with findings of neuropathy will be analyzed. Results from patients with T1D will be compared with results from healthy controls.

Conclusion: This project will investigate a possible association between B12 deficiency and NfL-levels with diabetic neuropathy in adolescents with T1D. Hopefully, in the future biochemical markers can be a useful screening method to earlier detect neuropathy.

Keywords: Paediatrics, Clinical neuroscience, Laboratory science

Flash talk session 14

Cardiovascular risks and benefits associated with Non-Steroidal Anti-Inflammatory Drug use following acute pericarditis: a Danish nationwide cohort study

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Kasper Bonnesen, Department of Clinical Epidemiology

Lars Pedersen, Department of Clinical Epidemiology

Vera Ehrenstein, Department of Clinical Epidemiology

Henrik Toft Sørensen, Department of Clinical Epidemiology

Morten Schmidt, Department of Clinical Epidemiology and Department of Cardiology at Aarhus University Hospital.

Introduction:
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are generally considered contraindicated in individuals with or at high risk of cardiovascular events, the exception being acute pericarditis where NSAIDs function as treatment. However, while reducing symptoms and recurrence of pericarditis, NSAID use may also increase the risk of other cardiovascular events. We aim to assess the cardiovascular benefit-risk balance of NSAID use in patients with first-time pericarditis.

Methods:
We conducted a cohort study based on Danish population-based nationwide registries. We identified all patients aged ≥18 between 1995–2016 with a first-time, primary or secondary, in- or outpatient diagnosis of pericarditis. We excluded patients with a redeemed prescription of any NSAID within 180 days prior to their hospital admission date.

We used a Cox proportional-hazards regression to calculate hazard ratios for the association between NSAID use and readmission for pericarditis, myocardial infarction, ischemic stroke, and all-cause death. We computed risks using the cumulative incidence function.

Results:
Pending.

Conclusion:
This is the first population-based study assessing the cardiovascular risks and benefits of NSAID use in patients with first-time pericarditis. The results will aid clinicians when deciding on pericarditis treatment.

Keywords: Epidemiology and biostatistics, Cardiovascular system, Inflammation

Does prenatal exposure to nitrate cause early puberty and poor semen quality?

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Background: The decreasing age at pubertal development and poor semen quality are two concerning aspects of reproductive health, and the causes for these are still not well understood. Growing evidence suggests that exposures in fetal life might impact reproductive health. Nitrate, a common component in vegetables and drinking water, is suggested to have a negative effect on the unborn child. When nitrate is ingested with nitrosatable drugs, teratogenic compounds can be formed. To our knowledge, this is the first study investigating potential effects on pubertal development and semen quality.

Aim: We aim to investigate if prenatal exposure to maternal intake of nitrate and nitrosatable drugs affects pubertal development in sons and daughters and semen quality in sons.

Methods: Our study population consists of mother-child pairs enrolled during pregnancy in the Danish National Birth Cohort in the period from 1996 to 2002. Information on pubertal development is available from 15,819 sons and daughters, who delivered half-yearly information on their current pubertal stage from age 11 years throughout puberty. Semen samples are analysed in 1,058 adult sons. Nitrate intake from diet together with nitrosatable drug use during pregnancy will be estimated by combining self-reported information with register information on prescribed drugs. Nitrate intake from drinking water will be estimated by linking yearly quality measurements on nitrate concentrations in Danish drinking water with the mother's residential address.

Perspectives: If nitrate is established as a potential cause of impaired reproductive health, regulations can be made.

Keywords: Epidemiology and biostatistics, Public health, Other

Comorbidity, Malnutrition, and Socioeconomic Markers as Risk Factors for Post-surgery Infections among Patients with Hip Fracture

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Hip fracture is a major and increasing burden on healthcare worldwide. In Denmark there have been improvements in quality of treatment and in-hospital care of hip fracture patients as well as a decrease in 30-day and 1-year mortality. Yet, an increase in risk of infection has been observed.

The risk of developing infection after hip fracture surgery depends on the interplay among multiple patient-, surgery-, and healthcare-related factors, many yet to be uncovered. It is unclear which factors contribute the most to the risk of infection in hip fracture patients and through which clinical pathways. In everyday clinical practice the risk factors comorbidity, malnutrition and low socioeconomic status seem to be of high importance and possible relationship.

We will collect data from Danish databases and examine how these three factors interrelate in regards to infection after hip fracture surgery and examine whether different comorbidity indices are predictive of infection, in order to aid clinical preventive measures.

Keywords: Epidemiology and biostatistics, Orthopedic surgery, Infection

Triglycerides in early type 2 diabetes and risk of cardiovascular disease: A Danish cohort study

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Aim: To investigate the association of triglycerides (TGs), including the interaction with low-density lipoprotein cholesterol (LDL-C), with risk of cardiovascular disease (CVD) in type 2 diabetes (T2D) patients.

Methods: Using medical registries, we studied patients residing in Northern Denmark diagnosed with T2D, 2002–2016. Patients were grouped based on their TG and LDL-C level 6 months after the first diabetes record. Patients were then followed until a hospital-diagnosed CVD event (myocardial infarction [MI], coronary revascularization [CR], stroke, and cardiac death), death, emigration, or study end. We used Cox regression to compute adjusted hazard ratios (aHRs), while controlling for CVD risk factors.

Results: Among 59,524 T2D patients, the rate of CVD events (median 5.8 years follow-up) for high (≥2.3 mmol/L) versus normal TGs (≤1.69 mmol/) was: 6.2 vs 5.0 per 1000 persons-years for MI, 9.4 vs 6.7 for CR, 6.9 vs 6.3 for stroke, and 9.9 vs 9.1 for cardiac death (aHRs: 1.25 [95% CI 1.13-1.40]; 1.31 [1.20-1.44]; 1.18 [1.07-1.30]; 1.17 [1.08-1.38]). Compared to patients with normal LDL-C(≤1.79 mmol/L)/normal TGs, those with normal LDL-C/high TGs had aHRs of 1.21 (0.92-1.58) for MI, 1.42 (1.14-1.76) for CR, 1.18 (0.94-1.47) for stroke, and 1.08 (0.91-1.29) for cardiac death. Those with high LDL-C (≥2.6 mmol/L)/normal TGs had aHRs of 1.60 (1.34-1.91), 1.92 (1.65-2.25), 1.10 (0.95-1.29), and 0.90 (0.80-1.02). Patients with high LDL-C/high TGs had aHRs of 1.80 (1.84-2.19) for MI, 2.32 (1.97-2.73) for CR, 1.29 (1.09-1.53) for stroke, and 1.03 (0.89-1.18) for cardiac death.

Conclusion: Elevated TGs associated with increased CVD risk. High LDL-C may further amplify that risk.

Keywords: Epidemiology and biostatistics, Cardiovascular system, Other

Fracture Risk in Danish Patients with Anorexia Nervosa: A 40-year-cohort-study

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Background:

Anorexia Nervosa (AN) is primarily a psychiatric disorder characterized by self-induced starvation, fear of weight gain, and a distorted body image causing severe undernutrition with secondary endocrine and metabolic changes, which may reduce bone mineral density (BMD) and increase the risk of bone fractures. AN is often diagnosed in adolescence which is a crucial time for obtaining maximal peak bone mass. Several previous studies have shown reduced BMD, but knowledge on fracture risk is sparse.

Methods:

From the Danish Health Registries we retrieved data on all patients diagnosed 1977-2017 with AN (Diagnosis code: F50.0 and F50.1) and a 1:10 age- and gender-matched population comparison cohort.

We computed cumulative incidence rates (IRs) of any fracture and specific fracture types per 1000 person-years in both cohorts during the study period and applied Cox proportional hazard model to compute hazard ratios as a measure of incidence rate ratios (IRRs) with 95% confidence intervals (CI), stratified by age and gender, comparing patients with AN with the controls.

Results:

We identified 14,774 patients with AN, including 93% women and 56% of the patients diagnosed at age 15-24.

Patients with AN had 30% more fractures than comparisons (17.0% vs. 13.0%)

We found an overall incidence rate ratio (IRR) for all fractures of 1.43 (1.37-1.49) for AN compared to comparisons. The fracture risk was increased on typical osteoporotic sites:

lumbar spine: IRR=2,40 (2.01-2.86), femur: IRR=2.56 (2.17-3.01) and forearm: IRR=1.54 (1.41-1.67)

Conclusion:

We found more fractures and overall increased fracture risk in patients with AN (43%) with highest risk at typical osteoporotic sites.

Keywords: Epidemiology and biostatistics, Molecular metabolism and endocrinology, Other

Impact of cancer-directed treatments on the risk of acute kidney injury: a population-based study

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Background: Acute kidney injury (AKI) is a common complication in cancer patients as approximately 27% of all cancer patients develop AKI during the first five years after the cancer diagnosis. Several cancer-directed treatments including cancer-directed surgery and anticancer drugs are linked to kidney impairment and may contribute to the high risk of AKI. However, for a large part of the treatments the evidence is based on case reports, non-comparative cohort studies or animal models. Consequently, the impact of numerous cancer-directed treatments on the risk of AKI in routine clinical care remains unclear and we aim to address this knowledge gap by examining the effect of such treatments on the risk of AKI using data from nationwide clinical registries.

Methods: We will apply a case-time-control design to evaluate the transient effect of cancer-directed treatments on the risk of AKI in cancer patients using data from the Danish medical registries from 2010 to 2020. In the case-time-control design, we will identify cancer patients with AKI within the first two years after cancer diagnosis and compare the use of treatment in the hazard period (1-30 days before AKI) with the use of treatment in the comparison period (61-90 days before AKI). A comparison group of cancer patients without AKI will be in included to adjust for time trends of exposure. We will use logistic regression to compute odds ratios.

Results: No results yet.

Perspective: Information about cancer treatment-related risk factors for AKI will be central in identifying potential modifiable risk factors as targets for prevention of AKI in cancer patients.

Keywords: Epidemiology and biostatistics, Nephrology, Oncology

Longitudinal alcohol consumption trajectories during adulthood and risk of female breast cancer – is it ever too late to change alcohol consumption behavior?

