

2011

# Book of Abstracts 2011



## Nobel Day Festivities 8<sup>th</sup> of December 2011



Traditionally, on 10<sup>th</sup> of December, the anniversary of Alfred Nobel's death, is awarded the Nobel Prize in Physiology or Medicine. Biomedicine shows attention to this day by organizing own research activities and festivities.

School of Health and Medical Sciences  
Department of Clinical Medicine  
Örebro University  
8<sup>th</sup> of December 2011

**Program Committee:**

Nikolaos Venizelos, Assoc. Professor

Allan Sirsjö, Professor

Elisabeth Hultgren Hörnquist, Professor





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## Preface

The "Nobel Day Festivities" were established 2009 by Biomedicine, Department of Clinical Medicine, School of Health and Medical Sciences at Örebro University, and is organized traditionally every year in order to notice the anniversary of Alfred Nobel's death (10th of December) with scientific activities including poster presentations and selected oral presentations by doctoral students, which are documented in this "*Book of abstracts*". Nobel day's activities are open and scheduled so that all students and personnel can attend the scientific activities. We warmly welcome you to enjoy all the good science that will be presented at Nobel Day.

The Organizers

Nikolaos Venizelos, Assoc. Professor  
Allan Sirsjö, Professor  
Elisabeth Hultgren Hörnquist, Professor

### Comparison of platelet aggregation during hibernation and non-hibernation in Scandinavian brown bears (*Ursus arctos*)

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**Objective:** Brown bears are free from thrombotic events despite several months of inactivity during hibernation, but information on the coagulation system in bears is scarce. Bears may serve as a comparative model for human thrombosis research, as inactivity is a known risk factor for venous thrombosis in humans. Our objective was to study primary haemostasis by impedance aggregometry in bears inactive during hibernation in winter, compared with their active state in summer.

**Methods and materials:** Whole blood was drawn from 6 wild brown bears (3 females, all bears between 2 and 3 years old) during hibernation in winter and during non-hibernation in summer. We analyzed samples within 3 hours by multiple electrode platelet aggregometry using three different agonists: adenosine diphosphate (ADP, 6.4  $\mu$ M), arachidonic acid (ASPI-test, 0.5 mM) or collagen (1  $\mu$ g/mL). Impedance, and thus aggregation, was quantified as arbitrary aggregation units (AU) after six minutes and area under the curve of arbitrary units (AUC).

**Results:** Platelet aggregation, expressed as AU and AUC, was markedly decreased during hibernation compared to non-hibernation. The differences were statistically significant for all the three different agonists using impedance aggregometry. Platelet count was moderately but statistically significantly reduced during hibernation compared to non-hibernation ( $146 \pm 47$  vs  $228 \pm 39 \times 10^9$  L<sup>-1</sup>,  $P=0.02$ ) but within this range the number of platelets most likely had little or no impact on platelet aggregation.

**Conclusion:** Platelet aggregation in brown bears is reduced during hibernation compared to their active state. This finding may contribute to the ability of bears to endure 6 months of inactivity without thrombotic complications.

If the basis for the specific biochemical mechanisms involved in reduced platelet aggregation in bears can be determined, this might translate into useful applications for human medicine

### Exposure to cigarette smoke induces overexpression of von Hippel-Lindau tumor suppressor in mouse skeletal muscle

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**Objectives:** Cigarette smoke (CS) is a well established risk factor in the development of chronic obstructive pulmonary disease (COPD). COPD is frequently accompanied by systemic manifestations, including reduced exercise tolerance, skeletal muscle wasting and decreased capillarization. In contrast to the obvious adverse effects of CS on pulmonary functions, the extent to which CS exposure contributes to development of the systemic manifestations of COPD remains largely unknown. Therefore this study aims to assess effects of chronic cigarette smoke exposure on skeletal muscle capillarization.

**Methods:** For this purpose, 129/SvJ mice were exposed to CS for 6 months and the expression of putative elements of hypoxia-angiogenic signalling cascade as well as skeletal muscle capillarization were studied. Additionally, functional tests assessing mice exercise tolerance were performed.

**Results:** Compared to the controls, skeletal muscles from CS-exposed mice exhibited significantly enhanced expression of von Hippel-Lindau tumor suppressor (VHL) and prolyl hydroxylase-2 (PHD2). In contrast, hypoxia-inducible factor-1 (HIF1- $\alpha$ ) and vascular endothelial growth factor (VEGF) expression were reduced, despite the increase in HIF1- $\alpha$  mRNA observed in response to CS exposure. Furthermore, decreased skeletal muscle capillarization was observed in CS-exposed mice. Functional test has shown that 6 months of CS exposure significantly reduced mouse exercise tolerance.

**Conclusion:** Taken together, the results implicate the role of CS exposure in the induction of VHL overexpression in skeletal muscles possibly leading to impaired hypoxic signal transduction and angiogenesis within peripheral musculature as well as subsequent exercise tolerance reduction.

#### References:

1. Gosker HR, Langen RCJ, Bracke KR, Joos GF, Brusselle GG, Steele C, et al. Extrapulmonary Manifestations of Chronic Obstructive Pulmonary Disease in a Mouse Model of Chronic Cigarette Smoke Exposure. *Am J Respir Cell Mol Biol.* 2009; 40(6):710-6.
2. Jatta K, Eliason G, Portela-Gomes GM, Grimelius L, Caro O, Nilholm L, et al. Overexpression of von Hippel-Lindau protein in skeletal muscles of patients with chronic obstructive pulmonary disease. *J Clin Pathol.* 2009; 62(1):70-6.

### Multilocus sequence typing of *Propionibacterium acnes* with diverse origin

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**Objectives:** *Propionibacterium acnes* is a Gram-positive, slow growing, anaerobic bacillus, predominantly found on the skin of adults. It is, however, considered an opportunistic pathogen and is mostly associated with acne vulgaris and rarely also severe infections. The aim of the present study was to obtain a well define multilocus sequence typing (MLST) protocol for *P. acnes*, in order to investigate the genetic heterogeneity of *P. acnes* isolates with diverse origin.

**Methods:** The MLST was based on internal fragments of nine housekeeping genes, *lac*, *oxc*, *fba*, *coa*, *zno*, *gms*, *pak*, *cob* and *cel*. All the MLST genes as well as *recA*, *tly* and *Tc12S* were PCR amplified and sequenced in 29 different *P. acnes* isolates with diverse origin including all known subtypes of IA, IB, II and III. Allele profiles for each gene based on the concatenated sequences were performed. To identify different sequence variants phylogenetic analysis was subsequently performed.

**Results:** The MLST analysis identified 23 sequence types within the collection. Furthermore, the phylogenetic trees showed a superior capability to discriminate *P. acnes* isolates when based on the concatenated sequences compared with analysis based on the sequence of each gene individually and also compared with only using *recA*, *tly* and *Tc12S*.

**Conclusion:** The results support the hypothesis that *P. acnes* is more diversified than the four major groups known up till now. Our data suggest that presented MLST-protocol is superior when investigating the heterogeneity of *P. acnes* isolates with diverse origin compared with using *recA*, *tly* and *Tc12S*.

**References:**

1. Perry AL, Lambert PA. (2006). *Propionibacterium acnes*. *Lett Appl Microbiol.* 42:185-8.

## Nitric oxide enhances the pro-inflammatory response in human renal epithelial cells by increasing IL-6 mRNA stability

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**Objective:** Nitric oxide (NO) and IL-6 are produced as part of the host response during urinary tract infection (UTI). IL-6 is believed to promote the inflammatory response but the precise function of NO in UTI remains elusive. The purpose of this study was to investigate whether NO could affect the inflammatory response in human uroepithelial cells by modulating IL-6 production and mRNA stability.

**Methods:** The human renal epithelial cell line A498 was infected with the uropathogenic *E. coli* (UPEC) strain IA2 and/or the NO donor DETA/NO. The IL-6 production and mRNA expression were evaluated by using ELISA and real time RT-PCR, respectively. IL-6 mRNA stability was evaluated by treating the cells with actinomycin D and analyzing the degradation by real time RT-PCR.

