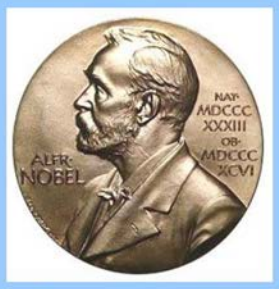
2017

Book of Abstracts

2017

Nobel Day Festivities

7th of December 2017



Traditionally, on 10th of December, the anniversary of Alfred Nobel's death, is awarded the Nobel Prize in Physiology or Medicine. School of Health and Medical Sciences shows attention to this day by organizing an own research activities and festivities.

School of Medical-, & Health Sciences
Örebro University, Örebro, Sweden
December 7, 2017

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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, Postdocs/Researchers, 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 Festivities, Örebro University 2017

The Committee

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The Ugandan Version of the Pediatric Evaluation of Disability Inventory (PEDI-UG). Part II: Psychometric Properties

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Objective: The Pediatric Evaluation of Disability Inventory (PEDI) has been recommended as a gold standard in paediatric rehabilitation[1]. A Ugandan version of PEDI (PEDI-UG) has been developed by culturally adapting and translating the original PEDI[2]. The aim of this study is to investigate the psychometric properties of the PEDI-UG in Ugandan children by testing the instrument's rating scale functioning, internal structure and test-retest reliability.

Methods: Two hundred and forty-nine Ugandan children (125 girls) aged six months to 7.5 years (Mean=3.4, SD=1.9) with typical development were tested using the PEDI-UG. Forty-nine children were tested twice to assess test-retest reliability. Validity was investigated by Rasch analysis and reliability by intraclass correlation coefficient.

Results: The PEDI-UG domains showed good unidimensionality based on principal component analysis of residuals. Most activities (95%) showed acceptable fit to the Rasch model. Six misfit items were deleted from the Functional Skills scales and one from the Caregiver Assistance scales. The category steps on the Caregiver Assistance scales' rating scale were reversed but functioned well when changed from a six-point to four-point rating scale. The reliability was excellent; intraclass correlation coefficient was 0.87–0.92 for the domains of the Functional Skills scales, and 0.86–0.88 for the domains of the Caregiver Assistance scales.

Conclusion: The PEDI-UG has good to excellent psychometric properties and provides a valid measure of the functional performance of typically developing children from the age of six months to 7.5 years in Uganda. Further analysis of all items, including misfit and deleted items, in children with functional disability is recommended.

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Changes in gut protein profiles associated with inflammatory bowel disease

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A conceptual model of conditional physical activity participation in adolescents with autism spectrum disorders

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Introduction: Physical inactivity is a big and current public health problem. Especially adolescents with an autism spectrum disorder (ASD) are less physically active. Only few of them achieve the recommendation of daily physical activity (PA) and many of them participate in fewer physical activities compared to typically developing peers. The reasons for not participating in physical activities depend on several factors, yet not comprehensively described from the adolescents' point of view. Therefore the purpose of this study was to describe how adolescents with an ASD perceive, experience and reflect on their participation in PA.

Participants and methods: Twenty-four adolescents, diagnosed with ASD without a co-occurring intellectual disability, aged 12-16 years, participated in the study. Data was collected using qualitative interviews and inductively analyzed using qualitative content analysis.

Results: The participating adolescents were a heterogeneous group in regard to their PA habits and preferences. However, all of them expressed that their willingness to participate in PA was conditioned regarding; what, where, when and with whom. The adolescents perceived varied challenges in the activity and the social context during PA, especially during the mandatory physical education. Perceived demands, freedom of choice, physical ability and sense of control affected their PA participation. The different aspects were conceptualized in an overarching theme: *Conditional participation in physical activities.*

Conclusions: The findings indicate that the adolescents' willingness to participate was associated with interacting and individual-related conditions. These, conditions to participate in PA can erroneously be interpreted as unwillingness to participate in PA at all. Thus aspects of autonomy and knowledge about individual conditions and needs have to be recognized when physical activity enhancing interventions are planned and offered for this population.

Validity and test-retest reliability of the Six-Spot Step Test in persons after stroke

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Background: Persons who have suffered a stroke often have hemiparesis with muscle weakness and spasticity, and consequently take more load on the non-paretic leg during standing. There is a need for a valid and reliable instrument that combines straight walking and taking load on each leg during single-leg standing. The Six Spot Step Test (SSST) includes walking 5 m and shoving blocks with one leg.

Purpose: The aim of the present study was to investigate construct convergent validity and test-retest reliability of the SSST in persons with gait and balance impairment after stroke.

Methods: The study was a cross-sectional study with measurement of dynamic balance and walking ability, which was repeated 3- 7 days apart, using a convenience sample of persons with diagnosis of stroke > 6 months previously. The measurements were made in a standardized order, starting with the Activities-specific Balance Confidence (ABC scale), followed by the Timed Stands Test (TST), the Four Square Step Test (FSST), the Dynamic Gait Index (DGI), the Time Up and Go (TUG) test, and the SSST. On the second test occasion only the SSST was performed.

Results: Eighty-one persons were included. Participants performed the SSST significantly faster during single-leg standing taking load on their paretic leg. The SSST demonstrated strong construct convergent validity with the TUG, DGI, and FSST instruments, and moderate convergent validity with the TST and the ABC scale. The test-retest was good. The Standard Error of the Measurements, SEM% values were between 14.7 and 20.0%, and the Smallest Real Difference, SRD%, ranged from 40.8% to 55.4 %, based on the lowest value calculated for the mean of four trials taking load alternatively on the paretic and non- paretic leg.

Conclusion: The SSST is a valid and reliable instrument for measuring walking balance post stroke and can be a complementary measure of gait and balance in stroke rehabilitation.

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Increased plasma Cathepsin S and Trombospondin-1 in patients with acute ST-elevation myocardial infarction

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Background and Objective. The role of cathepsins in the pathological progression of atherosclerotic lesions in ischemic heart disease has been described in detail more than a decade ago. Cathepsin S (Cat-S) is one of the 11 family members, which are lysosomal proteases that participate in numerous physiological systems. The expression and activity of these proteins are changed during various inflammatory diseases, including rheumatoid arthritis and atherosclerosis. The aimwas to examine changes in plasma cathepsin S (Cat-S) and trombospondin-1 (TSP-1 in patients with ST-elevation myocardial infarction (STEMI) before and after percutaneous coronary intervention (PCI)**.**

Materials and method: STEMI patients were divided into two groups depending on the degree of coronary vessel occlusion: those with closed (n = 90) and open culprit vessel (n = 40). Cat-S and TSP-1 were analyzed from peripheral venous blood samples drawn before, 1-3 days after and 3 months after PCI using enzyme-linked immunosorbent assay.

Result: In STEMI patients, plasma Cat-S and TSP-1 levels were initially high but declined rapidly over a period of 1-3 days. Although troponin-I were higher (P<0.01) in patients with closed culprit lesion, there were no differences in Cat-S and TSP-1 levels between the two patient groups (blood samples obtained before and shortly after PCI intervention). However, TSP-1 levels after PCI were significantly lower in the patient groups compared to healthy controls. Furthermore, in blood samples obtained 3 months after PCI, plasma Cat-S (but not TSP-1) was significantly higher (P<0.001) in patient with closed culprit lesion. There were no differences in demographic data, cardiovascular risk factors, between the two patient groups.