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Alcohol consumption has consistently been associated with risk of female breast cancer (FBC), which is the type of cancer that causes most deaths in women worldwide. However, most studies have assessed alcohol consumption at one point in time, typically at recruitment, or used a weighted average of alcohol intakes at different ages to reflect lifetime alcohol exposure. Such approaches do not reflect intra-individual variations in alcohol consumption across adulthood. Alcohol consumption behaviors fluctuate across the lifetime and these fluctuations may associate differently with the risk of FBC, and hormone receptor status subtypes. Using longitudinal data on alcohol consumption to identify consumption trajectories across adulthood by growth mixture models allows investigation of associations between different alcohol consumption patterns during adulthood and the risk of FBC. Thus, based on data from two large cohorts; the European Prospective Investigation into Cancer and Nutrition Cohort (EPIC) and the Diet, Cancer and Health Cohort (DCH), this Ph.D. project aims to determine alcohol consumption trajectories during adulthood and investigate associations between these trajectories and risk of FBC. Furthermore, based on the newly established cohort, Diet, Cancer and Health – Next Generations, this project examines whether trajectories similar to those determined in the DCH and EPIC cohorts can be found in young women today to estimate the future burden of FBC due to alcohol consumption. This project contributes to a better understanding of the role of alcohol consumption throughout a woman's life and the risk of FBC which may lead to a decreased population burden of FBC.

Keywords: Epidemiology and biostatistics, Public health, Oncology

Stability of diagnostic labelling of psychiatric outpatient visits: An investigation into the transition from the second (LPR2) to the third (LPR3) version of Landspatientregistret

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Background

In Denmark, data on hospital contacts are reported to Landspatientregistret (LPR). One of the most frequently used LPR parameters in psychiatric research is the main diagnosis (aktionsdiagnosen), which describes the most important (mental) disorder currently being treated. With the transition from the LPR2 (the second version of LPR) to LPR3 (the third version of the LPR) on the 15th of February 2019, the way main diagnoses were labelled in relation to outpatient visits changed substantially. Specifically, under the LPR2 paradigm, a connected series of outpatient visits were ultimately coded with only one main diagnosis, representative of this entire treatment course. With the advent of LRP3, coding regulation was updated. Since then, every single outpatient visit has been labelled with a main diagnosis to cover that specific visit only. This change in practice may have caused a destabilisation of diagnostic labelling that poses a threat to the many research activities that rely on the main diagnoses as either exposure or outcome.

Methods

Electronic health record data for all psychiatric hospital outpatient visits in the Central Denmark Region from the advent of MidtEPJ (2011) to the present day will be examined. Descriptive statistics will be applied to determine whether the transition from LPR2 to LPR3 has led to changes in the diagnostic.

Discussion

Data-analysis is ongoing. The initial results are promising with regard to diagnostic stability across the transition from LPR2 to LPR3. The final results will be shown at the PhD day.

Keywords: Other, Epidemiology and biostatistics, Medical technology and diagnostic techniques

Low-dose-Ketamine as an adjunct to morphine for acute pain in the ED: A protocol for a randomized, double-blinded, superiority trial

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Background: Sixty percent of the yearly 1.8 million emergency contacts to the Danish hospitals arrive from patients in pain. Still, ineffective analgesia is common in the emergency department (ED) and pain management is a challenging part of emergency medicine. Even more challenging are the needs of opioid-tolerant patients, as they need much larger doses of opioids for pain relief than others – which for a number of reasons they often do not receive. The difficulties in pain treatment in the ED, and in particular of opioid-tolerant patients, call for clinical studies investigating effect and safety of alternatives. Low-Dose-Ketamine (LDK) is found useful for pain reduction in the postoperative setting for both opioid-naïve and opioid-tolerant patients.

In this study we will evaluate the efficacy and safety of LDK as an adjunct to morphine for treatment of acute pain in the ED.

Hypothesis: LDK as an adjunct to morphine will be superior to morphine alone as regards of analgesic effect. The addition of LDK to morphine will result in a larger pain reduction for opioid-tolerant patients than opioid-naive patients.

Methods: A randomized, double-blinded trial, investigating the combination of LDK and morphine versus IV morphine alone as regards to analgesic effect.

160 patients fulfilling all inclusion criteria and no exclusion criteria will be divided in two groups (opioid-tolerant and opioid-naïve) and randomized in a 1:1 ratio.

Perspectives: This is the first study to examine the effect of LDK as an adjunct to morphine in a general patient population presenting to the ED with pain, and to compare the effect between opioid-tolerant patients and opioid-naïve patients.

Keywords: Pharmacology, Multimorbidity, Epidemiology and biostatistics

Flash talk session 15

Analysis of hormone receptors and HER2 for predicting tumor recurrence and progression in patients with non-muscle invasive bladder cancer.

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T. Ginnerup Andreasen, Department of Molecular Medicine; A. Taber, Department of Molecular Medicine; F. Prip, Department of Molecular Medicine; T. Steiniche, Department of Pathology; J. Bjerggaard Jensen, Department of Urology; and L. Dyrskjøt, Department of Molecular Medicine.

Introduction

Recent expression analyses of non-muscle invasive bladder cancer (NMIBC) tumors have shown high expression of transcription factors such as hormone receptors and tyrosine kinase receptors in patients with different molecular risks of recurrence and progression. The significance of these possible therapeutic targets remains to be investigated, as well as their potential functions as markers to identify molecular subgroups of NMIBC. The aim of this study is to explore the prognostic value of the androgen receptor (AR), progesterone receptor (PR) and HER2, by investigating the protein expression of these receptors in patients with NMIBC.

Materials and methods

Tissue microarrays (TMA) were constructed from selected tumor areas from transurethral resection samples of 167 patients with NMIBC. The TMAs were subjected to immunohistochemical staining for AR, PR, and HER2 as well as cytokeratin to distinguish the carcinoma cells from the stromal areas. To score the staining results digital pathology will be used via Visiopharm software. Cores will be aligned, regions of interest, e.g. tumor and stroma areas, defined, and the fractions of marker positive cells determined. The results will be correlated to clinical outcomes such as recurrence and progression.

Expected findings

Based on prior results from expression data, it is expected that high levels of HER2 is associated with progression and poor outcome. Increased levels of AR and PR are associated with low recurrence rates and high immune infiltration, respectively.

Keywords: Oncology, Urology, Other

Investigating stromal subtypes in the tumor microenvironment of localized prostate cancer using tissue microarrays

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Background: Prostate cancer (PC) is the most frequent cancer type in men in western countries. Non-metastatic PC patients can be treated by radical prostatectomy (RP). However, ~30% of RP patients relapse within ten years and current tools cannot predict which patients will relapse.

Recent research suggest that the stromal composition of the tumor microenvironment, especially cancer-associated fibroblasts (CAF), play a crucial role in PC progression. Thus, we hypothesize that we can identify high-risk RP patients based on differences in prevalence of CAF subtypes and in the stromal composition of PC.

Methods: We will use tissue microarrays (TMA) of RP specimens from AUH (n=803 in total). In these TMAs, 2 cancer cores and 2 adjacent normal (AN) cores are included from each patient. Additionally, we will create a multifocal TMA from RP specimens (n=50). In this TMA, we will include 3 cores from 2 distinct PC foci, 3 cores from AN tissue and 3 cores from prostatic intraepithelial neoplasia (pre-malignant lesion) from each patient. We will stain the TMAs by multiplex immunofluorescence (mIF) for selected stromal- and CAF markers. With mIF we can visualize up to 5 proteins in parallel and by digital pathology analysis we attain the localization and quantity of each protein.

Objectives: We aim to develop a biomarker that can predict relapse after RP to guide personalized treatment selection. We will investigate the stromal composition and the prevalence of CAF subtypes in PC in relation to recurrence-free- and overall survival by mIF in the two TMAs. Furthermore, we will investigate intra-tumour heterogeneity of pre-cancerous and cancerous lesions by mIF of the multifocal TMA.

Keywords: Oncology, Inflammation, Cell biology

Safety and effectiveness of direct oral anticoagulants in patients with nephrotic syndrome: A cohort study.

Sarah Kelddal, Department of Biomedicine

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Background: Thromboembolic events (TE) increase morbidity and mortality in patients with nephrotic syndrome. International recommendations advocate prophylactic anticoagulation in nephrotic patients at high risk of TE; however, no study has identified the best type of thromboprophylaxis. We aimed to assess the safety and effectiveness of direct oral anticoagulants (DOAC) in nephrotic patients.

Methods: Using medical carts, we evaluated TE and bleeding episodes in 21 nephrotic patients treated with DOAC between July 2016 and June 2021, at Department of Renal Medicine, Aarhus University Hospital. Nephrotic patients with a plasma albumin level less than 25 g/L who received DOAC as prophylactic anticoagulation or as treatment for a thrombosis were included. Patient records were used to obtain baseline characteristics and information about TE and bleeding episodes.

Results: We included 21 patients with nephrotic syndrome treated with DOAC. Nineteen patients received DOAC as thromboprophylaxis, and two patients received DOAC due to a previous thrombosis. During DOAC treatment (apixaban, n=10, or rivaroxaban, n=11), no TE were observed, whereas five minor (and no major) bleeding episodes were identified. When compared to non-bleeding patients, those with a bleeding episode were older (median 61 vs 50 years), more often female (80 %), and treated with DOAC for a longer time period (539 days vs 175 days). Neither the HAS-BLED score, nor the GN-risk-score accurately predicted the risk of minor bleeding events.

Conclusions: In this cohort study of patients with nephrotic syndrome, treatment with apixaban or rivaroxaban was associated with no TE and only minor bleeding episodes.

Keywords: Nephrology, Pharmacology, Other

Establishment of novel cellular biomarkers for activated and proliferating diabetic renal endothelial cells and tracking of their fate using serial intravital multiphoton microscopy

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Microvascular complications contribute to the pathogenesis of diabetic nephropathy (DN) and are associated with vascular remodeling. Renal endothelial cell (rEC) remodeling may contribute to capillary loss and tubule-interstitial fibrosis in DN via abnormal vessel sprouting and endothelial to mesenchymal transition (EndoMT), the transition of ECs into a myofibroblast-phenotype. However, as the renal endothelium has been difficult to assess in vivo, dynamic structural and functional aspects of rEC plasticity are poorly understood. Can rEC plasticity derive from any EC or are there specific subpopulations? What are the functional consequences of diabetic rEC remodeling and how does it contribute to tissue regeneration or injury?

Serial intravital 2-photon microscopy (2PM) of the kidney enables visualizing the same cells in a living animal over several weeks. Therefore, it uniquely allows detecting dynamic events such as cellular migration, proliferation, and functional changes over time.

