Danish Society for Pharmacology

10th Annual Meeting

Program

17 January 2018, kl. 10.00 – 21.00

Syddansk Universitet, Hovedindgangen
Auditorium 0100, Campusvej 55, Odense

The meeting is supported by a grant from:

Indhold

Information

Mødet er arrangeret af

Dansk Selskab for Farmakologi, en paraplyorganisation for:

- Dansk Selskab for Farmakologi og Toksikologi
- Dansk Selskab for Klinisk Farmakologi
- Dansk Selskab for Klinisk Kemisk Farmakologi
- Danmarks Farmaceutiske Selskab
- Dansk Selskab for FarmakoEpidemiologi

Praktiske Informationer:

- Frokost og kaffepauser er inkluderet i mødet
- Middagsbilletter kan købes på AU webshop
- Posters skal være sat op før symposiet starter
- Foredragsholderne bedes sørge for, at præsentationerne er klar i auditoriet senest 30 min før foredraget skal afholdes

Sekretariat:

- Institut for Biomedicin – Farmakologi, Att.: Jytte Kragelund, Aarhus Universitet,
  Bartholins Allé 6, 8000 Aarhus C.
  Tlf.: 8716 7604; e-mail: jk@biomed.au.dk

Program

09.30 Registration and coffee

10.00 Introduction to meeting: Niels Jessen, Aarhus University

Session 1 Population-based pharmacology I and BCPT Nordic Prize

Chairmen: Agnete Larsen and Niels Jessen, Aarhus University

10.05 BCPT Nordic Prize Lecture**:** *G protein coupled receptors in health and disease*
Thue W. Schwartz, University of Copenhagen

10:40 *Biobanks in Pharmacology*
Reimar W. Thomsen, Aarhus University

11:05 **Coffee**

Session 2 Oral presentations and Schou Memorial Lecture

Chairman: Kim Brøsen, University of Southern Denmark

11.20 O1. *Insight gained from genome-wide interaction and enrichment analysis on weight gain during citalopram treatment*
Henrik Thyge Corfitsen and colleague, Aarhus University and Psychiatric Research Unit, Herning

O2. *Lipid rescue for metoprolol-induced hemodynamic depression: A randomized clinical trial*
Kasper Meidahl Petersen and colleagues, Bispebjerg and Frederiksberg University Hospital

O3. *Adherence to selected national guidelines for use of expensive hospital drugs ("RADS guidelines")*
Lene Juel Kjeldsen and colleagues, Amgros I/S, Copenhagen

12.00 *Jens Schou Memorial Lecture*
Morten Andersen, University of Copenhagen

12:30 **Lunch**

Session 3 Population-based pharmacology II

Chairman: Steen Ingwersen, Novo Nordisk A/S

13:30 Key Note: *Pharmacometrics and Systems Pharmacology in drug discovery and development*
Piet Hein van der Graaf, Leiden University, The Netherlands

Session 4 **Posters and Coffee**

14:15-15:00 **Posters – Guided Tours**

Session 5 **15:00-16:00 Workshops - Parallel sessions**

1) **Pediatric Pharmacology**

Chairman: Helle Holst, Bispebjerg Hospital and University of Copenhagen

Model-based pediatric dose finding

Inclusion of biological mechanisms in population PK
Christian Hove Rasmussen, Certara Strategic Consulting

2) **Quantitative Pharmacology – From Drug Development to Clinical Applications**

Chairman: Rasmus Vestergaard Juul, Novo Nordisk A/S

Pharmacometrics in drug development
Rune Overgaard, Novo Nordisk

Case 1: Individualised dosing for controlled ovarian stimulation in IVF
Daniel Jonker, Ferring

Case 2: App for personalised risk assessment
Majken Hamann Sey, Novo Nordisk

16:15 **Break**

Session 6 **Hot topics in Danish Pharmacology – based on suggestions from the member societies**

Chairman: Ulf Simonsen, Aarhus University

16.30 (DSFE) *Pragmatic Trials*
Michael Busch-Sørensen, ApEHR

16.45 (DSK2F) *Vejledende terapeutiske intervaller for psykofarmaka – er de valide?*
Jan Borg Rasmussen, Filadelfia, Dianalund

17.00 (DSFT) *Milde analgetiske stoffer og reproduktive forstyrrelser*
David Møbjerg Kristensen, University of Copenhagen

17.15 (DSKF) *Medicinsk Cannabis*
Charlotte Uggerhøj Andersen, Aalborg and Aarhus University Hospitals

17.30 **Awards to best oral communication and best poster**
Niels Jessen, Aarhus Universiy

17.45 Drinks at the poster area

18:00 Dinner at the Campus Restaurant

Organizing Committee:
Agnete Larsen, Deidre Cronin Fenton, Maija Bruun Haastrup, Thomas Bo Jensen, Kim Dalhoff, Anders Jensen, Trine Meldgaard Lund, Zandra Ennis, Kenneth Skov, and Niels Jessen

Posters

A1: GROWTH HORMONE APPEARS TO BE POSITIVELY ASSOCIATED WITH ADIPOSE TISSUE FIBROSIS IN HUMANS

A. Bæk[1], M.C. Arlien-Søborg[2], J. Lebeck[1], N. Jessen[1,2], J.O.L. Jørgensen[1]
[1]Department of Biomedicine, Aarhus University and [2]Department of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark

A2: INVOLVEMENT OF SULFIDES AND KV7 CHANNELS IN GYY4137 AND HYDROGEN SULFIDE RELAXATION OF RAT MESENTERIC SMALL ARTERIES

A.G. Petersen[1], S. Abramavicius[2], N.S. Renaltan[1], M. Whiteman[3], E. Stankevicius[2], E.R. Hedegaard[1] and U. Simonsen[1].
[1]Department of Biomedicine, Aarhus University, [2]Institute of Physiology and Pharmacology, Lithuanian University of Health Sciences and [3]University of Exeter Medical School.

