SUSTAINABILITY IN HEALTH

ABSTRACT BOOK

Abstracts of papers accepted for poster presentation in the NorDoc PhD Conference

NORDOC PHD CONFERENCE

17. – 18. JUNE 2022
BERGEN, NORWAY

UNIVERSITY OF BERGEN
Faculty of Medicine

NorDoc
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COLOPHON

Abstract Book of the NorDoc PhD Conference
Bergen, 17. - 18. June 2022

SCIENTIFIC COMMITTEE

EDITOR

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This Book is available on the website: NorDoc PhD Conference

The Conference is funded by The Research Council of Norway and NORCE.

First published: 13th June 2022

The Research Council of Norway

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Locally tailored clinical guidelines and reoccurring training aimed to improve care at birth in Tanzania

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The ability of a country to meet the healthcare needs of its people depends largely on the knowledge, skills, motivation of the people delivering health services. A multicounty study in low and middle-income countries found disturbing results of generally low scores in knowledge, skills, and competency on basic intrapartum care, including partograph use, active management of the second stage of labor, and treatment of complications such as severe preeclampsia and postpartum hemorrhage. There are varying degrees of qualification and training for skilled birth attendants in low- and middle-income countries. Most health care providers who take care of women during labor either hold a diploma or certificate in general nursing or are doctors in the first years of clinical work or physicians with no specific training in midwifery and obstetrics care. The lack of adequate pre-service and in-house labor care training of healthcare providers appear to be a central contributor to the low level of relevant knowledge, skills, and competencies and is a key reason why many beneficial evidence-based practices are still not in place. Moreover, there is often a high staff turnover in maternity units resulting in loss of skills and training investments. Thus, the birth attendants holding the lives of others in their hands may lack the training required to act as skilled birth attendants; they are depending on unsupervised on-the-job learning for knowledge and skills improvement.

How sustainable is your project?

1. The project upscaled and continued assessing its feasibility to a wider range than how it was started. (more settings, population, and material supply).

2. The project extended by putting more budget, across borders, and more awards and multi-partners incorporated.

Profiling protein expression and ADP-ribosylation in breast cancer cell lines

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Since it was discovered that PARP inhibitors selectively target BRCA1/2 mutant cells, PARP inhibitors have been used to treat breast cancer patients with BRCA mutations. Further studies have shown that the effect of PARP inhibitors (PARPi) comes from their ability to trap PARP1 at DNA damage sites. Because PARP1-mediated ADP-ribosylation (ADPr) targets a variety of proteins after DNA damage stimulation, we wanted to elucidate whether changes in ADPr patterns contribute to PARPi sensitivity.

Therefore, we profiled the proteome and ADP-ribosylome in wild type and BRCA1/2 mutant cell lines with different PARPi sensitivities. We used mass spectrometry to characterize protein expression levels, as well as our Af1521-based enrichment to identify ADPr sites after H2O2-induced DNA damage. We identified 1011 and quantified 733 ADPr sites across the cell lines, with >90% of ADPr occurring on serines. We found that proteins involved in DNA damage response, nucleosome assembly, and RNA processing were enriched in the ADPribosylome, and that PARP1, histones and chromatin-associated proteins are the most abundant ADP-ribosylated proteins. Despite cell line differences in BRCA1/2 mutations and PARPi sensitivity, we find that a core ADPr signalling network is conserved across the cell lines. However, we detected site-specific differences in the PARPi-sensitive BRCA mutants, which we will further investigate to further elucidate how ADPr signalling contributes to PARPi sensitivity.

How sustainable is your project?

I am interested in attending this conference to learn how I could improve the sustainability while conducting basic research in a wet lab setting.

Automated pupillometry to detect cognitive motor dissociation after acute brain injury

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Automated pupillometry is well-established in the clinical setting for quantifying pupil motility with great precision at the bedside. Mental tasks such as mental arithmetic lead to pupillary mydriasis in conscious persons and are considered a surrogate marker for cognitive and emotional processes. Using a paradigm of standardized stimuli to evoke pupillary dilation, we investigated if automated pupillometry could detect covert consciousness in patients with acute brain injury. We established an automated pupillometry paradigm presenting patients and age- and sex-matched healthy volunteers to 1) their own facial reflection in a mirror, 2) a series of three different sounds, and 3) a mental task based on mental arithmetic to produce cognitive load. Automated pupillometry was performed on 91 patients (male 69%; median age 62; 45 neurological and 46 cut-off hospital cardiac arrest patients) and 25 volunteers. The total number of automated pupillometry recordings in patients was 688 (177 mirror; 174 auditory; 337 mental arithmetic), with 53 patients completing at least two series of stimuli. Pilot data on healthy controls demonstrate the feasibility of automated pupillometry to record pupillary dilation as a measure of brain activity. We hypothesize that automated pupillometry also may contribute to the clinical evaluation of unresponsive patients with acute brain injury by detecting residual consciousness in a subset of patients with cognitive-motor dissociation.

How sustainable is your project?

For 2016, CO2 emissions for MRI and CT calculated in 120 countries accounted for 0.77% of global emissions. 3 Tesla MRI produces 200 to 300 kg of carbon dioxide (CO2) equivalent. Automated pupillometry is a bedside tool that could reduce the need for brain imaging in unconscious patients.