I will establish novel cellular biomarkers for different rEC plasticity events and their functional consequences in vivo combining two techniques in diabetic mice: First, genetically labeled rECs will be subject to single cell RNA sequencing and marker screening. Next, serial intravital 2PM, followed by histological stainings, will then link the expression of the newly identified markers to dynamic structural and functional aspects of rEC remodeling in the same cells longitudinally.

The results will unravel the role of rEC plasticity in DN and decipher how their ability for remodeling contributes to either tissue regeneration or further inflammation and damage.

Keywords: Nephrology, Cardiovascular system, Animal models/disease models

Lysine-dependent modulation of protein endocytosis in the proximal tubule

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Proteinuria is a hallmark of kidney damage and the accumulation of proteinuria exacerbates kidney injury by impairing proximal tubular functions. Previous studies showed that lysine treated rats excreted more albumin- a one of the most abundant proteins in urine- in their urine, reflecting an inhibition in proximal tubular uptake mechanisms. Previous work by Birn and colleagues suggested that lysine administration inhibited the receptors responsible for albumin reabsorption. However, the entity of proteins endocytosed in the process remains to be elucidated. The central hypothesis of this work is that lysine influences function of reabsorption receptors, leading to less accumulation of proteins in the proximal tubule and therefore mitigating their detrimental effect on nephrons.

In this part project of my PhD, urine samples from patients with kidney disease before and after lysine treatment as well as heathy controls will be used. First, we will apply quantitative proteomics study on the urinary samples to explore the potential proteins involved in the lysine mediated process. Next, the proteins of interest will be tested in cultured proximal tubule cells. The response of the cells will be monitored and validated by immunoassays and possibly metabolomics study.

The results of the study will help explain how lysine changes albumin reabsorption by proximal tubules and identify proteins endocytosed in this process. The study of basic pathophysiological processes in the proximal tubule will offer new avenues for the treatment of kidney disease.

Keywords: Nephrology, Molecular metabolism and endocrinology, Cell biology

The effect of increased water intake on urinary tract infections in mice

Aimi Hamilton, Department of Biomedicine

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Urinary tract infections (UTIs) are common and during their lifetime, more than half of all women will experience at least one UTI. UTIs are most frequently caused by Escherichia coli localised to the urinary bladder. However, UTIs can ascend to the kidneys causing pyelonephritis and potentially life-threatening urosepsis. UTIs are generally treated with antibiotics, but patients are also encouraged to increase water intake during infection to support clearance of the bacteria. Increased water intake is also suggested as prophylaxis in various patient groups prone to UTIs. Here, we test if increased water intake indeed clears UTIs in mice.

We used a uropathogenic E. coli strain isolated from a patient with pyelonephritis and injected the bacteria directly into the bladder of anaesthetised female Balb/c mice. After the procedure mice were randomised to receive either regular food or gel-food containing 70% water. After 24 hours we removed the kidneys and plated them on LB-agar to assess the degree of pyelonephritis.

As expected, we found that mice with increased water intake had a 4-fold higher excretion of urine ($p<0.05$) and a 2-fold reduction in urine osmolarity from a mean of 1439 mOsm 95%CI(1218;1661) for mice on regular food to a mean of 668.7 mOsm 95%CI(587.7;749.6) for mice on gel-food ($p<0.0001$). Surprisingly, we found that mice with increased water intake presented with more bacterial colonies in their kidneys ($p<0.01$) and twice as many mice on gel-food developed pyelonephritis compared to mice on a regular diet (87.50% vs 43.75% respectively).

In conclusion, we found that an increased intake of water negatively affects ascending urinary tract infections in mice.

Keywords: Urology, Infection, Animal models/disease models

North-Reg Dwell Time study on Reduced BCG Dwell-Time in High Risk NMIBC

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Introduction:

Non-muscles invasive bladder cancer (NMIBC) accounts for the majority of newly diagnosed bladder cancer(BC). Adjuvant treatment of NMICB is instillations in the bladder with Bacillus Calmette Gurién (BCG). BCG is tuberculose vaccine, causing an immune reaction when instilled. The activation of the immune cells kills the remaining BC cells. Previous studies indicate that approximately 70 % of all patients treated with BCG experience side effects (SE) ranging in severity from mild to severe.

BCG treatment is well known to postpone, in worst case, time to cystectomy. Unfortunately, because of the severity of the SE some patients terminate their planned instillations before time.

Materials and methods:

This project will include 314 patient across a Nordic collaboration of four countries. The patients will be randomized 1:1, into an intervention and a control group. SE will be gathered each day during the instillation weeks with daily questionnaires sent on a text message directly to the patient. Before each instillation, an evaluation is performed, based on the reported SE. If the SE are of a certain severity, patients in the intervention group will be reduces in dwell time(DT). DT is the time the bladder is exposed to BCG. DT will always be 2 hours at the first instillation. The reduction in DT will be either 1 hour or 30 minutes depending on the severity of the SE.

Results:

Inclusion started in February and so fare 19 of the 314 patients have been included and randomized.

Conclusions:

We hope to show that reducing DT will decrease severity of SE caused by BCG instillations and thereby increase the number of patients completing all planned instillations.

Keywords: Urology, Other, Other

Research Protocol: En Bloc Resection of Non-Muscle Invasive Bladder Tumours

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Aim: To compare the surgical method of En Bloc resection to the conventional transurethral resection of non-muscle invasive bladder cancer (NMIBC) in terms of complete removal of tumour, specimen quality, and pathological certainty.

Background: NMIBC is a common disease with a 5-year recurrence rate reported as high as 64%. The cornerstone in the treatment of NMIBC is transurethral resection (TURB) where the tumour is dissected in pieces, removed from the bladder, and pathologically examined for potential muscle invasion. As the tumour is fragmented before removal, the method violates basic oncological principles and compromises pathological examination. Hence, TURB is possibly part of the mechanism causing recurrences. En Bloc resection (EBR), where the tumour is removed in toto, is supposed to overcome the flaws of conventional TURB, but large randomized trials are needed.

Methods: This project will be a multicentre randomised controlled clinical trial comparing EBR to conventional TURB. Patients with suspected NMIBC tumours with largest tumour diameter ≥2cm and ≤6cm will be randomised to either the intervention group, thus undergoing EBR, or the control group, undergoing conventional TURB. We intend to include 220 patients in total, 110 patients in each group. The RCT will be initiated in 2022.

Results: Pending. Final results are expected in 2024.

Conclusion: Pending.

Perspectives: If EBR can be shown to remove bladder tumours with better pathological quality and certainty, this could potentially spare patients from undergoing surgeries in the future, thereby reducing costs for both patients and society.

Keywords: Urology, Medical technology and diagnostic techniques, Other

Genomics, endocrine disruptors and clinical characteristics of infants with hypospadias

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Background: Hypospadias is the second most common congenital anomaly in males with severity ranging from mild with a distal urethral opening to severe cases with a meatus at perineal level. The aetiology remains largely unknown. Familial aggregation occasionally accompanied by undescended testis, testicular cancer and poor semen quality suggest a potential underlying genetic origin. Environmental influences likely contribute as the incidence is increasing.

Aim: To investigate possible causative mechanisms in the development of hypospadias across the clinical spectrum in males referred for hypospadias surgery.

Study design: This cross-sectional study includes boys with hypospadias (n=150) and a control group (n=50). Families are recruited at the first visit in the paediatric urology outpatient clinic at AUH when the boys are 3 to 5 months old. Parents are requested to answer a questionnaire (medical history, pregnancy, level of concern). Blood will be drawn from parents (mothers: analysis of endocrine disrupting chemicals (EDC) + future research) and children (hormonal activity + analysis of EDC). Urine is sampled from mothers and boys for analysis of EDC. When the hypospadias will be surgically repaired around 1 year of age, a foreskin biopsy and another blood sample will be sampled for genetic analysis.

Perspectives: Association of the hypospadias phenotype, sex hormone- and EDC-concentrations will be sought. Comparison of full genome sequencing and methylation analysis in different tissues may detect variations in epigenetic regulation, and thus explain the phenotypic diversity.

Results: Results are pending, preliminary data will be presented at the PhD Day.

Keywords: Urology, Paediatrics, Other

Late effects impact on Quality of Life after treatment for bladder cancer (CONQUER)

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Aim: To determine the prevalence of late effects and its influence on QoL following treatment for bladder cancer stratified by stage of the disease and treatment modalities.

Background:
Treatment of bladder cancer includes a variety of modalities spanning from conservative treatment with transurethral resection and instillation therapy to major surgery, radiotherapy, systemic oncological treatment and variations thereof. Each treatment has a risk of complications and impact on Quality of Life (QoL). This risk has been inconsistently described, and the impact on the patient's QoL has only been studied to a limited extend.

Methods:
This study uses a cross-sectional design to estimate late effects and its associated elements measured by a questionnaire survey with validated instruments such as EORTC-QLQ-C30/BLM30 and ICIQ-M/FLUTS(sex). National Patient Registry (LPR) will be used to identify the study population and for each patient we will sample 4 eligible references from the CPR registry. Patients are eligible if they are >18 yo, alive and have been diagnosed with primary bladder cancer (grade pT1 or higher) between 2015 and 2020. We expect to include ≈1400 patients and 5600 matched controls making this study the largest of its kind.

Results:
Results are expected in spring 2022.

Conclusion:
Still pending.

Perspectives:
Based on the data from this study, we will develop a new clinical tool, rating each late effect´s impact on QoL for each individual patient, thereby finding the patients with severely affected QoL due to treatment. Combined with the ability to offer existing low-cost treatment for the symptoms, this will be of great benefit for the patients.

Keywords: Urology, Oncology, Other

Flash talk session 16

Penetration depth and tissue concentration of cisplatin in relation to temperature and treatment time in a HIPEC procedure. Assessment in a novel experimental pig model.

Christina Harlev, Department of Clinical Medicine

Maiken Stilling, MD, PhD, Clinical Professor, Department of Orthopaedic Surgery, Aarhus University Hospital.

Peritoneal metastasis originating from gynecological malignancies are associated with poor prognosis. Previous studies have shown that cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is an effective treatment option but important basic factors for the HIPEC treatment remains poorly investigated.

The aim of this study is to establish a novel and reproducible porcine model to dynamically assess concentrations of the chemotherapeutic drug, cisplatin, during and after HIPEC procedure simultaneously from various target tissues by means of microdialysis. Microdialysis allows for sampling of the free and active concentration of cisplatin. While the pharmacokinetic profile in plasma is well characterized, the time course and tissue penetration depth of the locally applied drug remains unknown. In contrast to previous animal models, a large porcine model allows for the use of the same infusion and pump systems as used in the human HIPEC procedures.

