



# HEALTH SCIENCES

RIIKKA PELLINEN (ED.)

## *The First PhD student Symposium of the Faculty of Health Sciences*

*Health research within life span*

*Abstracts*

PUBLICATIONS OF THE UNIVERSITY OF EASTERN FINLAND

*Reports and Studies in Health Sciences*



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### **ABSTRACT**

The Faculty of Health Sciences offers high quality PhD training in the field of *Health and Well-being*, an area of expertise in the University of Eastern Finland. PhD training is offered by six Doctoral programs: Doctoral Programme in Nursing Science, Doctoral Programme of Public Health, Doctoral Programme of Clinical Research, Doctoral Programme in Drug Research, Doctoral Programme in Molecular Medicine, and Doctoral Programme in Nutritional Sciences. PhD students of the Faculty are integrated as researchers into the research groups at different departments of the Faculty. The unique structure of the faculty provides excellent opportunities for creating new research activities at the interfaces of clinical medicine, biomedicine, pharmacy and nursing science.

This book compiles the abstracts of the 1<sup>st</sup> PhD Symposium of the Health sciences to be held in Kuopio. Tietoteknia auditorium, on February 11, 2014.

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Biomedical Research; Clinical Trial; Ethics, Research; Congresses; Molecular Biology; Genetic Therapy; Genetic Vectors; Gene Transfer Techniques; Glioma/therapy; Vascular Endothelial Growth Factors; Collagen; Diabetes Mellitus, Type 2; Insulin; Sirtuins; Cardiovascular Diseases; Epilepsy; Neurodegenerative Diseases/therapy; Alzheimer Disease; Amyotrophic Lateral Sclerosis; Disease Models, Animal; Magnetic Resonance Imaging; Microarray Analysis; Signal Transduction; Placenta; Fetus; Vitamin D; Gene Expression Regulation; Gene Expression; Diet; Fatty Acids; Motor Activity; Metabolic Syndrome X; Pharmaceutical Preparations; Education, Pharmacy; Lifestyle; Depression; Drug Therapy; Nursing; Low Back Pain; Homocysteine; Physical Fitness; Lung Neoplasms; Osteoporosis, Postmenopausal; Neurodegenerative Diseases; Age Factors; Dentistry; Oral Health; Bone Marrow; Hyaluronic Acid; Parturition; Toxic Actions; Smoking; Quercetin; Ultraviolet Rays; Neoplasms; Sleep Disorders; Disphosphonates; Pharmacy; Sociology, Medical; Angiogenesis Inducing Agents; Adipose Tissue; Schizophrenia; Opioid Peptides; Stroke; Obesity; Pain; Patient Safety; Melanoma; Amines; Fermentation; Migraine Disorders; Amino Acids

# Contents

<b>PROGRAM.....</b>	<b>5</b>
<b>ORAL PRESENTATIONS .....</b>	<b>11</b>
<b>POSTERS.....</b>	<b>21</b>
<b>DOCTORAL PROGRAMMES.....</b>	<b>53</b>
DOCTORAL PROGRAMME OF CLINICAL RESEARCH.....	54
DOCTORAL PROGRAMME MOLECULAR MEDICINE.....	55
DOCTORAL PROGRAMME IN NURSING SCIENCE .....	56
DOCTORAL PROGRAMME OF PUBLIC HEALTH.....	57
DOCTORAL PROGRAMME IN DRUG RESEARCH.....	58
DOCTORAL PROGRAMME IN NUTRITIONAL SCIENCES.....	60
<b>NOTES .....</b>	<b>63</b>

# Program

## Tuesday, February 11

- 8.30-8.40 Vice Dean **Paavo Honkakoski**: Opening of the symposium  
*Chaired by docent Ville Leinonen and MSc Kati Väkeväinen*
- 8.40-9.00 **Happo Saara**: Clinical drug trials undergo a more thorough Research Ethics Committee analysis than other health research
- 9.00-9.20 **Karttunen Vesa** : Human placental perfusion in the studies on fetal exposure
- 9.20-9.40 **Ryynänen Jussi**: Pleiotrophy of vitamin D gene regulation in human monocytes and macrophages
- 9.40-10.10 *Coffee*
- 10.10-10.30 **Venäläinen Taisa**: Cross-sectional associations of food consumption with plasma fatty acid composition and estimated desaturase activities in Finnish children
- 10.30-10.50 **Tompuri Tuomo**: Physical activity and watching TV, but not cardiorespiratory fitness, are related to metabolic risk among 7 to 8 years old children
- 10.50-11.10 **Siitonen Pii**: Associations Between Beliefs About Medicines And Teaching About Medicine Education
- 11.10-11.30 **Järvelä Elina**: Applicability and Efficiency of Different Approaches in Lifestyle Interventions: Study Design of a Randomized Controlled Trial
- 11.30-12.30 *Lunch break (self-paid)*

**FACULTY OF HEALTH SCIENCES, 1<sup>ST</sup> PHD SYMPOSIUM 2014**  
**FEBRUARY 11, KUOPIO**

*Chaired by MSc (pharm) Henri Leinonen and Dr. Päivi Kankkunen*

- 12.30-12.50 **Härkänen Marja:** Multi-method approach for studying hospital patients' medication-related problems
- 12.50-13.10 **Lehtola Vesa:** Efficacy of movement control exercises versus general exercises on recurrent sub-acute nonspecific lowback pain in a sub-group of patients with movement control dysfunction. preliminary results
- 13.10-13.30 **Pletnikoff Paul:** Cardiorespiratory fitness is a better predictor of lung cancer than leisure-time physical activity: A population-based cohort study.
- 13.30-13.50 **Afrin Nadia:** Risk factors for falls with special reference to joint effects of health-related factors in postmenopausal women.
- 13.50-14.10 **Li Lili:** NOS1AP mediates excitotoxic neurodegeneration triggered by NMDA receptor-nNOS signaling
- 14.10-14.35 *Coffee*
- 14.35-14.40 **Lauri Mehtätalo:** Statistics teaching: what's offered at UEF
- 14.40-15.00 **Kokkonen Piia:** SIRT6 Regulators - New Possibilities in Treatment of Age-Related Diseases
- 15.00-15.20 **Martiskainen Henna:** Neuroprotective mechanisms of seladin-1/DHCR24 in Alzheimer's disease-related stress conditions
- 15.20-15.40 **Hakola Leena:** Determinants of maintained increase of aerobic exercise in aging men and women in a 4-year randomized controlled trial: The DR's EXTRA Study
- 15.40-16.00 **Tikkanen Päivi:** Grip strength and mortality in a random sample of community-dwelling older people
- 16.00-18.00 Posters and refreshments

**POSTERS**

1. **Fouad Y H Al-Sudani:** The association between unemployment and clinically determined oral health
2. **Arasu Uma Thanigai:** MAP KINASE BINDING DOMAINS AS REGULATORS OF NEURONAL PHYSIOLOGY AND PATHOLOGY
3. **Belt Heini:** Endothelial differentiation from iPSC
4. **Cui Lili:** Safety of intra-arterial delivery of bone-marrow mesenchymal stem cells in rats
5. **Deen Ashik Jawahar:** Rab10-mediated endocytosis of the hyaluronan synthase HAS3 regulates hyaluronan synthesis and cell adhesion to collagen
6. **Eloranta Aino-Maija:** Diet Scores in Relation to Metabolic Risk in Finnish Children Aged 6–8 Years – The Physical Activity and Nutrition in Children Study
7. **Emelonye Abigail:** Spousal presence in management of parturient pain in Nigeria
8. **Fashe Muluneh:** *In Vitro* and *In Silico* Prediction of Metabolism of a Hepatotoxic Pyrrolizidine Alkaloid Lasiocarpine
9. **Hartikainen Päivi:** Finnish Pharmacists' perceptions of their work on hospital wards
10. **Husso Tiia:** Small RNAs targeted to VEGF-A promoter are specific and potent modifiers of gene expression by epigenetic mechanisms
11. **Huuskonen Pasi:** The effects of maternal smoking on human placental proteome at term
12. **Hytti Maria:** Quercetin counteracts the cellular damage caused by HNE and inhibits inflammation in ARPE-19 cells
13. **Hämäläinen Lasse:** The gene expression profile of betaine and UVB-treated organotypic keratinocyte cultures
14. **Idehen Esther:** Cervical cancer screening awareness and participations among immigrant women in the Metropolitan area, Finland
15. **Ikävalko Tiina:** Craniofacial morphology but not excess body fat is associated with risk of having sleep-disordered breathing in 6-8 year old children – The PANIC Study
16. **Imtiaz Bushra:** Oophorectomy and risk of Alzheimer's disease among Hormone Therapy users and non users; A case control study
17. **Ishchenko Yevheenia:** Activation of P2X receptors by biphosphonate-induced ATP analogues
18. **Jauhiainen Suvi:** FLRT3 is induced by VEGFs in VEGFR-2-dependent mechanism and has novel role in the regulation of endothelial cell survival and angiogenesis
19. **Kaminska Dorota:** Adipose tissue *INSR* splicing in humans associates with fasting insulin level and is regulated by weight loss
20. **Kantanen Anne:** Quality of intrapartum care evaluated by women in labour and midwives



21. **Kivimies Kristiina:** Opiate use is associated with higher risk of rehospitalisation in schizophrenia
22. **Koponen Marjaana:** Incidence of antipsychotic use in relation to diagnosis of Alzheimer's disease among community-dwelling persons
23. **Korhonen Kristiina:** Amorphous perphenazine/PVP and perphenazine/Soluplus® formulations prepared by cryo-milling
24. **Korhonen Paula:** Interleukin-33 induces a Th2-type shift that is protective in a mouse model of cerebral stroke
25. **Kuosmanen Suvi:** The Effects of Genetic Variants on Nrf2 Binding
26. **Lindell-Osuagwu Leena:** Prescribing for off-label use and unauthorised medicines in three paediatric wards, before and after the EU Paediatric Regulation
27. **Liukka Mari:** Communication and feedback giving about adverse events
28. **Liukko Aino:** Characterization of memory CD4+ T cell responses to the dog allergen Can f 4 reveals a dominant epitope region
29. **Lopéz Maykel:** Glucokinase Regulatory Protein: role in the metabolism of glucose, amino acid and lipoprotein particles and their composition
30. **Luojus Maria:** Sleep duration associates with low serum zinc and increased high-sensitivity c-reactive protein levels in ageing men
31. **Martikainen Miika:** Novel Oncolytic Alphavirus Vectors with Increased Tumor Specificity
32. **Masarawah Amro:** Very low mammographic breast density predicts poorer outcome in patients with invasive breast cancer
33. **Mitkari Bhimashankar :** Functional recovery following intra-arterial delivery of human bone marrow derived mesenchymal stem cells after cerebral ischemia in rats
34. **Muuronen Antti:** Pericardial and intrathoracic adipose tissue measurements in risk profiling for stroke
35. **Paterno Jussi:** Biomarkers of Age-Related Macular Degeneration (AMD): Three new obesity related genetic loci are associated with advanced AMD
36. **Piippo Niina:** Intracellular protein aggregates induce inflammasome signaling in human ARPE-19 cells
37. **Piltti Juha:** Rho-kinase inhibitor Y-27632 decreases VEGF $\alpha$  gene expression in hypoxia conditions
38. **Porela-Tiihonen Susanna:** Postoperative pain after cataract surgery
39. **Poukka Mari:** Hyaluronan synthases 1 and 2 as prognostic factors in cutaneous melanoma
40. **Puljula Elina:** Bisphosphonates: How does the structure affect the ability to bind to hydroxyapatite?
41. **Raju Suresh:** The effect of TCF7L2 binding sequence variants
42. **Rauhala Leena:** Low dose UVB Irradiation Increases Hyaluronan Synthesis in Epidermal Keratinocytes via Sequential Induction of Hyaluronan Synthases *Has1-3*
43. **Rudgalvyte Martina:** Methylmercury exposure elicits alterations of endoplasmic reticulum stress genes in *Caenorhabditis elegans*
44. **Rytkönen Jussi:** Porous silicon - cell penetrating peptide hybrid nanocarrier for intracellular delivery of oligonucleotides
45. **Sahlström Merja:** Patient safety - how patients perceive it and how patients' role is seen by patients safety experts?

46. **Soininen Karoliina:** Quantitative analysis of the intracellular pharmacokinetics of anticancer drug doxorubicin and its liposomal formulations and a computational model of the intracellular PK/PD relationship
47. **Sousa Sofia:** Breast cancer tumour associated macrophages (TAM) modulation by free or liposome encapsulated nitrogen containing bisphosphonates (N-BP).
48. **Takabe Piia:** HAS3 overexpression downregulates MV3 melanoma cell line proliferation, migration and adhesion
49. **Takalo Mari:** High-fat diet increases tau expression and exon 10 inclusion in the brain of female mice
50. **Tella Susanna:** Critical incidents of learning patient safety – Finnish and British pre-registration nursing students’ experiences from clinical placements
51. **Toivanen Suvi:** The effectiveness of simulation method in intravenous medication competence -Evaluation of radiographers’ continuing education intervention
52. **Turtiainen Tarja:** Relations between approaches to teaching, perceptions of the teaching environment and pedagogical leadership in Finnish UASs
53. **Ucal ebahat:** New Methodology for Selective Acetylation of Primary Amino Groups
54. **Vaittinen Maija:** Down-regulation of calcineurin-like phosphoesterase domain containing 1 (CPPED1) expression improves glucose metabolism in adipocytes
55. **Wang Xijun:** Signaling mechanisms downstream of Rho contributing to neuron death
56. **Wirth Galina:** The therapeutic potential of members of the VEGF family on muscle recovery after ischemia insult in a mouse model of hypercholesterolemia
57. **Väkeväinen Kati:** Characterization of the microbial populations in atole agrio, a traditional Mexican fermented beverage
58. **Ylikangas Henna:** Insights on the structure-activity relationships of compounds binding to Large Amino Acid Transporter 1 (LAT1)
59. **Ylitörmänen Tuija:** The connection of nurse-nurse collaboration on nurses’ job satisfaction – a comparative mixed methods study between Finnish and Norwegian nurses
60. **Zaproudina Nina:** Vascular abnormalities in migraine



# *Oral presentations*

## **CLINICAL DRUG TRIALS UNDERGO A MORE THOROUGH RESEARCH ETHICS COMMITTEE ANALYSIS THAN OTHER HEALTH RESEARCH**

*Saara Happo (1), Arja Halkoaho (2), Tapani Keränen (3), and Soili Lehto (1, 4)*

*1. Department of Clinical Medicine, University of Eastern Finland, 2. Science Service Center, Kuopio University Hospital, 3. Department of Neurology, Kanta-Häme Central Hospital, 4.*

*Department of Psychiatry, Kuopio University Hospital*

Assessment of risk-benefit ratio is required for clinical trials as for other biomedical research. This task is conducted by Research Ethics Committees (REC). The latest revision of the Declaration of Helsinki points out a need for transparency of functioning of REC.

A total of 373 files of REC of Hospital District of Northern Savo 2009–2012 were analyzed to find differences in risk assessment between clinical drug trials and other health research. The type of study (e.g., drug trial or other health research), use of placebo and number of requested clarifications in different documents provided to REC were analyzed.

More clarifications are asked to clinical drug trial files than other health research files. Only 7% of clinical drug trial files did not require any clarifications, whereas 18% of health research passed without clarifications ( $p=0.027$ ). Compared with other health research, in clinical drug trials more clarifications were asked for informed consent (90% vs. 69%;  $p<0.001$ ) and ethical aspects (49 % vs. 16%;  $p<0.001$ ). Placebo drug trials were not asked more clarifications than other trials.

REC risk evaluation appears more thorough when assessing clinical drug trial files. This observation may be explained by a wish to protect patients by ensuring that informed consent includes the information a patient needs for making a decision to participate, and that the principal investigator has properly evaluated ethical aspects.

## **HUMAN PLACENTAL PERFUSION IN THE STUDIES ON FETAL EXPOSURE**

*Karttunen Vesa, Vähäkangas Kirsi*

*Faculty of Health Sciences, School of Pharmacy/Toxicology, UEF, Kuopio, Finland*

Pregnant mothers are exposed to a wide variety of compounds either in purpose, e.g. drugs and cosmetics, in food, water and air, or accidentally. The structure and function of human placenta differ more than any other organ from animal placentas. Because in Finland, placenta is discarded after birth, it can be used for experimental research. The method retains the structure of whole tissue and different cell layers. Earlier, placental perfusion was mostly used to study transplacental transfer of medical drugs but in recent years also environmental and food born carcinogens are being studied with increasing frequency. Human placental perfusion can be used to study transfer of compounds across the placenta, as well as the role of transporters, placental xenobiotic metabolism, and placental toxicity. The main obstacles of the method are that only term placentas are easily available, quite short timeframe, relatively low success rate, and the low recovery of lipid soluble compounds in perfusion equipment. Using human placental perfusion we have shown, for instance, that ethanol does not affect the transplacental transfer of the food carcinogen PhIP, or nicotine. We have also studied the perfusion method as a possible toxicity test system for fetal exposure.