A3: METABOLITE RECEPTOR SYNERGY IN ENTEROENDOCRINE SENSING OF DIETARY LIPIDS

Jeppe Pio Ekberg[1], Trond Ulven[2], Thue W. Schwartz[1]
[1]NNF Center for Basic Metabolic Research, Section for Metabolic Receptology, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3, 2200 Copenhagen, Denmark
[2]Department of Physics, Chemistry and Pharmacy, University of Southern Denmark, Campusvej 55, DK-5230 Odense M, Denmark

A4: COMPANION DIAGNOSTICS & ONCOLOGY DRUG DEVELOPMENT

Jan Trøst Jørgensen
Dx-Rx Institute, Baunevænget 76, 3480 Fredensborg, Denmark

A5: LIRAGLUTIDE INCREASES mRNA EXPRESSION OF NGB AND HMOX-1 BUT DOES NOT REDUCE THE IL-6 AND TNF-α RESPONSE IN LPS-STIMULATED ASTROCYTES

K. Bilde[1], B. DellaValle[1], J. Rungby[1,2], J. Palmfeldt[3], A. Larsen[1]
[1]Depart. of Biomedicine, Aarhus University, [2]Depart. of Endocrinology, Bispebjerg University Hospital, [3]Research Unit of Molecular Medicine, Aarhus University

A6: ORAL CONTROLLED RELEASE FORMULATIONS TO PATIENTS WITH GASTROINTESTINAL DYSFUNCTION – IS DRUG RELEASE AND ABSORPTION IMPAIRED?

L. Ladebo, A.M. Drewes, B. D. Steffansen, L.L. Christrup, A.E. Olesen
Department of Gastroenterology, Aalborg University Hospital, Aalborg, 9000, Denmark

A7: LOCALIZATION OF PREGNANCY ZONE PROTEIN WITHIN THE HUMAN – A POTENTIAL TARGET FOR RETINA PROTECTON?

L H Olesen[1,2], E. Emri[2] , A Larsen[1] & I Lengyel[2]
[1]Depart of Biomedicine Aarhus University, Denmark & [2]Centre for Experimental Medicine, The Queen's University Belfast, UK

A8: SHARP AGE LIMITS FOR AUTHORIZED MEDICINES MAY RESULT IN WIDE SPREAD OFF-LABEL USE

M. Andrulyte, O.J. Bjerrum
Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 2, 2100 Copenhagen and Copenhagen Centre for Regulatory Science

A9: PREGNANCY USE OF PRESCRIPTION MEDICATION IN DENMARK –A NEW ONLINE AVAILABLE STATISTICS 2000 TO 2016
Maja Laursen, The Danish Health Data Authority

A10: IMPACT OF TRIAL DESIGN ON THE ESTIMATION OF DRUG POTENCY AND POWER IN CLINICAL TRIALS OF HAEMOPHILIA WITH INHIBITORS
M.S Larsen, R.V Juul, M. Kreilgaard, A.T. Kristensen and U.S.H. Simonsson
Haemophilia PK & ADME, Haemophilia Research, Novo Nordisk A/S, Maaloev, Denmark

B1: COMPARISON OF CLINICAL INFORMATION SOURCES FOR DOSAGE RECOMMENDATIONS OF ANALGESICS IN PATIENTS WITH REDUCED RENAL FUNCTION
O. Bors[a], M.B. Houlind[b], C.Treldal[b], D. T. Thygesen[a], L. Colberg[a], M.H. Clemmensen[a].
[a]Medicine Information Centre, The Hospital Pharmacy Capital Region of Denmark, Copenhagen, Denmark. [b]Optimed, Clinical Research Centre, Hvidovre Hospital, Copenhagen, Denmark

B2: NICOTINAMIDE RIBOSIDE SUPPLEMENTATION IN OBESE MEN: AN INVESTIGATOR-INITIATED, RANDOMIZED,PLACEBO-CONTROLLED CLINICAL TRIAL OF INSULIN SENSITIVITY, SUBSTRATE METABOLISM, AND BODY COMPOSITION
O.L. Dollerup(1), B. Christensen, M. Svart, K. Sulek, S. Ringgaard, H.Stødkilde-Jørgensen, N. Møller, J.T. Treebak, N. Jessen
(1)Novo Nordisk Foundation Center for Basic Metabolic Research, Section of Integrative Physiology, University of Copenhagen, Blegdamsvej 3A, 2200 København N, Denmark

B3: CAN KCA3.1 ION CHANNEL BLOCKADE PROTECT AGAINST PULMONARY CIRCULATORY COLLAPSE AND OEDEMA?
PC Lind, AG Petersen, A Granfeldt, U Simonsen
Department of Biomedicine, Aarhus University, Aarhus, Denmark

B4: INTRAVENOUS PARACETAMOL IN NEONATES: SAFETY AND ENTHANOL-DRUG INTERACTIONS – PROTOCOL OF THE PARASHUTE TRIAL
Haslund-Krog S[1], Hertel S[2], Dalhoff K[1], Van Den Anker J[3], Henriksen TB[4], Holst H[1]
Department of Clinical Pharmacology, Bispebjerg Hospital[1], Neonatal Intensive Care Unit, Rigshospitalet[2], Division of Clinical Pharmacology, Children's National Health System, Washington DC, USA[3], Neonatal Intensive Care Unit, Dept Paediatrics, Aarhus University Hospital[4]

B5: PREVALENCE OF D-VITAMIN DEFICIENCY AMONG DANISH PREGNANT WOMEN – INDICATIONS OF NUTRITIONAL AND SEASONAL VARIATIONS
S.D. Justesen[2], A.L. Vestergaard[1,2], T. Volqvartz[1,2], S.K. Aagaard[1,2], M. F. Andreasen[3], I. Lesnikova[4], N. Uldbjerg[5], A. Larsen[2]*, P. Bor[1]*.
[1]Dept. of Obstetrics and Gynecology, Randers, [2]Dept. of Biomedicine, Aarhus University, [3]Dept. of Forensic Medicine, Aarhus University, [4]Dept. of Pathology, NC, [5]Dept. of Obstetrics and Gynecology, Aarhus, *Share senior authorship

B6: CENTRAL ROLE OF MUSCLE STEM CELLS IN REGENERATIVE FAILURE IN PATENTS WITH PERIPHERAL ARTERIAL DISEASE
T. Billeskov[1], J. Farup[2], N. Jessen[2], N. Eldrup[1], F. de Paoli[3]
[1]Dept. of Cardiothoracic & Vascular Surgery T, Aarhus University Hospital; [2]Dept. of Clinical Medicine, Research Laboratory for Biochemical Pathology, Aarhus University; [3]Dept. of Biomedicine, Aarhus University