The pigs will be operated with hysterectomy, bilateral salpingo-oophorectomy, omentectomy and removal of a 10 x 10 cm peritoneum at the anterior abdominal wall as in ovarian cancer surgery. Microdialysis catheters will be placed in tissues of the abdomen prior to the HIPEC procedure.

The concentration of cisplatin in dialysates, plasma and urine samples will be estimated by the use of UHPLC-MS. Pharmacokinetic data will be analyzed with non-compartmental analysis, and cisplatin plasma and tissue concentrations will be plotted as a function of time.

The study is in progress wherefore data will not be available for presentation, but the design, the animal model and the set-up will be presented.

Keywords: Animal models/disease models, Gynecology and obstetrics, Oncology

Deciphering the impact of a missing or extra X chromosome – studies of relevant genes in a zebrafish model

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Turner syndrome (TS) and Klinefelter syndrome (KS) are rare genetic conditions characterized by the loss or gain of one X chromosome, respectively. TS and KS are associated with several health problems including neurocognitive impairment and behavioral difficulties. Compared to the general population, TS women and KS men have an increased rate of mortality and morbidity, showing the severe consequences of these genetic conditions. The clinical phenotype is diverse within each karyotype variation and the underlying mechanisms are not well understood. Nevertheless, novel candidate genes which might play a key role in the phenotype of TS and KS have been identified in recently published DNA methylome and transcriptome studies of KS and TS patients. In this project, we aim to investigate four to 10 of these identified candidate genes in zebrafish models of TS and KS. Firstly, we will design and generate knockout and overexpression zebrafish models of TS and KS where the selected genes are investigated alone or in combination. Secondly, we plan to explore the neurocognitive and behavioral phenotype of these zebrafish in relation to attention-deficit/hyperactivity disorder (ADHD), social behaviour, autism spectrum disorder and anxiety. This study has the potential to provide a better understanding of the etiology and the pathogenesis of TS and KS and might also identify novel therapeutic targets. This is an important step for developing new, better, and personalized medicine and treatment options for TS and KS patients.

Keywords: Animal models/disease models, Genetic engineering, Basic neuroscience

Paragenetic inheritance of autoimmunity and neuropsychiatric sequelae

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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, targeting multiple organs, including the kidneys, skin and lungs, however, up to 75% of patients experience neuropsychiatric manifestations ranging from headache to cognitive impairment and psychosis. This is proposed to be caused by cross-reactive autoantibodies targeting the CNS.

Particularly infants of autoimmune pregnant women are at high risk, since maternal transfer of autoantibodies, combined with genetic predisposition, can negatively impact the development and health of the offspring. This may manifest as neurodevelopmental diseases such as autism spectrum disorders or even schizophrenia. Here, we used embryo transfers to examine the maternofoetal transfer of autoantibodies and autoimmune-induced activation of microglia in offspring; hereby, uncoupling environmental and genetic factors.

Normal C57BL/6J embryos were transferred to either 564Igi females, a murine strain presenting with SLE-like disease due to an autoreactive B cell receptor knock-in, or to healthy C57BL/6J females as controls.

A maternal transfer of both immunoglobulins and autoantibodies was measured using time-resolved immunofluorometric assays (TRIFMAs). We analysed germinal centers and plasma cells by flow cytometry, and microglia morphology and activation in the CNS of embryo transfer offspring were assessed using an immunohistochemical and immunofluorometric stain, respectively.

Keywords: Animal models/disease models, Basic neuroscience, Inflammation

The influence of vagus mediated immune modulation in the progression of Parkinson's Disease and disease subtypes

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In Parkinson's disease (PD) aggregated alpha-synuclein (ASYN) induces death of predominantly nigral dopaminergic cells, but also affects other neurons in the central and peripheral nervous system. In parallel, ASYN plays a central role in immune changes in PD affecting central and peripheral immune cells. ASYN pathology spread through anatomically connected neurons. Borghammer's team has proposed the existence of two PD subtypes, based on disease initiation point: 1) Body-first initiating in the gut and reaching the brain through the dorsal motor nucleus of the vagus (DMV), and 2) the brain-first, starting in the forebrain, spreading towards the midbrain, and eventually reaching the DMV. In both subtypes the vagus nerve (VN) is affected; early in the body-first, and late in the brain-first. Body-first patients appears to have a faster and more severe disease progression. Importantly, the VN is responsible for an anti-inflammatory modulation of the immune system through the inflammatory reflex. We propose that the loss of VN-mediated immunomodulation contributes to the differences in body-first vs. brain-first. We aim to determine the influence of the VN in the PD-associated immune response and neurodegeneration, by mimicking aspects of the brain-first and body-first PD subtypes in rats. To so we use injections of ASYN pre-formed fibrils (PFFs) into either the gut or brain. Furthermore, we will characterize immune changes in plasma and blood immune cells from patients with the two PD subtypes. Immune changes will be associated to neuronal dysfunction and phenotypic prestation, in order to evaluate the role of VN in PD.

Keywords: Animal models/disease models, Basic neuroscience, Inflammation

Diastolic adaptation and new treatment strategies in right heart failure

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Background: Right heart failure is the predominant cause of death in patients with pulmonary hypertension (PH). The underlying cause of the transition from a compensated disease stage to right heart failure remains elusive, but the development of right ventricular (RV) diastolic dysfunction may play a role in this deteriorating transition.

We hypothesize that diastolic stiffness is a significant pathophysiological factor in the development of right heart failure, and that RV diastolic dysfunction may be a potential treatment target.

Methods: Three studies will be conducted in the pulmonary trunk banding model of experimental RV failure:

In study A we will investigate the RV diastolic adaption to pressure overload in different rat strains.

In study B we will investigate the effects of the giant sarcomeric protein titin's isoform composition on RV deformation and development of right heart failure.

In study C we will investigate the effects of a SGLT2 inhibitor on RV diastolic adaptation to pressure overload.

State-of-the-art methods with high clinical relevance including echocardiography, magnetic resonance imaging, and invasive pressure-volume measurements will be used to evaluate disease development, RV diastolic function, and effects of interventions. Histochemical and molecular analyses will be performed to assess RV adaptation on molecular level.

Perspectives: The project will add to the understanding of the mechanisms and importance of diastolic deterioration in the development of right heart failure in PH. Further, the project will explore the potential of targeted RV therapies for patients with right heart failure with focus on improving RV diastolic function.

Keywords: Cardiovascular system, Animal models/disease models, Laboratory science

Na,K-ATPase-dependent cSrc kinase activation as a mechanism underlying impaired reperfusion following successful recanalization in stroke.

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J. Kalucka, Department of Biomedicine, Aarhus University; VV. Matchkov, Department of Biomedicine, Aarhus University.

Background: Yearly, almost 15 million people are affected by stroke. One-quarter of the patients with successful recanalization experience futile reperfusion which is an independent risk factor of impaired neurological outcome, yet the underlying mechanism remains unknown. Brain arterioles contribute to vascular resistance and are known to have an increased vascular tone in the penumbra, after recanalization, possibly preventing successful reperfusion. Furthermore, smooth muscle cells of arterioles in the penumbra have reduced abundancy of the Na,K-ATPase, and increased contractility due to potentiated sensitivity to intracellular Ca2+. The Na,K-ATPase activity is inversely proportional with cSrc kinase phosphorylation. Thus, we hypothesize that increased Ca2+ sensitivity of the contractile machinery in the smooth muscle cells in the penumbra causes vasoconstriction contributing to impaired reperfusion after recanalization.

Aim: To investigate the role of pial arteriole vasoconstriction in futile recanalization and to elucidate the underlying molecular mechanism that may provide new therapeutic strategies for improving stroke intervention.

Methods: Transient occlusion of middle cerebral artery in vivo in mice will be used to characterize the molecular mechanism underlying vasoconstriction in the penumbra using spatial transcriptomics and proteomics. Furthermore, we will visualize the vascular response with Laser Speckle Contrast imaging and interfere with the underlying mechanisms pharmacologically.

Perspective: This project may provide new targets for prevention strategies, improve the therapeutic regime in stroke, and thus, the outcome for stroke patients.

Keywords: Cardiovascular system, Animal models/disease models, Pharmacology

Molecular and physiological mechanisms behind anion-exchanger AE3-mediated regulation of the QT interval

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Short QT syndrome (SQTS) is a rare, genetically determined, severe cardiac disease with a high risk of syncope, ventricular fibrillation, and sudden cardiac death. We discovered that a loss-of-function variant in the SLC4A3 gene, which encodes the cardiac chloride-bicarbonate exchanger AE3, is associated with SQTS in patients. Previously, only six other genes, all encoding cation channels, have been known to be implicated in SQTS. Thus, the discovery of a SQTS-associated AE3 variant identifies a completely new disease mechanism for the development of SQTS.

In this study, we aim to create an optimized zebrafish model to facilitate in-depth functional characterizations of novel AE3 variants and investigate the molecular mechanism by which altered SLC4A3 function affects QT interval duration. Using CRISPR/Cas technology, we will generate novel knockout zebrafish lines and knockin zebrafish lines carrying selected AE3 variants. These zebrafish models will be used to explore the molecular and physiological mechanisms involved in AE3-mediated regulation of the QT interval. For this purpose, we will perform extensive molecular and physiological measurements on zebrafish hearts both in vivo and ex vivo, including ECG recordings and action potential, intracellular pH and calcium measurements in cardiomyocytes.

If successful, this project will provide valuable insights into the mechanisms behind AE3 involvement in the development of inherited heart disease and bring knowledge on the molecular and physiological role of AE3 in the regulation of QT interval and thereby potentially facilitate the development of brand-new treatment options for heart patients suffering from SQTS.

Keywords: Cardiovascular system, Animal models/disease models, Genetic engineering

DIVERSITY OF SMOOTH MUSCLE-DERIVED CELLS IN MOUSE AND PIG ATHEROSCLEROTIC LESIONS

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Background

Recent lineage-tracing studies in mice have revealed that smooth muscle cells (SMCs) in atherosclerotic lesions can acquire broad diversity of cellular phenotypes. It is still unknown whether the spectrum of SMC-derived phenotypes differs between species. The present study aimed to analyze whether SMC-derived cells of plaques in transgenic minipigs differ from those of mouse plaques.