Conclusion: Cat-S and TSP-1 levels are high during acute STEMI and this may contribute to new knowledge related to foregoing plaque rupture. Low levels of TSP-1 may be explained by anti-platelet drug treatment following STEMI. Elevated levels of Cat-S months after acute MI probably reflect the severity of the heart disease and may be important for prognosis. Future studies with large patient groups may reveal the causality of Cat-S and TSP-1 in myocardial infarction.

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Sex of older siblings and cognitive function

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Background: Number of older siblings is associated with lower cognitive function, possibly as a marker of material disadvantage. Sex differences may signal an influence of inter-sibling interactions.

Methods: The study used a national Swedish register-based cohort of men (n=644,603), born between 1970 and 1992. These men undertook military conscription examinations in late adolescence including assessment of cognitive function (intelligence). Cognitive function was assessed using three versions (used in different periods) of a written test. All versions included questions on inductive ability, linguistic understanding and spatial recognition. A nine-point normally distributed score was produced and nine indicates high cognitive function (general intelligence). Associations with siblings were investigated using linear regression with no siblings as the reference category.

Results: Male adolescents with lower average cognitive function have a larger number of older siblings, lower parental socioeconomic classification and mothers who gave birth before age 18 or who were older than average. Mean cognitive function are 5.30 for men with no older *male* siblings, and 5.12, 4.99 and 4.60 for men with one, two and three or more *male older* siblings, respectively. Mean cognitive function are 5.28 for men with no older *female* siblings, and 5.14, 5.00 and 4.65 for men with one, two and three or more *female older* siblings, respectively. After adjustment for numbers of younger siblings, year of conscription assessment, age/year of birth, European socioeconomic classification for parents and maternal age at delivery; the regression coefficients (and 95% confidence intervals) for cognitive function are -0.26 (-0.27, -0.25), -0.42 (-0.44, -0.40), and -0.72 (-0.76, -0.67) for one, two and three or more male *older* siblings, respectively, compared with none; and -0.22 (-0.23, -0.21), -0.39 (-.41, -0.37), -0.62 (-0.67, -0.58) for one two and three or more female *older* siblings, respectively, compared with none.
A larger number of *younger* siblings is not associated with lower cognitive function in the adjusted model.

Conclusions: Family size is associated with cognitive function: older male siblings may have greater implications than females due to their demands on familial resources or through inter-sibling interactions.

The impact of low socioeconomic status on coronary artery calcification

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Background: Low socioeconomic status has previously been associated with increased risk of subclinical coronary artery disease (CAD). Few studies have investigated a potential link of living in an area with low, as compared to high, socioeconomic status (SES) and subclinical CAD. The aim of this study was to investigate a potential relationship between socioeconomic residential area and coronary artery calcification (CAC), a marker of subclinical CAD.

Methods: We included 1067 participants with no previous history of CAD from the pilot study of Swedish CardioPulmonary bioImage Study (SCAPIS) between February and November 2012. Men and women aged between 50 and 65 were recruited from three high (n=541) and three low SES (n=526) areas in the city of Gothenburg (550,000 inhabitants). CAC score (CACS) was assessed with Agatston method utilising computed tomography and the individuals were classified into the following groups based on calcium score: no coronary calcification (NCC; n=625; mean age: 57) and any CAC (n=442; mean age: 59; females 31.5%, Males 68.5%).

Results: CAC was present in 244(46.3%) and 198(36.6%) individuals from low and high SES, respectively. Participants in low SES had a significant higher prevalence of diagnosed hypertension, diabetes, hyperlipidemia. In multivariate logistic regression model after adjusting for age and gender and cardiovascular risk factors, the odds for CAC was 18% higher among persons living in low SES areas (OR: 1.18, 95% CI, 0.87- 1.60).

Conclusion: In this cross-sectional study, we observed an association between living in a low SES area and coronary artery calcification. This effect was entirely explained by higher levels of CVD risk factors, indicating an effect of SES on the atherosclerotic process through increased burden of CVD risk factors. These results suggest that social inequalities in subclinical CAD might be reduced trough increased resources in low SES residential areas by targeting CVD risk factors. When assessing the risk of subclinical CAD, it may be relevant to target different risk factors in men and women.

A healthy diet rich in n-3 PUFAS enhances the effects of resistance training in elderly women

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Introduction: Aging is associated with a gradual loss of muscle mass and muscle function which contributes to a progressive loss of independence and the deterioration in quality of life. A strong predictor of functional status in elderly is the ability to rapidly generate muscle force (i.e. explosive capacity). Currently, resistance training is the most effective strategy to prevent the age related decline in muscle mass, maximal muscle strength and explosive capacity. In addition, recent data suggest beneficial effects of n-3 polyunsaturated fatty acids (n-3 PUFAs) as a therapeutic agent to reduce the age related decline in muscle mass and maximal muscle strength (Smith et al., 2015). The aim of the current randomized controlled trail was to investigate the effects of resistance training combined to a whole-diet approach rich in n-3 PUFAs on explosive force capacity and physical function in elderly women.

Methods: 63 healthy elderly women (65-70 yrs) were randomized into control (CON), resistance training (RT) and resistance training and healthy diet (RT-HD). Progressive resistance training was performed for 24 weeks at a load of 75%-85% 1RM. The healthy diet was based on current dietary guidelines in Europe and US, i.e. rich in wholegrain products, vegetables, fruits and fish with the following major adjustment: the n-6/n-3 ratio <2.

Results: Whole-body lean mass increased significantly by 1.5±0.5% in RT-HD only. Timed-up-and-go and single-leg-stance performance increased similarly in RT and RT-HD. Improvements in dynamic knee extension peak power and time to reach peak power (i.e. shorter time) occurred in both RT (+15.7±2.6% and -11.0±3.8%) and RT-HD (+24.6±2.6% and -20.3±2.7%) with the magnitude of changes significantly larger in RT-HD. Similarly, changes in squat jump peak force and rate of force development were higher in RT-HD (+58.5±8.4% and +185.4±32.9%) compared to RT (+35.7±6.9% and +105.4±22.4%).

Discussion: The current study present novel results showing that a healthy diet rich in n-3 PUFAs can optimize the effects of resistance training on lean mass and dynamic explosive force capacity in healthy elderly women.

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Epigenetic changes as prognostic predictors in endometrial carcinomas

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Objective: In Sweden, endometrial carcinoma is number five among female cancers, with 1,400 new cases per year. The diagnostic and prognostic markers for the high-risk subgroups with unfavorable prognosis are under intense debate worldwide. The aim of the present study was to address the epigenetic differences in a consecutive series of endometrial carcinomas comprising a low-risk group (FIGO-grade 1) and a high-risk group (FIGO-grade 3) with highly significant different treatment outcomes and survival rates.

Method: We used the Illumina Infinium HumanMethylation450 BeadChip to analyze the DNA methylation pattern and investigated its association with clinicopathological features important for defining the high-risk (FIGO-grade 3) and low-risk (FIGO-grade 1) groups of patients with endometrial cancer.

Results: We identified 2,224 differentially methylated CpG sites. Gene ontology analysis classified the hypomethylated genes in the high-risk group were to cell adhesion and membrane, and the hypomethylated genes to cell adhesion. Increasing methylation level in FIGO-grade 3 cancers was significantly ($P < 0.01$) associated with advanced tumor stage for CpG sites located in the *TBX2, CHST11, LRP5*, and *CIZ1/ DNM1* genes.

Conclusion: Our study identified specific DNA methylation signature in low-risk and high-risk endometrial tumors, and potential molecular biomarker genes associated with unfavorable clinical predictive and prognostic factors.