B7: CONSUMPTION OF THE HERBAL SUPPLEMENT GINGER IS POPULAR AMONG, DANISH PREGNANT WOMEN

T. Volqvartz[1,2], A.L. Vestergaard[1,2], S.K. Aagaard[1,2]; M.F. Andreasen[3]; I. Lesnikova[4]; N. Uldbjerg[5]; A. Larsen[2]*; P. Bor[1]* *Shared senior authorship
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B8: INTAKE OF THE SCANDINAVIAN LICORICE AMONG DANISH, PREGNANT WOMEN IN THE FIRST TRIMESTER

T. Volqvartz[1,2], A.L. Vestergaard[1,2], S.K. Aagaard[1,2]; M.F. Andreasen[3]; I. Lesnikova[4]; N. Uldbjerg[5]; A. Larsen[2]*; P. Bor[1]* *Shared senior authorship
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B9: VALIDATION OF THE ELECTRONIC PATIENT MEDICATION MODULE (EPM)—THE ADMINISTRATIVE DATABASE ON IN-HOSPITAL DRUG-USE IN THE CAPITAL REGION OF DENMARK

T.B. Jensen, E. Jimenez-Solem, R. Cortes, C. Betzer, S. Bøge Breinholt, K.M. Petersen, T.S. Petersen, J. Kjellberg, H.R. Christensen, J. Trærup Andersen
Dept. of Clinical Pharmacology, Copenhagen University Hospital Bispebjerg, Bispebjerg Bakke 23, 2400 CPH NV, Denmark

B10: DISSECTING GPCR INTERNALIZATION PATHWAYS USING A REAL-TIME INTERNALIZATION ASSAY

T.C. Møller, H. Bräuner-Osborne
Department of Drug Design and Pharmacology, Faculty of Health Sciences, University of Copenhagen, Universitetsparken 2, 2100 Copenhagen, Denmark

B11: A SPONTANEOUS CANINE MODEL OF CENTRAL NEUROPATHIC PAIN IN CAVALIER KING CHARLES SPANIELS

M.S. Thøfner[1], O.J. Bjerrum[2], J.R. Nyengaard[3], T.S. Jensen[4], M. Berendt[1]
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Abstracts

Free communications

Abstract O1

INSIGHT GAINED FROM GENOME-WIDE INTERACTION AND ENRICHMENT ANALYSIS ON WEIGHT GAIN DURING CITALOPRAM TREATMENT.

H. T. Corfitsen[1,2], A. Drago[2], [1]Aarhus University, Aarhus, Denmark [2.]Psychiatric Research Unit, gl. Landevej 49, 1 7400 - Herning, Denmark

Background: Weight gain is a possible side effect of the pharmacological antidepressant treatments. Defining antidepressant prescriptions based on personal genetic makeups would decrease the risk of weight gain and increase the quality of the current antidepressant pharmacological treatments. **Methods:** Clinical and genetic data from the STAR*D study were accessed through the NIMH, after permission. 643 individuals (63.45% females) were included in the present analysis. All patients received citalopram (40 mg/day). Weight gain was measured as "Weight (Increase) Within the Last Two Weeks" and ranges from 0 ("no weight change") to 3 ("has gained 5 pounds or more"). SNPs were excluded for allele frequency <0.01 and low genotype call rate. Deviations from the Hardy-Weinberg equilibrium were accepted under a P-threshold of 0.0001. The first 1000 SNPs, showing a stronger association with the phenotype were selected. The genes that harbored such variations were investigated for enrichment. **Results:** The axon guidance (p.adjust = 0.005) and the developmental biology pathway (p.adjust = 0.01) were enriched in variations associated with weight gain. The developmental biology pathway includes molecular cascades involved in the regulation of beta-cell development, and the transcriptional regulation of white adipocyte differentiation. A number of variations were harbored by genes whose products are involved in the synthesis of collagen (COL4A3, COL5A1 and ITGA1), activity of the thyroid-hormones (NCOR1 and NCOR2), energy metabolism (ADIPOQ, PPARGC1A) and myogenic differentiation (CDON). **Conclusion:** A molecular pathway analysis identified new candidate genes whose future investigation may provide insights in the molecular events that drive weight gain during antidepressant treatment.

Abstract O2

LIPID RESCUE FOR METOPROLOL-INDUCED HEMODYNAMIC DEPRESSION: A RANDOMIZED CLINICAL TRIAL

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Background: lipid rescue therapy (LRT) – i.e. rapid, high-dose lipid emulsion infusion– is recommended for poisonings with cardioinhibitory drugs, but our knowledge about efficacy and safety of LRT is limited. In a clinical trial we therefore investigated: 1) hemodynamic effects of LRT compared to matching placebo on metoprolol-induced hemodynamic depression, and 2) how the expanded plasma lipid-phase affected metoprolol pharmacokinetics.

Methods: ten male participants received in randomized order 60 mg iv metoprolol or placebo followed by LRT (6 ml/kg lipid emulsion) or placebo on four separate days (placebo+placebo, placebo+LRT, metoprolol+placebo, metoprolol+LRT). Primary endpoint was heart rates 90 min

after end of LRT/placebo. Exploratory endpoint related to hemodynamic effects of LRT alone and on metoprolol plasma concentration and cardio-inhibitory properties were also assessed.

Results: after metoprolol+LRT, average heart rates were 5.5 beats per minute (95% CI: 3.0-8.1) higher compared to placebo at study end ($p<0.001$). Average stroke volume and cardiac output was 4.1% (95 % CI: 1.0-7.3%, $p=0.01$) and 10.0% (95% CI: 4.7-15.4%, $p<0.001$) higher after metoprolol+LRT compared to metoprolol+placebo. LRT did not affect plasma metoprolol AUC ($p=0.78$). No serious adverse effects were observed.

Conclusion: during metoprolol-induced hemodynamic depression, LRT significantly increased heart rate and cardiac contractility. LRT demonstrated no effects on metoprolol pharmacokinetics or major safety issues.

Abstract O3

ADHERENCE TO SELECTED NATIONAL GUIDELINES FOR USE OF EXPENSIVE HOSPITAL DRUGS ("RADS guidelines")

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Background: The Danish health care system has used significant resources to develop and implement RADS-guidelines. Adherence is currently followed by aggregated drug use data, and consequently, knowledge about adherence to the RADS-guidelines at patient level is sparse.

Aim: The study sought to determine adherence to selected RADS-guidelines at patient level.