Ethnic disparities in use of secondary preventive medications poststroke in Denmark

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The aim of the study was to assess use and persistence of secondary preventive treatment after ischemic stroke comparing immigrants and Danish-born residents. A cohort of patients discharged with ischemic stroke diagnosis (n=106 224) by immigration status was identified from the Danish Stroke Registry between 2005 and 2018. We investigated use (claiming at least one prescription in 180-day post-discharge according to information from the Register of Medicinal Products Statistics) and persistence of treatment within 180 days thereafter using logistic regression and Fine and Gray model. Immigrants had lower odds of use of anticoagulants and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (odds ratio [OR], 0.66; 95% confidence interval [CI], 0.53–0.82 and OR, 0.87; 95% CI, 0.75–0.98, respectively) but had higher odds of use of beta-blockers (OR, 1.25; 95% CI, 1.02–1.53) than Danish-born residents after adjustment for age at stroke, sex, clinical and sociodemographic factors. Persistence of medication use did not differ between immigrants and Danish-born residents after adjustment for sociodemographic factors and comorbidities. Modest disparities in use of standard guideline recommended secondary preventive medications were observed when comparing immigrants and Danish-born residents with ischemic stroke. Furthermore, no differences in persistence of medication therapy were observed.

How sustainable is your research?

Disparities detected in immigrants provide a framework for improving poststroke medication use; hence, leading to a sustainable stroke care in this population.

CombiANTTM: antibiotic interaction testing made easy

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Efficient treatment of many infections is dependent on antibiotic combination therapies. Treatment strategies typically assumes that synergies from combinations are conserved within bacterial species and strains. Though, recent results show treatment effect is determined by specific drug–strain interactions that vary extensively and unpredictably both between and within bacterial species. To address this problem, we present a novel rapid quantitative method for antibiotic interaction – CombiANT. CombiANT consists of a 3D-printed agar plate insert that produces defined diffusion landscapes of 3 antibiotics, permitting quantification between all 3 antibiotic pairs in a single test. Image analysis yields fractional inhibitory concentration indices (FICis) with high accuracy and precision. A technical validation with 3 major pathogens, E. coli, P. aeruginosa, and S. aureus showed equivalent performance to checkerboard methodology with reduced assay complexity and costs. A synergy screening of 10 antibiotic combinations for 12 E. coli urinary tract infection clinical isolates illustrated the need for case-by-case treatment strategy. CombiANT could allow personalised large-scale diagnostics and we anticipate the method to facilitate clinical and basic research of antibiotic interaction testing.

Studying protein-protein interactions of acid-sensing ion channels

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Acid-sensing ion channel 1a (ASIC1a) is a proton-gated ion channel expressed in the central and peripheral nervous system. It plays an important role in physiological and pathological processes, such as pain, synaptic plasticity and necroptosis. The latter has been suggested to be mediated through a protein-protein interaction between ASIC1a and the receptor-interacting serine/threonine-protein kinase 1 (RIPK1). In an attempt to find novel ASIC1a interaction partners, our collaborators have previously used mass spectrometry to identify protein 1(P1) . protein 2 (P2) and protein 3 (P3) (naming due to confidentiality reasons). Here, we use immunoprecipitation to show that P1, P2 and P3 interact with ASIC1a, while we do not find evidence for the previously suggested interaction with RIPK1. In order to find the exact interaction site between P1 and ASIC1a, we incorporate the non-canonical photo-crosslinking amino acid AzF into a number of positions in the N- or C-terminus of ASIC1a and expose the cells to UV light in order to activate the crosslinkers. Although we do not observe successful photocrosslinking between ASIC1a and P1 or -P2 , the insertion of AzF at position C464 and L465 abolishes the interaction with P1, suggesting a potential site of interaction. Our data also suggest both C- and N- terminal half of P2 and P3 interact with ASIC1a.

How sustainable is your research?

Emerging evidences in research shows cellular proteins function as a part of the network of proteins and are often modulated by their interaction partners. My studies on the protein-protein interaction in ion channels, would pave way to understand one such regulatory network.

Deep Multi-Outcome Risk Prediction in Patients with Chronic Lymphocytic Leukemia

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The risk of infection, immune dysfunction due to the treatment process, and adverse events complicate the treatment process of patients with Chronic Lymphocytic Leukemia (CLL). Predicting any of these risks would improve the decision-making process during treatment. However, current predictive models only predict single output and ignore the dependencies among outcomes. We designed a multi-outcome deep model to jointly learn predicting multiple clinical outcomes including treatment initiation, the risk of infection, and the risk of death. We identified a cohort of 4149 patients and extracted features from laboratory, microbiology, pathology, clinical and CLLspecific patient data. The results showed that the multi-outcome models outperform single-outcome models in predicting treatment initiation, the risk of death, and marginally in predicting the risk of infection. Jointly learning to predict the risk of infection and the risk of death improved the performance of the both tasks which indicates an association between the risk of infection and the risk of death. In addition, a multi-outcome model designed to predict all the three outcomes achieved the best performance in predicting treatment initiation. These findings confirm the advantage of multi-outcome models over single-outcome models in predicting clinical outcomes. Furthermore, using multi-outcome approach, predictive models in clinical settings can go beyond simple prediction and discover dependencies among outcomes.

How sustainable is your project?

The ultimate goal of this research is to improve decision making process before initiating treatment via precision medicine. This ultimately help us to provide the best treatment option for all patients. Finally, our aim is to adopt fairness framework in our modeling approach.

How can we improve specialist health services for children with multireferrals? Parent reported experience.