Exploring gut health, well-being and diet in a Swedish population of general older adults

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Introduction: Gastrointestinal symptoms are common among elderly and are known to decrease the quality of life. In addition, elderly individuals particularly point out gut health as a factor influencing optimal functionality. Dietary patterns are known to influence gut health and have been associated to dyspepsia, irritable bowel syndrome and inflammatory bowel disease. Despite this, neither the prevalence of gastrointestinal symptoms nor the relationship between gut health, well-being and dietary factors have been thoroughly elucidated among free-living older adults. This is an important group to consider when investigating healthy ageing, since they are not yet dependent on elevated health care resources and with the right support might be able to maintain higher functionality for a longer time.

Aim: Our aim is to investigate the relationship between gut health, well-being and dietary intake in a population of free-living older adults.

Method: A cross-sectional observational study was performed with validated questionnaires regarding gastrointestinal symptoms, diet, stress, anxiety and depression. 302 participants (age ≥ 65 years), representing the general population, were enrolled in the study whereby 262 completed the study (median age 72, interquartile range 69-76, females 66%). Dietary intake was collected with a food frequency questionnaire and compared to national guidelines. The data is shown as percentage of study participants meeting the dietary recommendations. Statistical analysis included descriptive analysis for prevalence and median scores as well as a Spearman correlation. The study protocol was approved by the Ethics board (Uppsala, dnr 2012/309).

Results: 75% of the study population had at least one gastrointestinal symptom whereof 9% of severe grade. Well-being was generally high with low levels of stress, anxiety and depression. An inadequately low dietary intake was found for the following macronutrients: protein (56% of participants), fibre (85%) and unsaturated fats (>99%). Inadequately high intake was found for saturated fats (96%) and alcohol (28%). Significant correlations were found between increasing gastrointestinal symptoms and: depression, anxiety, stress and low protein and fibre intake. Another significant correlation was also seen between low stress levels and high protein intake.

Conclusion: Although the study population in general experienced high level of well-being, a majority of the participants experienced gastrointestinal symptoms. In addition, we identified that many elderly individuals had a low intake of fibre and protein, which correlated to increased gastrointestinal symptoms. Our results suggest that dietary interventions designed to increase gut health might be a cost-effective strategy to improve health and well-being among free-living older adults.

Arterial stiffness is associated to cardiorespiratory fitness and BMI – the Lifestyle, Biomarkers, and Atherosclerosis Study

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Background: The atherosclerotic process develops over long time, and begins already in childhood. It has been shown, that the extent of early changes in the large muscular arteries are associated with risk factors as hypertension, obesity and HDL-cholesterol concentration already in adolescence and young adulthood. Arterial stiffness is associated with the presence of cardiovascular risk factors and atherosclerotic disease. Carotid-femoral pulse wave velocity (PWV) is considered as the gold standard measurement of arterial stiffness. The association between PWV and cardiorespiratory fitness (CRF) is however inconclusive, especially in young adults.

Purpose: The aim of the present study was to examine the association between PWV and body mass index (BMI), and PWV and cardiorespiratory fitness (CRF), in young adults.
Methods: The 834 subjects in the study were self-reported healthy, non-smoking, age 18-25. Carotid-femoral pulse wave velocity was measured with applanation tonometry. CRF was measured by ergometer bike test to estimate maximal oxygen uptake (VO_2 max). BMI (kg/m^2) was calculated and categorized into underweight (<18.50), normal (18.50-24.99), overweight (≥25.00), or obese (≥30) according to classification by World Health Organization.

Results: The subjects with low CRF have significantly higher PWV than the subjects with medium or high oxygen uptake, $P<0.001$. The obese subjects have significantly higher PWV than the subjects in the other BMI categories, $P<0.01$. There is a tendency for a U-shaped association between PWV and BMI categories in women, however not statistically significant.

Conclusions: The inverse association between CRF and arterial stiffness is observed already in young adults, and is stronger than the association between BMI and arterial stiffness. The study result highlights the importance of high CRF, but also that underweight individuals may be a possible risk group that needs to be further studied.

Self-reported gastrointestinal symptoms among older adults are associated with increased intestinal permeability and psychological distress

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Objective: Despite the substantial number of older adults suffering from gastrointestinal (GI) symptoms little is known regarding the character of these complaints and whether they are associated with an altered intestinal barrier function and psychological distress. Our aim was to explore the relationship between self-reported gut health, intestinal permeability and psychological distress among older adults.

Methods: Three study populations were included: 1) older adults with GI symptoms (n=24), 2) a group of older adults representing the general elderly population in Sweden (n=22) and 3) senior orienteering athletes as a potential model of healthy ageing (n=27). Questionnaire data on gut-health, psychological distress and level of physical activity were collected. Intestinal permeability was measured by quantifying zonulin in plasma. The level of systemic and local inflammation was monitored by measuring C-reactive protein (CRP), hydrogen peroxide in plasma and calprotectin in stool samples. The relationship between biomarkers and questionnaire data in the different study populations was illustrated using a Principal Component Analysis (PCA).

Results: Older adults with GI symptoms displayed significantly higher levels of both zonulin and psychological distress than both general older adults and senior orienteering athletes. The PCA analysis revealed a separation between senior orienteering athletes and older adults with GI symptoms and showed an association between GI symptoms, psychological distress and zonulin.

Conclusion: Older adults with GI symptoms express increased plasma levels of zonulin, which might reflect an increased intestinal permeability. In addition, this group suffer from higher psychological distress compared to general older adults and senior orienteering athletes. This relationship was further confirmed by a PCA plot, which illustrated an association between GI symptoms, psychological distress and intestinal permeability.

DNA Launched Suicidal Flaviviruses as Therapeutic Vaccine Candidates

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Background: Chronic liver disease, resulting from Hepatitis B virus (HBV), Hepatitis D virus (HDV), or Hepatitis C virus (HCV) infections, contributes to a major health burden worldwide. The recent emergence of direct-acting antivirals against HCV infection shows high efficacy and safety whereas the relatively high cost of the treatment brings concerns about the accessibility, especially in the developing countries. Hence, there remains a need for developing low-cost and high-efficiency treatment options. The aim of this study is to develop therapeutic vaccine candidates against HCV using DNA based subgenomic flavivirus replicons as a delivery system.

Methods: Tick-borne encephalitis virus (TBEV), Langat virus (LGTV), West-Nile virus (WNV), or Kunjin virus (KUNV) replicon harboring a firefly *luciferase* gene as a reporter was expressed and characterized *in vitro.*

Results: WNV and KUNV replicons showed significantly higher replication compared to the negative controls, lacking a functional *viral RNA-dependent RNA polymerase* gene (NS5). Higher concentrations of TBEV replicon were required to demonstrate a significant increase compared to the negative control whereas no significant difference was detected for LGTV replicon. Replacing the *luciferase* gene with the HCV gene of interest demonstrated the HCV antigen expression after 48 h for KUNV replicon, after 72 h for WNV replicon, and after 96 h for TBEV replicon.

Conclusion: These results suggest that DNA based KUNV, WNV and TBEV replicons may function as carriers for the HCV gene of interest, and these replicons are selected for *in vivo* studies.

The effect of faecal microbiota transfer in patients with Irritable Bowel Syndrome on visceral hypersensitivity

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Objective: Irritable Bowel Syndrome (IBS) is a gastrointestinal disorder which affects about 10% of the worldwide population. Patients with IBS suffer from symptoms such as diarrhoea and/or constipation as well as abdominal discomfort, pain and cramps. The pathophysiology IBS is complex and not well understood. However, it is generally accepted that a dysregulation of the microbe-gut-brain axis is present in IBS. Common aberrations along this axis include an altered gut microbiota composition and increased perception of pain originating in the gastrointestinal tract. The aim of this study was to assess the effect of modulating the gut microbiota by faecal microbiota transfer (FMT) on visceral hypersensitivity.