Method: Six RADS-guidelines suspected to be associated with low adherence were selected by a project group for the study. The RADS-guidelines covered areas of gastroenterology, antimycotic treatment and urology. Data were collected retrospectively for a 3-month period (April-June 2016) by 12 pharmacists at 11 wards in 4 Danish regions. Patients were included according to inclusion criteria of the respective RADS-guidelines. When possible, all eligible patients at the respective wards were selected, otherwise a random sample of patients was included.

Results: Adherence to the RADS-guideline within the area of gastroenterology was 99% (80%-100%, n=71), adherence to antimycotic treatment could not be determined due to the nature of the guideline (n=51), but adherence to the three guidelines within urology were 99.4% (98.3%-100%, n=689), 98.3% (67%-100%, n=59) and 100% (n=161).

Conclusion: The study showed high adherence to all selected RADS-guidelines for all 4 regions. The unique Danish set-up for developing and implementing national guidelines for use of expensive hospital drugs seems successful. This national set-up has now been transferred to the Danish Medicines Council (Medicinrådet) from 1st January 2017. Some adjustments to the processes have been made, but the general idea of developing and implementing RADS-guidelines remains the same.

Poster Session

Poster A1

GROWTH HORMONE APPEARS TO BE POSITIVELY ASSOCIATED WITH ADIPOSE TISSUE FIBROSIS IN HUMANS

A. Bæk[1], M.C. Arlien-Søborg[2], J. Lebeck[1], N. Jessen[1,2], J.O.L. Jørgensen[1]
[1]Department of Biomedicine, Aarhus University and [2]Department of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark

Growth hormone (GH) is the endogenous ligand for the GH receptor. Exogenous GH agonist, Somatropin, is used to treat GH deficiency and some forms of growth retardation in children. In adults, excess GH causes acromegaly and results in metabolic dysregulation, increased mortality and substantial alterations in adipose tissue (AT). Fibrosis in AT can cause a dysfunctional tissue state associated with metabolic disorders and although GH seems to induce fibrosis in various tissues, its impact on AT fibrosis in humans is unexplored. Therefore, the aim of this project was to asses markers of AT fibrosis in patients with acromegaly before and after treatment.

Subcutaneous AT biopsies obtained from 17 acromegalic patients before and after treatment were examined for adipocyte size, extracellular matrix (ECM) content and expression of fibrosis-associated genes. Body composition was assessed by DEXA scans.

We recorded a significant decrease in ECM content and collagen gene expression after treatment by a median of 53.4 % ($P<0.05$) and 53.5 % ($P<0.05$), respectively. Although absolute fat mass was significantly increased after treatment by a median of 19.5 % ($P<0.01$), we observed no difference in adipocyte size. Lean body mass was significantly decreased by a median of 5.1 % ($P<0.001$).

In conclusion, excess GH causes a lean body composition and appears to induce AT fibrosis in humans, which likely contributes to a metabolically unhealthy leanness. Our findings point to AT fibrosis as a potential side effect of Somatropin treatment.

Poster A2

INVOLVEMENT OF SULFIDES AND KV7 CHANNELS IN GYY4137 AND HYDROGEN SULFIDE RELAXATION OF RAT MESENTERIC SMALL ARTERIES

A.G. Petersen[1], S. Abramavicius[2], N.S. Renaltan[1], M. Whiteman[3], E. Stankevicius[2], E.R. Hedegaard[1] and U. Simonsen[1].
[1]Department of Biomedicine, Aarhus University, [2]Institute of Physiology and Pharmacology, Lithuanian University of Health Sciences and [3]University of Exeter Medical School.

Hydrogen sulfide (H2S) is a gasotransmitter capable of regulating vascular tone. The slow releasing H2S donor, GYY4137, causes relaxation in mesenteric arteries but simultaneous measurements found no detectable traces of H2S. This question whether a sulfide-independent mechanism may contribute to the GYY4137 relaxation.

H2S released from GYY4137 was assessed in vitro by an ELISA assay, and wire myographs were used to examine the potential role of potassium (K) channels in the relaxation induced by GYY4137 or sodium sulfide (Na2S).

GYY4137 produced low levels of H2S at physiological pH and this release was independent of free thiols and rat mesenteric tissue. Both Na2S and GYY4137 induced relaxation, while this was not the case for a hydrolytic degraded GYY-analogue. KATP, BKCa, and KV7 channels were involved in Na2S relaxations whereas GYY4137 relaxation only involved KV7 channels. The thiol-containing amino acid, L-cysteine, significantly decreased Na2S relaxation and

abolished GYY4137 relaxation suggesting a link between the GYY4137 sulfide group and a target thiol group.

Taken together our results suggest that GYY4137 likely induces relaxation by a mechanism independent of H2S release. The mechanism underlying GYY4137 relaxation may involve direct transfer of a sulfide group to a target molecule leading to opening of KV7 channels.

Poster A3

METABOLITE RECEPTOR SYNERGY IN ENTEROENDOCRINE SENSING OF DIETARY LIPIDS

Jeppe Pio Ekberg[1], Trond Ulven[2], Thue W. Schwartz[1]

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The four fat metabolite sensors GPR40, GPR119, GPR120 and TGR5 belong to the family of G-protein coupled receptors. GPR119 and TGR5 couple via the Gs pathway, GPR120 couples both Gq and Gi, and recently we have shown that GPR40 can couple both Gq and Gs. We speculate that the four fat metabolite sensors have more influence on each other than previous thought. We show evidence that only the fat metabolite sensors GPR40, GPR119 and TGR5 act synergistically in the secretion of GIP and GLP1 and that GPR120 is able to block the TGR5 secretion of GIP and GLP1.

The GPR40 Gq+Gs agonist had the strongest effect on the incretin response. GPR120 activation showed no effect on GIP or GLP-1 secretion and, in combination with TGR5 agonist also blocked the effect of the latter on GIP and GLP1 secretion. Combination of GPR40(Gq), GPR119(Gs) and TGR5(Gs) agonists induced similar GIP and GLP-1 secretion as GPR40 Gq+Gs agonist only. GPR120 agonist given in increasing doses impaired the GIP and GLP1 release from TGR5 activation and was also able to decrease Olive Oil induced incretin release. No combinations were able to give the same GIP or GLP1 secretion as oliveoil. These data show that combining different intracellular signalling pathways, using activation different of G-proteins present on GIP and GLP1 cells, can amplify the incretin response.