## PLEIOTROPY OF VITAMIN D GENE REGULATION IN HUMAN MONOCYTES AND MACROPHAGES

Jussi Ryyänäinen, Sabine Seuter and Carsten Carlberg  
School of Medicine, Institute of Biomedicine, University of Eastern Finland

Genome-wide analysis of vitamin D receptor (VDR) location in undifferentiated THP-1 (monocytes) and PMA-differentiated THP-1 (M2-type macrophages) cells provided a new perspective on the physiological effects of 1,25-dihydroxyvitamin D<sub>3</sub> (1,25(OH)<sub>2</sub>D<sub>3</sub>). We selected the genomic regions of the primary VDR target genes *IL8*, *ASAP2*, *GOS2*, *CDKN1A* and *MYC* for detailed study of both immune and cell growth-related functions in context of the three-dimensional organization of chromatin. The gene for the chemotactic cytokine *IL8* (also called *CXCL8*) is located together with 8 other *CXCL* genes in the same chromosomal domain. A prominent VDR binding site controls the expression of *CXCL8*, *CXCL6* and *CXCL1* both in monocytes and in macrophages. In contrast, the chromosomal domain containing the *ASAP2* gene includes 3 VDR binding sites but it was found to be the only primary 1,25(OH)<sub>2</sub>D<sub>3</sub> target within the investigated genomic region. The cancer-associated 1,25(OH)<sub>2</sub>D<sub>3</sub> targets *GOS2*, *CDKN1A* and *MYC* are located in chromosomal loops containing 1 to 4 VDR binding sites. The size of the loops differs largely, suggesting an individual regulatory scenario for each VDR target gene. Our findings demonstrate the pleiotropic effects of 1,25(OH)<sub>2</sub>D<sub>3</sub>-mediated gene regulation in human monocytes and macrophages.

## CROSS-SECTIONAL ASSOCIATIONS OF FOOD CONSUMPTION WITH PLASMA FATTY ACID COMPOSITION AND ESTIMATED DESATURASE ACTIVITIES IN FINNISH CHILDREN

T Venäläinen<sup>1</sup>, U Schwab<sup>2,3</sup>, J Ågren<sup>1</sup>, V de Mello<sup>2</sup>, V Lindi<sup>1</sup>, AM Eloranta<sup>1,2</sup>, S Kiiskinen<sup>1</sup>, D Laaksonen<sup>3</sup>, T Lakka<sup>1</sup>

<sup>1</sup>Institute of Biomedicine, UEF, <sup>2</sup>Institute of Public Health and Clinical Nutrition, UEF, <sup>3</sup>Institute of Clinical Medicine, KUH

Plasma fatty acid (FA) composition is known to be a reliable indicator of dietary fat quality, but the associations with other dietary factors remain unknown in children. We investigated the cross-sectional associations of food consumption with FA proportions of plasma cholesterol esters (CE) and phospholipids (PL) and estimated desaturase activities among children. The subjects were a population sample of 423 children aged 6-8 years examined at baseline of The Physical Activity and Nutrition in Children (PANIC) Study. We assessed food consumption by food records and plasma FA composition by gas chromatography. Higher consumption of high-fibre grain products was associated with lower proportions of stearic, oleic and  $\gamma$ -linolenic acids and higher proportions of  $\alpha$ -linolenic acid, arachidonic acid, EPA and DPA. Consumptions of vegetable fat and high-fibre grain products were inversely associated and consumptions of candy, ice cream and pudding were directly related to estimated stearoyl-CoA-desaturase or  $\Delta 6$ -desaturase activity. The results of our study suggest that plasma FA composition is not only a biomarker for dietary fat quality but also reflects the consumption of high-fibre grain products and foods high in sugar among children.

## **PHYSICAL ACTIVITY AND WATCHING TV, BUT NOT CARDIORESPIRATORY FITNESS, ARE RELATED TO METABOLIC RISK AMONG 7 TO 8 YEARS OLD CHILDREN**

Tuomo Tompuri<sup>1,2</sup>, Juuso Väistö<sup>2</sup>, Niina Lintu<sup>2</sup>, Eero A. Haapala<sup>2</sup>, Virpi Lindi<sup>2</sup>, Timo A. Lakka<sup>1,2</sup>

<sup>1</sup>Department of Clinical Physiology & Nuclear Medicine, Kuopio University Hospital, Kuopio, Finland. <sup>2</sup>Inst. of Biomedicine, University of Eastern Finland, Kuopio, Finland

Physical activity (PA), watching TV (WTV) and cardiorespiratory fitness (CRF) have been linked to metabolic risk in children. However, most previous studies have used weight-proportional CRF measures that are confounded by adiposity. We investigated the independent associations of PA, WTV and CRF with metabolic risk in 479 children. We assessed PA and WTV using questionnaire and CRF by maximal workload scaled by lean mass (LM) from cycle ergometer test. LM and fat percentage (%BF) were assessed by DXA. Metabolic risk score (MetS) was computed using z-scores of waist circumference, fasting glucose, insulin, triglycerides and HDL cholesterol and blood pressure. Data were analyzed using multivariate linear stepwise regression. After adjustment for sex and growth maturation PA was inversely ( $\beta=-0.139$ ,  $P=0.002$ ) and WTV was directly ( $\beta=0.092$ ,  $P=0.035$ ) associated with MetS whereas CRF was not related to MetS. After further adjustment for %BF the association of PA was no longer statistically significant and the relationship of WTV was attenuated ( $\beta=0.078$ ,  $P=0.046$ ). Thus lower levels of PA and larger amounts of WTV were related to higher MetS, but these associations were partly explained by %BF. It is important to realize that CRF was not related to MetS. This emphasizes sense of lifestyle.

## **ASSOCIATIONS BETWEEN BELIEFS ABOUT MEDICINES AND TEACHING ABOUT MEDICINE EDUCATION**

Siitonen P<sup>[1]</sup>, Vainio K<sup>[1]</sup>, Kiviniemi V<sup>[2]</sup>, Keinonen T<sup>[3]</sup>, Hämeen-Anttila K<sup>[2]</sup>

<sup>[1]</sup>School of Pharmacy, UEF, <sup>[2]</sup>Finnish Medicines Agency, <sup>[3]</sup>School of Applied Educational Science and Teacher Education, UEF

Medicine education, i.e. teaching about rational use of medicines as a part of school health education, is one way to promote health literacy of children and adolescents. However, teachers' beliefs about medicines may have an effect on teaching about medicine related topics. The aim is to describe the associations between teacher's beliefs about medicines and teaching about illnesses and medicines related topics. Data was collected using a postal survey from a sample ( $n = 1700$ ) of Finnish primary and lower secondary school teachers in spring 2010. A response rate of 56% ( $n = 928$ ) was achieved. Teachers' beliefs about medicines were assessed using General part of the Beliefs about Medicines Questionnaire (BMQ). Multivariate logistic regression analyses were used. From the five illnesses and medicines related topics, one association was found. Teaching about basic knowledge of what medicines are was most likely among teachers who considered medicines as something harmful (OR 1.86, 95% CI 1.01-3.45). Although an association was found, other explanatory factors, i.e. teachers' experience of medicating their own child's long-term illness, seem to predict the teaching more than teachers' beliefs about medicines.

## **APPLICABILITY AND EFFICIENCY OF DIFFERENT APPROACHES IN LIFESTYLE INTERVENTIONS: STUDY DESIGN OF A RANDOMIZED CONTROLLED TRIAL**

*E Järvelä[1], E Sairanen[2], S Rantala[3], T Myllymäki[2], K Peuhkuri[3], E Mattila[4], K Kaipainen[4], L Karhunen[1], J Pihlajamäki[1], S Puttonen[5], H Järnefelt[5], J Laitinen[5], E Kutinlahti[7], O Saarelma[7], U Kujala[8], R Korpela[3], M Ermes[4], R Lappalainen[2], M Kolehmainen[1]*

*[1] Institute of Public Health and Clinical Nutrition, UEF; [2] Dept. Psychology, Uni Jyväskylä; [3] Institute of Biomedicine, Uni Helsinki; [4] VTT, Tampere; [5] Finnish Institute of Occupational Health, Helsinki and Oulu; [7] Duodecim Medical Publications Ltd; [8] Department of Health Sciences, University of Jyväskylä*

Common disorders metabolic syndrome and depression are related to lifestyle factors including diet, stress, physical activity and sleep. This study targets overweight and psychosocial stress with interventions based on cognitive behavioural therapy (CBT) and acceptance-commitment therapy (ACT). Overweight or obese people aged 25 to 60 years with psychological stress ( $\geq 3$  points, General Health Questionnaire-12) and access to Internet are recruited. They are randomly assigned to one of the study arms: group meetings with ACT principles, a mobile phone application with ACT principles, Virtual Health Check and Coaching with CBT principles via Internet, or no intervention. The effects of the 8-week interventions are measured at baseline, after intervention and after 6 months follow-up. Measurements involve psychological wellbeing, perceived and physiological stress, eating behavior, diet, physical activity, sleep, body weight and composition, blood lipids and metabolic risk factors and user experiences concerning technology. This multicenter study gives new insight into effectiveness and acceptability of psychological intervention methods, and new knowledge of different ways to deliver interventions for improving wellbeing.

## **MULTI-METHOD APPROACH FOR STUDYING HOSPITAL PATIENTS' MEDICATION-RELATED PROBLEMS**

*Marja Härkönen [1,2], Hannele Turunen [1,3], Katri Vehviläinen-Julkunen [1,3]*

*[1] Department of Nursing Science, University of Eastern Finland; [2] Finnish Doctoral Programme in Nursing Science; [3] Kuopio University Hospital*

Medication-related problems can be studied by using different methods. The aim of this presentation is to describe the use of three different research methods for identifying medication-related problems in hospital, and for studying the causes and contributing factors of detected problems. In the first phase of the study, medication-related incident reports (n=671) from a hospital during the year 2010 were analysed retrospectively. In the second phase, the structured observation method was used to examine medications (n=1058) administered by 32 nurses to 122 patients in spring 2012. In the third phase of the study, a retrospective review was conducted of patient records (n=463) randomly selected during 2011 by using the Global Trigger Tool method. Statistical analyses such as logistic regression analysis and Pearson's chi-squared tests were used. Each of the used study methods revealed different medication-related problems, and different information of the factors contributing to medication problems. Thus, combination of different methods was effective in adding the body of knowledge. The information can be used for developing patient safety in hospitals, for educational purposes, as well as for the purposes of further research.



## **EFFICACY OF MOVEMENT CONTROL EXERCISES VERSUS GENERAL EXERCISES ON RECURRENT SUB-ACUTE NONSPECIFIC LOW BACK PAIN IN A SUB-GROUP OF PATIENTS WITH MOVEMENT CONTROL DYSFUNCTION**

<sup>1</sup>Lehtola, Vesa <sup>2</sup>Luomajoki, Hannu <sup>3</sup>Leinonen, Ville, <sup>4</sup>Gibbons, Sean <sup>5</sup>Airaksinen, Olavi

<sup>1</sup> Dept of Physical and Rehabilitation Med, Inst of Clinical Medicine, UEF, <sup>2</sup> Zürich University of Applied Sci ZHAW, Inst for Physiotherapy, Winterthur, Switzerland, <sup>3</sup> Neurosurgery of NeuroCenter, KUH, <sup>4</sup> SMARTERehab, Neuromuscular Rehabilitation Institute, Newfoundland, Canada, <sup>5</sup> Department of Physical and Rehabilitation Medicine, Kuopio University Hospital

Practice guidelines recommend various types of exercise for chronic back pain but there are few head-to-head comparisons of these interventions. General exercise seems to be an effective option for management of chronic low back pain (LBP) but very little is known about the management of a sub-acute LBP within sub-groups. Recent research has developed clinical tests to identify a subgroup of patients with chronic non-specific LBP who have movement control dysfunction (MD).

We conducted a randomized controlled trial (RCT) to compare the effects of general exercise and specific movement control exercise (SMCE) on disability and function in patients with MD within recurrent sub-acute LBP.

64 subjects, (SMCE n= 30 and general exercises n= 34) concluded their interventions. Outcome measures for both groups improved after intervention. Mean changes in the Roland Morris Disability Questionnaire (RMDQ) were significantly different between the two groups in the favor of the SMCE group ( $p<0.01$ ). Mean change in disability, measured by RMDQ, was -6.8 (95% confidence interval -3.2 to -1.2) for the SMCE group and -4.4 (95% confidence interval -3.2 to -2.5) for the general exercises group.

Patients within a sub-group of MD benefit more through a specific individually tailored movement control exercise program than through general exercises immediately after three months intervention.

## **CARDIORESPIRATORY FITNESS IS A BETTER PREDICTOR OF LUNG CANCER THAN LEISURE-TIME PHYSICAL ACTIVITY: A POPULATION-BASED COHORT STUDY**

Paul Pletnikoff [1], Sudhir Kurl [2], Tomi-Pekka Tuomainen [3]

[1] Institute of Public Health and Clinical Nutrition, University of Eastern Finland

To examine cardiorespiratory fitness (CRF), leisure-time physical activity (LTPA) and the risk of lung cancer. Current literature on lung cancer risk with (LTPA) and (CRF) is sporadic. Previous reports have focused on (LTPA) or (CRF) to determine lung cancer risk. Our study will examine the associations of (LTPA), (CRF) and lung cancer.

A Population-based cohort study of 2232 men from Eastern Finland without cancer history. (LTPA) and (CRF) data was collected at baseline, with an average 20-year follow-up. The outcome was lung cancer. Men diagnosed with lung cancer (n=73) in the lowest quartile had a 2.8 fold increased risk (95% (CI) 1.14-7.22,  $p=0.024$ ) as compared to reference. This risk was similar for all VO<sub>2</sub>max quartiles. Within the cohort, every (3.77) mL/kg/min (1 SD) increase of VO<sub>2</sub>max was related to a decrease ((RR) 0.69, 95% CI 0.52 to 0.91) in lung cancer risk. The first quartile of (LTPA) was significant in the first model (95% CI 1.24-5.43,  $p=0.01$ ). Further adjustment provided no associations.

Conclusion: Increasing levels of (CRF) is protective against lung cancer. Increasing VO<sub>2</sub>max by (3.77) mL/kg/min (1 SD), may reduce lung cancer risk by 31%. (CRF) is a better predictor of lung cancer than (LTPA), up to 20-years later.

## **RISK FACTORS FOR FALLS WITH SPECIAL REFERENCE TO JOINT EFFECTS OF HEALTH-RELATED FACTORS IN POSTMENOPAUSAL WOMEN**

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This prospective population based cohort study investigates risk factors predicting falls in post-menopausal women. The study population consists of 11945 women from the Kuopio Osteoporosis Risk Factor and Prevention Study (OSTPRE) in Finland. The mean baseline age of these women is 52.3 (SD 2.9) years (range 47-56 years) and 68% are postmenopausal. About one thousand and fifty eight women (16.6%) had one fall and two thousand and seventy five women (19.6%) had two or more falls during the 5 year follow up. Among which about one thousand three hundred and sixty five falls are due to other than slip falls. Number of diseases, smoking, age and previous history of any kind of fractures are preliminary independent predictors of falls. Logistic regression analysis: presence of four or more diseases increases the risk of falling, OR= 2.1, p<0.000 and previous history of fractures also shows increase risk of fall, OR= 1.2, p=0.024. This study will continue to see the joint effects of other health related factors on falls.

Preliminary result of this study is increase number of diseases and history of previous fractures increase the risk of falls in postmenopausal women.

## **NOS1AP MEDIATES EXCITOTOXIC NEURODEGENERATION TRIGGERED BY NMDA RECEPTOR-NNOS SIGNALING**

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The ternary complex containing NMDA receptor (NR), PSD95 and nNOS mediates excitotoxicity, in part via p38MAPK dependent pathways. Mechanisms linking nNOS and nitric oxide to p38-mediated neuronal death have not previously been understood. Here we investigated excitotoxicity-evoked p38 activation mechanisms downstream of nNOS. We found that the unique PDZ domain binding pocket of nNOS is required for excitotoxicity. NOS1AP is an endogenous ligand of this pocket. Disruption of nNOS:NOS1AP interaction and knockdown of NOS1AP can reduce excitotoxic activation of p38 and subsequent neuronal death. We identified NOS1AP interacts with MKK3, the kinase required for excitotoxic activation of p38. Our results suggest that NOS1AP mediates the p38 activation evoked by NR-nNOS because it is able to recruit and supply p38-phosphorylating MKK3, thereby facilitating the activation of p38 by upstream signals. Based on our results, we designed a cell-permeable peptide that competes with NOS1AP for the PDZ domain of nNOS. This peptide inhibits NMDA-induced recruitment of NOS1AP to nNOS and doubles surviving tissue in a severe model of neonatal hypoxia-ischemia in rat. The highly unusual sequence specificity of the nNOS PDZ domain may provide opportunities for future generation of neuroprotectants.