Materials and methods

To describe and compare SMC-derived plaque cells in mouse and minipig atherosclerosis, we performed scRNAseq on atherosclerotic plaques from three 374Y-PCSK9 pigs and a healthy arterial media from a wildtype minipig as well as six plaques and underlying media from SMC-CreERT2 x TdTomato mice, in which SMC-derived cells can be identified by the expression of the TdTomato reporter. Bioinformatics analysis was conducted using Seurat v4 package in R. We integrated the datasets from mice and pigs to find common and specific SMC-derived cells.

Results

Alignment with mouse cells expressing the TdTomato reporter helped identify the pig SMC-derived cells. Within this family of putative SMC-derived cells, we identified two clusters of cells that were specific for pigs: stem-osteogenic (SERPINH1, COL6A3, IGF1 were highly expressed) (unique for atherosclerotic plaques), and inflammatory (ISG15, STAT1) – common for healthy media and plaques. We found no mouse-specific SMC populations.

Conclusion

Plaques from pigs have specific SMC populations that are not observed in mice. Future work is needed to analyze whether these are also present in human atherosclerosis and

whether they explain some of the differences in morphology between mouse and pig/human atherosclerosis.

Keywords: Cardiovascular system, Animal models/disease models, Cell biology

T Cell Recovery after Chemotherapy in Children, Adolescents and young Adults with Acute Myeloid Leukemia

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Background:

Myelosuppressive therapy is essential to obtain remission in acute myeloid leukemia (AML) but despite apparent efficacy of intensive therapy leukemic remnants may persist and expand into relapse. T cells exert anti-leukemic activity but current treatment regimens may hamper recovery of T cell function. Children mainly recover T cells from thymic output whereas adults maintain T cells by peripheral proliferation. Optimal T cell reconstitution may constitute a pivotal element in maintaining remission.

Aims:

We hypothesize T cell function to be affected by AML therapy and that optimal T cell reconstitution after AML therapy is age-dependent. We will investigate recovery of T cell quantities after AML therapy compared to a healthy cohort. We will explore the differences in T cell recruitment through thymic output versus peripheral cell expansion after AML therapy according to age, and the association between impaired immune reconstitution and risk of relapse.

Methods:

Patients between 0-50 years of age with de novo AML in remission at the end of chemotherapy are eligible. Blood sampled at monthly intervals from study participants have already been collected. Immunologically healthy children undergoing orthopedic surgery constitute the control group.

Thymic output and peripheral T cell expansion after AML therapy will be assessed by T cell receptor excision circles quantities and multiparameter flow cytometry with a proliferation marker.

Perspectives:

We aim to uncover the importance of optimal T cell reconstitution after AML therapy. Our results may guide the development of new treatment approaches and clinical handling of immune dysfunction after chemotherapy.

Keywords: Paediatrics, Oncology, Other

Co-chairs

Danish validation of a Retronasal Olfactory Powder Test and development of a Quick Retronasal Olfactory Test

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Introduction:
Quality of life, in olfactory impaired patients, is strongly associated with retronasal olfactory function. Familiarity with odors vary in different cultures and populations, so olfactory tests need to be validated.

Testing is time-consuming, so both a quick test and a thorough test is needed.

The aim of the study, was to validate the original retronasal powder olfactory in Denmark, and to develop a novel quick retronasal test for screening purposes.

Methods:
Ninety-seven participants were included in the study: 59 healthy controls and 38

patients with olfactory dysfunction. The test was modified by substituting unfamiliar odors and descriptors. Then the test was validated with a correct identification rate of 50%

in the original test and 90% in the quick test. Items with >90% correct identification

rate in the modified original test was included in the quick test - resulting in a 10-item

test.

Results:
The modified retronasal olfactory test achieved decent test characteristics with a 10th percentile cut-off value of 13: Sensitivity was 88.9%, specificity 83.0%, positive predictive

value 78%, negative predictive value 91.7% and ROC area of 0.86. The quick test achieved acceptable test characteristics with a 10th percentile cut-off value of 8.2: Sensitivity

was 72.2%, specificity 90.6%, positive predictive value 83.9%, negative predictive value

was 82.8% and ROC area 0.81.

Discussion:
Validation of both tests demonstrated satisfactory accuracy for the respective purposes. We recommend the quick test for screening and the modified test for thorough evaluation.

Keywords: Ear, nose and throat (ENT), Rehabilitation, Other

Attending to signs of readiness: A study of discharge decision-making in a medical ward

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In the context of the Danish welfare state and health care system, an increasing number of elderly and chronically ill people is enforcing a need for prioritizations in health care. A reduction in the amount and length of hospital admissions is one stated aim in policydiscourse. Previous studies have shown how health care professionals (HCP's) increasingly balance the needs of patients with management concerns of hospital capacity in their daily work. Attention to the daily practices involved in discharge decision-making is crucial to enhance health care quality and avoid re-admissions.

The study is based on three months of ethnographic fieldwork across three different medical wards, employing strategies of participant observation and conversations with nurses, physicians, coordinators and management. The data material is extensive field notes analysed through abductive analysis, where theory and empirical findings continuously inform each other in the process. Anthropological theories of care infrastructure inspire the analysis.

The study elucidates how decisions on discharge are negotiated in clinical settings where HCP's must simultaneously maintain standards of care and the flow of patients through the hospital. The study argues that this is done through the translation and prioritization of biomedical, clinical and embodied signs into "signs of discharge readiness".

The study discusses how negotiations of discharge readiness may co-produce inequalities in health, suggesting that more transparency on prioritizations and decision-making is needed, both in the planning of health care work, and in encounters with patients and their relatives.

Keywords: Qualitative research, Multimorbidity, Other

Socioeconomic disparity trends in end-of-life care for cancer and non-cancer patients: Are we closing the gap?

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Background: Socioeconomic disparities in end-of-life care have been reported across underlying diseases, but there is a paucity of information on potential time trends.

Objectives: To examine time trends in use of healthcare services at the end of life according to socioeconomic position in patients dying from cancer and non-cancer diseases.

Methods: We conducted a nationwide register-based cohort study among adults dying from cancer or non-cancer diseases in Denmark in 2006-2016. We obtained data on patients' educational and income level, and use of healthcare services within three months before death.

Use of healthcare services according to educational and income level was plotted by calendar year of death and compared by regression analyses adjusting for age, sex, comorbidity, cohabitation, and municipality.

Results: In both cancer (n=169,694) and non-cancer patients (n=180,350), we found limited socioeconomic disparities and no clear temporal trends in use of hospital, intensive care, emergency room, general practice, home care nurse, and hospice.

Among cancer patients, 1 percentage point more patients with high income level were affiliated with hospital-based specialist palliative care compared with patients with low income level in 2006/2007 (adjusted mean difference: 0.01 (95%CI: 0.01; 0.02)), whereas this was 12 percentage points in 2016 (adjusted mean difference: 0.12 (95%CI: 0.09; 0.14)).

Conclusion: Socioeconomic disparities in specialist palliative care tended to increase over time among cancer patients but were limited and without clear time trends in use of other healthcare services in both cancer and non-cancer patients.

Keywords: Epidemiology and biostatistics, Other, Oncology

Smoking is Associated with Infection Risk in Healthy Blood Donors

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BACKGROUND: The effect of smoking on infection risk has been little studied and mostly in smaller case-control studies examining specific infections. This leaves a gap in the knowledge on the effects of smoking on overall infection risk in healthy populations, possibly causing an underestimation of the dangers of smoking.

AIM: To examine the association of smoking with the risk of various infections in a large cohort of healthy blood donors.

METHOD: This cohort study used questionnaire and health register data from 123,799 healthy Danish blood donors. Multivariable Cox proportional hazards analysis was applied to estimate the association of current smoking and the risk of all-cause infection defined as hospital-based treatment for infection or redeemed prescriptions of antimicrobials stratified for time of birth and adjusted for relevant confounders.

RESULTS: The risk of infection in general was increased in current smokers when compared to non-smokers across all strata (hazard ratio estimates ranging from 1.27 to 1.36 for hospitalisation and 1.11 to 1.20 for redeemed prescriptions). Smoking was most strongly associated with abscesses (2.77) and skin infections (2.10). Furthermore, the risk of redeemed prescriptions of broad-spectrum antibiotics was increased (1.83) along with prescriptions against skin infections (1.40).

Conclusion: Current smoking was strongly associated with increased risk of hospital-based treatment of infection and redeemed prescription of antimicrobials. These findings warrant increased focus on infectious disease and smoking in addition to the focus on respiratory and cardiovascular consequences.

Keywords: Infection, Epidemiology and biostatistics, Public health

Sibling design: too good to be true?

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Background: An attenuation of association in a sibling design compared with an unpaired design is often attributed to removal of unmeasured confounding. Recent research challenge such interpretation by showing that attenuation of association due to random measurement error in exposure will always be higher in the sibling design than in the corresponding unpaired design.

Objective: We explored the impact of sensitivity (SE) and specificity (SP) of exposure ascertainment on the attenuation of association in the sibling design compared with the unpaired design.

Methods: We used simulation to mimic an observational study. The true risk ratio (RR), obtained with the SE and SP of exposure measurement equal 1.00, was set to 1.50. We then altered the SE and SP and, after each alteration, computed the RRs from an unpaired design and a sibling design.

Results: We illustrated the results using a 3D-graph (not shown). The results show that the sibling design RR is always closer to the null (RR = 1) than the corresponding unpaired design RR, regardless of the SE and SP. Further, the attenuation from the unpaired design RR to the sibling design RR is large when the SP is low and the SE is high (e.g., SP = 0.20, SE = 1.00, unpaired design RR = 1.41, sibling design RR = 1.24). However, when the SP is high and the SE is low the attenuation is small (e.g., SP = 1.00, SE = 0.20, unpaired design = 1.10, sibling design = 1.06).

Conclusion: The sibling design RR is closer to the null than the unpaired design RR regardless of the SE and SP of exposure ascertainment. Further, the size of the attenuation of association may depend on the SE and SP of the exposure ascertainment.

Keywords: Epidemiology and biostatistics, Public health, Pharmacology

Dissatisfaction with school toilets is associated with bladder and bowel dysfunction

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Background

Poor school toilet quality is reported as an issue in many countries, and has been correlated to toilet refusal in children. The aim of this study was to evaluate the association between school toilet quality and symptoms of bladder and bowel dysfunction (BBD).