Poster A4

COMPANION DIAGNOSTICS & ONCOLOGY DRUG DEVELOPMENT

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Over the past 20 years, we have experienced an increasing number of targeted cancer drugs being developed using the drug-diagnostic co-development model. In this model, a molecular diagnostic assay is developed in conjunction with the drug and used to define the patient population likely to benefit. For a number of targeted cancer drugs these companion diagnostic (CDx) assays have played a critical role in their successful development (Hersom M, Jørgensen JT. Ther Drug Monit. 2017 Oct 27. [Epub ahead of print]). These assays are not only important during the drug development process but they are likewise essential treatment decision tools after drug approval. The CDx assays have the individual patient as a point of reference and they are decisive for the move toward a more individualized pharmacotherapy as well as being an important element in the realization of precision medicine (Jørgensen JT. Ann Oncol. 2017 Nov 30. [Epub ahead of print]).

The increased use of predictive CDx assays in oncology drug development has also greatly influenced the clinical trial designs. Within the past few years, we have experienced an evolution

of the traditional drug-diagnostic co-development model where the different clinical development phases are fused together to form a kind of supersized phase I study. The US FDA have named this “seamless drug development”, and there are already several examples where this approach has resulted in regulatory approval of targeted cancer drugs, often using surprisingly small patient populations (Jørgensen JT, Hersom M. Clin Pharmacol Ther. 2017 Dec 2. [Epub ahead of print]).

Poster A5

LIRAGLUTIDE INCREASES mRNA EXPRESSION OF NGB AND HMOX-1 BUT DOES NOT REDUCE THE IL-6 AND TNF-α RESPONSE IN LPS-STIMULATED ASTROCYTES

K. Bilde[1], B. DellaValle[1], J. Rungby[1,2], J. Palmfeldt[3], A. Larsen[1]
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Brain tissue has limited capacity for regeneration and albeit necessary for tissue repair, inflammation in the CNS can often lead to irreversible secondary damage. This is prominent after neuronal trauma and in chronic neurodegenerative conditions like Alzheimer´s disease. Experimentally, glucagon-like peptide-1 (GLP-1) analogues limit brain trauma and improve memory in rodent models of Alzheimer´s disease. Astrocytes participate in neuroinflammation and tissue homeostasis, and have been shown to express the GLP-1 receptor, but the role of astrocytes in GLP-1 pharmacodynamics is not fully unraveled.

Here, an inflammatory model was established for two astrocyte cell cultures - a primary and immortalized DI TNC1 cells using LPS stimulation. Real-time PCR studies found no ameliorating effect of GLP-1 analogue liraglutide on *Il-6, Bax/Bcl-2* ratio, and *Tnf-α* mRNA expression, but a reduced response of *Il-1β* was seen in the primary culture. As the DI TNC1 cell line did not express *Il-1β*, this finding might reflect an effect of liraglutide on other cell types, most likely the microglia. Liraglutide increased mRNA expression of neuroglobin (*Ngb*) and heme oxygenase 1 (*Hmox-1*) but did not significantly affect mRNA expression of brain derived neurotrophic factor (*Bdnf*) and superoxide dismutase 2 (*Sod2*).

In conclusion, liraglutide affects neuroprotective genes like *Ngb* and *Hmox-1* by upregulating the mRNA expression but does not seem to reduce proinflammatory *Il-6* and *Tnf-α*.

Poster A6

ORAL CONTROLLED RELEASE FORMULATIONS TO PATIENTS WITH GASTROINTESTINAL DYSFUNCTION – IS DRUG RELEASE AND ABSORPTION IMPAIRED?

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Massive resection or widespread disease of the gastrointestinal (GI) tract has consequences for absorption of orally administered drugs in controlled release formulations (CRF). However, the influence of disease on drug absorption is not fully understood and therapy failure is common. Thus, the aim is to investigate the impact of GI-pathophysiology on net absorption and pharmacodynamics of oxycodone administered as an immediate release formulation and two different CRF in patients with GI disorders due to resection, chronic pancreatitis, and diabetes. Results will be compared to data obtained in healthy volunteers.

Five randomized, 3-armed, double-blinded, cross-over studies will be conducted in healthy volunteers and 4 patient groups. Transit time will be assessed with the SmartPill. Plasma levels of oxycodone will be used for pharmacokinetic evaluation. Pupillometry and mechanical muscle stimulation will be used for pharmacodynamic evaluation. Lastly, models will be developed to

explain if and why the release of drug and the absorption from different CRF are impaired in relation to different GI dysfunctions.

Fourteen healthy participants have been included. Data analysis awaits until all healthy participants and at least one patient group have completed the study. It is expected that evidence-based treatment guidelines will be established with recommendation for optimal choice of CRF to the specific populations investigated. Additionally, results will be extrapolated to CRF containing other drug classes than just opioids.

Poster A7

LOCALIZATION OF PREGNANCY ZONE PROTEIN WITHIN THE HUMAN – A POTENTIAL TARGET FOR RETINA PROTECTON?

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Age-Related Macular Degeneration (AMD) is a major cause of blindness in the aged population. A hallmark of AMD is drusen that are extracellular deposits in the sub retinal pigment epithelial (RPE) space. Drusen contain proteins, lipids, trace metals and hydroxyapatite (HAP), but the exact composition and how drusen are formed is not yet fully understood.

Recently we identified the presence of Pregnancy Zone Protein (PZP) in blood samples from AMD patients and found that PZP levels are higher in those who has the AMD-associated polymorphic form of complement factor H (Y402H). In addition, we found that PZP can bind to HAP using chromatography.

Interestingly, PZP is a highly preserved protease inhibitor related to inflammatory pathways including the complement system. Based on these findings we hypothesized that PZP might play a role in the eye and accumulate in the sub-RPE space by binding to the drusen associated HAP spherules but, PZP has not been reported in human eyes.

Here we examined PZP localization using cadaveric human eyes, selective antibodies and confocal microscopy. We found that PZP is indeed present in the human eye where it is localized to the ciliary body, outer plexiform layer of the retina and the retinal pigment epithelium. PZP was also localized to the HAP spherules in drusen. Therefore, PZP might become a new target for pharmacological intervention in combating drusen deposition and/or the dysregulation of the complement cascade, and therefore AMD.

Poster A8

SHARP AGE LIMITS FOR AUTHORIZED MEDICINES MAY RESULT IN WIDE SPREAD OFF-LABEL USE

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Off-label medicines can be described as medicines which are used outside the terms of its marketing authorization regarding indication, dosing, route of administration or group of patients. The latter off-label use was the main objective of this study.