**Results:** Stimulation of cells with DETA/NO (1mM) caused a significant ( $p<0.05$ ) increase in IL-6 production. Inactivated DETA/NO did not increase IL-6 production. UPEC-stimulated IL-6 production was further increased (by  $73\pm 23\%$ ,  $p<0.05$ ) in the presence of DETA/NO. The IL-6 mRNA expression increased  $2.1\pm 0.23$  fold in the presence of DETA/NO while the UPEC-induced increase was pronounced ( $17\pm 4.1$  fold). A synergistic effect of DETA/NO on UPEC-induced IL-6 mRNA expression was found ( $33\pm 11$  fold increase). These data were supported by IL-6 mRNA stability studies that demonstrated decreased degradation of IL-6 mRNA in the presence of DETA/NO.

**Conclusions:** The findings of this study suggest that NO may contribute to the host defense in UTI by enhancing the pro-inflammatory IL-6 production from uroepithelial cells by a mechanism involving increased IL-6 mRNA expression and stability.

## Interactions between retinoic acid and statin metabolism. Important role of CYP26B1

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**Objective:** There are several risk factors involve in development of Cardiovascular disease (CVD) among which include cholesterol whose accumulation in vessel walls leads to atherosclerosis progression. Currently antihyperlipidemic drugs such as statins are used to reduce CVD incidence through lowering blood cholesterol levels. Statins have also been shown to have anti-inflammatory effects not related to cholesterol metabolism. Recent studies have shown a relationship between cholesterol and retinoic acid (atRA) whereby cholesterol enhances retinoic acid synthesis while atRA has been reported to influence cholesterol flux. CYP26 is believed to be the most important regulator of atRA catabolism. Three human CYP26 isoforms exist: CYP26A1, CYP26B1 and CYP26C1. Vascular cells and atherosclerotic lesion express mainly CYP26B1. The aim of this study is to investigate the interaction between statins and atRA metabolism.

**Methods:** *Cells culture:* Aortic smooth muscle cells (AOSMC) were treated with different concentrations of statins ( Simvastatin, Rosavastatin, lovastatin, atorvastatin and fluvastatin ) ie 1 and 5 ng/ml for 24h

*QRT-PCR:* For analyzing expression of CYP26B1 and RAR $\beta$ .

*Transient transfection of COS-1 cells:* COS-1cells was transfected with CYP26B1

*HPLC:* Cell-associated [<sup>3</sup>H]atRA was measured using HPLC

**Results:** All tested statins increased the levels of atRA in AOSMC. This was associated with increased levels of atRA inducible genes, CYP26B1 and RAR $\beta$ . Statins also increased the levels of atRA in COS-1 cells over-expressing CYP26B1.

**Conclusion:** Statins induces atRA responsive genes, interfere with atRA catabolism via CYP26B1 and this could explain the effects of statins that are not related to cholesterol metabolism.



### The development and validation of a scale to assess sensory reactions in autism spectrum conditions

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**Objective:** To develop and validate a self assessment scale, tailored for sensory reactions in autism spectrum. A paradoxical lack of reactivity to sensory stimulation concurrently with overreactions to stimuli like sound or touch was recognized in early descriptions of the autism spectrum and has been confirmed in later research<sup>1</sup>.

**Methods:** Content analyzes of autobiographies and interviews. For scale reliability measures Cronbach's alpha will be used and for scale validity measures factor analysis.

**Results:** Text data were analyzed into categories and subcategories: hyper-reactivity, general overload, strong stimuli preferences, hypo-reactivity, inability to direct attention to stimuli, problems with stimuli from body/ movement and dealing with consequences of sensory reactions in daily life. A scale has been developed from the results and will be tested in a group of people with AST and a control group.

**Conclusions:** Our studies indicate that the individual sensory pattern should be assessed. This might be the case in the future since in the forthcoming DSM-V hyper- and hypo-reactivity and unusual sensory interests are proposed as sub-criteria for autism spectrum disorder. The individual sensory pattern is also important for planning of support.

**Reference:**

*I. Leekham, S. R., Nieto, C., Libby, S. J., Wing, L., & Gould, J. (2007). Describing the sensory abnormalities of children and adults with autism. **Journal of Autism and Developmental Disorders**, 37, 894-910*

## Risk of idiopathic dilated cardiomyopathy in 28,000 patients with celiac disease.

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## The role of platelets in inflammation at sites of infection – TLR2/1 mediated platelet adhesion on bacterial peptide-mimetic surfaces.

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**Purpose:** Platelets are nowadays considered to have important functions in inflammatory processes as key players of the innate immune system. Toll like receptors (TLRs), expressed on the platelet surface, recognize pathogen associated molecular patterns (PAMPs) and trigger immune responses. Pathogens are known to adhere to human tissues, e.g. atherosclerotic plaques, and form biofilms that causes a continuous immune response. Pam<sub>3</sub>CSK<sub>4</sub> acts as a ligand for TLR2/1 and thereby activates platelets. This study aims to investigate how adsorbed Pam<sub>3</sub>CSK<sub>4</sub> affects the adhesion and activation of platelets, and to clarify the role of adenine nucleotides in this process. Moreover, to study the release of interleukin-7 upon stimulation with Pam<sub>3</sub>CSK<sub>4</sub>.

**Methods:** To examine activation and granule secretion, Pam<sub>3</sub>CSK<sub>4</sub> was immobilized onto hydrophobic surfaces. Platelets were pre-incubated with a P2X<sub>1</sub>-antagonist, a P2Y<sub>1</sub>-antagonist, a P2Y<sub>12</sub>-antagonist or a phospholipase C- (PLC) inhibitor, before addition to Pam<sub>3</sub>CSK<sub>4</sub> coated surfaces. Cytokine-measurements were performed with hsELISA.

**Results:** A significant decrease in cell number was found when platelets were pre-incubated with MRS2159. Preliminary results indicate that inhibition of both the P2Y<sub>1</sub>-receptor (with MRS2179) and the P2Y<sub>12</sub>-receptor (with Clopidogrel) has an antagonizing effect on cell adhesion and spreading. Inhibition of the PLC signalling pathway did not alter the platelet response. Pam<sub>3</sub>CSK<sub>4</sub>-stimulation time- and dose-dependently increased the secretion of the pro-inflammatory cytokine interleukin-7.

**Conclusion:** TLR2/1-mediated adhesion of platelets is dependent on ATP-release while inhibition of P2Y<sub>1</sub>-receptors enhances platelet P2Y<sub>12</sub>-responses. These results further clarify TLR2/1-induced platelet activation and strengthen the role of the platelets as an active player in sensing bacterial infections.

## The mitochondrial solute carrier *SLC25A43* gene is frequently deleted in HER2-positive breast cancer and influences cell turnover and metabolism

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In breast cancer, overexpression of the human epidermal growth factor receptor 2 (HER2) is a potent activator of several signaling pathways, which increases cell survival and proliferation along with altered metabolism. These modified signaling systems contribute to an aggressive phenotype and poor survival. In an attempt to broaden the perspective, we searched for novel gene copy number variations implicated in HER2-positive breast cancer using whole genome array. One of the most frequent events found was a deletion at Xq24. The deletion covered an area harboring the gene encoding for the mitochondrial transport protein solute carrier (SLC) family 25A member 43. The current knowledge of the *SLC25A43* protein is limited but it has been suggested to be involved in cell metabolism. Further, *SLC25A43* has previously not been studied in relation to breast cancer. Therefore, we continued by confirming loss of heterozygosity within the *SLC25A43* gene in an extended cohort of HER2-positive tumors along with HER2-negative breast cancer, cervical- and lung cancer.

Working with the hypothesis that the *SLC25A43* expression could be affected in HER2-positive breast cancer, we used immunohistochemistry to show that protein expression of *SLC25A43* in fact varies widely between tumors.

Alongside, using *in vitro* models and staining the cells with the fluorochrome PKH67, we show that knockdown of *SLC25A43* by siRNA decreased cell turnover in normal breast epithelial cells MCF10A. In contrast, however, knocking down *SLC25A43* in HER2-positive breast cancer cell line BT-474 resulted in an increased cell proliferation. Furthermore, the gene expression of the metabolic mediators *GLUT1* and *ATP5B* increased after knockdown of *SLC25A43* of in MCF10A.