## **SIRT6 REGULATORS - NEW POSSIBILITIES IN TREATMENT OF AGE-RELATED DISEASES**

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SIRT6 is one of the seven human sirtuins and an epigenetic enzyme, the overexpression of which has been linked to lengthened lifespan of male mice. SIRT6 levels are downregulated in many human cancers, suggesting that it functions as tumor suppressor. Low levels of SIRT6 increase the amount of acetylated histone 3 (H3) which impairs the function of glycolytic genes, which in turn leads to tumorigenesis. Overall, SIRT6 controls the genomic stability and affects the glucose and lipid homeostasis. This makes SIRT6 an important player in multiple age-related diseases, such as type II diabetes, liver dysfunction and cancer. In addition, the physiological role of SIRT6 is not thoroughly studied. For this and for the drug design, new regulators of SIRT6 are needed.

As there were no regulators available for SIRT6, we explored the inhibition of SIRT6 with compounds from our in-house database. This led to the first micromolar inhibitors of SIRT6. At the moment we are developing an assay for SIRT6 deacetylation activity measurement based on the natural substrate H3. This assay has improved signal to noise ratio compared to other assays and it will enable more reliable SIRT6 regulator screening.

## **NEUROPROTECTIVE MECHANISMS OF SELADIN-1/DHCR24 IN ALZHEIMER'S DISEASE-RELATED STRESS CONDITIONS**

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Seladin-1/DHCR24 is suggested to have neuroprotective functions against A $\beta$ - and oxidative stress-induced apoptosis, and decreased levels of seladin-1 increase  $\beta$ -amyloidogenic processing of amyloid precursor protein (APP) during apoptosis. Thus, augmented seladin-1 expression may protect neurons from degeneration in Alzheimer's disease (AD). Here, we investigated whether seladin-1 overexpression has beneficial effects in different stress conditions *in vitro*.

Human SH-SY5Y neuroblastoma cells over-expressing APP751 isoform (SH-SY5Y-APP751) were transiently transfected with seladin-1. Apoptosis and ER-stress were induced by treating the SH-SY5Y-APP751 cells with staurosporine (STS) and tunicamycin (TM), respectively.

Over-expression of seladin-1 did not alleviate caspase-3 activation in STS-treated cells or CHOP induction in TM-treated cells and had no effect on APP processing. During STS-induced apoptosis, seladin-1 levels were significantly reduced when compared to vehicle-treated cells. Our results indicate that under the currently used conditions, seladin-1 over-expression did not alleviate STS- or TM-induced stress. The data suggest that induction of apoptosis significantly reduces seladin-1 levels, most likely due to degradation by activated caspase-3.

## DETERMINANTS OF MAINTAINED INCREASE OF AEROBIC EXERCISE IN AGING MEN AND WOMEN IN A 4-YEAR RANDOMIZED CONTROLLED TRIAL: THE DR'S EXTRA STUDY

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**Objective & introduction** Aim was to study determinants of maintained increase of aerobic exercise in older adults. **Methods** Participants (57-78 years) were from DR's EXTRA study, a population-based randomized controlled trial on health effects of exercise and diet. We included subjects in control group (n=169) and aerobic exercise group (n=185) with a low baseline exercise. Maintained increase of exercise was defined as  $\geq 60$  minutes more moderate-to-vigorous aerobic exercise per week reported at 2 and 4 years than at baseline. **Results & conclusions** Individuals in aerobic exercise group were more likely (OR 2.5 [95% CI 1.5-3.9]) to maintain increased exercise than those in control group. In aerobic exercise group those who were working at baseline were 2.5 times [1.2-5.3] more likely, while individuals aged  $\geq 68.4$  years old (0.4 [0.2-0.9]), having satisfactory health (0.5 [0.3-0.9]) or  $\geq 2$  chronic diseases (0.4 [0.2-0.9]) were less likely to maintain increased exercise than others. Intervention group modified associations of working status, age, depressive symptoms and light exercise with maintenance of increased exercise. Thus, intervention was efficient in increasing exercise independent of background variables. People near retirement were most responsive to exercise counseling.

## GRIP STRENGTH AND MORTALITY IN A RANDOM SAMPLE OF COMMUNITY-DWELLING OLDER PEOPLE

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The grip strength is commonly used as a predictor of mortality among older people. The aim of the present study was to evaluate the association between grip strength and mortality in a random sample of community-dwelling older people.

The Geriatric Multidisciplinary Strategy for the Good Care of the Elderly Study was conducted in Kuopio, from 2004 to 2007. Present analysis included 650 community-dwelling persons aged  $\geq 75$  years (mean age 81, 70% women). Grip strength was measured at the baseline of the study using a Saehan dynamometer. Deaths in the sample were recorded till the end of 2009. Hazard ratios (HR) for death in gender-specific grip strength tertiles were analyzed using unadjusted and age, Mini-Mental-State-Examination and Functional Comorbidity Index adjusted Cox's proportional hazard models.

Compared to the highest grip strength tertile, women in the lowest [HR 2.6 (95%CI: 1.57 to 4.30),  $p < 0.01$ ] and medium tertiles [HR 1.8 (95%CI: 1.06 to 3.10),  $p = 0.03$ ] and men in the lowest tertile [HR 2.7 (95%CI: 1.41 to 5.24),  $p < 0.01$ ] were at an increased risk of death. However, after adjusting for age and comorbidity, the association between grip strength and all-cause mortality no longer remained significant in either genders.



# *Posters*

## **THE ASSOCIATION BETWEEN UNEMPLOYMENT AND CLINICALLY DETERMINED ORAL HEALTH**

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The aim of this study was to assess whether unemployment was associated with poor oral health, and whether there was a difference in oral health according to unemployment's duration. As part of the Health 2000 Survey in Finland, we used data based on interviews, questionnaires, and clinical oral examinations, including the 30-63-year-old respondents ( $n = 4773$ ). Employment status was measured in its dichotomous form, employed vs. unemployed and unemployment further divided to long-term and short-term. We measured oral health in terms of numbers of missing, sound, filled, decayed teeth and teeth with deepened periodontal pockets ( $\geq 4$  mm,  $\geq 6$  mm). Models of Poisson and negative binomial regressions were fitted for oral health outcomes. Oral health-related behaviors, sociodemographic and socioeconomic factors were added as covariates. The unemployed had higher numbers of missing, decayed teeth and of teeth with periodontal pockets than the employed ones. The association remained consistent even after adjustments, and was mediated by oral health-related behaviors. Long-term unemployment showed stronger association with poor oral health than short-term. To conclude, the unemployed, especially the long-term ones, can be considered as a risk group for poor oral health.

## **MAP KINASE BINDING DOMAINS AS REGULATORS OF NEURONAL PHYSIOLOGY AND PATHOLOGY**

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Mitogen activated protein kinases have a fundamental impact on health and disease. These regulators of cell function act via post-translational modifications that either lead to new transcriptional programmes or act directly on existing cellular structures such as the cytoskeleton. This is achieved by distinct MAPK species compartmentalized into functionally distinct units by scaffold proteins. However, few MAPK scaffolds have been characterized. We have uncovered a family of proteins carrying a novel MAPKK interaction motif we previously identified. To characterize this family and determine the function of their protein interaction properties we apply quantitative pull down assay, live cell fluorescence microscopy, optogenetic regulators, RNAi knockdown rescue and small molecule screens. Investigations of the roles of compartmentalized MAPK regulation on cellular functions and behaviour potentially complements our present view of physiological and pathological events that ensue from either mutations in these proteins or external factors modifying their function. Some family members are associated with specific neurodegenerative disease proteins and investigating the functional relationships with the interacting proteins may thus lead to relevance in tackling neurodegeneration.

## **ENDOTHELIAL DIFFERENTIATION FROM IPSC**

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Conventional treatments of coronary artery disease, such as angioplasty and bypass surgery, are not always sufficient or suitable for all patients. Additionally, re-endothelialization of vessel walls may be impaired after coronary artery stenting. Therefore, it is essential to develop additional regenerative therapies to promote therapeutic angiogenesis in ischemic myocardium and endothelialization of stented vessels.

ESC and iPSC can divide indefinitely and they have the capacity to differentiate into any cell type. This ability gives great potential to regenerative medicine and personalized cell therapy. However, the pathway of EC differentiation from ESCs is not fully understood. Consequently, *in vitro* derivation of vascular cells from induced pluripotent cells and their characterization have proved to be difficult.

We have developed an efficient 2D EC differentiation method using human iPSC and ES cells. The protocol employs specific EC-favoring cell culture media and appropriate growth factors, such as VEGF-A, BMP-4 and TGF- $\beta$  inhibitor with precise dosage and timing. Characterization and functional assays of these EC includes cobble-stone morphology, EC-specific marker expression analyses by FACS, tube forming ability, uptake of acetylated LDL, NO production and Matrigel plug assay in immunodeficient mice. Laminar shear stress, hypoxia and FACS-sorting might also be important contributors in stable EC differentiation and maturing.

## **SAFETY OF INTRA-ARTERIAL DELIVERY OF BONE-MARROW MESENCHYMAL STEM CELLS IN RATS**

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Intra-arterial (i.a.) cell delivery for stroke is promising for clinical translation. Our aim was to explore a safe way for i.a. bone-marrow mesenchymal cell (BMMSC) delivery in rats.

Wistar rats (250-300 g) were sham-operated. They were divided into 7 groups according to different cell doses ( $0.25 - 1 \times 10^6$ ), infusion volume (0.5-1 ml) and infusion velocity (3-6 min). One group of rats was infused with  $1.0 \times 10^6$  cells labeled with iron oxide for *in vivo* tracking of cells. Cells were infused through the external carotid artery 48 h after sham-operation using laser Doppler flowmetry to monitor the local cerebral blood flow. MRI was performed 24 h after cell infusion to show possible micro-occlusions or hemorrhage. Limb placing test was performed to assess sensorimotor functions of rats. The rats were perfused 24 h after MRI.

There was a cell dose related decrease in cerebral blood flow, number of micro-occlusions and sensorimotor impairment. In addition, complications decreased with higher infusion volume and increased with longer infusion time. Iron-labeled cells were mainly located within and around the lesions.

Cell dose, infusion volume and velocity are important factors for safe i.a. cell transplantation.



## **RAB10-MEDIATED ENDOCYTOSIS OF THE HYALURONAN SYNTHASE HAS3 REGULATES HYALURONAN SYNTHESIS AND CELL ADHESION TO COLLAGEN**

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Hyaluronan synthase 3 (HAS3) is one among the three hyaluronan synthases family (HAS1-3), involved in the synthesis of an extracellular polysaccharide, hyaluronan (HA). Hyaluronan synthases are unique in that they are active only when located in plasma membrane, where they extrude the growing HA directly into cell surface and extracellular space. Therefore, traffic of HAS to/from plasma membrane is crucial for the synthesis of HA.

In this project, we have used live cell imaging, photoconversion and tracking, siRNA mediated gene knockdown, mass spectrometry and other standard molecular biology techniques.

Rab10 is associated with HAS3 in transport vesicles. Rab10 silencing blocked the retrograde traffic of HAS3 from plasma membrane to early endosomes, resulting in a significant increase of HA synthesis. Rab10 overexpression on the other hand suppressed HA secretion. The cell surface HA coat enlarged by Rab10 siRNA impaired cell adhesion to type I collagen, as indicated by recovery of adhesion following hyaluronidase treatment. The data indicate a novel function for Rab10 in HAS3-dependent HA synthesis, facilitating cell adhesion to type I collagen – processes important in tissue injury, inflammation and malignant growth.

## **DIET SCORES IN RELATION TO METABOLIC RISK IN FINNISH CHILDREN AGED 6–8 YEARS – THE PHYSICAL ACTIVITY AND NUTRITION IN CHILDREN STUDY**

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Diet scores can measure diets related to metabolic diseases in adults, but it is unknown whether they can be used to assess metabolic health in children.

Subjects were 413 6–8-year-olds. Diet was assessed by food records. We calculated Dietary Approaches to Stop Hypertension Score (DASH-S), Baltic Sea Diet Score (BSDS), Mediterranean Diet Score (MDS) and Healthy Diet Indicator (HDI) as reported formerly. The Diet to Assess Metabolic Risk in Children Score (DIMERIC-S), based on the results of The Physical Activity and Nutrition in Children Study, included a positive score for the oil intake and negative scores for the sugary drink, low-fat margarine and meat intakes. Metabolic risk was composed of waistline, fasting insulin, glucose, triglycerides and HDL cholesterol and blood pressure.

The risk of having a high metabolic risk did not differ in the quartiles of DASH-S, BSDS, MDS and HDI. The risk of having a high metabolic risk was 64% lower in the 3<sup>rd</sup> and 65% lower in the 4<sup>th</sup> quartile of the DIMERIC-S compared to the 1<sup>st</sup> quartile. The DIMERIC-S indicating a low oil intake and high sugary drink, low-fat margarine and meat intakes is related to a high metabolic risk in children, while diet scores developed for adults are not.

## **SPOUSAL PRESENCE IN MANAGEMENT OF PARTURIENT PAIN IN NIGERIA**

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The World Health Organization statistics show that about 800 women die every day from childbirth. Majority of these deaths occur in developing countries like Nigeria where maternal mortality is about 630 deaths per 100,000 births. In addition, Nigeria is a patriarchal society where childbirth is considered mainly as women issue. During parturiency the mother's pain management is given poor or no priority and spouse's participation during parturiency is low. Poor parturient pain inevitably leads to psychological and physical problems for mothers. The objective of the study is to examine the extent of effective use of spousal presence as a non-pharmacological intervention for parturient pain management in Nigeria.

A Cross-sectional study involving three groups; Parturient  $n = 150$ , their spouses  $n = 150$  and midwives working in the hospital  $n = 50$ . The research data will be collected from the maternity unit of the National Hospital Abuja Nigeria in 2014, through surveys, interviews, observations and the registry for a period of 12 months. Data analysis will be done statistically using SPSS 19 software and content analysis. Contributing to fresh knowledge and constitute a basis for improving health policies in respect of nursing practices in the administration of non-pharmacological management of parturient pain in Nigeria. This study is funded by grant from 24/7 technologies Ltd Nigeria.

## **IN VITRO AND IN SILICO PREDICTION OF METABOLISM OF A HEPATOTOXIC PYRROLIZIDINE ALKALOID LASIOCARPINE**

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Lasiocarpine is a heliotridine-type hepatotoxic pyrrolizidine alkaloid. On chronic exposure, it provokes severe toxicities such as hepatic megalocytosis in humans and in animals after metabolic activation. Here, we investigated the metabolism of  $100\mu\text{M}$  lasiocarpine in human (HLM) and pig (PLM) liver microsomes in the absence or presence of  $4\text{mM}$  reduced glutathione (GSH) in  $100\text{mM}$  potassium phosphate buffer,  $\text{pH } 7.4$  and NADPH. Moreover, in attempt to predict possible sites of metabolism, the alkaloid was docked in the active sites of crystal structures of human CYP3A4 and pig CYP2B enzymes. In LC/ESI-MS<sup>+</sup> analysis of the incubated samples, 11 different metabolites were observed both in HLM and PLM incubations. Five of the 11 metabolites were the primary metabolites formed by enzyme catalyzed ester hydrolysis ( $m/z$  238; 330) or oxidations ( $m/z$  398, demethylation; 428, N-oxidation; 428; oxidation). According to the area under LC/MS peak,  $m/z$  398 was the major metabolite in both species after 30 minutes incubation time followed by  $m/z$  428 and 238 in HLM and  $m/z$  330 in PLM; however,  $m/z$  398 seemed to be unstable in HLM incubations. In the presence of GSH, some of the metabolites were unstable and a GSH conjugate at  $m/z$  441[M-H] was detected. The rate of metabolism and level of the GSH conjugate were higher in HLM than in PLM incubations. Interestingly, the active site docking experiments predicted orientations consistent with major CYP mediated oxidations. These data suggest that the metabolism of lasiocarpine is catalyzed by several pathways which could influence the toxic characteristics of the alkaloid

## FINNISH PHARMACISTS' PERCEPTIONS OF THEIR WORK ON HOSPITAL WARDS

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Ward pharmacy requires an analysis of its state in order to develop the practice. Pharmacists are the best experts to report their job description. The aim of this study was to explore the perceptions of pharmacists working on wards about their tasks and opinions on the importance of tasks, time management, and distribution of work. A survey was conducted by sending e-mail with access to the survey to pharmacists (n=193). The pharmacists' current tasks and their importance were investigated with a list containing 23 tasks. The response rate was 51%. The most common tasks were stock management (93%) and providing drug information (91%). The most time-consuming tasks were stock management, dispensing oral drugs, and diluting intravenous drugs. The most important tasks were checking for drug interactions (94%), providing drug information (89%), and detecting problems in patients' medications (87%). Pharmacists would need more time for patient-oriented and informative tasks, and certain logistic and non-professional tasks could be transferred to pharmacy technicians. This study confirms that the job descriptions of pharmacists on wards center on logistic tasks, while clinical tasks are regarded as most important.