Methods

Pupils in Danish schools were invited to fill in online questionnaires regarding toilet habits, perception of school toilet standard/quality, and BBD symptoms. Teachers at the same schools were asked about quality characteristics of the toilets such as the year built/renovated, pupil to toilet ratio, and cleaning schedules.

Results

We recruited 19.577 children from 252 different schools. More than half of the children (50% of boys and 60% of girls) were unsatisfied with the toilet facilities. A fourth of children (28% of girls and 23% of boys) reported to avoid using the school toilets. We found a strong correlation between being unsatisfied with the school toilets, toilet avoidance and symptoms of BBD.

Conclusion

The majority of Danish children are unhappy with their school toilet facilities. Symptoms of BBD are associated with subjective toilet dissatisfaction and toilet visit postponement. As children spend a significant part of their day outside home, access to satisfactory toilet facilities is of utmost importance for their well-being.

Keywords: Paediatrics, Nephrology, Public health

The HOME-Health study (HOusing, environMEnt, and Health); Methodology, internal- and external validity of a Danish Cohort

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Most studies investigating indoor environmental quality (IEQ), health, and wellbeing are conducted within offices and not in residential areas, where we spend most of our time indoors. Commonly, quantitative measurements are presented, and few studies combine quantitative and qualitative measurements as a mixed method.

The HOME-Health study is a prospective cohort designed as a natural experiment aiming to investigate how building energy renovation affects residents' state of health, wellbeing, perception of IEQ, and IEQ-related behaviour and practice, and objective measurements of IEQ (i.e., temperature, humidity, air change rate, dust, and CO2). The study relies on data collected in two Danish cities involving residents living in social housing undergoing energy renovations. Several types of data collection methods were employed, including structured surveys, objective measurements of IEQ parameters, spirometry, and qualitative semi-structured interviews. Data collection is conducted seasonally (winter and summer), before and after the building renovations.

The HOME-health study presents data before building renovation (N=433) as building renovations are still ongoing. Internal validity shows that future analyses must be stratified by multi-family and terraced housing. Treating the study population as one entity, we find it representative to the Danish social housing population in terms of age, gender, persons per apartment, and immigration.

The final results from the HOME-Health study are expected to reveal how building renovations affect residents' health, wellbeing, perception of IEQ, behaviour of residents, and objective measurements of IEQ.

Keywords: Public health, Respiratory system, Allergy

The impact of hyperglycaemia on circulating erythrocyte glycosylation

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In diabetes, hyperglycaemia is responsible for various micro- and macrovascular late complications. An autoimmune response is proposed to be triggered by hyperglycaemia causing adverse effects in multiple organs. In type 1 diabetes patients, mannan-binding lectin (MBL), which is part of the innate immune system, has been associated with the development of diabetic nephropathy. High blood glucose may alter the glycosylation on circulating cells, which potentially changes the binding of MBL and other lectins. In this study, we aim to profile the characteristic of surface glycosylation on erythrocytes from hyperglycemic mice.

We induced diabetes in 8-weeks old wildtype male mice (n=10) by streptozotocin injections and included an age matched nondiabetic wildtype group (n=9). Over a period of three months, six blood samples were drawn from each mouse. Flow cytometry was used to quantify the binding of MBL and a panel of plant lectins to erythrocytes. The binding of MBL was detected with a secondary FITC labeled anti-MBL antibody. Anti-MBL-FITC binding to erythrocytes was expressed as Mean Flourescence Intensity (MFI) ratio= sample MFI/control MFI.

Our preliminary data are based on MBL's binding to erythrocytes. In diabetic mice, with blood glucose levels above 15 mmol/L the mean MFI ratio for MBL-FITC was 87.3 (95% CI: 73.7, 100.8) compared to the nondiabetic group, 100.3 (95% CI: 90.0, 110.6), p=0.10. Although insignificant, the result indicates less binding of MBL to erythrocytes from a hyperglycemic milieu compared to a nondiabetic milieu. In the near future, we will have results from a bigger mice study, including a panel of 15 lectins in addition to MBL.

Keywords: Molecular metabolism and endocrinology, Animal models/disease models, Inflammation

Impact and feasibility of high-intensity interval training in patients with coronary artery disease: a randomized controlled trial

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Purpose

Coronary artery disease (CAD) is the leading cause of mortality worldwide. Exercise training improves quality of life and reduces cardiovascular death and hospital admissions in CAD patients. We aimed to investigate the feasibility and efficiency of high-intensity interval training (HIIT) in patients with stable CAD.

Methods

In this randomized controlled trial, 142 patients with stable CAD and a mean age of 66.7 years completed the study, 64 in the HIIT group and 78 in the control group. HIIT was performed by training on a rowing ergometer 3 x week for 12 weeks. Prior to randomization and after 12 weeks, maximal oxygen consumption (VO2max), maximal pulmonary ventilation (VEmax) and maximal power output (Wmax) were determined in all patients. During the intervention period, the training load was defined as power output during training in week 3, 6 and 9. The average intensity was quantified and normalized to the average power that patients could sustain during a 5-min-all-out rowing performance test completed at week 5.

Results

Adherence to training was 97% (range 86-100%). The average relative power output was 72 ±19% during warm-up and 117 ±11 % during the interval bouts. Weekly training duration was on average 54 min. Compared to standard care, HIIT resulted in a significant ($p<0.001$) greater increase in VO2max, VEmax, and Wmax (197 mL/min [160;233], 13 L/min [11;16], and 23 W [19;27]).

Conclusion

Low volume HIIT performed as rowing significantly upregulated cardiorespiratory fitness (VO2max, VEmax, and Wmax) in patients with stable CAD compared to standard care. The exercise training on rowing ergometers was convenient and feasible for this frail patient group.

Keywords: Cardiovascular system, Rehabilitation, Inflammation

Does exercise rejuvenate the activation deficits of aged skeletal muscle progenitors?

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Introduction:

Skeletal muscle is highly sensitive towards biological aging as manifested by muscle atrophy and loss of regenerative capacity. This might be attributed to impaired activation of aged muscle progenitor cells, namely muscle stem cells (MuSCs) and fibro-adipogenic progenitors (FAPS). Although, exercise is commonly appreciated to attenuate such age-depended decay in skeletal muscle health, the effect of exercise on activation kinetics of MuSCs and FAPS remains unresolved.

Methods:

We randomized 23 healthy untrained individuals (67 +/- 5 years), to 6 weeks of bloodflow restricted exercise (BFRRE) or non-intervention control. Before and after the intervention muscle biopsies and tests of muscle function were performed. Fluorescence activated cell sorting (FACS) was used to quantify and isolate MuSCs and FAPS for subsequent in vitro assessment of activation kinetics. Furthermore, the abundance of subpopulation macrophages and endothelial cells was quantified during cell sorting.

Results:

Six weeks of BFRRE increased skeletal muscle function as assessed by 6-min walking capacity and maximal dynamic muscle strength ($p<0.05$). The results obtained from the FACS analysis and in vitro activation kinetics experiments will be available by the PhD-day 2022.

Discussion:

These findings will provide novel insight into how exercise might affect the functional dynamics of muscle progenitor cells. Furthermore, assessment of the mononuclear cell diversity within the skeletal muscle before and after exercise will elaborate on our understanding of how exercise might alleviate age-related decay of skeletal muscle health.

Keywords: Cell biology, Public health, Inflammation

How tidal volume and respiratory rate influence pulse pressure variation during mechanical ventilation

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Background: Fluid responsiveness is the ability to increase stroke volume in response to a fluid bolus. Fluid loading of non-fluid-responsive patients can be harmful, so predicting fluid responsiveness is of substantial clinical interest.

Mechanical ventilation induces cyclic variation in right- and left ventricular preload. If the heart is preload responsive, this results in stroke volume- and pulse pressure variation (SVV and PPV). Thus, PPV is a useful predictor of fluid responsiveness, but it is also affected by ventilator settings. Notably, using PPV to predict fluid responsiveness is often regarded unreliable if tidal volume is low (V_t < 8 ml/kg) or if the heart rate to respiratory rate ratio is low (HR/RR < 3.6). Recent trends in ventilator treatment are moving towards lower V_t and higher RR. This calls for better understanding of how ventilator settings influence pulse pressure variation.

Methods: During open abdominal surgery, we ventilated patients with 10 different combinations of tidal volume (4 to 10 ml/kg) and respiratory rate (10 to 31 min^{-1}) for 30 seconds each. For each setting we recorded pulse pressure variation. After returning to standard ventilation, patients were given a 250 ml fluid bolus. An increase in stroke volume (by pulse contour analysis) > +10% was considered a positive response.

Results: We included 52 subjects. PPV decreased close to linearly with lower tidal volume. Area under the ROC curve for PPV predicting fluid responsiveness was between 0.78 and 0.65.

Conclusion: PPV as well as its ability to predict fluid responsiveness is closely related to V_t. The relation to respiratory rate is more complex.

Keywords: Cardiovascular system, Medical technology and diagnostic techniques, Other

The Pharmacokinetics and Pharmacodynamics of Cannabis-Based Medicine

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Background:

- Cannabis-Based medicine (CBM) has been suggested as treatment for a wide range of diseases and symptoms.
- The use of CBM is rapidly increasing.
- The evidence of effect is sparse.
- The existing description of the pharmacokinetics (PK) and pharmacodynamics (PD) of cannabis (inhaled) is primarily derived from (healthy) recreational users.
- Oral CBM undergoes hepatic-first-pass metabolism.

Previously, no study has investigated PK/PD

- in oral capsule formulated CBM
- In a patient population.

Aim:

- To describe the PK/PD properties of oral CBM capsules

Methods:

- 28 patients diagnosed with multiple sclerosis.
- CBM treatment in steady state (THC, CBD or combined THC & CBD).

Blood samples are investigated for:

- Cannabinoids:

Δ9-Tetrahydrocannabinol (THC)

Cannabinol (CBN)

Cannabidiol (CBD)

And metabolites:

11-hydroxy-Δ9-tetrahydrocannabinol (THC-OH)

11- nor-9-carboxy-Δ9-tetrahydrocannabinol (THC-COOH)

Using high-throughput liquid chromatography-mass spectrometry (LC-MS-MS).