In conclusion, our findings reveal that *SLC25A43* is frequently deleted in HER2-positive breast cancer, suggesting that it might be an important mechanism in tumorigenesis. This hypothesis is supported by the findings of variation in *SLC25A43* protein expression in tumors along with its influences on cell turnover and metabolic markers.

## From self-centredness to self-agency. The substance of problems and changes described by patients after psychotherapy

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**Objective:** People use psychotherapy in different ways depending on how they perceive their problems and themselves.

**Methods:** Based on descriptions from people with recent experiences of psychotherapy, the aim of this study was to gain a deeper understanding of the participants' problems before psychotherapy and of changes after psychotherapy. Fourteen participants who were selected with variation according to age, gender, marital status, occupation, number of sessions and psychotherapy orientation (CBT and PDT) were interviewed after ending psychotherapy. A qualitative content analysis of the transcribed interviews was performed.

**Results:** Problems before psychotherapy showed an interaction between the categories *Overwhelming Emotions*, *Cognitive Problems* and *Problematic Behaviours*. The theme *Self-centredness* captured the latent content of the descriptions as being a person absorbed by having problems which become a hindrance to take optimal part in one's life context. Descriptions of changes were summarized in the categories *Emotions became balanced*, *Cognitive functions were activated* and *Possibility to influence one's own behaviour*, overlapping the two therapy orientations. The themes *Awareness of self-agency* and *Tools to handle problems* expressed the understanding of the descriptions of changes which made an optimal participation in the person's life context possible.

**Conclusions:** Gaining an awareness of self-agency and an ability to cope with problems were important findings according to the participants' statements in both therapy orientations in this study. Asking the same questions about problems and changes of problems to participants with experiences of different therapy orientations made it possible to gain an understanding of outcomes across the therapy orientations.

## Wwox expression predicts benefit from adjuvant tamoxifen therapy in randomized breast cancer patients.

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**Purpose:** Reduced or absent Wwox expression has recently been associated with tamoxifen resistance in breast cancer and also proposed as a candidate predictive marker for treatment. We aimed to investigate how Wwox expression correlates with outcome of tamoxifen treatment by examining tissue from 912 randomized breast cancer patients.

**Experimental design:** Paraffin embedded tissue from the patient's tumors were arranged on tissue micro array (TMA) and Wwox protein was stained using immunohistochemistry. After microscopic examination of the TMA, the results were analyzed with univariate Cox-regression, Kaplan-Meier survival curve and log-rank test using the Statistical package for the social sciences (SPSS).

**Results:** In the group of patients having a tumor absent of Wwox expression, there was no difference in recurrence-free survival between treated and untreated patients ( $P=0.812$ ). For patients having a tumor with moderate or strong Wwox protein expression, recurrence-free survival was improved in the treated group ( $P=0.001$  and  $P=0.003$  respectively). The test for interaction between Wwox and treatment demonstrated a decreased risk of recurrence for treated patients with a moderate or strong Wwox expression ( $HR=0.31$ , 95 % CI 0.10-0.98 and  $HR=0.28$ , 95 % CI 0.08-0.97, respectively).

**Conclusion:** Our results suggest that patients with high expression of Wwox have more benefit from treatment with tamoxifen.

### References:

1. Abdeen SK, Salah Z, Maly B, Smith Y, Tufail R, Abu-Odeh M, et al. Wwox inactivation enhances mammary tumorigenesis. *Oncogene* 2011, 30(36):3900-3906.

### ***Staphylococcus epidermidis* and *Staphylococcus aureus* induce changes in the expression of ENaC, CFTR, iNOS and mucin in human airway surface epithelial cells**

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**Background:** Air way inflammation is characterized by the imbalance of cytokines and nitric oxide production. The airway epithelium is covered by the airway surface liquid (ASL) and mucus. Presence of healthy air way surface liquid (ASL) depends upon the normal functioning Cl<sup>-</sup> efflux mainly via the cystic fibrosis transmembrane conductance regulator, CFTR, Na<sup>+</sup> influx via the epithelial Na<sup>+</sup> channel, ENaC, and mucin production. Gram positive bacteria *S. aureus* are more prevalent pathogen in the airways of newborns and in patients with compromised airway defenses. Staphylococci (CNS) with *S. epidermidis* as the predominating bacterial species have been recognized as a major cause of nosocomial infections in immunocompromised patients and in neonates.

**Aim:** In view of the interrelationship between CFTR, ENaC, mucins, and iNOS, the aim of the present study was to investigate the effect of the gram positive bacteria *S. aureus* and *S. epidermidis* on these proteins and to see if they are affected in a coordinated manner in a human bronchial epithelial cell line, and to investigate pro inflammatory capacities of these bacteria.

**Methods:** Confluent monolayers of cultured 16HBE were infected with 10<sup>4</sup> cfu/ml for 1h, 4h, 6h, 12h, 24h, and 36h. mRNA and protein expression was analysed by qRT-PCR, and western blotting respectively. Cell culture supernatant was used for cytokines, nitric oxide measurement by ELISA, and Griess assay respectively. Intracellular Ca<sup>2+</sup> concentration was determined by confocal microscopy.

**Results:** mRNA and protein expression level of CFTR was decreased significantly after 36h by *S. epidermidis* and more prominently by *S. aureus*, while *S. epidermidis* caused a significant increase in the mRNA and protein expression of  $\beta$ -, and  $\gamma$ - ENaC. Expression of iNOS was increased significantly but nitric oxide (NO) was not detected in the cell culture supernatant. MUC2, MUC5AC, and MUC5B mRNA expression was also increased by both Staphylococcus. Both *staphylococci* caused a decrease of the intracellular Ca<sup>2+</sup> concentration. We observed decrease in the release of cytokines along with the decrease in the number of viable cells during the course of infection.

**Conclusion:** We conclude that bronchial airway epithelium activity is probably effected in terms of Na<sup>+</sup>, Cl<sup>-</sup> and mucin secretion after infection with *S. aureus* and *S. epidermidis*. Furthermore 10<sup>4</sup> cfu/ml is not high enough concentration to induce production of NO by the healthy bronchial epithelial cells. *S. aureus* is more potent to make release of IL-6, IL-8 and TNF- $\alpha$  by bronchial epithelial cells as compared to *S. epidermidis*.

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## NLR expression in cystic fibrosis airway epithelial cells

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**Objective:** Apart from CFTR mutation, Cystic fibrosis (CF) is also associated with chronic airway infections with a number of bacteria, notably *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Burkholderia cepacia* and *Haemophilus influenzae*. These bacterial invasions usually provoke the innate immune system by host recognition of bacterial pathogens, in parts by membrane-bound receptors and intracellular nucleotide-binding oligomerization domain receptors (NLRs) and may play an important role in the pathophysiology of CF. The NLRs can be distinguished as the “nodosome” and “inflammasome” family. The “nodosome family” i.e., NOD1 and NOD2 mainly sense the bacterial peptidoglycan (PGN)-derived molecules resulting in the induction of inflammatory cytokines, chemokines and other anti-microbial molecules, while NLRP3 and NLRC4 inflammasomes detect and respond to a large range of pathogen-associated molecular patterns (PAMPs), including *S. aureus* LPS, *P. aeruginosa* flagellin, and damage-associated molecular patterns (DAMPs) such as ATP and uric acid crystals.

**Methods:** The aim of the current study was to investigate the expression of NOD1, NOD2, NLRP3 and NLRC4 by reverse transcription polymerase chain reaction in cystic fibrosis (CFBE) and bronchial epithelial cells (16HBE) under basal conditions and as well as after flagellin treatment.

**Results:** Under basal conditions, NOD1 expression was slightly up-regulated and the NOD2 and NLRP3 expression were significantly down-regulated in CFBE cells as compared to wild-type 16HBE cells. Flagellin caused a time-dependent decrease in the expression of NOD1, NOD2, and NLRP3 in CFBE cells, but a tendency to an increase in NLRC4 expression.