## SMALL RNAs TARGETED TO VEGF-A PROMOTER ARE SPECIFIC AND POTENT MODIFIERS OF GENE EXPRESSION BY EPIGENETIC MECHANISMS

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Small RNAs complementary to gene promoters have been shown to regulate gene expression. Transcriptional gene silencing but also induction of gene expression by double stranded RNAs involve epigenetic changes in the promoter but the exact mechanism of function has been elusive. We have reported that lentiviral shRNAs targeted to murine VEGF-A promoter are able to repress or induce VEGF-A expression both *in vitro* and *in vivo*. In this study we focus on clarifying the molecular mechanism behind this phenomenon.

We show that siRNA oligos and lentiviral shRNAs function in different ways in epigenetic regulation and that intact hairpin structure is needed for shRNA activity. We also show that 5-Azacytidine makes normally nonresponsive MS1 cells responsive to TGS. Importantly from therapeutic point of view, shRNA complementary to the promoter region upregulates all isoforms of VEGF-A, which likely leads to more natural response. Furthermore, we show by NGS and microarray analysis that the action of epigenetic RNAs is very specific on genome wide scale. In conclusion, RNA mediated manipulation of gene expression is a powerful and specific method to regulate target gene expression and is therefore a promising new method for gene therapy

## THE EFFECTS OF MATERNAL SMOKING ON HUMAN PLACENTAL PROTEOME AT TERM

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Maternal smoking reduces the birth weights of both the infant and the placenta and affects placental xenobiotic and steroid metabolism. Our objective was to examine the effects of maternal smoking on term placental proteome together with placental steroid-metabolizing activities. Fourteen term placentas, equally divided between smoker and non-smoker mothers, were evaluated. The placental proteome was analyzed using 2D-electrophoresis and the most consistent protein spots were identified by LC-MS/MS. Western blots were used for confirmatory analysis of altered proteins. Expression levels of placental steroid-metabolizing enzymes were analyzed by QPCR and with functional enzyme activity measurements. The top two networks affected by maternal smoking were 1) cell morphology, cellular assembly and organization, cellular compromise (15 hits) and 2) DNA replication, recombination, and repair, energy production, nucleic acid metabolism (6 hits). Proteins significantly up-regulated by smoking were SERPINA1, VIM, EFHD1 and KRT8 while down-regulated proteins were HBB, SERPINB2 and FGA. Catalytic activities of EROD and ECOD were increased and CYP19A1 activity was decreased by maternal smoking. Maternal smoking significantly affected term placental levels of at least 70 proteins.

## QUERCETIN COUNTERACTS THE CELLULAR DAMAGE CAUSED BY HNE AND INHIBITS INFLAMMATION IN ARPE-19 CELLS

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Age-related macular degeneration (AMD) is the leading cause of blindness in the western world. A driving factor of AMD is chronic inflammation, stimulated by life-long exposure to light and oxidative stress. Here we analyze the anti-inflammatory properties of Quercetin and determine the pathways by which it acts.

ARPE-19 cells were treated with 4-Hydroxynonenal (HNE) to simulate oxidative stress. Quercetin was added 1 hour after stimulation with HNE. The effects of the treatment on inflammation were measured with ELISA. Cell viability was assessed using the lactate dehydrogenase assay.

Quercetin decreased the levels of pro-inflammatory cytokines IL-6, IL-8 and MCP-1. It also protected the cells from HNE-induced toxicity, resulting in a decrease in LDH levels. Quercetin lowered the levels of phosphorylated p38 and of phospho-CREB but did not affect DNA binding of the NF- $\kappa$ B subunit p65.

Our results show that Quercetin can reduce the inflammatory response in retinal pigment epithelial cells by down regulating the mitogen activated protein kinase pathway and decreasing the phosphorylation of CREB. Furthermore, it is able to protect cells from death induced by oxidative stress. Quercetin may, therefore, be a valuable compound in finding a therapy for AMD.

## THE GENE EXPRESSION PROFILE OF BETAINE AND UVB-TREATED ORGANOTYPIC KERATINOCYTE CULTURES

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**Objective and introduction:** Ultraviolet radiation is known to inflict epidermal DNA damage. Betaine, also known as trimethylglycine is widely used in skin care products because of its moisturizing and protective properties, however, there are few studies addressing these effects in the skin. The purpose of this study was to investigate whether betaine tends to have a protective role against UVB.

**Methods:** Organotypic rat keratinocyte cultures were exposed to UVB (30 mJ/cm<sup>2</sup>), 10 mM betaine or their combination. Global gene expression was determined using Illumina RatRef-12 expression BeadChip. Based on the microarray data, 15 genes were chosen and their expression levels were confirmed using qPCR. In addition, the expression of keratin 2, keratin 10 and filaggrin were studied using western blotting and immunohistochemistry.

**Results and conclusions:** Biological processes altered by UVB were related to DNA replication, cell cycle and DNA repair whereas betaine treatment regulated TGF- $\beta$  signaling, response to cytokines and certain metabolic processes. Betaine significantly influenced the expression of keratin 2, but not the expression of other keratins or epidermal differentiation markers. In conclusion, betaine has some specific, unique effects on keratinocyte gene expression

## CERVICAL CANCER SCREENING AWARENESS AND PARTICIPATIONS AMONG IMMIGRANT WOMEN IN THE METROPOLITAN AREA, FINLAND

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**Objective:** To investigate African women's awareness and participations in the organized cervical screening program in the metropolitan region, Finland.

**Introduction:** Cervical cancer as described is one of most common cancers in women worldwide (1). Due to screening programs through pap tests and treatment offered to women at risk on a regular basis, the rates of cervical cancer have decreased in most developed world. The aim of Pap test screening is to reduce morbidity and mortality by providing early detection or diagnosis associated with the disease. Cervical cancer program is an essential portion in the Finnish health care system, thus decline of about 70–80% incidence and mortality rates of the disease (2).

The number of immigrants to Finland including women have increased in recent years. (3). Meanwhile, until now, study about immigrant women's participation in the organized screening for cervical cancer has not been published.

**Methods:** Study will utilize both qualitative and quantitative methods and samples of 20 and 200 women (30-45 of African origin) respectively, with Individual/team interviews. Qualitative content analysis and power analysis with the assistant of a statistician will be employed.

**Results:** This results will contribute to effective healthcare services render to immigrants' women in Finland.

**Conclusions:** It is imperative to assess how immigrant's women are participating in the screening program. Such assessment is vital to the creation of efficient public health interventions.

## CRANIOFACIAL MORPHOLOGY BUT NOT EXCESS BODY FAT IS ASSOCIATED WITH RISK OF HAVING SLEEP-DISORDERED BREATHING IN 6-8 YEAR OLD CHILDREN – THE PANIC STUDY

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**Objective & introduction:** To investigate the associations of craniofacial morphology and body fat with sleep disordered breathing (SDB) in a population sample of 491 Finnish children 6-8 years of age. **Methods:** Overweight and obesity were defined by International Obesity Task Force (IOTF) criteria. Body fat percentage was assessed by dual-energy x-ray absorptiometry (DXA). Craniofacial morphology was evaluated by an orthodontist and sleep was assessed by a questionnaire. **Results:** The prevalence of SDB was 9.9%. The median (interquartile range, IQR) of body fat percentage was 20.6 (17.4-27.1) in the girls and 15.0 (11.4-21.6) in the boys. Altogether 11.4% of boys and 15.6% of girls had overweight or obesity. There was no difference in the prevalence of overweight, obesity or body fat percentage between children with SDB and those without it. Children with tonsillar hypertrophy had a 3.7 times higher risk of suffering SDB than those with normal size tonsils after adjustment for age, sex and body fat percentage. Furthermore, children with cross bite had a 3.3 times higher risk of having SDB than those without cross bite, and children with a convex facial profile had a 2.6 times higher risk of having SDB than those with a normal facial profile. **Conclusion:** Abnormal craniofacial morphology, but not excess body fat, is associated with an increased risk of having SDB in 6-8 year old children. A simple model of necessary clinical examinations is recommended to recognize children with an increased risk of SDB.

## OOPHORECTOMY AND RISK OF ALZHEIMER'S DISEASE AMONG HORMONE THERAPY USERS AND NON USERS

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**Background:** Association of induced menopause with AD in context of HT use is ambiguous. **Objective:** To find out the impact of induced menopause carried out by oophorectomy, hysterectomy and radical hysterectomy on risk of AD and to find out the effect modification with HT use in a case control study. **Methods:** We conducted a nation- wide register based case control study using Finnish National Prescription Register and Special Drug reimbursement register linked to Hospital discharge register. AD cases were identified from Special Reimbursement Register and included women with verified AD diagnosis and each case matched by age, sex and region of residence to a control. Information on use of hormone therapy was collected from National Prescription Register and data on surgery was taken from Hospital discharge Register. **Results:** Induced menopause among post-menopausal women was not associated with increase in relative risk of AD. Long term HT use was associated with decrease in relative risk of AD as compared to short term use. **Conclusion:** Post-menopausal induced menopause after commencement of natural menopause might protect against AD irrespective of HT use. Long term HT use might protect against AD, favoring the critical window hypothesis.

## ACTIVATION OF P2X RECEPTORS BY BIPHOSPHONATE-INDUCED ATP ANALOGUES

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The main objective is to study the action of ATP analogues induced by bisphosphonates on pain transducing ATP-gated P2X receptors. Bone cancer pain, most troubling state, remains essentially intractable. Accumulating evidence suggests also involvement of P2X3 receptors in bone cancer pain. *Bisphosphonates* are efficient anti-bone cancer drugs which provide pain relief via still unknown mechanism. Trigeminal cell cultures will be prepared from Wistar rats (P10-P12). Cells will be plated on coverslips coated with poly-L-lysine and will be kept in culture medium in incubator (37°C with 5% CO<sub>2</sub>) for two days. HEK293 will be transfected with P2X3 or P2X7 receptor protein and membrane currents will be recorded using patch clamp technique.

We found that bisphosphonate induced agent ApppI induced a strong depressant action on P2X3 receptor mediated currents. Notably, in low (0.2 mM) calcium concentration the depressant action of ApppI was largely enhanced whereas in high concentration of extracellular calcium (10 mM) no currents suppression was found. We also observed the similar inhibitory action of ApppI on native P2X3 receptors expressed in trigeminal neurons. We discovered strong Ca<sup>2+</sup>-dependent inhibition of pain transducing P2X3 receptors by low nanomolar concentration of ApppI in trigeminal neurons and transfected HEK293 cells.

## FLRT3 IS INDUCED BY VEGFS IN VEGFR-2-DEPENDENT MECHANISM AND HAS NOVEL ROLE IN THE REGULATION OF ENDOTHELIAL CELL SURVIVAL AND ANGIOGENESIS

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Axon guidance-related factor fibronectin and leucine-rich transmembrane protein-3 (FLRT3) has been shown to regulate neuronal cell outgrowth after the injury of peripheral nerves. During morphogenesis FLRT3 has shown to regulate embryonic cell adhesion as well as directly interact with fibroblast growth factor (FGF) receptors and enhance their down-stream signaling in response to FGF-stimulation. Connection of FLRT3 to endothelial cell biology has not been previously reported.

We have recently studied the effects of mature form of VEGF-D (VEGF-D<sup>ANAC</sup>) in human umbilical vein ECs (HUVECs) by using Affymetrix Human Genome 2.0 Gene Chips, and found that FLRT3 mRNA is up-regulated in VEGF-D<sup>ANAC</sup>-treated HUVECs as compared to control cells. To confirm the findings HUVECs were stimulated with different recombinant human VEGFs and it was found that VEGFR-2-binding ligands (VEGF-A, -D, and -F) induce the expression of FLRT3 mRNA, however, VEGFR-1-binding PlGF did not have effects on its expression. Moreover, blockage of FLRT3 by siRNA techniques decreased the survival of HUVECs and the arrangement of the cells into capillary-like structures. Thus, according to our findings FLRT3 has novel role as a regulator of EC survival and *in vitro* angiogenesis.

## **ADIPOSE TISSUE *INSR* SPLICING IN HUMANS ASSOCIATES WITH FASTING INSULIN LEVEL AND IS REGULATED BY WEIGHT LOSS**

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Insulin receptor (*INSR*) exists in two protein isoforms resulting from alternative splicing of exon 11. The protein isoform containing the 12 amino acids insert, *INSR-A*, promotes cell growth whereas *INSR-B* predominantly regulates glucose homeostasis. In this study we investigated whether weight loss regulates *INSR* alternative splicing and the expression of splicing factors in adipose tissue. The relative ratio of the *INSR* gene splice variants was determined using the PCR-capillary electrophoresis method on adipose tissue samples from two weight loss intervention studies, Kuopio Obesity Surgery study (KOBS, n=108) and a very low calorie diet intervention (VLCD, n=32), and from a population-based Metabolic Syndrome in Men study (METSIM, n=49). The *INSR-B* mRNA variant expression increased in response to weight loss induced by both bariatric surgery ( $p=1\times 10^{-5}$ ) and VLCD ( $p=1\times 10^{-4}$ ) and correlated negatively with fasting insulin levels in the pooled data of the three studies ( $p=3\times 10^{-22}$ ). Additionally, we observed correlation with *HNRNPA1* ( $p=1\times 10^{-5}$ ), a known regulator of *INSR* exon 11 splicing. The effect of weight reduction on adipose tissue *INSR* splicing might be mediated by alterations in splicing regulators expression.

## **QUALITY OF INTRAPARTUM CARE EVALUATED BY WOMEN IN LABOUR AND MIDWIVES**

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Regardless of the WHO's and MSAH's recommendations of intrapartum care, increasing medicalization and decreasing number of maternity hospitals, the quality of intrapartum care has been studied little on a national level in Finland.

The aim of the study is to describe and explain the quality of intrapartum care in Kuopio University Hospital. The study will investigate women's and midwives' assessments about the different areas of quality of care and analyze if there is differences in the assessments between the groups.

This is a cross-sectional study with statistical method. The data will be collected with structured electronic questionnaires in 2014 - 2015 using a modified version of one Finnish quality care instrument called The Humane Caring Scale (HCS). In addition the patient record data will be used. The data will be analyzed with SPSS 21 statistical program.

The study will provide information about current intrapartum care culture and quality of it in Finland. The results can be applied to develop care more patient-centered and to allocate resources to those women, who need special support during childbirth.



## **OPIATE USE IS ASSOCIATED WITH HIGHER RISK OF REHOSPITALIZATION IN SCHIZOPHRENIA**

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This study examined the prevalences of illicit substance use among schizophrenia patients in Finland. The aim was also to find out the possible associations between illicit substance use and the risk of rehospitalization. Methods: Data were collected retrospectively from two different geographical sites in Finland (Helsinki and Kuopio), including both inpatients and outpatients. Data were collected from the patients' medical files, and substance use was defined either substance abuse or dependence. The study population consisted of 146 patients with ICD-defined schizophrenia. Results & Conclusions: The prevalence of use was 10.9% (16/146) for cannabis, 8.9% (13/146) for amphetamine, and 4.1% (6/146) for an opiate. Among patients with schizophrenia and substance use, the number of inpatient periods was about 1.5-fold when compared to non-users. The incidence rate ratio for hospitalizations was 2.9 (95% CI 2.47–3.63) for opiate use compared to non-users, 2.0 (1.71–2.41) for amphetamine use, and 1.6 (1.33–1.84) for cannabis use. The risk of rehospitalization was significantly higher for opiate use when compared with amphetamine use ( $p < 0.001$ ) or for cannabis use ( $p < 0.001$ ). The use of opiates is associated with significantly higher risk of rehospitalization than either amphetamine or cannabis use among patients with schizophrenia.