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The aim of the present descriptive study was to explore how to improve specialist health services for children with multiple referrals due to complex health complaints. Based on parent reported experiences of health services, we attempted to identify key areas of improvement. Parents/guardians of 250 children aged 6-12 years with multi-referrals to the Departments of Pediatrics and Child and Adolescent Mental Health at Haukeland University Hospital between 2013 and 2015 were invited. Their experience with the services their children received was collected through a questionnaire. Possible associations between overall experience and possible predictors were analyzed using bivariate regression.

148 (59%) out of 250 invited parents responded. Mean scores on single items ranged from 3.18 to 4.42 on a 1-5 scale, where five is the best possible experience. In the multiple regression model, perception of wait time, accommodation of consultations, providing adequate information about the following treatment, and collaboration between different departments at the hospital were all statistically significantly associated with parents overall experience of care.

The study support tailored interdisciplinary innovations targeting wait time, accommodation of consultations, communication regarding the following treatment and collaboration within specialist health services for children with multi-referrals due to complex health complaints.

Fair Pathways to net zero healthcare

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It is now clear that the health sector is not only at risk from climate change but also a major source of greenhouse gas emissions. In response, a growing number of healthcare systems have committed to mitigate their climate impact. To date, 18 countries have committed to developing net zero healthcare systems before 2050, comprising of high-, middle and low-income countries.

The work uses descriptive quantitative analysis to explore the multidimensional inequalities in health sector emissions. We use data sets from the Global Burden of Disease (disease burden), World Bank (emissions, income), Notre Dame Global Adaptation Initiative (climate vulnerability) and World Inequality Database (emissions inequality).

Healthcare's carbon footprint represents around 4-5% of global emissions. Current healthcare emissions show huge variation between countries and is projected to increase towards 2050. Delivering Universal Healthcare will increase carbon emissions, potentially increasing healthcare's global carbon footprint by up to 50%.

Given the huge variation in available financing, historical carbon emissions and unmet health needs, policy makers must pay close attention to inequality on the pathway to net zero healthcare.

How sustainable is your project?

My conceptual dimension of my project uses publicly available datasets. I am doing one long overseas research stay in 2023, rather than many small visits, and I'm using zoom for my qualitative interviews. Researching climate change, I try to do what I can to justify my travel.

When Should Countries Discontinue Intermittent Preventive Treatment Against Malaria in Pregnancy? A cost Effectiveness Analysis

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The world Health Organization recommends intermittent preventive treatment with sulphadoxine pyrimethamine (IPTp-SP) in addition to the basic strategy for controlling malaria and its effect during pregnancy, in areas of moderate to high transmission in Africa. The basic strategy includes delivery and use of insecticide-treated mosquito net (ITNs) and effective management of cases (ECM). Malaria transmission has been decreasing in sub-Saharan Africa countries. We calculated the cost-effectiveness of the IPTp-SP strategy at different levels of malaria transmission, to determine when it is no longer cost-effective.

We developed a decision tree to estimate incremental costs and health outcomes of maternal malaria infections and low birth weight between basic and IPTp-SP strategies. We modelled scenarios for five different levels of malaria transmission, estimated as parasite-prevalence from 19% to 1% among pregnant women at first antenatal care visit.

Compared to the basic strategy the IPTp-SP strategy delivered to a hypothetical cohort of 1,509,121 pregnant women in rural areas averted 290,733 DALY at an incremental cost of US$42,896. This yielded an ICER of US$0.15 per DALY averted when parasite-prevalence was 19%. The ICER was US$10, US$28, US$57, and US$166 per DALY averted when parasite-prevalence was 10%, 5%, 3% and 1 %.

Discontinuing the IPTp-SP strategy and recommending a basic strategy when parasite prevalence is below 3% is probably not cost-effective.

How sustainable is my research?

If we determine the level of malaria transmission below which provision of IPTp-SP is no longer cost effective. Resources reallocation to other interventions would contribute to improving the quality of life of the society.

Automated sequence analysis pipeline using Nextflow

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The advent of next generation sequencing (NGS) technologies has not only provided us with an abundance of data but has also presented us with a challenge of analyzing it. The paramount challenge in analyzing the copious amount of data is using the optimal resources from the myriad tools available. To overcome this, we propose an "Automated sequence analysis pipeline" which is optimized for DNA and RNA sequencing data. This pipeline is based on next flow scripting language and uses Anaconda package manager to manage the run environment. The whole pipeline is dockerized making it easier to deploy in all operating systems. We have developed pipelines to be used for germline DNA sequencing and RNA sequencing data. The specialty of the DNA pipeline is that it uses the combination of different variant callers and presents us with a consensus VCF output. This consensus calculation is implemented to get more dependable variants. The objective was to develop a scalable pipeline which integrates the fragmented tools and enhances reproducibility of the results. We have evaluated the pipeline with Genome in a bottle (GIAB) datasets and found the results to be consistent. The ease of installation facilitated by the pipeline enables computational reproducibility providing researchers more time for downstream analysis.

Social and environmental determinants of health among family caregivers of older adults in Finland

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Although the academic literature has focused on family caregivers' health outcomes, little is known about the social and environmental determinants of health and the extent to which they relate to health disparities among family caregivers caring for older adults. The purpose of the study was to describe the prevalence of diseases and the association with social and environmental determinants of health among family caregivers caring for older adults in Finland. Therefore, a cross-sectional analysis was conducted. The study participants were interviewed on sociodemographic factors, comorbidity, and the World Health Organization Quality of Life Questionnaire. Independent samples t-test, analysis of variance, and chi-square analyses were used to assess the social and environmental factors' association with health outcomes. Finally, a total of 126 family caregivers participated in this study. The mean age of study participants was 74 years, and most were female, married, and from an urban area. Family caregivers' older age and lower financial satisfaction were the main factors associated with the health inequalities. Older age was associated with age-related eye disorders, hearing impairment, coronary heart disease, and comorbidity. Family caregivers' lower financial satisfaction was associated with diabetes, depression, and higher body mass index. To enhance health equity, nurse-led interventions, a life course approach, and intersectional actions are required.