**Conclusion:** The results point to a compromised innate immune system in cystic fibrosis airway epithelial cells. The fact that activation of one NLR can influence the existence of others, and thereby making way for bacteria sensed by other NLR to colonize, is of greatest importance and might explain the succession of bacterial infections seen in CF.

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## Decreased density of muscarinic acetylcholine receptors in fibroblasts from children with Attention Deficit/Hyperactivity Disorder (ADHD)

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**Background:** Attention Deficit/Hyperactivity Disorder (ADHD) is a neurobehavioral disorder affecting both children and adults worldwide. It is believed that the neurotransmitters, dopamine and norepinephrine are involved in the pathophysiology of ADHD. Moreover, it is known that cholinergic activity can modulate dopaminergic activity in the brain. The aim of this study was to measure the density and affinity of muscarinic acetylcholine receptors (mAChRs) in children with ADHD.

**Methods:** Fibroblast cell homogenates from 11 boys with ADHD, fulfilling the DSM-IV diagnostic criteria and from 9 matching controls were used in the study. The maximal binding capacity ( $B_{\max}$ ) and the equilibrium dissociation constant ( $K_D$ ) of mAChRs were determined by radioligand binding assay, using the mAChR antagonist <sup>3</sup>H-QNB. Due to non-normally distribution of the calculated data, three outliers were identified by the MAD<sub>E</sub> method (two in the ADHD group, both with a non-hereditary ADHD and one in the comparison group), and were therefore excluded from the statistical analyses (Student's unpaired t-test).

**Results:** A significantly lower  $B_{\max}$  for the binding of the muscarinic antagonist <sup>3</sup>H-QNB was observed in the fibroblasts from the children with ADHD when compared to controls ( $p=0.01$ ), but the  $K_D$  did not differ between the two groups ( $p=0.40$ ).

**Conclusions:** The present results indicate a reduced density of mAChRs, in fibroblasts from children with ADHD, which might be a contributing factor to the disorder. However, further studies are needed to confirm these observations.

## Altered tryptophan and alanine transport in fibroblasts from boys with Attention Deficit/Hyperactivity Disorder (ADHD): an in vitro study

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**Background:** The catecholaminergic and serotonergic neurotransmitter systems are implicated in the pathophysiology of attention-deficit/hyperactivity disorder (ADHD). The amino acid tyrosine is the precursor for synthesis of the catecholamines dopamine and norepinephrine, while tryptophan is the precursor of serotonin. A disturbed transport of tyrosine, as well as other amino acids, has been found in a number of other psychiatric disorders, such as schizophrenia, bipolar disorder and autism, when using the fibroblast cell model. Hence, the aim of this study was to explore whether children with ADHD may have disturbed amino acid transport.

**Methods:** Fibroblast cells were cultured from skin biopsies obtained from 14 boys diagnosed with ADHD and from 13 matching boys without a diagnosis of a developmental disorder. Transport of the amino acids tyrosine, tryptophan and alanine across the cell membrane was measured by the cluster tray method. The kinetic parameters, maximal transport capacity  $V_{\max}$  and affinity constant  $K_m$  were determined. Any difference between the two groups was analyzed by Student's unpaired t-test or the Mann Whitney U test.

**Results:** The ADHD group had significantly decreased  $V_{\max}$  ( $p = 0.039$ ) and  $K_m$  (increased affinity) ( $p = 0.010$ ) of tryptophan transport in comparison to controls. They also had a significantly higher  $V_{\max}$  of alanine transport ( $p = 0.031$ ), but the  $K_m$  of alanine transport did not differ significantly. There were no significant differences in any of the kinetic parameters regarding tyrosine transport in fibroblasts for the ADHD group.

**Conclusions:** Tryptophan uses the same transport systems in both fibroblasts and at the blood brain barrier (BBB). Hence, a decreased transport capacity of tryptophan implies that less tryptophan is being transported across the BBB in the ADHD group. This could lead to deficient serotonin access in the brain that might cause disturbances in both the serotonergic and the catecholaminergic neurotransmitter systems, since these systems are highly interconnected. The physiological importance of an elevated transport capacity of alanine to the brain is not known to date.

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### Wound healing

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#### **Objective:**

The aim was investigate how keratinocytes regulate fibroblast genes involved in extracellular matrix remodelling, in a more *in vivo*-like condition. We used a keratinocyte-fibroblast organotypic skin culture model to elucidate possible anti-fibrotic effect of keratinocytes during epidermal generation.

#### **Methods**

The organotypic skin cultures were grown for up to 7 days. To study how epidermal regeneration progressed, the organotypic cultures were snap-frozen and sectioned for morphology as well as staining for epidermal differential markers keratin 10, keratin 14, involucrin and loricrin. Expression of 12 genes important for the modulation of the extracellular matrix were analysed with real-time PCR.

#### **Result**

The organotypic skin culture formed a skin equivalent within 7 days. The stratified keratinocyte layer expressed the late epidermal differentiation markers keratin 10, involucrin, and loricrin. The basal layer expressed the keratin 14 as expected.

A set of twelve experiments were performed analysing fibroblast gene expression. 11 out of 13 genes were significantly regulated by keratinocytes, either in the presence or absence of TGF.

#### **Conclusion:**

Our results demonstrate mechanisms by which keratinocytes affect fibroblasts to act catabolically on the extracellular matrix in the reepithelialisation process. This adds understanding to the observations that reepithelialisation and epithelial transplantation reduces scar formation.

#### **References:**

1. Koskela A, Engström K, Hakelius M, Nowinski D, Ivarsson M. Regulation of fibroblast gene expression by keratinocytes in organotypic skin culture provides possible mechanisms for the antifibrotic effect of reepithelialization. *Wound Repair Regen.* 2010 Sep-Oct; 18 (5):452-9.

**Collagenous colitis patients demonstrate a Th1/CTL-associated gene expression profile with increased frequencies of Ki67<sup>+</sup> proliferating and CD45RO<sup>+</sup> activated/memory CD8<sup>+</sup> and CD4<sup>+</sup>8<sup>+</sup> mucosal T cells.**

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**Objective:** Microscopic colitis (MC), comprising collagenous colitis (CC) and lymphocytic colitis (LC), is a common cause of chronic diarrhoea. Our aim is to characterize the intestinal mucosal lymphocytes in CC patients.

**Methods:** Lamina propria lymphocytes (LPLs) and intraepithelial lymphocytes (IELs) isolated from mucosal biopsies from CC patients (n=3-7) and 3-13 healthy individuals were phenotypically characterized by flow cytometry. Expression of different genes involved in T helper (Th) cell differentiation was investigated by qRT-PCR on mucosal biopsies from 7 CC, 3 ulcerative colitis (UC), 19 diarrhoea patients and 13 healthy controls.

**Results:** The frequencies of CD8<sup>+</sup> and CD4<sup>+</sup>8<sup>+</sup> double positive (DP) LPLs as well as IELs were increased in CC patients compared to controls. In addition, the frequency of proliferating Ki67<sup>+</sup>CD8<sup>+</sup> as well as activated/memory CD45RO<sup>+</sup> CD8<sup>+</sup> and DP LPL and IEL T cells were increased in CC patients. In contrast, the frequency of CD4<sup>+</sup> LPLs was decreased. Still the CD4<sup>+</sup> population consisted of higher frequencies of CD45RO<sup>+</sup> as well as Ki67<sup>+</sup> cells. Likewise to CD4<sup>+</sup> LPLs, CD19<sup>+</sup> B and plasma cells (CD38<sup>++</sup>CD138<sup>+</sup>) in the LP of CC patients were decreased, but the frequency of proliferating CD19<sup>+</sup>Ki67<sup>+</sup> cells in CC patients was not different from healthy controls.

Quantitative RT-PCR on mucosal biopsies revealed increased expression of genes encoding T-bet, IFN- $\gamma$  and IL-12, involved in maturation of Th1 and CD8<sup>+</sup> cytotoxic T lymphocytes (CTLs) in CC patients compared to healthy controls. In contrast to UC patients, there was no increased expression of genes involved in Th17 differentiation, i.e. IL-6, IL-17, ROR- $\gamma$ , or IL-23.