## **INCIDENCE OF ANTIPSYCHOTIC USE IN RELATION TO DIAGNOSIS OF ALZHEIMER'S DISEASE AMONG COMMUNITY-DWELLING PERSONS**

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To determine the incidence of antipsychotic use in relation to diagnosis of Alzheimer's disease (AD). The study cohort consisted of all community-dwelling residents in Finland diagnosed with AD in 2005 and one matched control ( $n=12258$ ). The mean age of cohort was 79.3 years and 63.7% were women. Data on all antipsychotics dispensed between 1995 and 2009 were extracted from the prescription register. The rate of new antipsychotic users/100 person-years was calculated up to 8 years before and 4 years after AD diagnosis. During the follow-up, 2191(35.7%) persons with AD initiated antipsychotic use. Among persons with AD the incidence was four times higher compared with the controls and started to significantly increase two to three years before diagnosis. Incidence was highest among the persons with AD during the first six months after AD diagnosis but remained stable among the controls. In conclusion, incidence of antipsychotic use starts to increase already few years before AD diagnosis which might be associated with early neuropsychiatric signs of AD. The highest rate of new users occurs directly after AD diagnosis. This type of prescribing practice is a concern as antipsychotics have been associated with serious adverse drug events.

## **AMORPHOUS PERPHENAZINE/PVP AND PERPHENAZINE/SOLUPLUS® FORMULATIONS PREPARED BY CRYO-MILLING**

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Low dissolution rate limits the bioavailability of many drugs. One way to overcome this problem is to convert crystalline drugs into their more soluble amorphous counterparts e.g. by mechanical activation. A common approach is to prepare an amorphous drug/polymer solid dispersion. Perphenazine (PPZ) is a poorly soluble drug whose dissolution rate can be improved by a solid dispersion technique. Polyvinylpyrrolidone K30 (PVP) is a very commonly used carrier in solid dispersions, whereas Soluplus® is a rather new polymeric solubilizer. In this study, solid dispersions of PPZ/PVP (4/1 m/m) and PPZ/Soluplus (1/4 m/m) were prepared by cryo-milling. Physical properties of the cryo-milled samples were analyzed by DSC, FTIR and XRPD. Fresh samples were stored at 4°C RH 0%, ambient RH 0%, 40°C RH 0% and ambient RH 60% in order to evaluate their stability. The study demonstrated the possibility to prepare amorphous 4/1 PPZ/PVP and 1/4 PPZ/Soluplus dispersions by cryo-milling. All PPZ/Soluplus and PPZ/PVP dispersions stored at 4°C RH 0% were found to remain amorphous for at least 105 days. Other PPZ/PVP dispersions showed recrystallization of PPZ at earlier time points of the study. Thus, 1/4 PPZ/Soluplus solid dispersion might be a promising candidate for further formulation studies.

## **INTERLEUKIN-33 INDUCES A TH2-TYPE SHIFT THAT IS PROTECTIVE IN A MOUSE MODEL OF CEREBRAL STROKE**

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Cerebral stroke is one of the leading causes of disability and death. Ischemia induces inflammation both in the brain and the periphery, contributing to the outcome of stroke. A Th1-type response is thought to be neurotoxic whereas a Th2 response and anti-inflammatory cytokines, such as IL-4, appear to be beneficial. The aim of this study was to test whether Interleukin-33 (IL-33), a cytokine that has been shown to induce the Th2 response, would be protective in a mouse model of cerebral stroke. IL-33 was administered intraperitoneally to Balb/c mice either one week prior to or immediately after permanent middle cerebral artery occlusion (pMCAO). Neuronal damage was imaged by MRI and the mice were sacrificed either 1 or 3 days post ischemia. Tissues and plasma were analyzed by immunohistochemistry, flow cytometry and RT-PCR. IL-33 reduced the lesion size regardless of whether the treatment was started before or after pMCAO. The treated mice had increased IL-4 levels in plasma, spleen and cortex and diminished astrocytosis in the brain peri-ischemic area. Blockade of the increase in IL-4 by anti-IL-4 antibody partly prevented the protection. Our results show that IL-33 is protective against ischemic insult and may represent a novel therapy for stroke.

## THE EFFECTS OF GENETIC VARIANTS ON NRF2 BINDING

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The majority of SNPs identified in genome-wide association studies (GWAS) are located in the noncoding DNA. One of the mechanisms by which these may affect disease susceptibility is through alterations in cis-regulatory elements that bind transcription factors. Nrf2 is a transcription factor that binds to antioxidant response elements (AREs) together with Maf F, G, or K and regulates genes involved in antioxidant defense and xenobiotic metabolism. The objective of this study is to investigate the effects of sequence variation in ARE on the binding of Nrf2.

Interactions between the Nrf2-MafG complex and DNA were modelled using molecular dynamics simulations. Existing Nrf2 ChIP-seq datasets were analyzed to study the sequence variation in the datasets. The binding of the Nrf2-Maf - heterodimers into systematically varied ARE sequences was investigated by custom-made protein binding microarrays. This data resulted in a tool that is used to identify sequence variations likely to lead to changes in the Nrf2 binding. We identified the sequence variations leading to drastic changes in Nrf2 binding. Alterations in DNA binding properties of Nrf2 may affect the expression of target genes and thereby disease susceptibility.

## PRESCRIBING FOR OFF-LABEL USE AND UNAUTHORISED MEDICINES IN THREE PAEDIATRIC WARDS, BEFORE AND AFTER THE EU PAEDIATRIC REGULATION

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Prescribing for off-label use and unauthorised medicines was common in the paediatric wards of the Kuopio University Hospital in 2001. The objective was to evaluate the possible impact of the European Paediatric Regulation (came into force in 2007) that aims to reduce such use of medicines. Therefore, we repeated the study in 2011 as it was conducted 10 years earlier. Prescriptions for patients were reviewed prospectively during a 2-week period in each of the three wards; neonatal intensive care unit, general paediatric ward and paediatric surgical ward in April and May 2011. The medicine's authorising status of all prescriptions was determined according to the approved summary of product characteristics valid during the study in Finland. The prescribing for off-label use and unauthorised medicines was more prevalent in 2011 than in 2001. The proportion of patients with at least one prescription for off-label use or for an unauthorised medicine was significantly higher, 79% in 2011, compared to 58% in 2001 ( $p<0.001$ ). For newborns significantly more prescriptions were for off-label use in 2011 than in 2001 (51% vs. 22%;  $p<0.001$ ). The legislation has had only minor or no impact on the authorising status of medicines commonly used in paediatric inpatients in specialised care.

## COMMUNICATION AND FEEDBACK GIVING ABOUT ADVERSE EVENTS

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To improve patient safety in health care the first step is to create a safety culture among staff. Staff will not speak about errors or report incidents if they have to be afraid of being disciplined or punished. The aim of this study was to find out how much staff and managers communicate about adverse events and how much staff gets feedback about them. This cross-sectional study was carried out in one district of social and health services in Finland in 2011. The data were collected by The Hospital Survey on Patient Safety Culture web-based questionnaire from hospital staff (N=1319) giving an overall response rate 36% (n=481). Half of respondents were nurses (51%), 12% ward managers and 6% were doctors. The rest were other health care professionals. Almost half (46%) of respondents have not reported about adverse events in last year. 73 % thought that staff will freely speak up if they see something that may negatively affect patient care. More than half of respondents (57%) were informed about errors that happen in their unit and every third (28%) got feedback about changes that were made based on event reports. It seems that in the study organization staff can speak out about problems that may risk patient safety. More attention is needed in feedback giving.

## CHARACTERIZATION OF MEMORY CD4+ T CELL RESPONSES TO THE DOG ALLERGEN CAN F 4 REVEALS A DOMINANT EPITOPE REGION

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The recently characterized dog lipocalin allergen Can f 4 has turned out to be an important dog allergen in terms of IgE reactivity. However, the human T cell reactivity to Can f 4 has not been examined previously. The objective of this study was to characterize memory CD4+ T cell responses to Can f 4 in allergic and nonallergic individuals and to identify dominant T cell epitopes of Can f 4 suitable for peptide-based allergen immunotherapy. Allergen-specific CD4+CD45RO+ memory T cell lines from allergic and healthy subjects were established with recombinant Can f 4 allergen and stimulated with 48 overlapping 16-mer Can f 4 peptides. The epitope specificity, proliferation and phenotype of the T cell lines, were analyzed. We observed a higher frequency and functional avidity of Can f 4 specific memory CD4+ T cells in the peripheral blood of allergic subjects. The epitope region localized between the amino acids 43-67 of Can f 4 was recognized as immunodominant, as the T cell lines a majority of allergic donors with diverse HLA backgrounds recognized at least two overlapping peptides covering this region. Can f 4-specific memory CD4+ T cells of allergic subjects differ functionally from those of nonallergic subjects and recognize a dominant epitope within Can f 4. A peptide containing the immunodominant epitope (p43-67) is a potential candidate for peptide-based immunotherapy of dog-sensitized subjects.

## **GLUCOKINASE REGULATORY PROTEIN: ROLE IN THE METABOLISM OF GLUCOSE, AMINO ACID AND LIPOPROTEIN PARTICLES AND THEIR COMPOSITION**

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Single Nucleotide Polymorphisms (SNPs) of Glucokinase Regulatory Protein (GCKR) gene associate with the levels of glucose, lactate, amino acids and the composition of lipoprotein particles, which increases the risk of Type 2 Diabetes. GCKR is strongly expressed in the liver and it is the main allosteric inhibitor of glucokinase (GCK), the enzyme that phosphorylate glucose in the first step of glycolysis. After glucose uptake, GCK is released from GCKR and phosphorylates glucose to glucose-6-phosphate. The increase in glucose-6-phosphate is in equilibrium with fructose-6-phosphate which binds to GCKR and promotes re-formation of the inhibitory GCKR-GCK complex. This inhibition is a fast and short term mechanism of controlling GCK activity. Molecular mechanisms of the regulation of GCKR-GCK inhibitory interaction are well understood, but the molecular mechanisms by which GCKR regulates lactate formation, amino acid metabolism and lipoprotein particle size and composition are unknown. In this project we will investigate the role of GCKR in the metabolic networks using hepatic cell lines and primary hepatocytes. Our preliminary data indicated that GCKR down-regulation produces a fast and drastic increase in lactate production. The completion of the project will provide an integrative view of the functional relationship between GCKR and the main metabolic routes in the liver. It will also enlighten the mechanisms by which GCKR gene variants contribute to diabetic traits.

## **SLEEP DURATION ASSOCIATES WITH LOW SERUM ZINC AND INCREASED HIGH-SENSITIVITY C-REACTIVE PROTEIN LEVELS IN AGEING MEN**

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Zinc (Zn) and copper (Cu) modulate N-methyl-D-aspartate glutamate receptor (NMDA) activity, and have thus been suggested to affect sleep duration. In addition, inflammatory processes, also regulated by the same trace elements, are related to altered sleep duration. However, data on the association between sleep and micronutrients is scarce. Population-based data was collected during 1984-1989 from 2586 men (aged 42-60 years) living in Eastern Finland. The participants reported their sleep duration based on hourly categories. The levels of Zn, Cu and high-sensitivity c-reactive protein (hsCRP) were measured. Analyses of covariance were conducted with adjustments for age, cumulative smoking history (pack-years), alcohol consumption (g/wk), Human Population Laboratory depression scale scores, physical activity (kcal/d) and body mass index. Significant associations between sleep and serum levels were observed in Zn (p-value 0.006, lowest values in  $\leq 6$  h of sleep) and log<sub>e</sub> hsCRP (p-value 0.033, highest values in  $\leq 6$  and  $\geq 9.5$ -10 h of sleep). Low serum Zn level is associated with short sleep possibly due to modulation of inflammatory systems or NMDA activity. Those with short or long sleep had higher levels of hsCRP, which may support the hypotheses of inflammation behind that association.

## NOVEL ONCOLYTIC ALPHAVIRUS VECTORS WITH INCREASED TUMOR SPECIFICITY

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Avirulent Semliki forest virus (SFV) vector VA7 has been shown potency as oncolytic agent in immunocompromised cancer models, including glioma. However, in syngeneic glioma models displaying normal type-I interferon (IFN) response, the oncolytic efficacy was poor. Recently, neurovirulent alphaviruses have been shown to inhibit the induction of IFN response in cells. Here we studied if neurovirulent strains of SFV can be used to engineer potent but safe oncolytic agents. Inhibition of JAK/STAT-pathway in Vero(B) cells was studied by western blot. Oncolytic potency was tested *in vitro* by measuring cytopathic effect (CPE) in CT-2A mouse astrocytoma cell line. Tissue de-targeting *in vivo* was studied by infecting BALB/c mice with SFV4 carrying miR124 or miR122 target sequences. The neurovirulent SFV4 inhibits STAT1 phosphorylation thus disrupting type-I IFN mediated signaling. SFV4 displayed increased CPE in IFN-beta treated CT-2A cells *in vitro* compared to VA7. SFV4-miRT124 was detected to dominantly infect oligodendrocytes showing only limited replication in neurons. We conclude that neurovirulent SFV4 shows increased oncolytic potency *in vitro* and that safety of such virus can be increased by miRNA-mediated de-targeting.

## VERY LOW MAMMOGRAPHIC BREAST DENSITY PREDICTS POORER OUTCOME IN PATIENTS WITH INVASIVE BREAST CANCER

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To examine the prognostic value of mammographic breast density (MBD) and tumor features and their relationship with established prognostic factors in selected patients with invasive breast cancer. This study is based on a database of 278 breast cancer patients treated in Kuopio University Hospital during 2002–2008. Altogether 139 consecutive HER2-positive breast cancer patients were first selected and subsequently complemented with HER2-negative patients (n=139) matched for age and time of operation. Mammograms were analyzed in consensus by 5 radiologists to evaluate tumor features and MBD according to the Breast Imaging Reporting and Data System (BI-RADS). Breast density was dichotomized into Very Low Density (VLD; BI-RADS 1) or Mixed Density (MID; BI-RADS 2+3+4). Mammographic features were then compared with established prognostic factors and outcome of the patients. 50 deaths occurred during the follow up time, of which 40 (14,4%) were from breast cancer. Patients with VLD breasts had a significantly worse prognosis compared to patients with MID breasts (disease free survival 75.6% vs. 90.7%,  $p<0.01$ ; and overall survival 75.5% vs. 90.2%,  $p=0.01$ ). The association remained significant even after correcting for age ( $\leq 50$  and  $>50$  years). No other mammographic feature was prognostically significant. In Cox regression analysis VLD proved to be an independent poor prognostic feature second only to HER2 positivity. Previously, high breast density has been shown to be a significant risk factor for breast cancer. However Very Low Breast Density is associated with poorer outcome.

## **FUNCTIONAL RECOVERY FOLLOWING INTRA-ARTERIAL DELIVERY OF HUMAN BONE MARROW DERIVED MESENCHYMAL STEM CELLS AFTER CEREBRAL ISCHEMIA IN RATS**

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Intravascular cell therapy is a promising approach for the treatment of stroke. Our aim was to study intra-arterial delivery (i.a.) of human bone marrow derived mesenchymal stem cells (BMMSC) to see whether this is efficient route to target cells in the brain and facilitate behavioral recovery in stroke rats. To study biodistribution of BMMSCs, cells were labeled with <sup>111</sup>In-oxine and infused through the external carotid artery (ECA) 24 h after sham-operation or middle cerebral artery occlusion (MCAO). SPECT imaging was carried out 20 min and 24 h after infusion to track cells. To assess behavioral effects of cells, BMMSCs (1x10<sup>6</sup>) were infused into the ECA on postoperative day 2 or 7 followed by assessment of sensorimotor outcome during the 42-day recovery period. I.a. infusion of human BMMSCs resulted in immediate cell localization in the brain, however, most of the signal relocated to liver and spleen during next 24 h. Cells did not seem to promote functional recovery in MCAO rats, when the sticky label test, cylinder test or Montoya's staircase were used as an outcome measure. Intra-arterial delivery of human BMMSCs produces efficient localization in the brain, but this is not translated to behavioral recovery in MCAO rats.

## **PERICARDIAL AND INTRATHORACIC ADIPOSE TISSUE MEASUREMENTS IN RISK PROFILING FOR STROKE**

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Our purpose was to investigate the representativeness of single slice area measurements compared to three-dimensional fat volume assessments and the associations between intrathoracic fat measurements and established risk factors for stroke. Cardiac CT was performed on 110 patients with stroke/TIA. Pericardial (PAT) and intrathoracic (IAT) adipose tissue areas were measured from slices at the level of left main coronary artery (LMCA) and the coronary sinus (CS). 3D-volume measurements were performed in 20 patients. Correlations between fat areas and markers indicating pro-inflammatory and pro-coagulative potential were analyzed 3 months after stroke. Single-slice measurements of the IAT at the level of LMCA correlated more strongly with volume measurements than at the level of CS while for PAT there was no significant difference between the sites. PAT and IAT areas correlated with von Willebrand Factor antigen and Interleukin 6. Measurement of fat area using single slice at the level of LMCA reflects accurately true intrathoracic fat volume and is a recommended measurement site. PAT and IAT are correlated with chronic inflammation and coagulation markers indicating pro-inflammatory and pro-coagulative potential of intrathoracic fat.