How sustainable is you project?

Sustainability can be applied to this project. Family caregivers' good health status is essential to maintain caregiving in the future. Therefore, it is necessary to assess family caregivers' health inequalities and find solutions to narrow these avoidable health disparities.

A sweet fact: having glucose in urine is normal

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There is no quantitative culture in urinalysis. A wide usage of glucose test strips (with detection limits as high as 5.6 mmol/L) in clinical use has led to an apparent misconception, including contemporary renal physiology textbooks, that normal human urine does not contain glucose. Using quantitative NMR spectroscopy, we analysed overnight spot urine samples from two independent population cohorts: the Northern Finland Birth Cohort 1966 and 1986 with 4,482 (age 46 years, 43% men) and 1,010 (age 33 years, 42% men) participants, respectively. Most of the participants studied here were normoglycaemic (serum fasting glucose <5.6 mmol/L). We were able to detect and quantify glucose in 99.1% of these 5,492 urine samples and the concentration distributions were almost identical, slightly positively skewed with a median relative concentration of 24.2 and 22.5 mM per 1 mM creatinine in NFBC1966 and NFBC1986, respectively. The relative concentrations appeared slightly higher for women. These direct quantitative molecular data unequivocally shows that glucose is always present also in the urine of normoglycaemic individuals. This is a fundamental issue that should be acknowledged and corrected in elementary teaching materials. The present newly introduced methodology – feasible in large-scale epidemiology and clinical studies – opens a novel possibility to study completely unexplored urinary glucose concentrations at the population level.

How sustainable is your project?

Urine has been regarded as waste for a long time. Actually, non-invasive urine samples contain potential source of information not available in routine blood samples, urinary metabolites has potential in epidemiology and translational medicine.

Childhood Cancer Risk Among Children with Major Birth Defects By Sex

Dagrun Daltveit[1], Kari Klungsøyr[1,2], Anders Engeland[1,2], Anders Ekbom[3], Mika Gissler[3,4], Ingrid Glimelius[5], Tom Grotmol[5], Laura Madanat-Harjuoja[6,7,8], Anne G Ording[9], Henrik T Sørensen[9], Rebecca Troisi[10]

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Worldwide, 400,000 new childhood cancer cases are diagnosed each year. The underlying causes are largely unknown. Childhood cancer is more common among children with birth defects, suggesting a common aetiology. Whether this association differs by sex is unclear. To identify associations between birth defects and childhood cancer overall and by sex.

We performed a population-based nested case-control study in four Nordic countries in the period 1967-2014. Cases were defined as live-born individuals in the birth registries, with a subsequent cancer diagnosis registered in the cancer registries. Controls were matched on country and year of birth, and selected among persons alive, living in the country and cancer-free at time of data linkage. We estimated relative risks of cancer by odds ratios from logistic regression models with 95% confidence intervals.

More than 20,000 children were diagnosed with cancer during the study period. The risk of cancer was higher among children with chromosomal (10-fold) than non-chromosomal defects (2-fold). The association between birth defects and childhood cancer was stronger among females (3-fold) than males (2-fold).

The birth defect–cancer associations were stronger among females than males. Further studies on the underlying mechanisms are needed.

Characteristics of rapid plaque progression in patients with symptomatic non-obstructive coronary artery disease

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Coronary artery plaque progression is associated with increased risk of cardiovascular events. Characteristics of rapid plaque progression in non-obstructive CAD remain unexplored.

We identified 23 patients (61±11 years, 44% women) with non-obstructive CAD undergoing clinically indicated serial CCTA with >1 year interscan interval from the Norwegian Registry of Invasive Cardiology. All coronary segments were analyzed at baseline and follow-up using a semi-automated analysis software. Rapid plaque progression was defined as the highest tertile of annualized plaque volume progression (>1.0% per year). Total and compositional plaque volume were assessed for each coronary artery segment.

Patients with rapid plaque progression had higher calcium score, segment involvement score and prevalence of left main stem disease at baseline compared to patients without rapid plaque progression (all $p<0.05$). Baseline compositional plaque volume in the rapid progression group was characterized by significantly less fibrous plaque($p<0.05$). Patients with rapid plaque progression had faster progression of fibrous plaque and noncalcified plaque compared to patients without rapid plaque progression (all $p<0.05$). At follow-up, 43% of patients with rapid plaque progression developed obstructive CAD, compared to the no progression group ($p<0.05$).

Rapid plaque progression in non-obstructive CAD is characterized by faster progression of noncalcified plaque.

How sustainable is your project?

Advanced plaque analysis by CCTA enables precise assessment of plaque subtypes in coronary artery disease, which could contribute to optimize risk stratification and identify individuals with high risk of rapid plaque progression in non-obstructive CAD.

The importance of time since last meal when measuring blood biomarkers: Results from the Hordaland Health Study

Åslaug Anfinsen[1], Hanne Rosendahl-Riise[1], Ottar Nygård[2], Grethe Tell[3], Per Magne Ueland[3], Arve Ulvik, Adrian McCann[3], Jutta Dierkes[1], Vegard Lysne[2]

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Dietary intake has pronounced effects on biomarker concentrations in the hours after dietary intake, and the current practice in epidemiological studies of distinguishing between fasting- and non-fasting samples when evaluating biomarker data may be inadequate.