Methods: In this randomised double-blind placebo-controlled trial, 16 patients with IBS were included. Half of the patients received faecal material from a healthy donor (treatment group), while the other half received their own faecal material (placebo group). The faecal material was administered into the caecum by whole colonoscopy. In addition to completing questionnaires for assessing IBS symptoms, the patients underwent a barostat procedure at baseline and 8 weeks after FMT. The barostat method assesses visceral hypersensitivity by measuring visceral sensation caused by intestinal balloon distension. VAS-scores for pain, discomfort and urge were fit to a logistic function model and evaluated at fixed pressures of 20, 30, 40, 50 mmHg. These values were compared before and after FMT using paired sample t-tests, and between treatment and placebo using two-sample (independent group) t-tests, respectively.

Results: No statistically significant differences in the patients' perception of pain and discomfort were found before and after FMT, neither in the treatment nor the placebo group. The perception of urge was significantly scored lower by the placebo group than the treatment group at 30, 40, 50 mmHg. Even though a relief in symptoms after FMT was found in the treatment group compared to baseline, this was not associated with decreased visceral hypersensitivity.

Discussion: FMT with healthy donor material seems to have a beneficial effect on the symptom scores in IBS patients. However, this decrease in symptoms does not seem to be mediated by reduced hypersensitivity. Further analyses need to be performed to study what contributes to the positive effect of FMT in IBS patients.

Ambulance nurses experiences of non-conveying patients to another level of care

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Novel purine analogues with dual platelet inhibitory functions

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Targeting IL-6/IL17A in vascular inflammation using Affibody molecules

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Objective: Atherosclerosis is the most common underlying cause of the cardiovascular diseases (CVDs) characterized by cholesterol deposition and activated immune cells in the vessel wall. The balance between pro- and anti-inflammatory cytokines play a decisive role in the progression of atherosclerosis. Interleukin (IL) 6 and IL17A pro-inflammatory cytokines are important contributors in the atherosclerosis pathology. The aim of this project is to block cytokines IL6 and IL17A using Affibody molecules in vascular inflammation.

Methods: The small protein module termed Affibody molecules were used to block IL-6 and IL17A cytokines in human primary aortic smooth muscle cells (SMCs) and mouse 3T3 fibroblast cells. The pro-inflammatory cytokines monocyte chemoattractant protein-1 (MCP-1) and GRO-α proteins were analysed as readout for IL6 and IL17A respectively, measured by ELISA. We used Apolipoprotein E deficient ($ApoE^{-/-}$) mice as model of atherosclerosis to determine the blocking efficacy of the Affibody molecules.

Results: Our *in vitro* data demonstrates that both IL6 and IL17A induces MCP-1 and GRO-α proteins respectively in human primary aortic smooth muscle cells (SMCs). The IL6 and IL17A mediated release of MCP-1 and GRO-α was completely abrogated by Affibody molecules, specific for IL6 and IL17A. We also show here that IL17A induces GRO-α release in mouse 3T3 fibroblast cells and this IL17A mediated GRO-α release was markedly reduced by inhibition of an Affibody specific for mouse IL17A.

Conclusion: In conclusion, our data suggest that IL6 and IL17A Affibody molecules can block IL6 and IL17A cytokines in cell culture system and we are currently exploring their efficacy *in vivo* using $ApoE^{-/-}$ mice that spontaneously develops atherosclerosis.

The life-style, biomarker and preclinical atherosclerosis study: inter-individual variations in platelet sensitivity towards ADP, epinephrine and nitric oxide

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Introduction: Platelet aggregation and secretion can be induced by a large number of endogenous activators, like collagen, ADP and epinephrine. Conversely, the blood vessel endothelium constitutively release platelet inhibitors such as nitric oxide (NO) and prostacyclin. NO and prostacyclin are also well-known vasodilators and on that account contribute to alterations in local blood flow and systemic blood pressure. In this study we investigated platelet responses and blood vessel parameters in young, healthy individuals participating in the LBA study (life-style, biomarker and preclinical atherosclerosis study). The ultimate goal of the LBA study is to identify the earliest signs and risk factors in atherosclerosis.

Results: A sub-population of platelet preparations from young individuals responded strongly to low concentrations of ADP and epinephrine but not collagen. Furthermore, both ADP- and collagen-induced aggregation and ATP secretion were positively correlated to diastolic blood pressure and mean arterial pressure. When a NO-releasing S-nitrosothiol was combined with high doses of these platelet agonists, the results indicated for sub-populations of NO-sensitive and NO-insensitive individuals. This difference in responsiveness towards NO was not dependent on menstruation cycle or gender. Moreover, the aggregatory response to high dose collagen in combination with NO correlated to flow-mediated vasodilation of the arteria brachialis.

Conclusion: Platelet responsiveness to ADP, epinephrine and NO differs between young individuals. Moreover, platelet reactivity may have a significant effect on vessel tension homeostasis and systemic arterial blood pressure.

Successful return to work after acquired brain injury: support person's perception of supporting

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Introduction and aim: Return to work (RTW) after acquired brain injury (ABI) is a demanding process for the client and need support. This study's aim was to understand the support person's perception of supporting clients with ABI to a successful RTW.

Method: Nine persons who acted as support persons in the vocational rehabilitation (VR) process were chosen by clients with ABI participating in a previous study. Three of the support persons had a formal mandate to support the client by the employer and six of them were characterized as providing informal support. All the support persons had different kind of work. Semi structured interviews were conducted and analyzed by latent content analysis.

Findings: The analysis elicited three themes describing the support person's perception in the assistance for the client to successfully RTW: (i) Commitment, (ii) Adaptation and (iii) Cooperation. Within each of the theme multiple mechanisms were identified, reflecting the complexity that the VR process had for the client. The mechanisms were about strategic issues, reflection and decision making. The support persons experienced that their role was extra valuable for the client in contexts where adaptation and cooperation was required. Commitment built on social relations is linked to sustainability of the support.

Conclusion: Support persons play a multi-dimensional role which is important for client with ABI to successfully RTW.

The Biochemical Characterization of Lithium-associated Hyperparathyroidism (LHPT): Disturbances in calcium homeostasis reveals both hypercalcaemia and hypocalcaemia

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Introduction: Today, more than 15,000 individuals are treated with lithium in Sweden. Prevalence studies demonstrate that 15-20% of lithium patients develop hypercalcaemia, analogous to primary hyperparathyroidism. Not only is Lithium-associated hyperparathyroidism (LHPT) a poorly defined condition and management recommendations equivocal, but calcium homeostasis may be affected in a more complicated fashion than merely elevated PTH secretion. Hitherto, *hypo*calcaemia has not been described as an associated adverse reaction of lithium treatment. The current study aims to examine in detail calcium homeostasis principally with regards lithium duration.

Methods: Medical records of all 297 lithium treated patients in Jönköping (with treatment duration ≥1.5 years) regarding calcium homeostasis were examined and information on gender, age, lithium treatment duration, Levothyroxine treatment was obtained. 8262 calcium values were retrieved.