Four drugs were chosen for investigation and collection of two years prescription data from five community pharmacies in DK. Diclofenac, mirtazapine and quetiapine is authorized for patients >18 years; desmopressin can only be prescribed for patients <65 years. For data extraction, CITO software and SQL code were used during spring 2017.

The number of off-label prescriptions found for diclofenac, mirtazapine and quetiapine patients below 18 years correspond to 145 out of 7518 examined which represents 2%. Of those 145

prescriptions 50 (35%) were prescribed for patients <14 years. Of all (n=925) desmopressin prescriptions 17% were dispensed for elderly (>65). Of these prescriptions 95% (n=159) were off-label.

Thus, 65% of the three examined medicines prescribed for children were dispensed for patients between 14-18. An interpretation could be that general practitioners do not see the physiological difference to use it for patients >14 compared to an adult person of 18 years. In elderly, prescribing of desmopressin could lead to hyponatremia. With 95% of elderly receiving desmopressin this may pose a risk.

To conclude, monitoring of off-label prescriptions is needed since off-label prescribing may present an additional risk. However, if the age limits in the label are taken too serious this could lead to undertreatment.

Poster A9

PREGNANCY USE OF PRESCRIPTION MEDICATION IN DENMARK –A NEW ONLINE AVAILABLE STATISTICS 2000 TO 2016

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We performed a linkage between the Medical Birth Register during 2000-2016 and data on prescription medicines use from the National Register of Medicinal Products Statistics using the unique civil registration number.

Calculated figures are number of women and number of women per 1000 pregnancies. Medications are presented at substance level (ATC level 5) as well as higher levels. The statistics demonstrates medicine use before pregnancy and during pregnancy split in trimesters and split by age groups. For comparison we show medicines use in a control group –ten women per pregnant woman with the same age and region of residence.

The statistics is free available online in both a Danish and English version, includes 55,000 to 66,000 pregnancies per year and will be updated yearly. It can be found at http://esundhed.dk/sundhedsregistre/LSR/Sider/LUG01.aspx

Poster A10

IMPACT OF TRIAL DESIGN ON THE ESTIMATION OF DRUG POTENCY AND POWER IN CLINICAL TRIALS OF HAEMOPHILIA WITH INHIBITORS

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Historically, clinical trials of haemophilia with inhibitors (HwI) have been challenged by the small patient population. New approaches to clinical trial methodology and statistical modelling could potentially be used for study optimization. Therefore, we evaluated the impact of different trial designs and study conditions on the estimated drug potency and power, and compared traditional statistical methods with repeated time-to-event (RTTE) modelling in terms of power.

Bleeding information from a clinical trial of 23 haemophilia patients with inhibitors treated on-demand was used to develop a baseline RTTE model using NONMEM. Clinical trial simulations for a hypothetical anti-haemophilic drug were performed using different trial designs (parallel-group, placebo-controlled parallel-group, crossover and placebo-controlled crossover designs) and study conditions, including sample size, study duration and dose levels. The precision and accuracy of the estimated drug potency (EC_{50}) and power for different trial designs, study conditions and statistical methods (RTTE modelling, *t*-test and negative binomial regression) were evaluated.

The developed baseline RTTE model accurately described the clinical data. The crossover designs displayed up to four-fold higher precision of the estimated EC_{50} and three-fold higher power relative to the parallel-group trial designs. Furthermore, RTTE modelling provided a higher power relative to the traditional statistical tests.

Crossover designs in combination with RTTE modelling can reduce the required sample size and study duration, while ensuring high power and precise estimation of EC_{50}, in clinical trials of HwI.

Poster B1

COMPARISON OF CLINICAL INFORMATION SOURCES FOR DOSAGE RECOMMENDATIONS OF ANALGESICS IN PATIENTS WITH REDUCED RENAL FUNCTION

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Objective: To assess and compare dosage recommendations for analgesics in patients with reduced renal function (eGFR < 50 mL/min/m^2).

Methods: The clinical information sources pro.medicin.dk, The Renal Drug Handbook, Renbase® and UpToDate® was used to find dosage recommendations for Codeine, Tramadol, Fentanyl, Morphine, Oxycodone, Acetylsalicyllicacid, Diclofenac, Ibuprofen, Naproxen and Paracetamol. Dosage recommendation was grouped by eGFR ranges: <10, <30 and <50 mL/min/m^2 and indexed by: (A) no need for adjustment, (B) dose adjustment required, (C) contraindicated or should be avoided. Kohen's Kappa and Fleiss' Kappa test was used to quantify agreement between the clinical information sources. Kappa values < 0.2 were considered poor agreement, values between 0.21 to 0.40 as fair, 0.41 to 0.60 as moderate, 0.61 to 0.80 as good and 0.81-1.00 as very good agreement.

Results: The agreement for dosage recommendations between all sources was 0.45; 0.64 and 0.17 for eGFR <10; <30 and <50 mL/min/m^2. Highest agreement was found between pro.medicin.dk and Renbase® (0.44 — 0.66). Lowest agreement was found between Renbase® and The Renal Drug Handbook (0.11 — 0.51). Finally, Renbase® was found to have the most conservative dosages recommendations.

Conclusion: Dosage recommendation for analgesics to patients with reduced renal function varies between different clinical information sources. Especially at eGFR between 30 — 50 mL/min/m^2 the choice of source has significant impact on dosage recommendation.

Poster B2

NICOTINAMIDE RIBOSIDE SUPPLEMENTATION IN OBESE MEN: AN INVESTIGATOR-INITIATED, RANDOMIZED, PLACEBO-CONTROLLED CLINICAL TRIAL OF INSULIN SENSITIVITY, SUBSTRATE METABOLISM, AND BODY COMPOSITION

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Animal studies suggest a positive role for nicotinamide riboside (NR) on insulin sensitivity in models of metabolic disease. NR, a nicotinamide adenine dinucleotide (NAD+) precursor, is a member of the vitamin B3 family and is available as an over-the-counter supplement. To test if NR supplementation improves insulin sensitivity in obese humans we conducted a randomized,

placebo-controlled, double-blinded, and parallel-group designed clinical trial. 40 healthy, sedentary males with a body mass index (BMI) > 30 kg/m2, age- range 40-70 were randomly assigned to 12 weeks of NR (1,000 mg twice daily) or placebo treatment.