**Conclusion:** CC patients have higher frequencies of CD8<sup>+</sup> and CD8<sup>+</sup>4<sup>+</sup>, Ki67<sup>+</sup> proliferating and CD45RO<sup>+</sup> activated/memory T cells in the intestinal mucosa. In addition CC patients demonstrate increased expression of a Th1/CTL-associated gene profile.

### Important processes in treatment for eating disorders – adolescent's experiences

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#### **Objective:**

The aim of the study is to examine how adolescents who suffered from eating disorders perceive their received treatment and which treatment processes – facilitating as well as complicating – concerning recovery they emphasises in their narratives.

#### **Methods:**

In collaboration with four Swedish units specialized on treatment for eating disorders we intend to recruit and interview 20 former patients in order to gather narratives about their treatment. Participants should have been between 13 and 19 years old when treated and without a diagnosis when treatment ended. Treatment should have ended for at least six months and not longer than two years ago. We intend to select the sample for a variety of age, sex, form of treatment etc. Interpretation will be carried out using Max van Manen's (1997) hermeneutic-phenomenological method, according to which people's lived experience is the focus.

#### **Results:**

As this is an ongoing study, there are no results to present.

#### **Conclusions:**

Since there are no results to present and therefore not possible to draw any conclusions I would like to mention something about expected clinical implications. When it comes to eating disorders a decision on treatment should be based on individual aspects such as age, family situation, duration of illness etc. Knowing which treatment processes former patients perceive as important can be helpful when it comes to decide which treatment interventions to use for which patient and what to focus on in an ongoing treatment.

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## ***P. gingivalis*-induced aggregation and ROS production in whole blood is dependent on gingipains**

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**Objective:** A large body of data accumulated over the past several years suggests that the periodontal pathogen *Porphyromonas gingivalis* is associated with cardiovascular disease. We have previously demonstrated that *P. gingivalis* induces aggregation and reactive oxygen species (ROS) production in whole blood, and that the anti-inflammatory mediator lipoxin A<sub>4</sub> inhibits these responses by modulating platelet-neutrophil interaction through a down-regulation of the surface expression of CD11b/CD18 on neutrophils (1). Furthermore, *P. gingivalis*, unlike other periodontopathogenic bacteria, has been shown to trigger platelet aggregation, mainly through the interaction between bacterial gingipains and protease-activating receptors (PARs) on the platelets. Since platelet aggregation precedes thromboembolic events, this is an important pathogenic feature of the bacterium.

**Methods:** In order to investigate the effect of gingipains on *P. gingivalis*-induced cell activation in whole blood, platelet/leukocyte aggregation and ROS production was examined by lumiaggregometry.

**Results:** This study shows that leupeptin, a protease inhibitor of gingipains, inhibits *P. gingivalis*-induced aggregation and ROS production in whole blood. Supernatants of bacteria suspensions induced no ROS-production, but an aggregatory response that was also inhibited by leupeptin.

**Conclusions:** *P. gingivalis*-induced aggregation and ROS production in whole blood is mainly dependent on gingipains. However, since bacterial supernatants (containing soluble gingipains) stimulate only aggregation, this suggests that a gingipain/PAR-mediated mechanism in combination with phagocytosis of whole bacterium is a prerequisite for inducing a respiratory burst and an inflammatory response. These findings may contribute to new strategies in the prevention and treatment of periodontitis-induced inflammatory disorders, such as atherosclerosis.

### **References:**

1. Emma Börgeson, Johanna Lönn, Ida Bergström, Veronika Patcha Brodin, Sofia Ramström, Fariba Nayeri, Eva Särndahl, and Torbjörn Bengtsson. (2011). Lipoxin A<sub>4</sub> Inhibits *Porphyromonas gingivalis*-Induced Aggregation and Reactive Oxygen Species Production by Modulating Neutrophil-Platelet Interaction and CD11b Expression. *Infect Immun.* 2011 Apr;79(4):1489-97.

## Investigation of UVA/Riboflavin Photosensitization as an Infectious Therapy

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**Objective:** To evaluate the efficacy of riboflavin photoactivation by ultraviolet light A (UVA) as a treatment for corneal infections.

Riboflavin photosensitization is currently in clinical practice, through the procedure Collagen Crosslinking (CXL), for treatment of corneal ectasia. The same mechanism is also utilized in transfusion medicine to minimize the risk for an associated infectious transmission by elimination of possible contaminants<sup>1</sup>. Several case reports have reported management of recalcitrant corneal infections by applying CXL<sup>2</sup>.

**Methods:** The clinical response was assessed in two studies, one retrospective case series and a prospective pilot study. In the latter study CXL was evaluated as primary therapy for bacterial keratitis. Antimicrobial efficacy of riboflavin excitation by ultraviolet dosages and the wavelength implemented clinically was investigated in two articles. Eradication experiments comprised three different bacterial strains in fluid solutions, commonly isolated as pathogens in corneal infections. Effects of riboflavin and UV were independently examined as well as the two factors in combination. Finally, growth inhibition of the protozoa, *Acanthamoeba castellanii*, was investigated in a similar setup.

**Results:** In clinical keratitis a reduced inflammation, retardation of corneal melting, and initiation of epithelial healing was observed shortly after the photoactivation treatment. In the pilot study, 14 out of 16 patients could be managed without antibiotics. Antimicrobial evaluation showed an extensive eradication of all tested bacteria as a consequence of the interaction between UVA and riboflavin. Regarding *Acanthamoeba* growth inhibition could be induced by ultraviolet light solitarily, with no further effect by addition of riboflavin.

### References:

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## Prevalence of HTLV 1/2-infection among injecting Drug Users in Stockholm, Sweden, 2007-2008

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**Background:** Human T-cell Lymphotropic Virus type 2 (HTLV-2) infection has been demonstrated among some native Indian population in North and South America, and in rare cases in Africa (ref). It is rare in the general population in Europe. However, high prevalence rates have been found among intravenous drug users (IVDU) in both the US and several European countries (ref). In studies in early 1990s among IVDUs in Stockholm, HTLV-2 prevalence rates of 2,3% and 3,2 % were found, while HTLV-1 was rare (ref). We have now, in 2007-2008, performed a new study in a similar population in Stockholm, Sweden.

**Objective:** To study if HTLV-2 is still relevant among IVDUs in Stockholm. Of so, to see if risk factors are similar as in 1994.

**Methods:** Serum samples from IVDUs in Stockholm, during the years 2007-2008 (n=1079) were collected and investigated for HTLV-1/2 antibodies. The samples were also analysed for Hepatitis B surface antigen (HbsAg) and core antibodies (anti-HBc), Hepatitis C (HCV), antibodies and HIV antigen/antibodies. Data regarding age, sex, current drug use, country of origin, detention and homelessness were collected. The data were compared to the data from the early 1990s.

**Results:** Among 1079 investigated subjects, 35 were found to be positive for antibodies against HTLV-1 and/or HTLV-2, giving an overall HTLV-prevalence of 3,2%. Of these, two had antibodies to HTLV-1, 28 to HTLV-2 and 5 had non-typeable antibodies to HTLV. All HTLV-positive individuals were also HCV antibody positive, 26% were HIV positive and 77% were positive to anti-HBc. i.e. The HTLV-positive individuals were 10 years older than the HTLV negative group (mean age). The majority of the HTLV positive individuals had Swedish origin, and they were all active drug users, 68% using amphetamine.

**Conclusion:** The prevalence among IVDUs in Stockholm, Sweden 2007-2008 is 3,2%, which is similar to the prevalence in this group in the early 1990s. The HTLV positive IVDUs are about ten years older than the HTLV negative IVDUs (mean age). 100% of the HTLV positive in this group are positive to HCV antibodies, 26% are positive to HIV antigen/antibodies.