Results: 193 (65%) women and 104 (35%) men were included. The average age is 57 years (21-92 years) with an average treatment duration of 15 years (1.5-45).196 calcium values before lithium treatment initiation were retrieved, on average 2.3 mmol / l (2.02-2.54). During treatment period 120 patients (40%) remained normocalcaemic. 20% developed or were strongly suspected of LHPT. 15% had 2-5 elevated calcium values, 13% had 1-15 (median=6) calcium values below 2.15mmol/l and 7% had both hypo- and hypercalcaemic episodes. 12 of 18 LHPT patients (67%) had low (<4mmol) 24-hour urine calcium levels (0.8-3.9).

Conclusion: The prevalence of hypercalcemia is at similar levels to previous studies. This is the first description of hypocalcaemia being associated with LHPT and possibly reflects a more complicated parathyroid dysfunction than previously known. The biochemical profile of LHPT is in many ways similar to Familial Hypocalciuric Hypercalcemia (FHH).

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A diverse outcome of Caspase-1 activation

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Antimicrobial effect of plantaricins on *Staphylococcus epidermidis*

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Introduction: *Staphylococcus* belongs to the skin normal flora of humans and can become pathogenic when breaching the epithelial barrier. It has the ability to evade host immune response and antibiotics through different mechanisms. Therefore, there is a need for alternative therapeutic agents for preventing such infection. Ribosomally synthesized antimicrobial peptides (Bacteriocins) produced by *Lactobacillus plantarium*, which can destabilize inner cell membrane and cause bacterial death, has become a focus of possible alternative treatment. In this study, plantaricin EF and JK, class IIb bacteriocins, are investigated for their antimicrobial activity against *S. epidermidis*.

Methods: CD measurements with and without liposomes were used to study the secondary structure of different combinations of plantaricins. The permeabilizing potential of plantaricins on liposomes was detected by CF release and lysis of *S. epidermidis* was investigated microscopically by using Sytox Green. The inhibitory and bactericidal effects of plantaricins in combination with different antibiotics (vancomycin, gentamycin, and teicoplanin) were determined by the broth microdilution assay.

Results: CD spectra analysis showed that all plantaricins adopted α-helical structures. Lysis of liposomes was significantly enhanced when plantaricins were combined with their cognate peptides, which also significantly increased *S. epidermidis* lysis compared to each individual peptide that had poor antimicrobial activity. Plantaricin EF was found to be more efficient than JK at inhibiting *S. epidermidis* growth. Furthermore, plantaricin A displayed antimicrobial activity and potentiated membrane permeabilization when combined with EF and JK. Interestingly, addition of plantaricin EF reduced the MIC values of all three antibiotics by more 30-fold, while plantaricin JK caused a reduction of 2 and ~7-fold of gentamycin and teicoplanin, respectively.

Conclusions: The plantaricin peptides A, E, F, J- and K were able to permeabilize gram positive bacteria. Plantaricins EF was found to be more effective than JK against *S. epidermidis*. Sub-MIC concentrations of plantaricin EF were most sufficient in reducing the concentrations of different antibiotics and enhancing their inhibitory and bactericidal activity. This study suggests that plantaricins of *L. plantarum* could potentially be used together with traditional antibiotics in prevention and treatment of local infectious caused by *Staphylococcus*, such as chronic wounds.

A combination of a betalactam antibiotic and a single dose of aminoglycoside seems favorable in the treatment of sepsis

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Background: The discussion of whether to use a combination of betalactam antibiotic and an aminoglycoside or not, in the treatment of sepsis is still prevalent. Previous studies have only shown significant benefit of the combination regarding to septic shock. This retrospective study, proceeding from patients having positive bloodcultures, aims to investigate if there is a reduced risk of mortality if the combination of a betalactam antibiotic and an aminoglycoside is used in cases of bacteremia, during sepsis or septic shock.

Material/methods: All patients having positive bloodcultures within the Region of Örebro county in 2011-01-01 to 2012-12-31,a total of 1450 patients, were evaluated. Exclusion criteria were: patients with obvious focus of infection, hospital aquired infections, by positive blood cultures already known pathogens, those who did not receive any antibiotics, patients <18 years of age or patients having positive blood cultures regarded as contamination. In all 301 individual cases were included. Sepsis and septic shock were defined according to SEPSIS-3; i.e. an acute change of SOFA-score $\geq$ 2 points.

Results: Betalactam monotherapy in patients with sepsis or septic shock was associated with a significant higher risk of mortality within 28 days of follow up compared to the group treated with the combination of a betalactam antibiotic and an aminoglycoside, OR 3,3, 95 % CI (1,6-6.9), p =0,001). Within the group of patients with septic shock OR between monotherapy or combination therapy was 14.0, 95 % CI (0.24-833), p=0,21. This group included only 19 patients. In the subgroup of patients with bacteremia not meeting Sepsis-3 criteria (n=28), no mortality was observed.

Conclusions: This study supports combination therapy with a betalactam and an aminoglycoside compared to betalactam monotherapy, in the treatment of sepsis and septic shock with initially unknown focus.

Effects of Resampling and Sequencing Depth in Microbiome Analysis

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Random shotgun sequencing of DNA obtained directly from the environment has revealed profound microbial novelty and diversity. Culture-independent Next Generation Sequencing method presents an exciting means to elucidate microbial dynamics, which invariably determine human health and global biogeochemical processes [Franzosa, E.A. et.al.,2015]; making it an important tool for microbiome analysis, regarding composition and functional prediction. However, sequencing costs often set limits to the amount of sequences that can be generated and, consequently, the biological outcomes that can be achieved from any such attempt [Sims D. *et.al*..2104].

We try to find out the optimal sequencing depth capable of capturing microbial richness by applying resampling the entire data set at different depths; and compare analysis results, using widely acknowledged classification and prediction tools. Our studies show that there is a major shift in classification and prediction potential, across different sequencing depths, which in turn affects the final output.

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The effect of high-intensity exercise on various biomarkers of the intestinal barrier.

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The effect of butyrate on tryptophan transport - a potential role in microbiota-gut-brain interactions

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Background: The gut-brain axis is a bidirectional communication system between the gut with its microbiota and the brain. Gastrointestinal and psychological problems often affect each other reciprocally. Clinically, gastrointestinal disorders such as irritable bowel syndrome are frequently associated with psychological problems, whereas neuropsychiatric disorders such as autism are often accompanied by intestinal symptoms.
From a mechanistically point of view, the gut-brain interaction includes endocrine, immune and neural pathways. On the one hand, the brain applies these mechanisms to influence several gut targets. On the other hand, the gut microbiota can modulate brain function, for instance by the production of short-chain fatty acids which are neuroactive bacterial metabolites, or altered systemic tryptophan levels. One of the short-chain fatty acids, butyrate, has been shown to positively influence intestinal and neurological functions. This suggests butyrate as a key mediator in the microbiota-gut-brain interaction.

Aim: The aim of this project is to understand by which mechanisms butyrate can affect the central nervous system, with a special focus on the function and expression of tryptophan transport system, one of the biomarker for neuropsychiatric disorders.

Methods: Fibroblast have previously been shown to be a valid model system to study the gut-brain axis, among others, as they express several neuronal-specific enzymes and receptors. In this project, primary adult human dermal fibroblasts (LGC Standards GmbH, Germany) were cultured until confluency and thereafter treated with regular medium supplemented with butyrate in different concentrations (20 mM, 40 mM) for one or six hours, or stressed with regular medium supplemented with H_2O_2 (10 µM) for one hour, respectively. These conditions were either conducted alone or in combinations.

Results: Transporter assays showed that H_2O_2 incubation decreased the tryptophan transport capacities. These processes were rescued by butyrate treatment. The gene expression of the two major tryptophan transporters, Solute Carrier Family 3 Member 2 (SLC3A2) and Solute Carrier Family 7 Member 5 (SLC7A5), was not altered by incubation with H_2O_2 for one hour. However, butyrate treatment for six hours upregulated the expression of SLC7A5, while it had no effect on the expression of SLC3A2.