To describe biomarker concentrations during the first seven hours after dietary intake, focusing on amino acids, lipids, one-carbon metabolites, and biomarkers of vitamin status. Methods: We used cross-sectional data from 5835 participants in the Hordaland Health Study. Estimated marginal geometric mean metabolite concentrations were plotted as a function of time since the last meal, up to 7 hours, adjusted for age, sex, and BMI.

A considerable variation was observed for most biomarker concentrations during the first 7 hours after dietary intake. We observed a common pattern among several of the amino acids and one carbon metabolites with the highest concentrations being observed during the first three hours after dietary intake. Blood lipids and lipid-soluble vitamins were largely stable, except for phylloquinone and triglycerides, where highest concentrations were observed one hour after dietary intake.

Our findings suggest that the effect of dietary intake should be accounted for be accounted for by noting the exact time since the last meal, instead of categorizing samples into fasting and non-fasting.

Targeting AML by the Leukemic Matrisome Interface

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Acute myeloid leukemia (AML) is an aggressive form of haematological cancer. The matrisome plays a crucial role in transitioning from normal haematopoietic- to leukemic stem cells (LSC). In the bone marrow, LSC interact with osteoblasts (OB) and actively create a leukemic niche to evade chemotherapy and thus allow relapse. We investigate the composition of the leukemic matrisome interface (LMI) between AML cells (AMLs) and OB and the intercellular communication networks responsible for LMI formation.
We established an AML-OB co-culture (CC) model with human KG1a-GFP AMLs and murine MC3T3-dTomato OB. The CCs are treated with the anti-leukemic drug Ara-C, analysed via confocal microscopy, flow cytometry and qPCR for AML and OB marker expression and investigated for LMI changes by mass-spectrometry.
Our results show that in CCs AMLs and OB form morphological distinct layers. A top layer with floating AMLs, a middle layer and bottom layer where AMLs and OB have physical contact. At the OB-AML interface, in addition to loosely attached typical round shaped AMLs; flat, macrophage-like AMLs appear and OB acquire a pleiomorphic shape. In line with these changes, we observed a hindered osteogenic differentiation and drastic changes in the matrisome.
These findings validate our in vitro model which inexpensively and scalarly recreates the patients' bone marrow minimal AML niche, deepen our understanding of leukemogenesis and will help unveil new therapeutic targets for AML patients.

How sustainable is your project?

We developed an in vitro co-culture model to mimic the acute myeloid leukemia (AML) patients minimal leukemic bone marrow niche. This allows us to reduce in vivo studies to find new therapeutic targets to a minimum.

ATRAID, a highly glycosylated protein localized to membranous cellular compartments

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All-trans retinoic acid-induced differentiation factor (ATRAID) is a well conserved, poorly characterized gene, its expression induced by all-trans retinoic acid. Two transcripts are listed in NCBI, the transcript 3 (isoform C) and transcript 1 (isoform A). The difference between them is lacking N-terminal signal peptide in isoform A. Both isoforms are predicted to contain several N-glycosylation sites. ATRAID binds to NELL-1 at the nuclear envelope of human osteoblasts and dental pulp cells decreasing proliferation by reducing the expression of cyclin D1 and increasing differentiation. In ARPE-19 cells, ATRAID accelerates cellular senescence, its expression has increase in RPE-cells derived from aged mice. ATRAID locates to the mitochondria of ARPE-19 cells and binds to NRF2. Its overexpression induces morphological changes and functional disruption in mitochondria. Moreover, it is shown that ATRAID binds with lysosomal proteins, LAMP1 and SLC37A3. Complex of ATRAID/SLC37A3 is required for releasing of nitrogen-containingbisphosphates (N-BPs) from the lysosome to the cytoplasm. In this study, we aim to find more about ATRAID. We produced transgenic cell lines expressing ATRAID with a cterminal Flag-tag. Western blotting revealed ATRAID is highly N- glycosylated. The combination of subcellular fractionation and ICC showed that ATRAID is absent from the cytosol and the nucleus and is located in the plasma membrane and intracellular vesicles or compartments.

Dietary intake and adherence to dietary guidelines in the Hordaland Health Studies

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The Hordaland Health Studies (HUSK) is a community based observational study, initially conducted in 1992-93. The second round of the study, HUSK2 was conducted between 1997-1999. From 2018 to 2020, men and women born 1950-51 who had previously participated in HUSK2 were invited to participate in HUSK3. Dietary intake was assessed in HUSK2 and HUSK3 via food frequency questionnaires (FFQs). An inadequate dietary intake is considered a modifiable risk factor for age-related decline in muscle strength and mass, and the time span between HUSK2 and HUSK3 represents a crucial time for disease prevention. We aim to explore dietary changes and adherence to food-based dietary guidelines in the 1950-51 cohort of HUSK.

In HUSK3, 2192 participants were followed up, out of which 1704 completed the FFQ. There was a statistically significant increase in the daily intake of fruit and berries, vegetables, meat, total fish, and fatty fish from HUSK2 to HUSK3. A statistically significant decrease was observed in the daily intake of milk and yoghurt. The total HUSK3 cohort showed the following adherence to dietary guidelines: fruits and berries (66%), vegetables (75%), red meat (6%), total fish (91%), fatty fish (34%), wholegrain (50% in men vs 56% in women), and energy percentage of added sugar (96%). Preliminary analyses indicate an increased intake of most food groups and fairly high adherence to FBDGs in the cohort.