## **New high-sensitivity troponin I and T assays in stable coronary artery disease. Initial results of biological and analytic variation**

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### **Objective**

Determination of cardiac troponin (cTn) is important for the diagnosis of acute myocardial infarction (AMI) and stratification of the risk for future adverse cardiac events. Guidelines advocate serial testing of cTn and at least one sample above the 99th percentile of normal followed by a rising or falling pattern and a 20% change from baseline as an indication for myocardial injury. Recently, high-sensitive (hs) cTn assays have been introduced, allowing a more reliable detection of cTn below the 99th percentile. In order to identify better biomarkers and because of lack of previous studies our aim was to determine long-time and circadian biological variation of cTn in patients with stable coronary disease.

### **Methods**

Twenty-three patients participating in the clinical “PUMI” study were included. All patients were suspected of stable angina pectoris and referred for coronary angiography. One day prior to coronary angiography the patients were admitted to hospital, a standard ECG was taken and continuous multilead ST-segment monitoring was performed for 24 hours. Following an interview about chest pain, blood samples were taken and the blood pressure was measured repeatedly every four hours for a total of six times. The initial blood sample was taken between 08.00 and 10.00 am and all samples were frozen and analysed later with hs-cTnI and hs-cTnT assays.

### **Results**

Preliminary study results are expected for presentation on December 8, 2011.

**Predictors of time to relapse/recurrence after electroconvulsive therapy (ECT) in patients with major depressive disorder – a population based cohort study.**

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**Objective:** The aim of the study is to define predictors of relapse/recurrence after electroconvulsive therapy, ECT, for patients with major depressive disorder.

**Methods:** A study of all patients (n=486) treated by means of ECT for major depressive disorder was performed. The data derive from a Regional Quality register in Sweden. Psychiatric hospitalisation or suicide were used as markers for relapse/recurrence.

**Results:** The relapse/recurrence rate within one year after ECT was 34%. Factors associated with increased risk of relapse/recurrence included co morbid substance dependence and treatment with benzodiazepines or anti-psychotics during the follow up period.

**Conclusions:** Within the first years after ECT relapses/recurrences leading to hospitalisation or suicide are common. Treatment with lithium might be beneficial while benzodiazepines, antipsychotics or continuation ECT do not seem to significantly reduce the risk of relapse/recurrence.

**Reference**

1. Axel Nordenskjöld, Lars von Knorring, and Ingemar Engström, "Predictors of Time to Relapse/Recurrence after Electroconvulsive Therapy in Patients with Major Depressive Disorder: A Population-Based Cohort Study," *Depression Research and Treatment*, vol. 2011, Article ID 470985, 7 pages, 2011.  
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## The effect of NO-donors on chloride efflux and intracellular $\text{Ca}^{2+}$ concentration in cystic fibrosis airway epithelial cells

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Since previous studies showed that the endogenous bronchodilator, S-nitrosglutathione (GSNO), causes a marked increase in CFTR-mediated chloride ( $\text{Cl}^-$ ) efflux and improves the trafficking of CFTR to the plasma membrane, and that also the NO-donor GEA3162 had a similar, but smaller, effect on  $\text{Cl}^-$  efflux, it was investigated whether the NO-donor properties of GSNO were relevant for its effect on  $\text{Cl}^-$  efflux from airway epithelial cells. Hence, the effect of a number of other NO-donors (SNP, SNAP, DETA-NO, and DEA-NONOate) on  $\text{Cl}^-$  efflux from CFBE ( $\Delta\text{F508}/\Delta\text{F508}$ -CFTR) airway epithelial cells was tested.  $\text{Cl}^-$  efflux was determined using the fluorescent MQAE-technique. Possible changes in the intracellular  $\text{Ca}^{2+}$  concentration were tested by the fluorescent fluo-4 method in a confocal microscope system. Like GSNO, SNP had no immediate effect on  $\text{Cl}^-$  efflux, but after 4h incubation with the NO-donor, an increased  $\text{Cl}^-$  efflux was found (in the order SNAP > DETA-NO > DEA- NONOate > SNP). The effect of DEA-NONOate on  $\text{Cl}^-$  efflux was not significant, and the compound may have (unspecific) deleterious effects on the CFBE cells. None of the compounds that had a significant effect on  $\text{Cl}^-$  efflux caused significant changes in the intracellular  $\text{Ca}^{2+}$  concentration. Incubation of CFBE cells with SNP caused a two-fold increase of CFTR mRNA. Furthermore SNAP and DETA-NO (100 $\mu\text{M}$ ) caused a significant increase in CFTR mRNA expression in the presence of L-cysteine. Incubation with NO-donors decreased the expression of the  $\alpha$ - and  $\beta$ -subunits of ENaC in CFBE. In conclusion, the effect of GSNO on  $\text{Cl}^-$  efflux is, at least in part, due to its properties as an NO-donor, and the effect is likely to be mediated by CFTR, not by  $\text{Ca}^{2+}$ -activated  $\text{Cl}^-$  channels.

**Keywords:** Nitric oxide donors, cystic fibrosis, airway epithelium, CFTR, ENaC, calcium.

## Platelets regulate the expression of fibroblast genes involved in extracellular matrix turnover, reepithelialisation and myofibroblast differentiation in a three-dimensional *in vitro* model

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**Objective:** Platelet-rich-plasma is a promising treatment for impaired healing conditions such as chronic wounds but clinical trials give contradicting results and the underlying molecular processes are poorly described. This study aims to investigate the effects of isolated platelets on the expression of fibroblast genes involved in extracellular matrix (ECM) turnover, epithelialisation and myofibroblast differentiation.

**Methods:** Human skin fibroblasts were cultured in a three-dimensional collagen gel, separated from thrombin- or collagen-activated platelets by a semi-permeable membrane. Fibroblast mRNA expression of 14 genes coding for ECM structural proteins, proteases, protease inhibitors as well as keratinocytes growth factor (KGF) and  $\alpha$ -smooth muscle actin ( $\alpha$ SMA) was analysed by real-time PCR. The level of transforming growth factor  $\beta$ 1 (TGF- $\beta$ 1) in the culture medium were analysed with ELISA.

**Results:** The amount of released TGF- $\beta$ 1 was dependent on platelet number and increased with incubation time. Platelets had significant effects on various ECM regulating genes but no specific effect with respect to fibroplasia could be discerned. KGF was significantly upregulated in early culture while the myofibroblast-specific marker  $\alpha$ SMA was differently regulated over time.

**Conclusion:** Although we found that platelets have significant effects on various genes crucial for ECM homeostasis, no specific net effect on fibroplasia could be discerned.

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## Association of Genetic Variants in the NLRP3 region with Expression of Proximal Genes and Myocardial Infarction

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**Objective:** Vascular inflammation is a key component for the manifestation and pathogenesis of atherosclerosis that subsequently leads to MI. Studies have shown the association of NLRP3 with various inflammatory diseases and vascular inflammation. A recent study has linked the SNPs from the regulatory region of NLRP3 to an inflammatory disease<sup>1</sup>. We investigated tissue specific association between these SNPs and expression level of all genes within 200kb search window surrounding the SNPs. We also investigated the association of these SNPs to Myocardial Infarction (MI).

**Methods:** We investigated 4 SNPs, rs4353135, rs4266924, rs6672995, and rs10733113 previously found to be associated with inflammatory disease<sup>1</sup>. eQTL analysis was performed in liver, aorta, carotid atherosclerotic plaque, mammary artery, and PBMC<sup>2</sup>. The genotyping of MI patients (n=550) and controls (n= 1035) was done using Taqman SNP assays.

**Results:** Our study demonstrated that rs4353135 and rs4266924 were significantly associated with mRNA levels of Zinc finger protein namely ZNF496 rather than NLRP3. On the other hand, rs6672995 and 10733113 were significantly associated with expression of both NLRP3 and ZNF496. The association between the SNPs and the levels of ZNF496 and NLRP3 were mainly found in plaque and PBMC. Only rs4353135 showed association to MI (p=0.06). When differentiated the cohort based on gender, the association was significant in males (p=0.004) and not in females. No significant association was found for the other SNPs towards MI.