Conclusion: These findings suggest that gut-derived butyrate can alter tryptophan transport which potentially might affect central nervous system function.

Long term results of early myoelectric prosthesis fittings – a prospective case-control study

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Background: Children with upper limb reduction deficiency (ULRD) are recommended to be fitted with hand prosthesis at an early age because it encourages motor learning and prosthetic integration into the body scheme. Early fitting of a passive prosthetic hand is supported by the literature but the age for introducing an active, myoelectric, hand varies and is more controversial. In Scandinavia the myoelectric hand prosthesis is introduced to the child at the age of 3 years, but in North America it is recommended that the fitting takes place as early as 10-15 months of age.

Aim: To compare prosthetic skill, prosthetic use and risk for rejection over time between children fitted with MEP before or after 2½ years of age.

Methods: Prospective case-control design. Cases were nine children fitted with MEP before age 2½ years whereas controls, 27 children, were fitted with MEP from age 2½ years. The Skills Index Ranking Scale was used to classify prosthetic skill and prosthetic use was categorised based on wearing time and pattern. Independent samples tests were used to compare data between groups. To estimate and compare risk of prosthesis rejection between groups and over time, survival analysis was used.

Results: Cases showed prosthetic skill early, but controls did catch up at age 3½. Cases had a significant ($p = 0.040$) decrease in prosthetic use at age 9. In the long term, cases had a higher percentage of rejecting their prosthesis.

Discussion & Conclusion: Considering a young child's development of prosthetic skill and prosthetic use over time, this study shows no additional advantages from fitting a myoelectric hand prosthesis very early. So, in conclusion, a recommended age for fitting myoelectric hand prosthesis in children is from 2½ years of age, with further consideration taken to the individual psychosocial and motor development.

The effects of butyrate on induced hyperpermeability in human colonic mucosa

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The intestinal permeability is an indicator of intestinal barrier function and an increased permeability has been associated with several diseases such as irritable bowel syndrome, inflammatory bowel diseases, coeliac disease or type 2 diabetes. Strengthening the barrier function and keeping the intestinal permeability at a normal level could therefore be used in prevention or treatment of these diseases. Butyrate, a short-chain-fatty acid produced by specific members of the intestinal microbiota, has previously been shown to reduce permeability and strengthen the barrier function in cell culture experiments and animal models. However, data from clinical experiments is very scarce.

In this study, butyrate's ability to decrease stress-induced hyperpermeability in human colonic biopsies was tested in an *ex vivo* setting. For this, mucosal biopsies from the sigmoid colon of 10 healthy volunteers were preincubated with 5 or 25 mM butyrate in Ussing chambers. The mast-cell degranulator compound 48/80 was used to induce tissue hyperpermeability. Transepithelial electrical resistance (TER) as well as the paracellular and transcellular permeability were measured after 0, 30 and 60 minutes.

Butyrate, at both concentrations, did not reduce the induced paracellular or transcellular hyperpermeability after 60 minutes. This contrasts previous results from cell culture and animal experiments and might be explained by the relatively short time of butyrate incubation, hence indicating that butyrate might not have an acute effect on intestinal permeability.

The Interpreting of Relayed Calls through the Service Bildtelefoni.net- Interaction and the Joint Construction of Meaning[1]

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Objective: The service Bildtelefoni.net enables people who use Swedish Sign language (SSL) on videophones to interact, via an interpreter, with people who use telephones and vice versa; interpreting in video relayed calls. The interpreter works in a studio and views the person who uses SSL through a videophone on a screen. The interpreter also hears the person who speaks Swedish on the telephone via a headset.
The overall aim of the research project was to describe, analyse and discuss participants' interaction and joint construction of meaning within interpreting in video relayed calls.

Methods: Dialogism and Conversation Analysis (CA) were used as theoretical and methodological frameworks in order to investigate the interactional phenomena. The data consists of 25 authentic calls collected from the regular service of Bildtelefoni.net.

Results: Positioning of the interlocutors emerges in and through the interaction in intricate and context-dependent ways, which enriches the understanding of the interaction. However, the interpreter is primarily responsible for, and able to manage and administrate the turn-organisation and sanctioning utterances by means of different techniques and strategies. The interpreter's headset and the text-function serve as interactional resources in video relayed calls; in the auditive as well as in the visual arena. The interpreter has got several demands and responsibilities in the interaction: as a representative of the service, as a provider of instructions, as a technical facilitator, and as a mediator. However, the implications of the research are that the interaction of video relayed calls is a complex process, the existence of which requires a sophisticated co-operation among all of the interlocutors: the interpreter, the user of the videophone, and the user of the telephone. The interpreter, however, has a special position in this context, based on certain obligations and demands to manage the interaction in relation to the service.

Conclusion: The interpreter has a key-function, at the same time as all participants are involved in an intricate joint construction of meaning in video relayed calls, created on a moment-to-moment basis.

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Environmental barriers to participation and facilitators for use of three types of assistive technology devices

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Background: In rehabilitation, assistive technology (AT) is prescribed in order to improve activity and participation for individuals with disability. Research shows that many devices are not used to the extent or to the benefits expected. The aim of this study was to compare the presence of environmental barriers to participation and facilitators for AT use and study the relation between barriers and AT use in three different types of AT devices.

Methods: A cross-sectional survey was conducted. Inclusion criteria were: ≥1 year experience as user of myoelectric prosthesis (MEP), powered mobility device (PMD), or assistive technology for cognition (ATC) and age 20-90 years. The survey contained the Swedish version of Craig Hospital Inventory of Environmental Factors and a study-specific questionnaire focusing on facilitating factors. Overall, 156 participants answered the survey. Non-parametric tests were used for comparisons.

Results: Barriers to participation were significantly lowest in MEP users (md=0.12; $p<0.001$), and highest in ATC users (md=1.56; $p<0.001$-$p=0.048$). A positive correlation between fewer barriers and higher use of MEP was seen ($r=0.30$, $p=0.038$). Compared to the other groups, users of ATC with more use reported more barriers for participation. The greatest barriers to participation were: *Natural environment*, *Surroundings*, and, *Information*. Most support came from *Relatives* and *Professionals.*

Conclusions: There is a difference in how users of different AT devices experience the environment in terms of barriers for participation and facilitators for use. The environment may facilitate AT use but barriers in the environment can still restrict participation in AT users. Future research should comprise the influence of AT use on participation.

Activation of JAK/STAT3 and PI3K pathways are crucial for MCP-1 induction by IL6 trans-signaling in human endothelial cells

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IL6, a pleotropic cytokine released from wide variety of cells, acts on target cells by binding to either a membrane bound receptor (IL6R) or its soluble form and a signal transducing receptor gp130. Signaling via the membrane-bound receptor is referred to as classic-signaling and has been related to regenerative and anti-inflammatory functions. Whereas IL6 signaling via the soluble receptor (referred to as trans-signaling) has been linked to pro-inflammatory effects leading to chronic inflammatory diseases including atherosclerosis. During atherosclerosis, IL6 contributes to development and destabilization of plaque and its blockade has been shown to have immense therapeutic significance though associated with some adverse outcomes.

In this study, we used human vascular endothelial cells to elucidate molecular differences in classic- versus trans-signaling of IL6 and relate that to its pro-inflammatory impacts. We revealed, using flow cytometry and ELISA, that human endothelial cells express both IL6R and gp130 on their surface and release the soluble forms.