Results (awaiting)

PK parameters

- Max. plasma conc. (Cmax)
- Min. plasma conc. (Cmin)
- Average plasma conc. (Cavg)
- Mean steady state area under the curve (AUC0-24)
- Time to Cmax (Tmax)/Time to Cmin (Tmin)

PD parameters

- Pain Intensity
- Pain Intensity Difference
- Pain relief
- Patient and investigator global evaluating

Discussion

- The PK and PD of CBM in a patient population will be described.
- The description of the metabolism of cannabinoids is highly relevant and interesting for future studies or treatment guidelines.
- The oral formulation of CBM may be beneficial for patients who requires e.g., pain relief during a longer period of time.

Keywords: Rehabilitation, Pharmacology, Other

The effects of CRMP2 knock out on structure and function of white matter in a mouse model of Schizophrenia

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Schizophrenia (SZ) is a complex neuropsychiatric disorder, with many unanswered questions. Myelination is essential to keep signal transduction and communication within the brain at an optimal level. There is evidence for impaired myelination in several neuropsychiatric disorders including SZ. Here we focus on CNS demyelination as a component of SZ, using a Collapsin Response Mediator Protein 2 (CRMP2) conditional knock out mouse (cKO) model. CRMP2-cKO mice show several SZ-like clinical signs and a reduced CNS myelination. Focusing on the largest white matter structure in the brain, corpus callosum (CC), we investigated potential changes in function with multielectrode electrophysiology. Reduced compound action potential amplitude and slope were observed indicating impaired signal transduction. At the structural level, the volume of CC in cKO mice was reduced. Our data showed that this was not caused by a decrease in the number of oligodendrocytes. Ultrastructure was investigated in 3D axonal and myelin reconstructions of image stacks acquired by Serial Block Face Scanning Electron Microscopy, implementing an image-segmentation pipeline. Nodes of Ranvier parameters (node length and volume, myelin thickness and axon diameter) are currently being analyzed in cKO and control animals. Together our findings indicate that CRMP2 plays a role in white matter function in a SZ model. The mechanisms by which this happens are still uncertain. Our project has implemented analysis methods to shed light on the role of myelin defects in SZ. These analyses-pipelines can be used in our future work on genetic models of neuropsychiatric disorders.

Keywords: Animal models/disease models, Clinical neuroscience, Laboratory science

Reliability and validity of the translated Gait Outcomes Assessment List for Danish children with cerebral palsy

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Aims: To translate the Gait Outcomes Assessment List (GOAL) into Danish, evaluate its reliability and validity in children with cerebral palsy (CP), and investigate the correlation between the GOAL questionnaire and the Challenge.

Methods: The translation process followed four-stages: translation, synthesis, back-translation and review. Children and parents respectively answered the GOAL for test-retest reliability. Evaluation of face and discriminative validity between GMFCS levels. Concurrent validity between child and parent baseline GOAL and between GOAL and Challenge were investigated.

Results: Fifty-nine children (34 boys), 5 to 18 years mean age 10.6 (SD 3.5) were included, 34 in GMFCS level I. Test-retest was excellent for children (n=33) ICC= 0.91 (95% CI 0.83-0.95) and good for parents (n= 40) ICC= 0.82 (95% CI 0.65-0.90). Parents and professionals perceived the GOAL relevant. The GOAL discriminated between GMFCS levels: Children (p=0.00) and parents (p=0.07). Concurrent validity between children and parents GOAL showed to be significant (n= 46) 0.72 (p<0.001). Concurrent validity between GOAL and Challenge (n =41) was significant for parents 0.34 (p=0.03) but not significant for children 0.30 (p=0.06).

Conclusion: Child and parent GOAL both in conjunction with the Challenge can provide meaningful in assessing, planning and evaluation rehabilitation for ambulatory children with CP.

Keywords: Paediatrics, Rehabilitation, Medical technology and diagnostic techniques

Proton therapy dose distributions around cardiac implant leads measured with 3D dosimeters and films

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Due to their proximity to lymph nodes, cardiac implantable electronic device leads can present a challenge to target coverage in proton therapy of breast cancer patients. Moreover, shortcomings in treatment planning dose calculations when modelling the interaction of proton beams with metal components can result in greater uncertainty in the delivered dose. The aim of this study was to dosimetrically investigate the dose degradation caused by two types of leads with 3D radiochromic dosimeters and 2D gafchromic films.

3D dosimeters were fabricated from silicone, curing agent, chloroform and leucomalachite green. Leads of two different widths (Ø1.6 mm and Ø2.2 mm) were used. Films were placed 1 cm above and 1 cm below the leads. The setup was CT-scanned and imported to Eclipse where two spot-scanning proton therapy plans were prepared using 2.5 or 7.5 cm thickness solid water (SW) build-ups, such that the leads were positioned at the spread-out Bragg peak.

With respect to dose degradations, the largest underdosage (12%) was observed for the Ø2.2mm lead and 7.5 cm SW, while the smallest underdosage (6%) was observed for the Ø1.6mm lead and 2.5 cm SW. Underdosage was localised behind the leads in the beam direction and had approximately the same width and shape as the leads themselves. No overdosage due to backscatter radiation could be observed with neither films nor radiochromic dosimeters.

Both leads caused dose degradations, with the smallest shadowing effect measured for the Ø1.6 mm lead. Since underdosage was localised in the beam direction downstream of the leads, its effect could be minimized in patient plans by using more than one field at different incidence angles.

Keywords: Oncology, Other, Other

Use of Photodynamic diagnosis (PDD) at primary TURB: Potential influence on recurrence and progression rates in NMIBC in a registry-based study using a country cohort

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Background: Treatment effect and long-term outcome of non-muscle invasive bladder cancer (NMIBC) rely largely on diagnostic accuracy, which may be enhanced using photodynamic diagnosis (PDD) for transurethral bladder resection (TURB).

Objective: To describe recurrence and progression rates according to PDD-use at department-level in an unselected, national cohort of NMIBC patients.

Design: We identified Danish patients with NMIBC as initial diagnosis in 2010-2017 via the Danish National Patient Registry (DNPR), dividing them into four exposure groups depending on the percentage usage of PDD at primary TURBs of the treating department.

Participants: Among 17,546 NMIBC patients (76% men, 24% women), 577 were excluded due to cystectomy immediately after primary TURB or re-TURB, leaving 16,969 patients in the cohort.

Outcome measurements: Risk difference (RD) for recurrence and progression rates after two and five years depending on PDD-exposure group.

Results and limitations: RD for recurrence after two years was 11% [95%CI: 9; 13] (45% in the low-PDD-use group; 34% in the high-PDD-use group). After five years, RD was 16% [95% CI: 14; 18] (56% vs. 40%). RD for progression after two and five years was 8% [95%CI: 6; 9] (18% vs. 10%) and 13% [95%CI: 11; 15] (26% vs. 13%), respectively. Inter-exposure group RDs in recurrence and progression rates were statistically significant. Limitations apply mainly to design and lack of information regarding visual impression at TURBs.

Conclusions: PDD at primary TURB in an everyday setting may lower recurrence and progression of NMIBC irrespective of instillation therapy and patient characteristics.

Keywords: Urology, Other, Other

Associations between the IGF-related proteins STC2 and PAPP-A and mortality in a cohort of type 2 diabetes patients

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Background

Pregnancy-associated plasma protein-A (PAPP-A) has repeatedly been shown to be associated with the development of CVD and atherosclerosis. PAPP-A is an enzyme that indirectly activates Insulin-like growth factor I (IGF-I). The protein Stanniocalcin-2 (STC2) can irreversibly bind and inactivate PAPP-A. Thus, PAPP-A and STC2 are indirect regulators of IGF-I activity.

This study examined associations between the IGF-related proteins; PAPP-A and STC2 with mortality in a cohort of type 2 diabetes (T2D) patients.

Study Design and Patients

This retrospective cohort study included 1284 participants with type T2D from the Danish arm of the ADDITION study. Subjects were followed for 5 years with a median diabetes duration of 6.07 years [5.15; 6.84] at study entry. Measurements of STC2 and PAPP-A were performed on blood samples, drawn at inclusion. Study outcome was all-cause mortality.

Results

During follow-up 114 subjects died. Survival analysis was performed by Cox Proportional Hazards model using the log2-transformed STC2 and PAPP-A variables (log2STC2; log2PAPPA). The unadjusted hazard ratio (HR) was 2.52 (95 % CI 1,5-4,1; p<0.001), for log2STC2 and 2,83 (95% CI 2,09-3,85; p<0.001) for log2PAPP-A. After adjustment for age, gender, waist measurement, diastolic blood pressure, smoking, cardiovascular comorbidity, cholesterol, creatinine and HbA1c both STC2 and PAPP-A remained associated with all-cause mortality; HR=1.8 (95% CI 1,06-3,05; p=0.03) for log2STC2 and HR=2.82 (95% CI 1,99-3,99; p<0.001) for log2PAPP-A.

Conclusion

STC2 and PAPP-A associated with all-cause mortality in a cohort of T2D patients.

Keywords: Molecular metabolism and endocrinology, Cardiovascular system, Epidemiology and biostatistics

FECUNDABILITY

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Background: In 2009, Human papillomavirus (HPV) vaccination was included in the Danish Childhood Vaccination Programme. The vaccine is recommended for girls aged 12 years and is offered free of charge. HPV is a sexually transmitted virus, which can cause infection in the female genitalia. Most HPV infections resolve spontaneously, but in some women the infection persists. Previous studies have indicated a possible link between HPV infection and decreased fertility. By investigating the association between HPV vaccination and fecundability, defined as the probability of conceiving per menstrual cycle, we can gain an insight into whether prevention of HPV infections protects female fertility.

Aim: To investigate the influence of HPV vaccination on fecundability among Danish couples trying to conceive.

Method: The study is a prospective cohort study (n=13,806) based on two Danish preconception cohorts, “SnartGravid” and “SnartForældre”. Women complete a screening questionnaire, a baseline questionnaire and bimonthly follow-up questionnaires for up to 12 months, providing information on socio-demographics, reproductive and medical history, lifestyle, and pregnancy status. We will obtain data on HPV vaccination before study entry from The National Health Insurance Service Register and the Register of Medicinal Product Statistics. We will analyse the association between HPV vaccination and fecundability using a proportional probability regression model. The computed fecundability ratios and corresponding 95% confidence intervals express the difference in the per-menstrual cycle probability to conceive between vaccinated and unvaccinated women.