## **BIOMARKERS OF AGE-RELATED MACULAR DEGENERATION (AMD): THREE NEW OBESITY RELATED GENETIC LOCI ARE ASSOCIATED WITH ADVANCED AMD.**

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AMD is the leading cause of central blindness in elderly in the Western countries. It has a complex multifactorial etiology, including aging, genetic factors, smoking, hypertension and atherosclerosis. Moreover, obesity has been considered to increase the risk for AMD. We hypothesize that the genetic variations shown to be associated with obesity might also be involved in the pathogenesis of AMD. For studying that, a cross-sectional clinical data from 350 advanced AMD cases and 720 controls were collected. All subjects were > 65 years old, and without diabetes mellitus. We genotyped 40 newly associated obesity related loci using Sequenom iPlex platform. Of the 40 SNPs analysed, PTBP2 (rs1555543), GNPDA2 (rs10938397), HOXC13 (rs1443512) and MAP2K5 (rs2241423) were found to associate with AMD in the Finnish population. These new findings give suggestive evidence that the link between AMD and obesity could be partly explained by genetic factors. Besides providing new interesting insights into pathogenic mechanisms of AMD, these findings may also help to reveal possible targets for intervention and useful diagnostic biomarkers in the future.

## **INTRACELLULAR PROTEIN AGGREGATES INDUCE INFLAMMASOME SIGNALING IN HUMAN ARPE-19 CELLS**

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Age-related macular degeneration (AMD) is a progressive eye disease in which dysfunction of retinal pigment epithelial (RPE) cells plays a major role in the vision loss. Currently, almost 90% of AMD patients have no therapy available which largely results from the lack of knowledge on the molecular pathogenesis of the disease. In the present study, we have examined the ability of intracellular protein aggregates to activate the inflammasome signaling in human ARPE-19 cells. ARPE-19 cells were grown into confluence and exposed to MG-132 and Bafilomycin A (BafA) in order to inhibit proteasomal degradation and autophagy, respectively. Thereafter, inflammasome signaling and cytokine production were determined with ELISA and western blot techniques. Additionally, caspase-1 enzyme activity and cell viability were monitored with appropriate commercial methods. Our results show that intracellular protein aggregation resulted in the caspase-1-dependent release of IL-1 $\beta$ . Concurrently, the inflammasome receptor protein NLRP3 became upregulated, and intracellular levels of 4-hydroxynonenal (HNE)-protein adducts were increased. Moreover, already low concentrations (1 pg/ml) of IL-1 $\beta$  were able to induce a secondary response by promoting the production of IL-8. Our findings suggest that inflammasome activation becomes induced after a decline of intracellular degradation systems in human ARPE-19 cells, and IL-1 $\beta$  produced by the cells has biological effects towards chemokine production.



## **RHO-KINASE INHIBITOR Y-27632 DECREASES VEGFA GENE EXPRESSION IN HYPOXIA CONDITIONS**

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Rho-kinase inhibitor Y-27632 is a potential drug whose medical activity has been studied in relation to both human physiology and different diseases. The novel findings have revealed that Rho-kinase inhibitor Y-27632 supports gene expression, which maintains the normal chondrocyte phenotype. If this kind of ability could be connected to patient originated pluripotent stage cells, it could offer a novel solution to use direct cellular differentiation process in order to produce repair of cartilage tissue. In this study, we have focused on the short period biological responses of the Rho-kinase inhibitor Y-27632 to human primary foreskin fibroblasts. Fibroblast cells were exposed to 1  $\mu$ M and 10  $\mu$ M Rho-kinase inhibitor Y-27632 treatments under normoxia and 5% oxygen condition, which mimics cartilage tissue conditions. Rho-kinase inhibitor Y-27632 decreased vascular endothelial growth factor VEGF $\alpha$  gene expression in hypoxia conditions but did not seem to induce expression of the chondrocyte specific genes like type II collagen and aggrecan, which could be necessary for cellular cartilage therapies. In addition, Rho-kinase inhibitor Y-27632 treatments have caused the decrease of the vinculin-associated focal adhesions according to immunocytochemical stainings.

## **POSTOPERATIVE PAIN AFTER CATARACT SURGERY**

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Cataract surgery is the most common surgical procedure in eye practice. The modern surgery with phacoemulsification technique is considered as a minor procedure with an uneventful and pain-free recovery. However, in the previous literature, little attention has been paid to pain and other postoperative ocular symptoms, and the data on the incidence of these symptoms are conflicting. The study was a prospective follow-up clinical trial. Data on ocular symptoms and pain management was collected before and after surgery using Brief Pain Inventory-based questionnaire form. The follow-up points were at first hours, one day, one week and six weeks after surgery. 196 Patients who underwent first-eye unilateral cataract surgery were included. During the first postoperative hours, 34% of patients reported ocular pain. Most had mild pain, but 9% had moderate or severe pain. 45% Of patients reported new ocular symptoms had developed after surgery. In conclusion, at least 1/10 patients can have significant pain after surgery, and 1/5 can have moderate or severe ocular irritation symptoms, which may last up to 6 weeks. Thus, patients should be provided appropriate counseling on pain and pain management as part of postoperative care.

## **HYALURONAN SYNTHASES 1 AND 2 AS PROGNOSTIC FACTORS IN CUTANEOUS MELANOMA**

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Hyaluronan (HA) is a large extracellular matrix molecule, which has shown to contribute to cancer development. In our previous work we showed that the expression of hyaluronan synthases 1-2 (Has1-2) is decreased in malignant melanoma compared to benign lesions. In the present study, our objective was to compare the immunohistological data with patient clinical data in order to analyze whether the expression of Has1 or Has2 has prognostic value in melanoma. The material consisted 140 specimens, including superficial (Breslow thickness <1mm) and deep (Breslow >4mm) melanomas and lymph node metastases of melanoma. The samples were stained with antibodies against HAS 1-2 and hyaluronan degrading enzyme hyaluronidase 2. The immunostaining results were tested with  $\chi^2$  -test for correlation with clinicopathological parameters. The expression of Has1 and Has2 was decreased in deep melanoma and metastases compared to superficial melanoma. Our results indicated that the recurrence of melanoma associates with decreased expression of HAS 2 ( $p=0.025$ ,  $\chi^2$  -test). In addition, decreased expression of HAS 2 associates with melanoma caused death ( $p=0.016$ ), suggesting that declined Has2 expression correlates with poor outcome of the disease.

## **BISPHOSPHONATES: HOW DOES THE STRUCTURE AFFECT THE ABILITY TO BIND TO HYDROXYAPATITE?**

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Bisphosphonates (BPs) are synthetic molecules containing a P-C-P backbone. When in the bloodstream, BPs are rapidly taken up by the bone tissue where they can prevent the resorption of bone. BPs have several medical applications; not only are they used in the treatment of osteoporosis and other skeletal disorders but also for bone imaging when linked to a gamma-emitting radioisotope. Recent studies have also showed evidence of BPs' direct effects on cancer cells. The problem is BPs' negative charge and their high affinity for bone tissue, which is why BPs are poorly taken up by cells in the soft tissue. Esterification of the BP phosphate groups can reduce the negative charge of the molecule and thus increase their cell permeability. Some of these esterified BPs have shown promising results in inhibiting tumor progression. We have systematically studied the effect of different ester-groups to BPs' ability to bind to hydroxyapatite by a  $^{31}\text{P}$  NMR spectroscopy based method. The results of this study give strong basis for rational design of novel BPs that are targeted for cancer therapy.

## THE EFFECT OF TCF7L2 BINDING SEQUENCE VARIANTS

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Polymorphisms in the DNA binding sequences of a known Type 2 Diabetes (T2D) risk gene, the transcription factor TCF7L2, may be involved in the etiology of the disease. We aim to investigate the effects of these polymorphisms on the DNA binding of TCF7L2 to provide a basis for their functional characterization. We generated singly and multiply mutated oligos for the TCF7L2 binding consensus and performed an ELISA based method where biotinylated oligos are arrayed onto a glass slide, measured for background fluorescence using SYBR Green and, after applying in-vitro translated TCF7L2 protein, a primary antibody for TCF7L2 and a labeled secondary antibody, for specific fluorescence. Processed fluorescence intensities provided a matrix of variant effect on the TCF7L2 binding sequence that will be mapped to the nine publically available and one new TCF7L2 ChIP-seq dataset to evaluate their functional significance of on TCF7L2 chromatin occupancy. We identified a core sequence for TCF7L2 that is highly sensitive to variation. These results provide tools for the identification of novel regulatory polymorphisms that may alter the expression of TCF7L2 target genes and thereby have an effect on the etiology of T2D.

## LOW DOSE UVB IRRADIATION INCREASES HYALURONAN SYNTHESIS IN EPIDERMAL KERATINOCYTES VIA SEQUENTIAL INDUCTION OF HYALURONAN SYNTHASES HAS1-3

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Hyaluronan, an integral component of the extracellular matrix, responds strongly to different kinds of injuries in the epidermis of skin. Here, the effects of acute ultraviolet B (UVB) exposure on hyaluronan content and molecular mass, and expression of genes involved in hyaluronan metabolism were defined in monolayer and differentiated, organotypic 3D-cultures of rat epidermal keratinocytes. The signaling pathways regulating the response were also characterized. In monolayer cultures, UVB consistently increased secretion of hyaluronan into the culture medium (2-3-fold) and regulated the mRNA expression of the hyaluronan synthases *Has1-3* as well as the degrading enzymes *Hyal1-2*. Interestingly, silencing of *Has2* and especially *Has3* clearly decreased the UVB-induced accumulation of hyaluronan. p38 and CaMKII pathways were found to be involved in the UVB-induced up-regulation of *Has2* and *Has3* expression, respectively, and their inhibition reduced hyaluronan deposition. In organotypic cultures, UVB treatment also activated hyaluronan metabolism and shifted hyaluronan toward a smaller size range. The data show that exposure of keratinocytes to acute, low dose UVB triggers changes in hyaluronan metabolism that are an important part of the adaptation of keratinocytes to radiation injury.

## **METHYLMERCURY EXPOSURE ELICITS ALTERATIONS OF ENDOPLASMIC RETICULUM STRESS GENES IN *CAENORHABDITIS ELEGANS***

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Methylmercury (MeHg) is an environmental toxicant that causes embryonic, developmental and neurological defects. During ER stress, unfolded or misfolded proteins accumulate on ER and activate the Unfolded Protein Response (UPR) which is critical in animal development, while unresolved protein folding results in initiation of apoptotic pathways.

Following MeHg exposure (10  $\mu$ M), RNA-seq, quantitative RT-PCR, toxicity assays, and transcript splicing were performed. RNA-seq produced 35.5 million and 41.1 million sequence reads which revealed 541 genes up- and 261 genes down-regulated by MeHg treatment. Of these, Activated in Blocked Unfolded protein response (ABU) gene family members (7/15) were found to be significantly down-regulated. MeHg toxicity assays were also performed on UPR gene *ire-1*, *pek-1*, *atf-6* and *xbp-1* mutants. Our results highlight specific molecular mechanism(s) of MeHg toxicity in *C. elegans* that may be conserved in humans.

## **POROUS SILICON - CELL PENETRATING PEPTIDE HYBRID NANOCARRIER FOR INTRACELLULAR DELIVERY OF OLIGONUCLEOTIDES**

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Major obstacle in the use of oligonucleotide drugs is the delivery of these large and negatively charged biomolecules through cellular membranes into the cytosol and the nucleus. As of lately, mesoporous silicon (PSi) has become of interest in drug delivery due to its biocompatibility and tunable properties. In this study, PSi-nanoparticles, with thermal stabilization and subsequent aminosilane modification, were utilized as an oligonucleotide delivery platform. Splice correcting oligonucleotides (SCOs), a type of oligonucleotide drug, were loaded into the positively charged PSi-nanoparticles up to 14,3% (w/w). The fast loading is driven by electrostatic interactions, the loading efficiency being 100% within 5 minutes. The nanoparticles were able to deliver and release biologically active SCO inside cells *in vitro*, when formulated together with novel cell penetrating peptide (NickFect51). The biological effect was monitored with splice correction assay and confocal microscopy utilizing HeLa pLuc 705 cells. Contrary to commercial counterpart, the use of PSi-carrier platform in oligonucleotide delivery did not reduce the cell proliferation. Additionally, the oligonucleotide cargo was shown to be protected against proteolytic digestion inside the porous nanocarrier.

## **PATIENT SAFETY - HOW PATIENTS PERCEIVE IT AND HOW PATIENTS' ROLE IS SEEN BY PATIENTS SAFETY EXPERTS?**

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Patient safety has been studied extensively, but so far little research has focused on patients' views. Patients' views are important because patients have a perspective of the whole treatment process. The purpose of this study is to investigate day surgery patients' experiences of patient safety (PS) and patients' participation in promoting patient safety. In addition, the purpose is to find out how PS experts evaluate patients' role in the promotion of PS. This study has a mixed method approach with three different data. Data will be collected from 1) day surgery patients with a PEPS (Patients' Experiences of Patient Safety) -questionnaire 2) patients' and their relatives' written reports of safety incidents and 3) patient safety experts' views on patient's role and on the empowerment of patients to participate in the promotion of safe care. A quantitative data will be analyzed statistically including factor analysis and a logistic regression. Qualitative data will be analyzed by content analysis. The expected results of the study can be utilized in the development of patient-centered health care services and in particular, to empower patients to participate in their own care and promotion safer care. The results can be utilized also in healthcare workers education.

## **QUANTITATIVE ANALYSIS OF INTRACELLULAR PHARMACOKINETICS OF DOXORUBICIN AND ITS LIPOSOMAL FORMULATIONS AND A COMPUTATIONAL MODEL OF THE INTRACELLULAR PK/PD RELATIONSHIP**

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In order to be active the drug needs to access the target cells and inside the cells to be transported to the site of action. However, the uptake mechanisms may affect the sub-cellular distribution of the drugs. Small drug molecules are able to enter cells via passive diffusion through plasma membrane, whereas nanoparticles have to utilize endocytosis as internalization mechanism. In addition, the methods studying the intracellular pharmacokinetics are often based on semi-quantitative detection such as fluorescence. In this study we utilized quantitative mass spectrometer (HPLC-MS/MS) for studying the intracellular kinetics of anti-cancer drug doxorubicin (DOX) as such or as pH-sensitive liposomal DOX formulation (L-DOX) in rat glioma cell line. The results showed that at 2  $\mu\text{M}$  concentration the cellular and nuclear uptake levels of free and L-DOX were almost equal. However, at 8-fold higher DOX concentration (16  $\mu\text{M}$ ) the cellular and nuclear uptake levels of free DOX were 6.3-fold and 5.3-fold higher, respectively, than levels of L-DOX. This indicates that the endocytosis pathways, which liposomes are utilizing, were saturated at high concentration. Interestingly, the change in the exposure concentrations (8-fold difference) did not correlate with the observed changes in free DOX concentrations at the cellular (12-fold difference) and nuclear (24-fold difference) level. This suggests that at low concentration multidrug resistance mechanisms, such as efflux transporters, are inhibiting the cell uptake process of free DOX. At the moment, similar kinetic studies are carried out with the commercially available pegylated liposomal DOX formulation (CAELYX®). In addition, the similar time-dependency of the toxicity with the free DOX, L-DOX and CAELYX® was observed by the cell viability assay. Free DOX and L-DOX showed equal toxicity ( $\text{IC}_{50}$  0.37 and  $\text{IC}_{50}$  0.35  $\mu\text{M}$ , respectively) whereas CAELYX® was significantly less toxic compared with free DOX and L-DOX (35-fold and 37-fold, respectively). Finally, the computational PK/PD model which describes the time-dependent intracellular kinetics of free DOX and its liposomal formulations, and the cell death induced by the drug will be built up with Berkeley-Madonna software and be fitted to the data with Extended Least Squares method.

## **BREAST CANCER TUMOUR ASSOCIATED MACROPHAGES (TAM) MODULATION BY FREE OR LIPOSOME ENCAPSULATED NITROGEN CONTAINING BISPHOSPHONATES (N-BP)**

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Breast cancer (BC) is no longer seen as a disease solely due to cancer cells. The immune system cells that infiltrate primary tumours and after BC cell education co-migrate to other sites, are essential in the formation pre-metastatic niches in organs such as lungs and bones. Tumour associated macrophages (TAM) resemble the M2 polarization state leading to an anti-inflammatory, immunosuppressive response, opposed to the classically activated M1 polarization leading to inflammation. Bone is a common site of BC metastasis, mostly because of the vicious cycle between resorbing osteoclasts and circulating BC cells that stimulate each other in such niche. Therefore, anti-resorptives like bisphosphonates (BP) e.g. zoledronate (ZOL), have been used to prevent/manage BC bone metastasis.