These findings suggested that both classic- and trans-signaling can take place in human endothelial cells. Next, we investigated pathways engaged by classic- and trans-signaling of IL6 by stimulating human endothelial cells with IL6 alone or in combination with its soluble receptor respectively. During classic signaling, we observed a dose-dependent increase in activation of JAK/STAT3 pathway. Meanwhile in trans-signaling, we observed activation of PI3K and ERK/MAPK pathways in addition to markedly increased activation of JAK/STAT3 pathway. Further, we showed that only activation of trans-signaling leads to expression/release of MCP-1 from endothelial cells. By blocking those pathways, we confirmed that the MCP-1 induction by IL6 trans-signaling is mediated through JAK/STAT3 and PI3K pathways.

Put together, our findings indicate that both classic- and trans-signaling of IL6 can take place in HUVECs and that activating trans-signaling involving JAK/STAT3 and PI3K pathways is crucial for MCP-1 induction.

CBD: An integrative and interactive colorectal cancer biomarker database

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Colorectal cancer (CRC) is one of the most common type of malignancies and major course of cancer death worldwide. Although accumulating evidence from a huge amount of individual molecular studies has improved early diagnosis, better therapy and predicting prognosis in CRC, the clinical importance of the biomarkers has been need to be further clarified. In this study, we construct an integrative and interactive database for CRC biomarker: CBD (http://sysbio.suda.edu.cn/CBD/) in which all the identified CRC biomarkers and their relevant information have been collected from 1115 published articles in PubMed. The main functions for CBD are to search, display and analysis CRC biomarkers. CBD users can also send the new identified biomarkers to our database manager via the submission page.

In this version of CBD, 870 biomarkers with 1134 biomarker information records were concluded. There were 35 DNA, 94 RNA, 583 protein, and 158 other biomarkers according to the biological category. The CBD was constructed under MySQL server with Apache as HTTP server, and HEML, PHP and JavaScript languages were used to implement the web interface. Multiple statistical analysis for the CBD inside data have been conducted in different ways like the biological category, source and application of biomarkers; the region, race, number, gender, and age of samples; the location and stage of CRC; the experiment method, result, author, published year and journal of researches. MiRNA-Gene and Protein-protein interaction network were used to explore the relationship between different biomarkers, and Geno ontology and KEGG pathway enrichment analysis were conducted to understand these biomarkers in systemic biological level.

The users can use these result as a base to further analysis CRC biomarkers in more detailed direction, by which some new CRC biomarkers may be identified. The biomarker functions in the CRC diagnosis, therapy, and prognosis can be analysed according to the guide of P4 medicine.

In conclusion, the CBD will provide a new valuable tool to search and analysis CRC biomarkers for the researchers and clinicians.

Quantitative 16S rDNA Droplet Digital PCR for determination of bacterial load and duration of DNAemia in bloodstream infections

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Background: Droplet digital PCR (ddPCR) can be used for absolute quantification of bacterial DNA load in blood. The 16S rDNA gene is present in all bacteria, and can be used for detection of bacterial DNA by PCR, with or without subsequent sequencing for species identification. We hypothesized that quantification of the bacterial DNA load by 16S rDNA gene ddPCR can be useful in the management of bloodstream infections (BSI). In this study we compared a quantitative *16S r*DNA ddPCR with species specific ddPCR:s for quantification of the bacterial DNA load during BSI caused by *Staphylococcus aureus, Escherichia coli* or *Streptococcus pneumoniae*.

Material/methods: Patients with blood culture positivity for *S. aureus* (n=27), *E. coli* (n=28) or *S. pneumoniae* (n=30) were included in the study. Blood samples for PCR were collected on admission, on day 1-2, 3-4, and 6-8, respectively. When a patient was PCR negative in both methods, no further PCR analysis was performed. The admission sample was missing in several cases. DNA was extracted from 1 mL frozen EDTA whole blood with 20 % Glycerol using Blood Pathogen Kit (Molzym) on the Arrow (Diasorin). Extracted DNA was subjected to species specific ddPCR:s for *S. aureus* (*nuc*), *E. coli* (*uidA*) and *S. pneumoniae* (*lytA*), and to a general ddPCR using the16S rDNA gene. The droplets were generated and analyzed with QX200 Droplet generator/ reader (BioRad).

Results: The two methods showed discrepant results in some individual samples, but were significantly linearly related, r=0.95 (p<0.001) for *S.aureus* PCR results, r=0.78 (p=0.005) for *E.coli* PCR results and r= 9.55 (p<0.111) for *S.pneumoniae* PCR results.
The bacterial DNA load measured by 16S rDNA ddPCR on day 1-2 was higher in patients with sepsis (SOFA score >2) than in patients without sepsis (SOFA score <2) in the entire study cohort (1.70 [0-4.67] versus 0 [0-2.24], p=0.007 and in the sub-groups of patients with BSI caused by *S.aureus* (2.61 [0-4.50] versus 0 [0-2.01], p=0.008 and *E.coli* (1.70 [0-4.67] versus 0 [0-0], p=0.04).

Conclusions: 16S rDNA ddPCR appears to be a promising method for DNA quantification in BSI. Future studies should evaluate if repeated determination of bacterial DNA load can be useful in sepsis management.

Faecalibacterium Prausntzii inhibits inflammation in Crohn's disease

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Low 25-Hydroxyvitamin D predicted emergency caesarian section due to prolonged labour

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Screening history in elderly women diagnosed with cervical cancer

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Discovering of Bone Morphogenetic Protein Signaling Pathways in Obesity in Mice

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Objective: The bone morphogenetic protein (BMP) pathway is one of the multiple signaling pathways that are part of the adipose lineage differentiation. BMP signaling components, such as BMP-4 and BMP-2 in particular, have been linked to white adipogenic differentiation. This presentation will be presenting data from two studies, in which the gene expression of the known BMP signaling components will be investigates in adipose tissue of chow fed mice and high fat/high sucrose (HF/HS) fed mice.

Method: This study is a retrospective study conducted by analysis of data collected as part of the Hybrid Mouse Diversity Panel (HMDP) database, generated at the University of California, Los Angeles. In the two chosen studies all mice were adult, male and fed with chow respectively HF/HS diet for 8 weeks.

Results: BMP-2 and -4 had high expression both in mice fed with chow and HF/HS diet. BMP-2 was the ligand that increased between the diets and BMP-4 had no significant change. The rest of the known ligands decreased. The antagonist in the signaling pathway with highest expression were Matrix gla protein and Gremlin-2. Matrix gla protein and Chordin increased and the rest decreased when comparing between the mice fed with chow and HF/HS diet.

Conclusions: Overall this study was a preliminary overview of the differences in the expression of BMP signaling components in the obese mouse. It shows that the HF/HS diet has an impact on BMP gene expression. Further studies are needed.

Notch signaling pathways may protect against diet induced obesity

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Objective: Obesity is a global health problem, affecting people of all ages. The condition is caused by several known and unknown factors from genetics to diet and energy consumption. Recently, studies have shown improved glucose metabolism and loss of body weight when inhibiting Notch 1 [1], a transmembrane receptor involved in numerous developmental processes. However, there is limited research on Notch signaling pathways during the induction of obesity. Our objective is to compare diet-induced obese mice to lean chow-fed controls with regards to the expression of genes involved in Notch signaling.