Insulin sensitivity (M-value during a hyperinsulinemic euglycemic clamp), the primary end-point measure, was not affected by NR treatment. NR did not affect endogenous glucose production and glucose uptake (measured with tritiated glucose) or oxidation of glucose. Similarly, NR supplementation had no effect on resting energy expenditure, lipolysis (measured with tritiated palmitate), oxidation of lipids, body composition, or hepatic lipid content. No major adverse events during NR treatment were recorded throughout the trial.

These data do not support a role for NR supplementation to improve insulin sensitivity and reduce the risk of type 2 diabetes in obese humans. NR supplementation in doses of 2,000 mg/daily appears safe in healthy humans, and future studies may determine whether NR supplementation have positive effects on other outcomes than insulin sensitivity.

Poster B3

CAN KCA3.1 ION CHANNEL BLOCKADE PROTECT AGAINST PULMONARY CIRCULATORY COLLAPSE AND OEDEMA?

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ARDS is a severe condition characterized by acute inflammation and an increased alveolar-capillary permeability resulting in non-cardiogenic lung oedema and hypoxemia.

Currently, no pharmacological interventions exist that target directly the underlying pathophysiology of the disease, thus elucidating the need for novel pharmacological entities. However, our research group has recently shown that KCa3.1 and TRPV4 ion channels play a crucial role in the development of the disease, and KCa3.1 channel blockers seem to be a promising potential target for treating the disease.

For in vivo studies, a model of acid-induced ARDS will be established in mice. Post acid-instillation, mice will be randomised to either saline or a KCa3.1 blocker (Senicapoc, RA-2, TRAM-34). Outcomes will be inflammatory markers in BAL fluid, histological scoring, blood gas analysis, lung function parameters and the degree of lung oedema.

For in vitro studies, murine pulmonary arteries (300-500 µm) will be mounted in isometric wire myographs for tension recording. As in ARDS, pulmonary arterial relaxation will be induced by KCa3.1 channel activation, and a dose-response-curve will be established for a series of KCa3.1 blockers.

10% of patients admitted to an intensive care unit have ARDS with a high mortality. Current treatment methods show no reduction in mortality and are thus unsatisfactory. This preclinical project will investigate novel drugs for pulmonary circulatory collapse and oedema, and the perspective is that a successful development of new drug candidates will reduce mortality and morbidity from the disease.

Poster B4

INTRAVENOUS PARACETAMOL IN NEONATES: SAFETY AND ENTHANOL-DRUG INTERACTIONS – PROTOCOL OF THE PARASHUTE TRIAL

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Introduction: There is very limited data on the pharmacodynamics and safety of i.v. paracetamol especially in neonates receiving > 72 hours treatment.

Objectives: *Primary:* To explore the safety of prolonged use (> 72 hours). *Secondary:* 1. Efficacy measured with the COMFORTneo pain scores. 2. Drug-excipient interaction with ethanol (CYP2E1 inducer) i.e. co- administration with phenobarbital.

Endpoints: *Primary:* Plasma paracetamol, paracetamol metabolites and liver biomarkers (ALAT, PP,bilirubin). *Secondary:* Pain scores (COMFORTneo pain scale). Levels of oxidative metabolites and of p- ethanol in patients receiving phenobarbital in addition to paracetamol within 24 h of measurement.

Design: A multicenter phase IV safety trial. *Participants:* Neonates of all gestational ages and up to 44 completed week's postmenstrual age admitted to the NICU at Rigshospitalet University Hospital or Aarhus University Hospital. **Sample size:** 120 eligible patients.

Intervention: I.v. paracetamol will be administered following the normal procedures. Plasma samples are collected by heel prick or opportunistic sampling.

Study duration: January 2018 – December 2018

Funding: Funded by Department of Clinical Pharmacology and Regionernes Medicinpulje. EudraCT: 2017-002724-25

Poster B5

PREVALENCE OF D-VITAMIN DEFICIENCY AMONG DANISH PREGNANT WOMEN – INDICATIONS OF NUTRITIONAL AND SEASONAL VARIATIONS

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Vitamin D deficiency during pregnancy has been linked to adverse pregnancy outcomes like preeclampsia, recurrent pregnancy loss, gestational diabetes, fetal growth restriction, and preterm birth.

In a prospective cohort study, placental tissue, maternal blood, and infor-mation regarding lifestyle were collected from 224 pregnant women at Randers Regional hospital. Recruitment took place in week 10-14 of gestation. 25-hydroxy vitamin D (VD) levels were analyzed using liquid chromatography mass spectrometry.

Of the 224 women included, only 58% had a sufficient VD level (≥75 nmol/L) in the blood, even though all participants were taking some form of vitamin supplement. Of the remaining 42%, 12.1% were very VD deficient (≤50 nmol/L). Both seasonal and dietary habits were reflected in the VD levels. VD levels were lower in women included in autumn-winter. A positive correla-tion was found between the consumption of fish oil and VD, as 71.4% of the women taking fish oil tablets had sufficient VD levels. Increased pre-pregnancy BMI was negatively correlated to VD level (P=0.04).

Conclusion: 42% of the pregnant women had suboptimal VD levels. VD sta-tus was affected by seasonal differences and dietary supplements supporting a need for a more individual approach to VD supplementation among pregnant women.

Poster B6

CENTRAL ROLE OF MUSCLE STEM CELLS IN REGENERATIVE FAILURE IN PATENTS WITH PERIPHERAL ARTERIAL DISEASE

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Lower extremity peripheral artery disease (PAD) leads to ischemia during exercise and is associated with degeneration of skeletal muscle. Despite surgical treatment, the skeletal muscle function does not return to the pre-ischemic state. Successful skeletal muscle regeneration is dependent on a pool of muscle stem cells (MuSCs) which are influenced by the systemic as well as the local microenvironment. When encountered with dysfunction of the MuSCs, the skeletal muscle regeneration is impaired and the muscle undergoes fatty-degeneration (accumulation of fibrosis and adipocytes).

We hypothesize that PAD leads to MuSC dysfunction due to chronic ischemia. In consequence, the muscle is unable to recover resulting in muscle fibre atrophy and accumulation of fibrosis adipocytes.

Muscle biopsies will be collected from PAD patients (n=24) admitted to revascularization surgery and controls (n=24). PAD follow up biopsies will be collected at 3 months. Immuno histochemistry is used for fibre cross-sectional area, in vivo MuSC content/activity and fibrosis/adipocyte quantification. Fluorescence activated cell sorting is used to quantify and isolate primary MuSCs. Cell culture experiments is used to determine the proliferative and differentiation capacity of MuSC and to evaluate the degree of MuSC senescence.