We aimed to explore liposome encapsulation of ZOL to target BC TAM, in order to modulate their polarization status from M2 to M1. *In vitro* experiments with murine BC conditioned medium (4T1 cell line) and murine macrophage (M $\phi$ ) cell line (J774) were conducted. qPCR and multiplex ELISA of M1 and M2 markers show that ZOL-LIP increases some M1 markers. To further assure the potential clinical relevance of these findings, studies with the orthotopic 4T1.luc2 Balb/c mouse model are being conducted. The effects of ZOL and ZOL-LIP in a neoadjuvant context will be assessed. To the date preliminary results show no effect of ZOL or ZOL-LIP in the primary tumour growth. Ongoing we are checking the effects on M $\phi$  involvement in metastasis formation.

## **HAS3 OVEREXPRESSION DOWNREGULATES MV3 MELANOMA CELL LINE PROLIFERATION, MIGRATION AND ADHESION**

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Hyaluronan (HA) is an important molecule in tumor stroma. It is produced by plasma membrane-bound enzymes (HAS1-3), which extrude HA-chain into the extracellular space. In many cancers the content of HA is altered, suggesting an important role for HA in tumorigenesis. Aim of the present work was to study the influence of HAS3 overexpression on MV3 melanoma cell behavior. HAS3-inducible MV3 cells were generated by Lentiviral transduction. The influence of HAS3 overexpression on MV3 cell proliferation, migration and adhesion was studied. Protein phosphorylation was analyzed with phosphokinase array and Western blot. Secreted HA in the culture media was measured using HA-ELSA assay. Increased HAS3 expression resulted in over 20-fold increase in secreted HA. This associated with 30% reduction in cell proliferation and reduced cell adhesion and migration rates. Phosphokinase array showed that the phosphorylation of SRC-kinases, STAT3 and STAT5 was decreased by 20% in HAS3 overexpressing cells. Taken together, HAS3 overexpression in MV3 cells decreases cell proliferation, migration and adhesion, possibly due to lowered SRC-kinase activity that influences cell proliferation and regulates focal adhesion kinases.

## HIGH-FAT DIET INCREASES TAU EXPRESSION AND EXON 10 INCLUSION IN THE BRAIN OF FEMALE MICE

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Type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) are risk factors for each other, but the underlying molecular mechanisms are not well understood. Intraneuronal deposits of tau protein are a common feature of several neurodegenerative diseases, including AD. Moreover, aberrant splicing of tau exon 10 leads to the altered ratio of four-repeat (4R) vs. three-repeat (3R) isoforms in these diseases. To investigate the effects of both genetic and high-fat diet (HFD)-induced diabetic phenotype on tau expression and alternative splicing, we used the AD mice (APdE9) cross-bred with the T2DM mice overexpressing insulin-like growth factor 2 in pancreas. HFD, regardless of the genotype, significantly ( $p \leq 0.00001$ ) induced 4R-tau and 3R-tau mRNA expression and increased 4R-tau vs. 3R-tau mRNA ratio in the temporal cortex of the female mice. Increased 4R-tau and 3R-tau expression significantly associated with impaired memory and reduced exploratory activity. All these effects were independent of the peripheral metabolic changes. Our study indicates that the HFD independently of T2DM or AD background induces the expression and exon 10 inclusion of tau in the brain of female mice. These data suggest that tau-related pathological mechanisms may be affected by active dietary choices.

## CRITICAL INCIDENTS OF LEARNING PATIENT SAFETY – FINNISH AND BRITISH PRE-REGISTRATION NURSING STUDENTS' EXPERIENCES FROM CLINICAL PLACEMENTS

Susanna Tella<sup>1</sup>, Nancy-Jane Smith<sup>2</sup>, Pirjo Partanen<sup>1</sup>, Hannele Turunen<sup>1,3</sup>

<sup>1</sup> UEF, Department of Nursing Science, <sup>2</sup> University of Salford, Salford, UK, <sup>4</sup> Kuopio University Hospital

Clinical placement learning covers at least half of the nursing programme in Europe and has an important role in pre-registration nursing students' learning and understanding of patient safety. Understanding pre-registration nursing students' learning about patient safety during their clinical placements is limited. The aim was to characterize and compare Finnish and British nursing students' experiences of learning about patient safety during their clinical placements in health care organizations. Inductive content analysis was used to analyze Finnish (n=22) and British (n=32) last year pre-registration nursing students' written critical incidents (CI), positive or negative nature, relating to patient safety. The students described their CIs' as having negative and positive aspects. The most events were first seen as negative but reflection enabled positive learning and reinforced the importance of patient safety. The CIs occurred from the first to the last year of education. Identified themes included 1) preventing errors and 2) acting safely after an error. The main difference between Finnish and English students related to the type of CIs. *Conclusion:* Reflecting patient safety must be systematic during clinical placements, but also afterwards in academic settings to support students' professional development. Results endorse equipping nursing students with competence to prevent errors and act safely after an error has occurred.

## **THE EFFECTIVENESS OF SIMULATION METHOD IN INTRAVENOUS MEDICATION COMPETENCE -EVALUATION OF RADIOGRAPHERS' CONTINUING EDUCATION INTERVENTION**

*Suvi Toivanen [1], Kerttu Tossavainen [1], Hannele Turunen [1]*

*[1] Department of Nursing Science, University of Eastern Finland*

It has been estimated that 10 % of the patients treated in hospital suffer from adverse events of which significant part relates with pharmacotherapy. To ensure medication competence of health care professionals and to promote patient safety there is need to develop new and effective teaching methods. The aim of this study is to evaluate the effectiveness of simulation education in radiographers' theoretical intravenous medication competence and to compare simulation and e-learning methods on immediate and sustained learning. This quasi-experimental intervention study used mixed methods design. The participants (N = 219) consisted of radiographers of three university hospitals. The education for experimental group was simulation and for comparison groups e-learning. The data was collected (2012-2013) with a knowledge-based test in three different phases: before, after and half years after the education. The data analyses include descriptive statistics and comparing the differences between groups. Qualitative data were collected by interviews. The analysis method is content analysis. Results of this study provide important information of simulation method in pharmacotherapy education compared to current teaching methods and thus help to develop patient safety promoting teaching methods.

## **RELATIONS BETWEEN APPROACHES TO TEACHING, PERCEPTIONS OF THE TEACHING ENVIRONMENT AND PEDAGOGICAL LEADERSHIP IN FINNISH UASS**

*Tarja Turtiainen, PhD student [1], Terhi Saaranen, University lecturer, docent[2], Santtu Mikkonen, Statistician, PhD [3], Hannele Turunen, professor[2]*

*[1] Department of Nursing Sciences UEF, MAMK University of applied sciences, [2] Department of Nursing Sciences UEF, [3] Department of Applied, Physics, UEF*

The purpose of this study is to examine relations between approaches to teaching, teaching environment and pedagogical leadership among health care, social and sport teachers in the universities of applied sciences (UASs) in Finland. This information is needed while the UASs are in reforming process in Finland. The data were collected using three international questionnaires: The Approaches to Teaching, The Perception of Teaching Environment and The Leadership for Academic Work. The equivalence of the instrument was improved by forward-back translations, the expert evaluations and a pilot study. The sample consisted of 1072 teachers, of which 439 returned the questionnaire by post; the respondent rate was 41%. The data analyses include descriptive and multivariate methods and the structural equation modelling. The construct validity of the questionnaires was evaluated by exploratory and confirmatory factor analysis and the reliability by the Cronbach alpha coefficient indicating the alpha values being good, over .80. The initial results will be ready by February 2014. Findings can be used to develop the leadership of teaching and learning in UASs.



## NEW METHODOLOGY FOR SELECTIVE ACETYLATION OF PRIMARY AMINO GROUPS

Sebahat Ucal[1], Janne Weisell[1], Alex Khomutov[2], Jouko Vepsäläinen[1]

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Selective acetylation of primary amino groups is a useful method in synthetic organic chemistry as well as in medicinal chemistry. These kind of acetylation reactions of primary amines with esters are already known but have required the use of catalysts or reagents such as pincer-ruthenium complex, nitrogen heterocyclic carbenes and manganese (III) bis(2-hydroxyanil)acetylacetonato complex. As the catalysts commonly used in the acetylation of amines, can be expensive, toxic and difficult to prepare and/or isolate the catalyst from the reaction. We have recently developed a new methodology for selective acetylation of primary amino groups without the requirement of any catalysts. Briefly, phenyl acetate has been demonstrated for the first time to be a new highly selective acetylating agent in acetonitrile in room temperature at 30 min. Our reaction shows high selectivity for primary -NH<sub>2</sub> groups over primary -OH or secondary -NH groups. Moreover, it is very efficient way to synthesize diacetylated polyamines, the natural products of polyamine acetylating enzyme, without any additional step(s), and thus, simplifies the synthesis of these compounds.

## DOWN-REGULATION OF CALCINEURIN-LIKE PHOSPHOESTERASE DOMAIN CONTAINING 1 (CPPED1) EXPRESSION IMPROVES GLUCOSE METABOLISM IN ADIPOCYTES

Maija Vaittinen [1], Marjukka Kolehmainen [1], Jussi Pihlajamäki [1], Matti Uusitupa [1], Leena Pulkkinen [1]

[1] Department of Clinical Nutrition, University of Eastern Finland (Kuopio Campus)

We have shown that *CPPED1* expression is downregulated in adipose tissue (AT) after weight reduction in persons with features of metabolic syndrome. However, the function of *CPPED1* in AT is unknown. In this study we aimed to investigate the localization of *CPPED1* protein expression in cultured SGBS preadipocytes and adipocytes, and to elucidate the role of *CPPED1* in adipocyte glucose metabolism. Immunofluorescence was used for *CPPED1* protein localization in SGBS preadipocytes and adipocytes. The effect of reduced *CPPED1* expression by RNAi technique on insulin action was measured using insulin-stimulated glucose uptake. Furthermore, the effect of *CPPED1* knock-down on the expression of genes related to adipocyte function was studied in SGBS adipocytes by RT-qPCR and western blot. *CPPED1* protein expression was localized in cytoplasm of preadipocytes and adipocytes. The *CPPED1* knock-down increased insulin-stimulated glucose uptake, the expression of genes/proteins involved in glucose metabolism and tended to increase adiponectin secretion into the conditioned medium. We demonstrate that *CPPED1* is a novel molecule involved in adipocyte biology and glucose metabolism, possibly via adiponectin-mediated mechanisms.

## **SIGNALING MECHANISMS DOWNSTREAM OF RHO CONTRIBUTING TO NEURON DEATH**

*Xijun Wang, Michael Courtney*

*Molecular Signaling Laboratory, Dept of Neurobiology, A.I.Virtanen Institute, UEF*

Increasing evidence converges on the involvement of Rho GTPases in neuronal cell death which is associated with various neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and Amyotrophic Lateral Sclerosis. Our previous work suggests the contribution of Rho to neurodegeneration, but the downstream proteins targeted by Rho recruiting cell death signals and the subsequent events they mediate remain to be elucidated. This project aims to investigate signaling mechanisms regulating neuronal death that are mediated by activated Rho and determine the Rho effectors and other downstream mediators responsible as they may be targets for therapeutic interventions in brain diseases. High throughput microscopy and image analysis using fluorescence resonance energy transfer (FRET) reporters were applied to primary neuron cultures. Combining this with a panel of effector-selective Rho mutants, the structural regions and residues of Rho contributing to neuronal cell death were mapped. An independent strategy used a plasmid-based RNAi knockdown to identify candidate neurodegenerative Rho effectors. The Rho residues most strongly implicated in neuronal cell death are consistent with the candidate Rho effectors identified via RNAi knockdown, and these candidates are being further explored.

## **THE THERAPEUTIC POTENTIAL OF MEMBERS OF THE VEGF FAMILY ON MUSCLE RECOVERY AFTER ISCHEMIA INSULT IN A MOUSE MODEL OF HYPERCHOLESTEROLEMIA**

*Galina Wirth<sup>1</sup>, Petra Korpisalo<sup>1</sup>, Hanne Hakkarainen<sup>1</sup>, Timo Liimatainen<sup>1</sup>, Seppo Ylä-Herttuala<sup>1,2</sup>*

*<sup>1</sup>Department of Biotechnology and Molecular Medicine, UEF, <sup>2</sup>Research Unit, KUH*

The aim of angiogenic therapy in ischemic disorders is to stimulate vessel growth in areas of poor vascularization in an attempt to increase blood supply and to support tissue recovery. We aimed to investigate the muscle recovery potential of AdhVEGF-A and -D<sup>ANAC</sup> after acute ischemia in a mouse model of hypercholesterolemia. Limb ischemia in LDLR<sup>-/-</sup>ApoB<sup>100/100</sup> mice was induced by ligation of both femoral artery and vein, followed by intramuscular injection of AdhVEGF-A, hVEGF-D<sup>ANAC</sup> or control LacZ. Gene transfer with hVEGF-A or -D<sup>ANAC</sup> had no beneficial effects on perfusion recovery of ischemic calf muscle. Surprisingly, the overall perfusion in AdhVEGF-A group was significantly reduced on d7. Although hVEGF-A transduced limbs were the most edemic, the edema formation failed to statistically explain the poor vessel functionality in this group. Moreover, gene transfer had minor positive effect on morphological recovery of calf muscle. In fact, AdhVEGF-A muscles were predominantly necrotic on d4 in comparison with control group. Although AdhVEGF-A gene transfer induced capillary enlargement in the ischemic calf muscle, enhanced angiogenesis failed to translate to either improved perfusion or accelerated muscle recovery beyond the natural recovery response.

## CHARACTERIZATION OF THE MICROBIAL POPULATIONS IN ATOLE AGRIO, A TRADITIONAL MEXICAN FERMENTED BEVERAGE

K Väkeväinen[1], A Valderrama[2], J Espinosa[3], D Centurión[3], T Sainz[4], G Díaz-Ruiz[2], A von Wright[1], C Plumed-Ferrer[1], C Wachter[2]

[1]Institute of Public Health and Clinical Nutrition, University of Eastern Finland, [2]Universidad Nacional Autónoma de México, [3]Universidad Juárez del Estado de Tabasco, [4]Universidad Autónoma Metropolitana

Food fermentations are cost-effective ways to improve the microbiological safety, nutritional value and organoleptic properties of products. However, these processes should be controlled and predictable. This can be achieved by applying defined microbes (starters) to stabilize the fermentations. Lactic acid bacteria (LAB) are commonly found in both traditional and starter-guided fermentations. The aim of this study was to characterize the microbial populations of a traditional fermented Mexican beverage, atole agrio. Atole agrio is prepared from ground maize and water through a 6–12 hour spontaneous fermentation. Since there is no previous publication on the fermentation of atole agrio, this research provides the first results. Total mesophiles, LAB, yeasts, molds and Enterobacteriaceae were measured by plating technique during fermentation, as well as the pH. The results showed relatively low levels of LAB (6.7 log cfu/ml) throughout the fermentation. The average level for total mesophiles was 8.3, yeasts and molds 6.9 and Enterobacteriaceae 5.8 log cfu/ml. The pH decreased from 7.5 to 4.5. Due to the short fermentation time, the microbial community remained relatively stable. However, increasing the initial level of LAB could improve the organoleptic properties of atole agrio.

## INSIGHTS ON THE STRUCTURE-ACTIVITY RELATIONSHIPS OF COMPOUNDS BINDING TO LARGE AMINO ACID TRANSPORTER 1 (LAT1)

Ylikangas H, Peura L, Malmioja M, Gynther M, Huttunen KM, Leppänen J, Laine K, Lahtela-Kakkonen M, Rautio J, Poso A

School of Pharmacy, Faculty of Health Sciences, University of Eastern Finland

LAT1 is a transmembrane protein located at the blood-brain barrier (BBB) where it ferries prize nutrients from blood to brain. Its natural substrates are neutral amino acids with hydrophobic side chain. LAT1 is also involved in brain delivery of drug molecules mimicking amino acids (e.g. levodopa, gabapentin). Broad substrate specificity and high expression at the BBB make LAT1 a promising carrier of poorly penetrable drugs into the brain via prodrug technology. In order to design new LAT1-substrates it is crucial to identify key features required for high affinity. Here, 3D quantitative structure-activity relationships (QSAR) of a series of LAT1-substrates were analyzed using pharmacophores and comparative molecular field analysis (CoMFA). LAT1-affinity measured with *in situ* rat brain perfusion was used to determine biological activity of the compounds. The resulting 3D pharmacophore identified molecular features beneficial for efficient LAT1-binding. Moreover, statistically significant CoMFA was generated which suggests chemical modifications improving LAT1-affinity. As a result, five new high-affinity prodrugs were designed and their affinity successfully predicted with CoMFA. 3D QSAR models generated are useful in optimization and rational design of new LAT1-mediated prodrugs.