**Conclusion:** In contrast to the earlier findings, our study shows the association of the SNPs with the expression of ZNF496 rather than NLRP3. The association of the variants with the expression of genes is tissue dependent. The association of the SNPs for the risk of developing MI requires to be confirmed in larger cohort studies. Overall, our findings suggest a potential role of ZNF496 in the pathophysiology of cardiovascular disease.

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## ***Propionibacterium acnes* Activates Caspase-1 in Human Neutrophils**

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*Propionibacterium acnes* is a Gram-positive, slow growing, anaerobic bacillus, predominantly found as a commensal on the skin and mucous membranes of adults. It is, however, considered an opportunistic pathogen; mostly associated with acne vulgaris but rarely also with severe infections such as infective endocarditis, prosthetic joint infections and deep sternal wound infections following cardiothoracic surgery. In addition, *P. acnes* has recently been found in high frequency in prostate tissue from patients with prostatitis and prostate cancer. The NOD-like receptors (NLR) act as intracellular sensors of microbial components, and a number of various bacteria have been found to induce assembling and activation of NLR-inflammasomes; leading to a pro-inflammatory response. The present study investigated if *P. acnes* activates inflammasomes.

*P. acnes* isolates (n=29) with diverse origin were used as stimuli for peripheral blood cells obtained from blood donors. The activity of inflammasomes was determined by measuring caspase-1 by flow cytometry.

A significant amount of caspase-1 was found in neutrophils upon *P. acnes* stimulation, whereas only a modest activation was seen in monocytes. The response among different blood donors varied significantly, almost 5-fold. In addition, *P. acnes* of various origins showed considerable variation, however, the commensal isolates showed a stronger response compared with the invasive.

In conclusion, although regarded as a harmless commensal of the skin, *P. acnes* strongly activates the inflammasome of human peripheral neutrophils.

## Psychiatric Intensive Care

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**Objective:** The concept of psychiatric intensive care units (PICU) in Sweden is not clearly defined, however it is the most specialized form of psychiatric care. Few international studies describe the caring aspect of the PICU based specifically on caregivers' experiences.

**AIM:** The aim of this study is to describe what characterises the core of a PICU in Sweden and to describe the care activities provided for patients admitted to the PICU.

**Methods:** Critical incident technique was used as the overall research method. Eighteen caregivers at a PICU participated in the study by completing a semi-structured questionnaire. In-depth interviews with three nurses and two assistant nurses also constitute the data.

**Results:** An analysis of the content identified four categories that characterize the core of PICU: dramatic admission, protests and refusal of treatment, escalating behaviours and temporarily coercive measure. Care activities for PICU were also analysed and identified as controlling – establishing boundaries, protecting – warding off and supporting – giving intensive assistance and structuring the environment.

**Conclusions:** We interpret that psychiatric intensive care units could be considered as a specific level of care with short length of stays and rapid improvement. In the PICU, there are possibilities for the patient to be intensively cared for in a safe manner due to the specific environment and closeness to a caregiver

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## Autoantibodies to Transglutaminase 6 in children with cerebral palsy

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### Objectives

In a previous study of children with cerebral palsy (CP) we found elevated levels of celiac disease (CD)-related markers, mainly IgG antibodies to TG2 and gliadin.

The majority of these children did not have enteropathy based on routine histological or extended immunohistochemical analysis of small bowel biopsies. Recent studies have identified transglutaminase 6 (TG6) as the preferential target of the immune response in adults with cerebellar ataxia as a consequence of gluten sensitivity, independent of intestinal involvement. The aim of this study was to investigate whether children with CP have circulating antibodies against TG6 in the absence of evidence of classical CD.

### Methods

Sera from 96 children with CP age range 18 months to 24 years were available for analysis. None of these children had any co-morbidity for CD such as type 1 diabetes mellitus or dermatitis herpetiformis. 36 subjects age range 2-18 years were used as controls. Sera were analysed for IgA and IgG class antibodies to TG6 using the established ELISA.

### Results

Twelve children tested positive for TG6 antibodies (13%). 1 control subject tested marginally positive for anti-TG6 IgG and one for anti-TG6 IgA. In the subgroup of CP patients with tetraplegia the prevalence of TG6 antibodies was significant (35%).

### Conclusion

In the subgroup of children with the most severe form of CP we found a significant prevalence of anti-TG6 antibodies. The aetiology of this remains unclear. One can speculate that autoimmunity against TG6 may result from early brain damage and associated inflammation

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## ERG Rearrangement Metastasis Patterns in Locally Advanced Prostate Cancer

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**Objectives:** To investigate multifocal prostate cancer (PCa) to determine its predilection for metastasis, using *ERG* rearrangement as marker of clonality. A hallmark of PCa is that distinct tumor foci may arise independently, which has important biological and clinical implications. Recent studies characterizing *ERG* rearranged PCa possessing intrafocal homogeneity but interfocal heterogeneity support this hypothesis.

**Methods:** We studied 26 patients who underwent prostatectomy and lymphadenectomy with at least two distinct PCa foci and one lymph node (LN) metastasis. Each focus was assessed for size, Gleason score, *ERG* rearrangement, and TMPRSS2-*ERG* transcript.

**Results:** Fifteen of 26 cases exhibited interfocal homogeneity with regard to *ERG* rearrangement (ie, presence vs absence of *ERG* rearrangement). *ERG* rearrangement was present in all foci for six and absent in all foci for nine cases. Two cases revealed interfocal heterogeneity with regard to rearrangement mechanism (ie, rearrangement through insertion or deletion). Eight of 26 cases revealed interfocal heterogeneity with regard to rearrangement status. In all cases with at least one *ERG* rearranged focus, we found the corresponding LN metastasis harboring an *ERG* rearrangement. Interestingly, in a subset of cases the rearrangement status in the LN did not correspond to size or Gleason score. All but two *ERG* rearranged foci had detectable TMPRSS2-*ERG* transcript levels.

**Conclusions:** When multifocal PCa demonstrates both *ERG*-positive and *ERG*-negative foci, the positive foci have a greater predilection for metastasis. Larger studies are needed to confirm the potential additional risk an *ERG* rearranged focus confers on the likelihood of disease progression.

## The role of NLRP3 and CARD8 in the regulation of IL-1 $\beta$ in Vascular Smooth Muscle cells

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### Objective

Chronic inflammation of the arterial wall is the underlying cause of atherosclerosis thus implicating the immune system to play an integral role in atherogenesis, although the initiation mechanisms that underpins atherogenic inflammation remains to be elucidated. IL-1 $\beta$ , an important mediator of cellular differentiation, proliferation and apoptosis is known to be activated from its inactive form by the inflammasomes. Inflammasome activities are implicated to depend on a plethora of moieties including NLRP3 and CARD8 which have been reported to be associated with several inflammatory diseases. The aim of this study was to examine the role of NLRP3 inflammasome and CARD8 protein in the regulation of TNF- $\alpha$  induced IL-1 $\beta$  in Human Aorta Smooth Muscle Cells (AOSMC).

### Methods and Results

In this study, AOSMC were transfected with SiRNA targeting the NLRP3 and CARD8 genes, followed by TNF- $\alpha$  treatment. We found that TNF- $\alpha$  induces IL-1 $\beta$ , IL-1Ra and NLRP3 genes but not CARD8. The knock down of NLRP3 gene significantly decreases IL-1 $\beta$  and increases IL-1Ra expression and release while CARD8 knock down increases IL-1 $\beta$  and IL-1Ra mRNA expressions but decreases IL-1 $\beta$  protein release.

### Conclusion

Our results suggest that NLRP3 and CARD8 interplay in IL-1 $\beta$  expression and release in AOSMC and could possibly be potential future targets for treatment of atherosclerosis and other inflammatory diseases.

## Reciprocal struggle in person transfer tasks - Caregivers' experiences in dementia care

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**Objective:** Dementia is one of the main conditions to be associated with a severe activity limitation among older people and one of the main reasons older people access special care units. This presentation will be presenting caregivers experiences' of person transfer situations involving people with dementia.

**Method:** Qualitative focus group interviews were conducted. Ten caregivers, five in each focus group participated. Data were extracted in phrases and sentences using content analysis.