Keywords: Gynecology and obstetrics, Epidemiology and biostatistics, Public health

Sortilin as a Biomarker for Cardiovascular Disease Revisited

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Genetic variants in the SORT1 locus (encoding sortilin) are strongly associated with risk of coronary artery disease (CAD). Circulating sortilin has therefore been proposed as a biomarker for cardiovascular disease. Multiple studies have reported associations between sortilin levels and cardiovascular outcomes but the findings are not consistent. The aim of this study was to evaluate sortilin as a biomarker for CAD in a cohort of 1,173 patients with symptoms suggestive of CAD. Plasma sortilin was measured using two methods: ELISA and the OLINK Cardiovascular II panel. We found a relatively poor correlation (0.21) between the two. In addition, genotyping and whole-genome sequencing (WGS) was performed. Regression analysis of sortilin levels identified two independent cis protein quantitative trait loci (pQTL) on chromosome 1p13.3, one being a well-established risk locus for CAD. Incorporating rare variants from WGS did not identify any additional pQTLs. None of the traditional CAD risk factors, such as sex, age, smoking, and statin use, associated with sortilin level. Further, there was no association between sortilin level and coronary artery calcium score or disease severity. Sortilin did not improve discrimination of obstructive CAD, when added to a clinical pretest probability model. Overall, our results indicate that studies using different methodologies for measuring circulating sortilin should be compared with caution. In conclusion, the well-known SORT1 risk locus for CAD is linked to lower plasma sortilin levels, measured with ELISA; however, sortilin is not a useful biomarker for CAD in a clinical setting of low- to intermediate-risk chest-pain patients.

Keywords: Cardiovascular system, Other, Other

Insomnia in depression and the efficacy and appropriateness of ball blankets: an industrial PhD

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Introduction
Depression is a global health issue affecting around 4% of the population. Depression is often accompanied by insomnia. Sedatives used to treat insomnia have side effects, why non-pharmacological treatments may be needed.

Aim
To investigate patients' experiences of depression-related insomnia and sleep interventions, and to test the efficacy and appropriateness of the Protac Ball Blanket ® (PBB).

Methods
Study 1 is a systematic review on patients experiences of depression-related insomnia and pharmacological and non-pharmacological sleep interventions. It is conducted in accordance with the JBI Methodology for systematic reviews of qualitative evidence.

Study 2 is a crossover trial. Patients (n=45) are randomized to a 2-week sleep period with the PBB followed by a 2-week control period. Group 2 works vice versa.

The primary outcome is changes in Total Sleep Time. Secondary outcomes are changes in other sleep outcome measures, PRN medicine, quality of sleep, insomnia severity and symptoms of depression and anxiety. Data collection: Actigraphy, sleep diaries and questionnaires. A paired, two-sided t-test to compare the means of the differences in the outcomes will be performed.

Study 3 is a qualitative study. The aim is to investigate how patients (n=12) with depression-related insomnia experience sleeping with a PBB, focusing on the blanket's mechanism of actions and its perceived influence on patients' sleep quality. Data will be collected using semi-structured interviews and analyzed using content analysis.

Perspectives
PBB is potentially a supplement or alternative to sedatives, but evidence for the efficacy is needed.

Keywords: Psychiatry, psychology and mental health, Qualitative research, Public health

Aquaporin mediated regulation of cell-cell adhesion and polarity proteins in in-vivo models of breast cancer

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Aquaporin water channels (AQPs) facilitate the transport of water across cellular membranes and are critical for the regulation of body water homeostasis. Dysregulation of AQPs is correlated to poor prognosis in a multitude of cancers including metastatic breast cancer. Cancer development and progression are associated with loss of cell-cell adhesion and cellular polarity along with accelerated cancer cell migration. AQPs are involved in cellular adhesion but their role in the regulation of cell adhesion and polarity proteins in breast cancer is yet unraveled. In this study, the MCF-7 breast cancer cell line was used to generate new cell lines with overexpression of AQP1, AQP3, AQP5 as well as relevant AQP5 point-mutants. Growth of 3D spheroids was followed by microscopy and subsequently immunostained for the cell adhesion protein γ-catenin and the polarity protein Scribble, to study their localization, along with western blotting to quantify their protein levels. Preliminary data indicates that AQPs differentially regulate both γ-catenin and Scribble in breast cancer cells. Further studies are required to understand the underlying mechanism of AQP mediated regulation of cell adhesion and polarity in breast cancer.

Keywords: Oncology, Cell biology, Animal models/disease models

Kidney function before and after acute kidney injury: a nationwide population-based cohort study

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Background

Acute kidney injury (AKI) is a common and serious condition defined by a rapid decline in kidney function. Data on changes in long-term excretory kidney function following AKI are sparse. We, therefore, examined the changes in estimated glomerular filtration rate (eGFR) from before to after AKI in a population-based setting.

Methods

Using a Danish population-based laboratory database, we included individuals with a first-time AKI identified by an acute increase in plasma creatinine (pCr) during 1 April 2010 to 31 December 2017. We restricted to individuals with an outpatient baseline eGFR within 8-365 days before AKI and three or more outpatient pCr measurements both before and after AKI. We stratified individuals by baseline eGFR level (≥/< 60 ml/min/1.73m2) and used two separate linear regression models to estimate and compare individual eGFR slopes and eGFR levels before and after AKI.

Results

Among individuals with a baseline eGFR ≥60 ml/min/1.73m2 (n=64,759), first-time AKI was associated with a median difference in eGFR level of -5.6 ml/min/1.73m2 (interquartile range (IQR), -16.1 to 1.8), and a median change in eGFR slope of -0.7 ml/min/1.73m2/year (IQR, -2.9 to 1.5) when comparing the period after AKI with the period before AKI.

Correspondingly, among individuals with a baseline eGFR <60 ml/min/1.73m2 (n=32,987), first-time AKI was associated with a median difference in eGFR level of -2.2 ml/min/1.73m2 (IQR, -9.2 to 4.3), and a median difference in eGFR slope of 1.5 ml/min/1.73m2/year (IQR, -2.9 to 6.5).

Conclusion

First-time AKI is associated with changes in both eGFR level and eGFR slope. The magnitude and direction of the changes depend on baseline eGFR.

Keywords: Nephrology, Epidemiology and biostatistics, Cardiovascular system

Impact of bimaxillary surgery on pharyngeal airway – a five-year retrospective study

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The Pharyngeal (PA) airway is indirectly affected by bimaxillary orthognathic surgical procedures due to hard-and soft tissue repositioning. However, in the literature, long-term stability studies are lacking. The aim of the present study was to evaluate PA changes in dentofacial deformity patients following bimaxillary orthognathic surgery at a five-year follow-up. Fifty patients from a retrospective study cohort 2012-2014 were included. Cone beam computed tomography images before - immediately - and five years after surgery, respectively, were assessed. Primary outcome variables were PA parameters, total -, retropalatal -, and oropharyngeal volumes, cross-sectional area, and minimal hydraulic diameter. Secondary outcome variables comprised PA soft tissue - and skeletal movements and self-reported questionnaire on sleep breathing disorder. The results showed a significant increase in the PA volume immediately after surgery, which remained stable at five-year follow-up ($P < 0.01$). A mandibular advancement of over 5 mm and epiglottis upward movement over 1mm influenced positively the PA and oropharyngeal volume ($P = 0.02$). While, over 5mm upward movement of the hyoid bone and 1 mm increase in hydraulic diameter influenced positively the PA volume ($P = 0.03$). The observed increase in airway volume, the cross-sectional area and the hydraulic diameter were not reflected in the sleep-breathing self-reported assessment. In conclusion,

bimaxillary surgery enlarged the PA volume significantly and remained stable five years after surgery.

Keywords: Dentistry, Respiratory system, Other

COVID-19 outbreak among Danish hospital employees: What are the sources?

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Background: During the early COVID-19 pandemic, Regional Hospital West Jutland experienced a considerable COVID-19 outbreak among hospital employees.

Aims: To investigate occupational- and personal exposure to COVID-19 among the infected employees during the first year of the pandemic.

Methods: Hospital employees with confirmed COVID-19 infection were invited to participate in a web-based survey. We analyzed occupational and personal exposure to COVID-19 for all respondents. Additionally, we analyzed healthcare activities, as well as use of personal protective equipment when in contact with confirmed or suspected COVID-19 patients. The analyses were stratified by two groups; respondents working in COVID-19 wards and respondents working in general wards.

Results: Data from a total of 163 respondents were analyzed. The most pronounced source of COVID-19 exposure was contact with confirmed or suspected COVID-19 patients (76.1%). Surprisingly, as for the use of personal protective equipment in aerosol-generating procedures, adherence to guidelines was considerably better in COVID-19 wards than in general wards (93.10% vs. 36.36%).

Conclusion: This study shows that hospital employees with COVID-19 most likely acquired the infection through contact with COVID-19 patients. With regard to prevention measures, employees in general wards were less inclined to use personal protective equipment than employees working in COVID-19 wards. This difference in behavior is surprising, since the general wards also treated COVID-19 patients and assisted in aerosol-generating procedures.

Keywords: Infection, Other, Infection

Room temperature Magnetoencephalography (MEG) using optically pumped magnetometers (OPM)

Preliminary setup enabling measurements in patients with amyotrophic lateral sclerosis (ALS)

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MEG is most commonly measured using superconducting coils (SQUIDS) that requires liquid helium cooling the system is reliable but expensive and large. In recent years a new technology using OPM have shown that collection MEG signals using smaller individual sensors at room temperature is feasible with almost the same sensitivity as SQUIDS. This allows the collection of MEG data in a much more flexible manner.

This study aims to use an active/passive paradigm that was made for the SQUID based MEG system at AUH and adapt the use of OPMs with the goal of reproducing similar cortical signals.

Still in the preliminary phase of the study and early stages of OPM technology presents a host of challenges to overcome to enable reliable measurements and set up when measuring patients with amyotrophic lateral sclerosis (ALS).

A custom made sensor array and mounting system (SAMS) have been created to enable the OPM sensors to be places millimeters from the head of the subjects without any contact. The control of distance and movement is key in getting strong signals for usable SNR. The SAMS also enables the sensors (currently up to 16) to be placed over any location of the head or body of the subject. The individual OPM sensors allow the array to be configured in a multitude of shapes since it is 3D-printed.

OPMs still requires heavy magnetically shielded rooms to obtain usable SNR, but the flexibility of OPMs and SAMS should make testing inside a shielded room both easier and more comfortable for the subjects, as well as cheaper to obtain and run for the departments. The OPM/SAMS also allow for studies that are currently impossible using SQUID systems.

Keywords: Basic neuroscience, Clinical neuroscience, Medical technology and diagnostic technique