Methods: We used data from the database Hybrid Mouse Diversity Panel [2]. We selected expression data for genes involved in the canonical pathways of Notch in adipose tissue and obesity phenotypes (e.g. body fat percentage, insulin levels and liver weight). Mice had been fed either a chow or a high fat-high sucrose diet for 8 weeks. We investigated differences in Notch pathway gene expressions between dietary groups and potential correlations between the components and obesity phenotypes within each group.

Results: All components of the Notch pathway were differently expressed in the diet-induced obese mice compared to lean controls ($p<0.001$); eight components were significantly upregulated and only one was downregulated. 14 significant correlations were found between Notch pathway components and obesity phenotypes in the obese mice, 12 of them were negative and showed lower obesity, insulin levels and liver weight.

Conclusion: For the obese mice, having a higher expression of key Notch pathway components may have a protective effect against obesity when challenged with a high fat-high sucrose diet.

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The correlation between glycated Hemoglobin A1c and time spent in glucose target range; a multicenter study

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Objective: 78% of Sweden's children and adolescents with type 1 diabetes use continuous glucose monitoring (CGM) or flash glucose monitoring (FGM) to monitor their glucose levels. HbA1c is considered as golden standard to evaluate patient's glycemic control the past two to three months. The CGM/FGM device enables physicians and patients to access a large amount of stored glucose data, such as the time patients have spent in the glucose target range (4 – 8 mmol). Time spent in target range could be an important factor predicting future diabetes complications. However, the relationship between time spent in glucose target range and HbA1c is currently unknown. The aim of this study was to examine this relationship.

Methods: Glucose data for the past 60 days were collected for 63 children and adolescents with CGM/FGM using Diasendâ, an internet based platform. HbA1c and data regarding study sample was collected from SWEDIABKIDS, Sweden's pediatric diabetes quality registry. Data was analyzed using linear regression analysis in SPSS.

Results: 23 patients were excluded due to CGM/FGM usage less than 80% of their time. We found a negative linear correlation between time in glucose target range and HbA1c ($r^2 = 62.2\%$, $p < 0.001$). This implies that 62.2% of HbA1c's variation could be explained by time spent within glucose target range.

Conclusion: Our study shows a linear correlation between time spent in glucose target range and HbA1c. This finding suggest that time spent in glucose target range may work as an addition to HbA1c to asses glycemic control.

Is electroconvulsive therapy an effective treatment for postpartum depression?

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PCSK9 and Mortality in Hemodialysis patients

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Using ultrasonography to diagnose peritonsillar abscesses

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Objective: Today the golden standard of diagnosing a peritonsillar abscess (PTA) is a fine needle aspiration (FNA). FNA is painful, potentially risk full, and has a high frequency of type 2 errors (10-24%) [1]. Ultrasonic (US) examination of the peritonsillar room is a new method to diagnose PTA, and this study aim to evaluate if US examination is equal to FNA.

Materials and methods: The same ultrasonic machine (Flex Focus 500) and equipment will be used throughout the whole study. There is two ways of examining the peritonsillar area, through the transcervical view and the intraoral view. All ultrasonic examinations will be performed by the same practitioner. On all patients, there is a follow-up time regarding if there actually was an abscess or not, examining final clinical diagnosis.

Results: 18 subjects and 20 separate cases of suspected PTA were included, where 7 cases had PTA confirmed by FNA, whereas the US-examination found 10 positive cases. This results in a sensitivity of 70% and specificity of 100% for the US-examination, compared to FNA. During the follow up, these three patients later turned out having a PTA, resulting in a sensitivity of 100% and a specificity of 100% when comparing US with final clinical PTA diagnosis.

Conclusion: Transcervical US examination of patients with suspected PTA is a procedure with high sensitivity (100%) and high specificity (70%), when compared to FNA in diagnosing PTA. Also, US-examination has an even higher specificity than FNA when comparing with final clinical PTA diagnosis. In 50% of the cases, US-examination managed to rule out PTA, which could result in fewer unnecessary FNA:s in the future.

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Cellular membrane transport of Phenylalanine in fibroblasts from patients with Phenylketonuria (PKU)

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MicroRNA as an alternative treatment strategy against uropathogenic E. coli

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Objective: The choice of treatment against uropathogenic *E. coli* (UPEC) has become problematic due to the increasing antibiotic resistance. Hence, new strategies are urgently needed for treatment of urinary tract infections caused by multidrug-resistant UPEC. MicroRNAs (miRNAs) are short RNA molecules that are found in all cells. In recent years, the interest for miRNA has increased due to their ability to block the production of proteins. A recent study showed that miRNA released from intestinal epithelial cells are able to penetrate gut bacteria and influence their growth (1-2). It is well known that host cells can release various antimicrobial factors (mainly proteins and peptides), but that human miRNA can affect bacterial growth is a completely new and unexplored field of research. The type-1 fimbriae is an important virulence factor used by UPEC to colonize the human bladder and the aim of this study was to investigate if miRNAs can inhibit type-1 fimbriae-mediated adhesion of UPEC.

Method: The UPEC strain CFT073 was cultured in the presence or absence of miRNA mimics that target the type-1 fimbriae. Type-1 fimbriae-mediated adhesion was then evaluated by mixing 0.05% yeast with the miRNA-exposed bacteria. The adhesion was evaluated by aggregometry.

Results: With *in silico* prediction analysis, two miRNAs were identified that in theory could bind to the UPEC type-1 fimbriae adhesin *fimH*. miRNA1 was able to significantly ($p<0.05$) inhibit type-1 fimbriae-mediated adhesion in CFT073 after 6h, resulting in decreased yeast aggregation. The negative control (scrambled miRNA) had no significant effect. After 24 h, both miRNA1 and miRNA2 significantly ($p<0.05$) inhibited type-1 fimbriae-mediated adhesion.

Conclusion: Synthetic miRNA mimics were able to impair adhesion mediated by the type-1 fimbriae, an important virulence factor utilized by UPEC to colonize the human bladder.

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Differential Poliovirus Receptor expression in 2D and 3D Renal Carcinoma cultures.

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Objective: Renal Cell carcinoma (RCC) accounts for more than 90% of kidney cancers (1). Natural killer (NK) cells are Innate immune cells that play a vital role in tumor eradication through cytotoxicity and release of pro-inflammatory cytokines (2). NK cells specifically recognize Poliovirus Receptor (PVR) as a ligand that is over expressed in tumors. However, NK cell based immunotherapies to treat solid tumors have been largely unsuccessful (3). The objective of the study was to first characterize the tumor cell line that is most susceptible to NK cytotoxicity. After the characterization, NK ligand (PVR) expression would then be compared between both the two and three dimensional RCC cultures.

Methods: Comparison of cytolytic activity of IL-2 activated NK cells against three different tumor cell lines (LUTC-2, ACHN, A498) was assessed using the chromium (51Cr) release assay. PVR expression was then compared between 2D and 3D A498 RCC cultures after accumax treatment using flow cytometry analysis.

Results: A498 cell line had the highest susceptibility to NK cell recognition and cytotoxicity. A significant down regulation of PVR was observed in 3D model as compared to the 2D RCC cultures, this statistical significance was evaluated by two-way ANOVA test ($P \leq 0.001$).

Conclusions: These results show that A498 RCC is an appropriate model for studying in-vitro NK cell-tumor interactions. There was also differential PVR expression between the 2D and 3D RCC models and these mechanisms are poorly understood. Therefore, further studies into the PVR down-regulation mechanisms in NK and 3D tumor interactions are required to improve NK-cell based immunotherapy.

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Author Index, Nobel Day's Festivities 2017

Author Index, Nobel Day's Festivities 2017

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Abstract Poster Page nr

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