Sustainable work participation after rehabilitation. Preliminary results

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Function, coping resources and health are central factors in rehabilitation after injury or sickness. To investigate how these factors are associated with sustainable work participation during 12 months after rehabilitation is the aim of this study.

A sample of 412 employed patients (≤ 67years) referred to inter-professional rehabilitation in western Norway were included. In surveys patients reported mental (MCS) and physical (PCS) function (SF-36), self-perceived health (EQ-VAS) and coping resources (SOC-13). Data on work participation was retrieved from Statistics Norway; sustainable work participation was defined as no sick leave beyond 16 days during 12 months after rehabilitation. Ordinal regression was used to analyse association between sustainable work participation and MCS, PCS, EQ-VAS and SOC-13, adjusted for age, sex and diagnoses.

The levels of MCS and PCS (SF-36) were found to be associated with sustainable work participation; OR 0.96, 95% CI 0.92-0.99, p = 0.004 and OR 0.93, 95% CI 0.90-0.97, p < 0.001, respectively (Pseudo R2 = 0.1133). EQ-VAS and SOC-13 were significant in crude analysis, but not in the fully adjusted model.

Achieved higher level of mental and physical function were associated with sustainable work participation 12 months after inter-professional rehabilitation. This suggest that rehabilitation for functional improvement can promote sustainable work participation after injury or sickness

How sustainable is your project?

In this project, we are investigating sustainability in work participation after rehabilitation. We are presenting a preliminary definition of sustainable work participation after rehabilitation and preliminary results.

Extracellular vesicle signaling in induction of nephrogenesis

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Nephron formation (nephrogenesis) is occurring through a complex reciprocal interaction of signaling molecules between the ureteric bud (UB) and metanephric mesenchyme (MM). How the UB and MM cells are interacting is unclear and the signaling molecules include Wnts and cell growth factors. The study identifies a novel way of signaling interaction happening via secreted extracellular vesicles (EVs) during nephrogenesis using mouse model. EVs mainly include exosomes (40-100 nm) and microvesicles (100-1000 nm). Our study showed EVs based communication between UB and MM cells during nephrogenesis. Both UB and MM cells were found to secrete EVs. In this study, UB cells were used to tag secreted EVs with green fluorescence (UB-PalmGFP cell line). We showed that palmGFP-containing EVs, secreted by UB cells, are found in the developing nephrons. The UB cell line derived EVs increased the survival and competency of MM cells and enhanced nephrogenesis. The functional role of EVs was studied by inhibiting biogenesis of EVs by drugs (GW4869, RBC8 and BQU57) and knock out/down of genes involved in biogenesis of EVs (Rab35, RalA/B). The results showed that genetic inhibition of EVs is partly inhibiting nephrogenesis (inhibited nephrogenesis), suggesting that UB derived EV signal is important for the nephrogenesis. In addition, when the EVs were provided to the inhibited nephrogenesis, they significantly boosted nephrogenesis which confirms the significant role of EVs during nephrogenesis.

How sustainable is your project?

In my doctoral study project we used novel technologies which saved hundred of animals from being sacrificed for research purposes. In this project, we generated our own cells and then those cells were being used to avoid the usage of mouse tissues.

Strong and steady – preventing functional decline and falls among older adults together with volunteers

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Falls account for the largest proportion of injuries among older adults above 65 years and can have vital consequences like decrease in functional capacity and loss of independence. In addition, falls contribute to substantial costs in health care. Exercise with focus on improving strength and balance have shown to be the most effective single measure to prevent falls among community-dwelling older adults.

With an increasing proportion of older people in the society, without necessarily being more health care professionals to deal with them, there will be a growing pressure on health care services. Physiotherapists have knowledge about exercise interventions and have traditionally delivered these. But can physiotherapists use their knowledge to take another role in the preventive work?

With funding from the Norwegian Directorate of Health, a new exercise concept called Sterk og stødig (Strong and steady) was developed as a collaboration between NTNU and the physiotherapy department in Trondheim municipality. Physiotherapists use their knowledge to train and guide volunteers that are instructors to exercise groups. As part of the concept course modules for both the physiotherapists and the volunteers are made. In this way one physiotherapist can guide five instructors that reaches 50-100 older adults with a quality assured exercise offer. Today Sterk og stødig have been implemented in about 100 Norwegian municipalities.

How sustainable is your project?

One way to ensure sustainability for the future health care services is to change the way health care professionals use their knowledge.

Phase separation and particulate leaching integrated 3D printing of porous scaffolds for tissue engineering applications

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3D printed scaffolds for bone tissue engineering must possess multiscale porous structure to promote cell attachment, proliferation, and tissue formation. Although, 3D printing technologies enable fabrication of reproducible and precise 3D complex structures, they are incapable to induce micropores within deposited filaments. The aim of this study was to 3D print polycaprolactone (PCL) scaffolds with internal multiscale microporosity by integrating non-solvent induced phase separation (NIPS) and salt-leaching techniques (SLT). Briefly, 30% (w/v) PCL solution was prepared by dissolving PCL in acetone with and without 7 or 14% (w/v) NaCl. After printing, scaffolds were washed in DI water to leach the salts out for 14 days. The accuracy and quality of the printed scaffolds were assessed with a stereomicroscope. Scaffolds demonstrated 20% shrinkage after drying. To quantify porosity, pore volume and pore size, micro-CT was conducted. PCL scaffolds with 14% NaCl exhibit significantly higher pore volume with larger pore size compared to that with 7% and without salts. However, there is no significant difference in overall porosity between the salt added groups whereas they are porous than neat scaffolds. Morphological characterization utilizing scanning electron microscope (SEM) confirmed the porous structure of the printed scaffolds. In conclusion, combining NIPS and SLT with 3D printing technology is promising strategy to tailor porosity of tissue engineering scaffolds.