Poster B7

CONSUMPTION OF THE HERBAL SUPPLEMENT GINGER IS POPULAR AMONG, DANISH PREGNANT WOMEN

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Background: Ginger is perceived as a safe antiemetic in pregnancy. However, studies indicate that ginger may increase risk of bleeding, interacts with medical treatments and affect the fetal testosterone metabolism. Despite the increased access to ginger based products, the use of ginger among Danish pregnant women is currently not known.

Materials and methods: 225 pregnant women at weeks 12-14 of gestation completed a questionnaire on lifestyle and habits including their use of herbal supplements between June until December 2016.

Results: A total of 11.2% (n=25) reported use of ginger products in the first trimester. 2.7% (n=6) self-administered ginger to relieve symptoms of nausea and vomiting. Besides, 10.3 % (n=23) took ginger as shots, tea, tablets or oil without specifying the cause of intake. As many as 28.0% (n=7) of the women taking ginger also used prescription drugs.

Conclusion: Over one in ten of the Danish pregnant women uses ginger regularly. To minimize the risk of adverse pregnancy and fetal outcomes due to ginger consumption, possible adverse effect should be investigated and interactions with other medical treatments taken into consideration in prenatal counseling to ensure a sensible intake.

Poster B8

INTAKE OF THE SCANDINAVIAN LICORICE AMONG DANISH, PREGNANT WOMEN IN THE FIRST TRIMESTER

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Background: Licorice consumption in pregnancy may cause several adverse effects as hypertension and preeclampsia. In addition, fetal exposure is associated with lower intelligence quotient, attention deficit and pubertal advancement for girls in later life. Despite U.S Food and Drug Administration currently has determined pregnant women should not eat licorice root or large amounts of licorice, the use of licorice among Danish pregnant women has never been investigated.

Materials and methods: A cohort of 225 pregnant women were included at gynecological and obstetric department, Randers Regional Hospital from June until December 2016. The use of licorice was investigated based on a questionnaire on lifestyle and habits also specifically addressing this issue.

Results: More than a third of the women 37.8% (n=85) reported eating licorice a couple of times per week and as many as 7.1% (n=16) consumed licorice on a daily basis. Only 12.4% (n=28) reported no intake of licorice.

Conclusion: Danish, pregnant women have a very high consumption of licorice. There seems to be a need for an obstetric attention to maternal licorice intake, since prenatal exposure may cause several adverse pregnancy and fetal outcomes.

Poster B9

VALIDATION OF THE ELECTRONIC PATIENT MEDICATION MODULE (EPM)—THE ADMINISTRATIVE DATABASE ON IN-HOSPITAL DRUG-USE IN THE CAPITAL REGION OF DENMARK

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Registries on in-hospital drug-use are sparse, especially those that can be linked to nationwide registries. In this study, we validate EPM (Electronic Patient Medication module)—the electronic administrative database on in-hospital drug-use covering the Capital Region of Denmark.

The research database (EPM-research) is an adaptation of the database underlying the electronic administrative database for in-hospital drug-use (EPM-clinic). Our validation was comprised of two studies. Study 1: Accordance of registration between EPM-clinic and EPM-research was investigated by analyzing randomly chosen historical patient records. Study 2: Workflows and real-life registration practices were investigated through visits to three different departments. An observer followed a nurse while administrating drugs. This information was compared with EPM-research. The primary endpoint for both studies was accordance of active ingredient. Proportions with 95%-confidence intervals (CI) were calculated.

In study 1, 227 historical drug administrations were identified and reviewed, resulting in an accordance of registration of 100.0% (CI 98.4%-100.0%). In study 2, 176 drug administrations

were observed of which 173 were recorded with identical active ingredient, resulting in 98.3% (CI 95.1%-99.6%) accordance of data.

Conclusions: Our validation of the EPM-research showed very high accordance. The database will be useful in future research.

Poster B10

DISSECTING GPCR INTERNALIZATION PATHWAYS USING A REAL-TIME INTERNALIZATION ASSAY

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Activation of G protein-coupled receptors (GPCRs) usually triggers internali-zation and subsequent recycling to the membrane or degradation. This is a key regulatory process that protects receptors against overstimulation and allows fine-tuning of GPCR activity by changing the desensitization/resensitization balance. It is also an important mechanism from a drug development perspective, because it can severely limit the therapeutic effect of a drug.

We have used a real-time lanthanide resonance energy transfer (LRET) based assay to monitor GPCR internalization. The assay runs in 384-well plate format and is highly efficient compared to the traditional microscopy-based assays. We have used a range of chemical inhibitors and activators and dominant negative mutants to investigate the internalization pathways of the β_2-adrenoceptor (β_2AR) and to establish a toolbox for dissecting the internalization pathways of other GPCRs.

We find that the β_2AR internalization is dependent on dynamin and protein kinase C, but independent of actin and GRK2. These tools can be readily applied to study the internalization pathways of other GPCRs.

Poster B11

A SPONTANEOUS CANINE MODEL OF CENTRAL NEUROPATHIC PAIN IN CAVALIER KING CHARLES SPANIELS

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Aim: To assess, if symptomatic syringomyelia characterized by spontaneous or evoked scratching directed at the neck and paroxysmal pain manifestations (vocalisation) is associated with mechanical allodynia, if pregabalin as monotherapy is useful, if the spino-thalamic tract is involved

Methods: A prospective case-control study quantifying the mechanical nociceptive threshold with monofilaments. A histological characterisation and stereological quantification of spinal cord structural damage. An agency (DMA) approved randomized double-blind placebo-controlled crossover study to evaluate the analgesic efficacy of pregabalin in dogs with syringomyelia-related central neuropathic pain.

Results: Median mechanical nociceptive threshold is not significantly different between cases and controls. Comparative studies of grey and white matter changes between induced rodent models of syringomyelia and canine cases after initial pilot staining of serial spinal cord sections.

Still unblinded, the studied group of dogs can clearly be separated into two symptomatic different groups promising a positive result of the treatment.

Discussion: The ongoing characterisation of this potential spontaneous model of central neuropathic pain has shown, that the clinical phenotype of chronic pain is as diverse in canine as in human patients for which reason assessment of the relationship between sensory threshold and behavioral indicators of pain should be multi-dimensional

Deltagerliste (pr. 14. januar 2018)

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