**Result:** One theme was condensed: 'Reciprocal struggle in the person transfer task'. Three sub-themes emerged: 'Communication strategies', 'Environmental factors', and 'The goal may be inaccessible'.

**Conclusion:** Person transfer situations involving people with dementia can fluctuate, therefore the ongoing challenge will be to ensure a dynamic approach based on the person with dementia's different needs at different times. Behavioral markers hold for identification of antecedents and consequences and measures need to be developed in domains including social interaction, psychomotor aspects of function and environmental factors. These measures would allow us to link better the antecedents to the consequences of the behavior and by those tailoring interventions to facilitate person transfer situations involving people with dementia. .

## Paternalism, self-determination and reciprocity. Staff ethics in the encounter with patients in psychiatric inpatient care

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There are many ways staff may create encounters with patients, but in medical ethics there are three basic perspectives which have been dominant; paternalism, self-determination and reciprocity. The aim of this study is to illuminate statements made by staff in relation to the three basic perspectives in medical ethics.

Thirteen psychiatric clinics participated from child- and adolescent psychiatry and adult psychiatry and 177 persons wrote an ethical diary during one week. The analysis was made in NVivo 8 with theory-guided content analysis. The statements were categorized by placing them in a theme within one of the perspectives.

The final themes in paternalism were 1) to maintain and restore the health of the patient, 2) to give good care 3) to take responsibility. The themes in self-determination were 1) the patient's right to autonomy and to be informed, 2) respecting the patient's integrity and 3) human rights. The themes in reciprocity were 1) to involve patients in the formulation and implementation of their care and 2) building trust between staff and the patient. There were also encounters where these ethical ideals were not respected by staff. There were statements about assaults against patients, lying to patients, and objectification of patients.

Despite an awareness of patient's rights, paternalism appeared to be the dominant perspective in these clinics. There were only a few statements about reciprocity. Staff could fairly routinely use subtle coercion and thereby reduce the patient's right to autonomy. These results have proved useful in ethical discussions with staff.

## Effects and experiences of warm versus cold skin disinfection

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**Objective:** In clinical praxis, and during surgical skin preparation, patients often comment on the cold experience of the skin preparation. This pilot study aimed to compare warm versus cold skin disinfection with a chlorhexidine solution on bacterial growth, skin temperature and the experience of the disinfection.

**Methods:** A random experimental study with crossover design including ten healthy volunteers. Intervention consisted of preheated skin disinfection (38°C). Controlgroup received cold (20°, roomtemperature) skin disinfection. Bacterial samples were taken with a rayon swab (Copan Italia SpA). Skin temperature was measured using a digital thermometer (Exacon A/S, Denmark). To measure experience, a 10cm semantic differential scale was used comprising anchor words from negative to positive ('0' to '10'). Statistics; Paired sign-test was used for analysing skin temperature. Wilcoxon signed-ranks test for experiences.

**Results:** One of ten bacterial samples showed growth in both groups. No significant difference in skin temperature between the groups. However there was a greater difference in skin temperature (baseline) when using 20°C skin disinfection,  $p=0,021$ . The experience of 38°C is more pleasant compared with 20°C skin disinfection,  $p=0,001$ .

**Conclusions:** This pilot study support that preheated skin disinfection is more pleasant for awake persons. This study will be the base for a larger random clinical trial with similar aim.

## The transcription factor zinc finger protein 496 is required for human umbilical vein endothelial cell function *in vitro*

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**Objective:** Zinc finger protein 496 (Znf496) is a co-transcription factor which belongs to the classic zinc finger protein family, and is located at chromosome1q44. This region contains various genes associated with Crohn's disease and familial cold urticaria. In general, Znf496 contains a SCAN domain, a KRAB domain and four repeated C2H2 Zinc fingers. However, the exact function of Znf496 is still unknown. Previously, we showed that the Znf496 mRNA expression level is associated with myocardial infarction (MI) and is expressed in endothelial cells. Thus, in this presentation, the data from Znf496 knock-down (Znf496KD) human umbilical vein endothelial cells (HUVECs) will be presenting, in which HUVECs with Znf496KD or without (controls) was investigated. Data from cell morphogenesis, proliferation, migration and tube formation will also be presented.

**Method:** In the present study, Znf496 was knocked-down in HUVECs with siRNA followed by the investigation of cell behaviors like morphogenesis, proliferation, migration and tube formation. Data from Znf496KD group and controls was recorded by photos and analyzed difference with two tailed t test.  $P < 0.05$  was considered as a significant difference.

**Results:** We found that the knock-down of Znf496 in HUVEC's abolished the proliferation, migration and tube formation ability of the cells.

**Conclusion:** We therefore suggest that Znf496 is necessary for endothelial cell homeostasis. The findings in this study may therefore contribute to elucidate the role for the development of diseases where angiogenesis plays a central role, like cancer and cardiovascular diseases.

### Åldersrelaterad makuladegeneration (AMD) - en riskfaktor för muskuloskeletala problem.

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AMD är den vanligaste orsaken till nedsatt syn i västvärlden. AMD påverkar i första hand det centrala synfältet i området som benämns "macula" där vi har bäst synskärpa. Det medför att synskrävande uppgifter är svåra att genomföra, t.ex. att läsa, se på TV. AMD patienter beskriver ofta besvär från stela och trötta muskler i nackområdet ofta i samband med dålig kroppskontroll och balans. Dessa besvär kan bero på långvarig anspänning och hög koncentration. Symptom påminner mycket om de problem som kan noteras vid långvarigt intensivt bildskärmsarbete, där muskuloskeletala besvär från nacke skuldra inte heller är ovanliga. I nyare forskning har dessa muskulära problem förknippats med en förhöjd visuell ansträngning.

**Syfte:** Att undersöka om det finns ett samband mellan nedsatt/ ansträngd synfunktion och muskuloskeletala besvär i nacke/ skuldra området.

**Metod:** En grupp AMD patienter i åldersspannet 65-85 år (N= 24) jämfördes med en åldersmatchad referensgrupp med åldersnormal syn (N= 24).

Datainsamlingen bestod av optiska data och två frågeformulär. Det ena formuläret hade inriktning mot muskulära och posturala besvär, det andra formuläret (VFQ-NAS ; The Visual Functioning Quality- Near Activity Subscale) ger mått på den visuella funktionen.

**Resultat:** Korrelationen synrelaterade och muskulära besvär var signifikant (Spearman's rho= 0,502;  $p < 0,001$ ). Multipel Regressionsanalys gav ytterligare stöd för att synfunktionen har stor påverkan på muskuloskeletala problem i nacke skuldra. I besvär analysen noterades även att AMD patienterna hade mer problem i alla områden.

**Slutsats:** Resultaten stöder att det finns en koppling mellan visuella noterade problem och muskuloskeletala problem axel/ skuldra.

## Recolonisation of the skin following pre-operative disinfection and impact of plastic adhesive drapes

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During surgery the surgical site will be prepared with chlorhexidine in alcohol, 5mg/ml and draped with disposable sterile drapes. Total sterilisation of the skin is not possible and the sources of contamination can be both the patient's own skin flora and from the surgical team. At the end of a cardiac surgery bacteria will almost always be present in the surgical wound. There are various strategies to prevent dislocation of the skin flora into the wound, e.g. the use of plastic adhesive drape. The aims of this study were to measure the time to recolonisation and to study if there was any difference in bacterial growth on the skin with or without plastic adhesive drape. Repeated bacterial sampling was conducted after preoperative disinfection during six hours in ten volunteers. Bacterial samples from the skin on the participants' chest were taken at eleven occasions. Recolonisation was detected after 30 minutes on the skin with plastic drape and after 60 minutes without plastic drape. There was a statistical difference in total numbers of positive culture samples between skin with or without plastic drape, 25/80 versus 6/80,  $p < 0.0001$ . In conclusion, the use of plastic drape seems to increase the recolonisation on the skin. A recolonisation also seems to start earlier with plastic drape than without. However, further research on recolonisation of the skin with plastic adhesive drape in a real context i.e. during surgery is needed.

Keywords: Plastic adhesive drape, Recolonisation, Skin



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