Combining Radiation and Immunotherapy to control solid tumor growth: Testing the role of tumor size using in vivo model

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Combining conventional cancer therapies facilitate synergistic anti-tumor activity, where clonal heterogeneity and immune escape mechanism of solid tumor resistance could be prevailed. The radiation induces direct cell damage while also exposing tumor associated antigens. This activates immune cell infiltration and cancer cell recognition, which would further enhance checkpoint blockage therapy.

Preclinical C3H mammary carcinoma in vivo model was used to compare the tumor growth delay caused by combining proton radiation with Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) therapy against individual therapy. Treatments were started when tumors reached sizes of 50-400 mm3 and included single dose of proton radiation (20 Gy) followed by 4 CTLA-4 injections (10mg/kg). Tumor growth time to 1000 mm3 was the end point for this study.

Median time (days) of tumor growth of all the groups was determined. Anti-CTLA-4 alone group only had a small effect in the smallest tumors while a much-enhanced response was obtained when it was combined with proton radiation. As the tumor size increases, the effect of combination becomes less apparent. Radiation only group has shown to delay growth of larger tumors, but no benefit of combination could be observed.

Tumor size at start of the treatment clearly played a significant role, with smaller tumors showing the greatest enhancement between combinations and their respective controls.

How sustainable is your project?

The in vivo experiments are planned kepping in mind the prinicple of the 3R rules, and there is great relavence for clinical translation for combining radiation and immunotherapy, and thus further experiments are also planned, not only in preclinical setting, but also for human clinical trials.

Cardiovascular mortality among persons with advanced chronic kidney disease: a nationwide cohort study

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Chronic kidney disease (CKD) and diabetes are both well-established risk factors for cardiovascular disease and mortality. The aim of this study was to examine the risk of cardiovascular mortality among persons with advanced CKD with and without diabetes.
In a nationwide registry-based matched cohort study, we identified all Danish persons aged ≥ 18 years with advanced CKD between 2002 and 2018. Non-exposed persons with eGFR ≥ 30 mL/min/1.73m2 were matched on birthyear and sex. Multivariate Cox regression was performed to calculate standardized risk of cardiovascular mortality.
We included 135,824 persons with advanced CKD. The mean age was 76 years. 31,991 (23.6%) had diabetes with a mean duration of 9.7 years. For persons with diabetes, the standardized absolute risk (95% CI) of cardiovascular mortality was 9.6% (9.3-9.8) after 1 year and 28.4% (27.9-29.0) after 5 years. Compared to age- and sex matched persons, the corresponding relative risk (95% CI) was 3.1 (3.0-3.1) and 2.2 (2.2-2.3), respectively. Among persons without diabetes, the standardized absolute 1- and 5-year risk was 7.7% (7.6-7.8) and 23.7% (23.4-23.9), respectively. The corresponding relative risk was 2.5 (2.4-2.5) and 1.9 (1.8-1.9).
Persons with advanced CKD had a two- to three-fold increased risk of cardiovascular mortality compared to the background population, with the greatest risk among persons with concomitant diabetes.

Effect of Semaglutide in Abdominal Aoric Aneurysm Development

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Abdominal Aortic Aneurysm (AAA) consist of a localized dilatation of the aorta, corresponding to an increase by 50% of the normal artery diameter. Interestingly, diabetes mellitus (DM) and metformin treatment seem to have a protective effect for AAA development. Glucacon-like peptide 1 receptor agonists (GLP-1Ra) are a class of antidiabetic drugs that mimic endogenous GLP-1 action. Liraglutide, a long-acting GLP-1Ra (once daily subcutaneous administration in type 2 diabetic patients) pre-vents abdominal aortic aneurysm (AAA) in apolipoprotein E (ApoE) deficient mice infused with Angiotensin II. Semaglutide is a GLP-1Ra with improved half-life, allowing for once weekly subcutaneous administration, thus be-coming more convenient for patients. This manuscript aims to discover if Semaglutide is as effective as Liraglutide in preventing AAA development. AAA was induced in ApoE deficient mice by subcutaneous infusion of 1000 ng/kg/min of AngII, through a mini-osmotic pump, for 28 days. Mice were divided into two experimental set-ups: a rescue trial, where treatment with Semaglutide began one week after disease induction, and a prophylactic trial, where treatment started simultaneously with disease induction. Results indicate that Semaglutide does not have an effect in aneurysm growth, but rather acts by preventing rup-ture in the early stages of disease development. However, further studies are necessary to clarify Semaglutide’s effect and mechanisms of action in AAA development.

Relevance of sustainability in basal research

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What is the purpose of medical research? Pharmaceutical companies might claim a genuine interest in helping patients and advancing healthcare, but this is obviously coupled with economical interest. The latter is reflected in how companies prioritize their research on projects that are expected to be economically profitable. What is desirable for our species as a whole might be another matter entirely, but with skyrocketing expenses for medical research the economical aspect cannot be overseen. Basal research on the other hand is aimed towards acquisition of new knowledge for the mere purpose of expansion of our common base of knowledge. Historically both basal research and targeted research have contributed to breakthroughs in diagnosis and treatment. With increasing costs related to advanced medical research it is however becoming necessary to prioritize research that is expected to have a larger overall benefit. The relation between cost and benefit is one way of evaluating sustainability of a project, but estimating these determining parameters can be difficult. Especially for basal research projects this can prove to be difficult since consequences of any findings might not be immediately evident. My research can be classified as a combination of basal and targeted research. I focus on cancer patients being treated with different modalities of immune therapy, and I use mass cytometry to evaluate changes in immune profile in blood and tissues during treatment.