## **THE CONNECTION OF NURSE-NURSE COLLABORATION ON NURSES' JOB SATISFACTION -A COMPARATIVE MIXED METHODS STUDY BETWEEN FINNISH AND NORWEGIAN NURSES**

*Tuija Ylitörmänen, <sup>1,2</sup> Tarja Kvist, <sup>1</sup> Hannele Turunen, <sup>1,3</sup>*

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Today collaboration in healthcare is strongly supported by policymakers to ensure high quality of patient care. Collaboration among registered nurses (RNs) is important considering the wellbeing of the RNs, as poor interaction levels cause job dissatisfaction. The aim of this study is to investigate the connection of nurse-nurse collaboration on nurses' job satisfaction in Finland and Norway. A concurrent triangulation strategy of mixed method is of choice to form a more complete understanding of the topic. Quantitative and qualitative data will be collected concurrently in spring 2014 by open-ended interviews and two questionnaire surveys: the Nurse-Nurse Collaboration Scale (Dougherty & Larson, 2010) and the Job Satisfaction Scale (Kvist et al., 2012). The target group is RNs working on wards in university hospital in Finland and Norway. Sample size is determined by power of 0,8 and an alpha of 0,05 (95%). The data will be analyzed statistically and by inductive content analysis and then compared for differences and conjunctions, finally combining the data's for interpretation. Results can be applied in the development of the RNs collaboration and interaction skills and in improvement of job satisfaction. The outcomes can be of use to support the workplace health promotion.

## **VASCULAR ABNORMALITIES IN MIGRAINE**

*Nina Zaproudina [1,2], Matti Närhi [1,2], Jukka A Lipponen [3], Mika P Tarvainen [3], Pasi A Karjalainen [3], et al.*

*[1] Institute of Biomedicine/Physiology, [2] Institute of Dentistry, [3] Department of Applied Physics and [4] Department of Neurobiology, A. I. Virtanen Institute, UEF, and [5] Department of Physical and Rehabilitation Medicine, Kuopio University Hospital, Kuopio, Finland*

Vascular changes in migraine remained a matter of active debate. In present studies, we searched for the possible new markers of the headache-associated vascular changes. Skin temperature values of face and hands and their nitroglycerin-induced changes were examined using infrared thermography and the 2-dimensional distribution of blood pulsation wave in the facial area was exposed with the Blood Pulsation Imaging technique in migraineurs (n 13) and healthy women (n 30). Nitroglycerin-induced headache was associated with a long-lasting increase of the facial skin temperature, especially in the nose area, due to its' lower baseline level. The lower acral skin temperatures were found in migraineurs compared to the controls. In addition, a transverse progress of blood pulsation wave was found in the face of migraineurs in contrast to synchronous blood perfusion in healthy women. Overall, our studies reveal disturbances in the peripheral blood flow and lateralization of facial blood perfusion in migraineurs. These specific signs of the vascular dysregulation in migraineurs open new dimensions for the studies of vascular processes accompanying migraine.



# *Doctoral Programmes*

## DOCTORAL PROGRAMME OF CLINICAL RESEARCH

The Doctoral Program of Clinical Research (DPCR, [uef.fi/dpcr](http://uef.fi/dpcr)) is a multidisciplinary program that covers all the specialties in clinical medicine. The purpose of the program is to support the process of doctoral theses, particularly those related to clinical research or clinical materials. It serves researchers in all health care units that are part of the special responsibility area (ERVVA) of Kuopio University Hospital (KUH) and cooperates with The National Graduate School of Clinical Investigation (CLIGS).

The purpose of the training provided by the doctoral program is to create professionals with skills for independent and team-based clinical research projects. Therefore, it is recommended that all doctoral students in the DPCR attend the courses Introduction to Clinical Research (1 ECTS) and Seminar series of the Graduate School of Clinical Research (2 ECTS) as well as Introductory Course for a Clinical Researcher (5 ECTS; web-course) provided by the Science Service Center of KUH. In addition, it is recommended that all doctoral students attend and present their results in at least one international scientific conference.

Students apply in the DPCR according to UEF instructions (deadlines annually 31.8., 30.11., 28.2. and 31.5.). The Applicant should have either completed or currently ongoing applicable Master's degree (MD etc.) and ongoing or planned research project suitable for doctoral dissertation project with a research plan approved by supervisors for the doctoral dissertation.

The leader of the DPCR is Professor Juhani Nuutinen ([juhani.nuutinen@kuh.fi](mailto:juhani.nuutinen@kuh.fi)). The contact persons are the Coordinator of the Doctoral Program, docent Ville Leinonen ([ville.leinonen@kuh.fi](mailto:ville.leinonen@kuh.fi)) and Project Coordinator Saara Happonen ([saara.happonen@kuh.fi](mailto:saara.happonen@kuh.fi)).

## **DOCTORAL PROGRAMME MOLECULAR MEDICINE**

The Doctoral Program in Molecular Medicine (DPMM) is an interdisciplinary doctoral training program with the purpose of training researchers as international experts in modern biomedicine. Molecular medicine studies the causes and mechanisms of origin of diseases on a molecular level and strives to find methods to treat and prevent these diseases.

Research fields in the program range from basic laboratory sciences and diagnostics to applied clinical research. The doctoral program concentrates on the research of major diseases, such as cardiovascular diseases, type 2 diabetes, obesity, neurological diseases, inflammations, and cancer, as well the possibilities provided by stem cell technologies in the treatment of various diseases.

DPMM offers high quality PhD training by organizing scientific courses, seminar series and providing PhD supervision. PhD students work as researchers in the groups belonging to the program.

Doctoral training is organized by A. I. Virtanen Institute and School of Medicine in the University of Eastern Finland. Director of DPMM is Academy Professor Seppo Ylä-Herttuala. Contact person: Coordinator Joanna Huttunen, joanna.huttunen@uef.fi



## **DOCTORAL PROGRAMME IN NURSING SCIENCE**

### **– systematic education for future researchers and experts**

Katri Vehviläinen-Julkunen, professor, director of the Doctoral Programme in Nursing Science; Tarja Kvist, PhD, university researcher; Reeta Lamminpää, PhD -student, MSc

### **Why doctoral education in nursing science?**

Doctoral education in nursing started in 1930's in the United States of America. The need for PhD prepared nurses has been globally evident. Changes in the health care systems and new innovations in care settings as well as several challenges in the society are highlighting the need for a systematic doctoral education. PhD educated nurses with researcher training are needed in clinical practice, leadership positions and educational institutions as well as in research. In Finland, since 1979, doctoral education has been offered in nursing and health sciences. Since then a total of 100 PhDs have got their doctoral degree in UEF.

### **What UEF is offering and how networking is arranged?**

In the University of Eastern Finland doctoral education in nursing science is arranged within the framework of the Doctoral Programme in Nursing Science (DPNursing) provided by the Faculty of Health Sciences. The programme arranges PhD-courses and seminars in the field of nursing science discipline and transferrable skills. The purpose of the DPNursing is to train excellent, internationally oriented researchers and experts with doctoral education for a variety of national and international duties. Other aims are to improve their research careers and to strengthen multidisciplinary research. Annually 6-8 doctoral degrees are granted.

The Doctoral Programme (DPNursing) in UEF works in close cooperation with the Finnish Doctoral Education Network in the field (a network of five universities – University of Eastern Finland, University of Oulu, University of Tampere, University of Turku and Åbo Akademi). The network has been financed by the Academy of Finland. The Network coordinates doctoral courses in nursing science with the participating universities. Annually 6-8 courses with 6 ECTS are offered by the network. Courses are held by international and national experts. The course calendar includes topics such as qualitative and quantitative research methods, action research, perspectives on preventive nursing and nursing education research, health services research and research ethics. Doctoral training involves an opportunity for collaboration in multidisciplinary doctoral programmes, too. Students can benefit from training and education provided by international networks and doctoral schools.

### **How to apply?**

Students are selected to the programme twice a year. Students apply the right to perform postgraduate studies in the Doctoral Programme in Nursing Science according to UEF instructions (deadlines annually 30.11. and 31.5.). Application form and instructions can be found at UEF Graduate School Internet site.

**DOCTORAL PROGRAMME OF PUBLIC HEALTH**  
**-Top Quality Research with a Mission of Health Promotion**

Jussi Kauhanen, Juha Lindfors

Institute of Public Health and Clinical Nutrition, University of Eastern Finland;

The Doctoral Programme in Public Health (DPPH) at the University of Eastern Finland introduces doctoral students to a multidisciplinary world of health-related phenomena and research. Students enter our programme with different backgrounds and prior degrees. Health itself, however, is always at focus in our training, as well as health promotion as the practical goal. But the research methodology and theoretical foundations can be tracked to multiple scientific disciplines. Students are often surprised to learn that there may be various ways to solve scientific problems, and this in part makes the doctoral training in public health so fascinating. The main educational goal of the Doctoral Programme is to train academic professionals to meet high international standards in scientific research, higher education, public sector administration, NGO's, and private sector, both in the settings of national and international cooperation. Our doctoral student body is a sort of microcosm, since currently about half of the students are non-Finnish in origin. So multiculturality is yet another word to describe us.

Do you find these to be interesting prospects for you? Then go ahead and contact us at:

<http://www.uef.fi/en/dpph/etusivu>

# DOCTORAL PROGRAMME IN DRUG RESEARCH

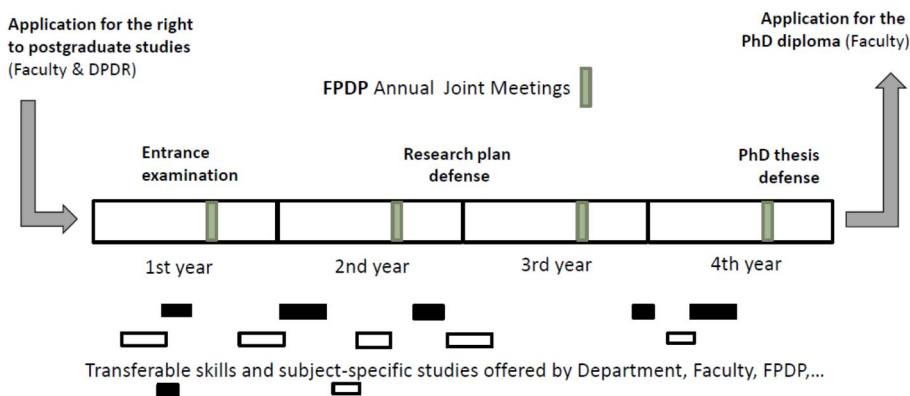
## -in a nutshell

The Doctoral Programme in Drug Research (DPDR) is a multidisciplinary programme that covers all topics of drug research and toxicology at the UEF. DPDR is an active member in the national FinPharma network.

## Studies at the DPDR

DPDR students will perform their studies according to the degree requirements of the programme which are listed in the UEF postgraduate study guide. After receiving acceptance from the Faculty, DPDR student design their personal study plans (**Figure**) and begin training in transferable skills and subject-specific areas that are provided by the Faculty and DPDR, FPDP and other Doctoral programs, respectively. *FPDP joint meetings* contribute to networking and career development.

The *entrance examination* guarantees that basic knowledge about research and activities in pharmacy is obtained and the *research plan defense* provides practice for the actual PhD defense and also a valuable source of scientific input to research problems.



Degree	Transferable skills studies	Subject-specific studies	Total ECTS
PhD (Pharm) and PhD	10-20	20-30	40
D Med Sci and DDS	5-15	15-25	30

**Figure.** Post-graduate study process at the DPDR.

## Research at the DPDR

Research in the School of Pharmacy (<http://www.uef.fi/en/farmasian-laitos/research>) has been organized into six strategic research areas, to which research groups belong:

- Drug design and discovery
- Drug-like properties of drug substances (ADMET research)
- New drug formulations and process analysis techniques (PAT)
- Evaluation of efficacy of drug treatment
- Neurobiology and pharmacology
- Toxicology

The PhD students conduct their research in projects associated with these areas under the guidance of their supervisors. Increasingly, cross- and multidisciplinary research projects

## National collaboration

The FinPharma Doctoral Program (FPDP; [www.fpdp.fi](http://www.fpdp.fi)) is a national network for coordinated training in drug research and toxicology for PhD students. The main participating Doctoral Programs are from Universities of Helsinki, Eastern Finland, and Turku. Some supervisor and student members belong to Universities of Oulu, Tampere, Åbo Akademi and Jyväskylä. With 38 positions funded by the Ministry of Education and about 300 active PhD students, FPDP is the second largest Doctoral Program in Finland. FPDP activities are organized in four sections (Drug Discovery, Pharmacy, Clinical Drug Research and Toxicology).

FPDP enhances national and international networking by the four sections' courses and other activities, by awarding travel grants to domestic and international courses and laboratory visits and by cooperation with the pharmaceutical industry, regulatory authorities and societies.

All members of the local Doctoral Programs belong automatically to the FPDP, conform to its regulations, and can utilize its activities.

FPDP is directed by professor Raimo Tuominen and the coordinator is Ilkka Reenilä, both at the University of Helsinki.

## **DOCTORAL PROGRAMME IN NUTRITIONAL SCIENCES**

The purpose of the Doctoral Programme in Nutritional Sciences is to provide interdisciplinary doctoral training for students of nutritional sciences and its neighbouring disciplines who are interested in the interlink between nutrition and health and the relevancy of nutrition in the promotion of health and treatment of diseases. The main research lines at the Unit of Clinical Nutrition are 'Diet and Chronic Disease', 'Food and Health' and 'Food Biotechnology and Safety' and they all serve the common goal to identify the role of diet, foods and food components in the maintenance of health and treatment of diseases. Besides routine clinical methods, we also apply the systems biology tools to analyze the underlying tissue-level effects of the studied dietary modifications. Main food items in our studies have been whole grains, fish and berries. More information:

<http://www.uef.fi/en/nutrition/research>.

At the moment around 20 students belong to the Doctoral Programme in Nutritional Sciences. Their background education on master level is in most of the cases nutrition, but there are also students with the background of e.g. medicine, food chemistry, molecular biotechnology, animal physiology or molecular biology.

### **How to apply and postgraduate training**

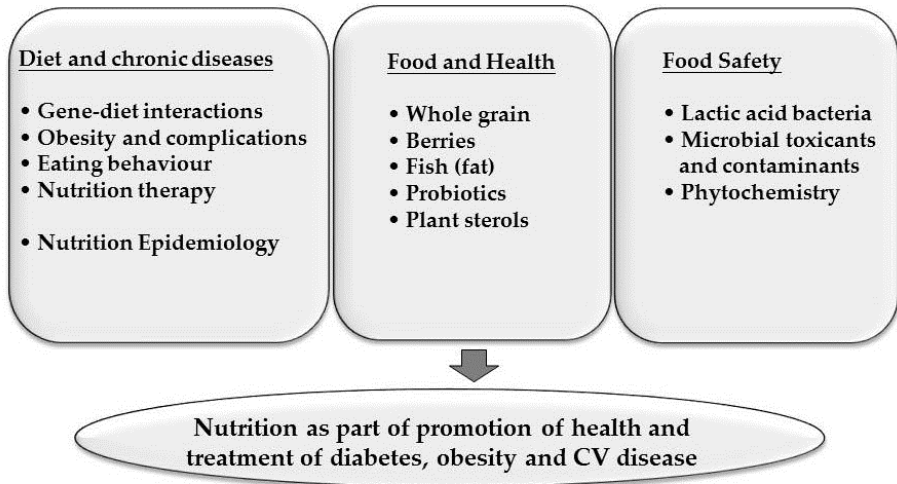
Students apply the right to perform postgraduate studies in the Doctoral Programme in Nutritional Sciences according to UEF instructions (deadlines annually 31.8., 30.11., 28.2. and 31.5.). More instructions:

<http://www.uef.fi/en/dpntr/hakeminen>.

The following degrees are available for PhD students graduating from the programme: Licentiate of Philosophy, Doctor of Philosophy, Licentiate of Health Sciences, Doctor of Health Sciences, Doctor of Medicine and Doctor of Dental Sciences.

Students perform their postdoctoral studies according to the degree requirements of the programme. Degree requirements and postgraduate courses offered by UEF graduate school and Doctoral programmes can be found in WebOodi or in the UEF postgraduate study guide. More information:

<http://www.uef.fi/en/dpntr/jatkokoulutus>.



Research areas at the Unit of Clinical Nutrition

**Contact information**

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