How sustainable is your project?

In my poster I will briefly discuss what parameters are relevant for evaluating sustainability. Furthermore, I will evaluate my project using these same parameters, and discuss how I can try to narrow the gap between my academic research and clinical application.

Tyrosine hydroxylase deficiency: developing precision medicine approaches to treat rare metabolic disorders

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Tyrosine hydroxylase deficiency (THD) is a rare, but debilitating neurometabolic disease associated with defective dopamine (DA) synthesis. THD belongs to the family of Dopa-responsive dystonias (DRD), where supplementation of LDOPA - the lacking enzyme product of TH and precursor to DA - is used to ameliorate the most severe symptoms, in some cases, leading to their complete resolution. When successful, the currently available options for medical intervention merely bypass enzyme dysfunction without addressing the root cause. However, as a subset of patients with severe cases of THD has poor or no response to L-DOPA, an urgent demand manifests for more precisely tailored treatment options. A further complication clinicians face is that THD patients often exhibit complex and variable phenotypes where symptoms overlap with cerebral palsy and other metabolic disorders, often resulting in late or inadequate intervention. For a viable precision medicine (PM) approach to become attainable and address the shortcomings of current therapeutic strategies, a combination of improved selection of treatment options and more accurate genotypephenotype mapping are required. We provide an update on this underdiagnosed illness related to its expanding phenotype, prevalence, ongoing efforts to develop novel therapeutics and describe how different modeling approaches can be used for the improvement of genotype to phenotype predictions and for in silico testing of treatment strategies.

3D window screens to create window double screen traps for mosquito control

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Mosquitoes are a notorious vector for several deadly infections such as malaria. Contemporary mosquito control method relies heavily on insecticide-based approaches. The excessive usage of insecticides has led to the emergence of insecticide resistance in mosquitoes which now is a huge threat for major vector control campaigns. In this growing scenario of insecticide resistance, demand for a more sustainable insecticide-free mosquito control approach is higher than ever. To address this, we have been working on a novel method which focuses on blocking mosquito-host contact by using a state of the art screened (3D screens) window. We used commercial screen materials made of polyester and polypropylene to design novel mosquito screens that provides remarkable additional benefits to those commonly used in house screening. The novel design is based on a double screen setup made of a screen with 3D geometric structures parallel to a commercial mosquito screen creating a trap between the two screens. Owing to the design of the 3D screen, mosquitoes can penetrate the 3D screen from one side but cannot return through the other side, making it a unidirectional mosquito screen. Therefore, the mosquitoes are trapped inside the double screen system. As of now, the efficacy of 3D screens in capturing mosquitoes has been tested in phase I laboratory studies (2015) and phase II semi field trial (2016-2017). A large-scale phase III community trial is in progress in north-eastern Tanzania.

How sustainable is your research?

The novel approach for mosquito control we are evaluating at the moment is based on sustainable approach itself. We are not relying on contemporary insecticide based approach but rather focusing on chemical free, environmental friendly and sustainable physical screening and trapping system.

Response of Stem Cells to 3D bioprinted Alginate-Gelatin-based Structures

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In the recent years, three-dimentional (3D) bioprinting has attracted a great attention in the field of tissue engineering. Hydrogels based on alginate (Alg) and gelatin (Gel) have been extensively used for extrusion-based 3D bioprinting as they are biocompatible natural materials. One of the challenges in the bioprinting of cell-laden hydrogels (bioinks) is to find a suitable crosslinker that can enhance the strength of bioprinted structures without affecting cell viability negatively. This study aims to compare the effect of different crosslinkers for Alg-Gel-based bioinks on stem cell viability and proliferation. Here, human mesenchymal stem cells were bioprinted in Alg-Gelbased bioink and crosslinked with calcium chloride (CaCl2) alone or double crosslinked with either genipin (GP) or transglutaminase (TG). All the crosslinking methods maintained good stability of the biorinted structures for 7 days. LIVE/DEAD staining, PicoGreen and alamarBlue assays were performed over 7 days to evaluate the viability, metabolic activity and proliferation of cells. The results obtained from these assays demonstrated that cells have better viability, higher metabolic activity and proliferation in the bioinks that were double crosslinked with CaCl2 and TG. This preliminary data highlights the promising potential of double-crosslinking of Alg-Gelbased bioink with CaCl2 and TG for bioprinting applications.

How sustainable is your project?

Using 3D bioprinter for tissue engineering applications has been started a few years ago in our group; and after each research project new data is being built. What has been achieved in the present research will be added to the previous data to build-up more results for a larger project.

Mortality, stroke recurrence and functional dependency after first – ever ischemic stroke in Central – Norway

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Stroke incidence and mortality have drastically decreased in Norway. Aims. Provide updated estimates on mortality, recurrent stroke, and functional dependency among patients with firstever ischemic stroke, and assess prognostic factors associated with poor outcome with focus on vascular risk factors, stroke characteristics, function, age, and comorbidity burden. MIDNOR-STROKE is a multicenter prospective study including patients with first-ever ischemic stroke admitted to stroke units during 2015-2017. Data on survival, stroke recurrence and functional disability (i.e. Modified Rankin scale (MRS)) were collected during hospital stay and 12 months. Patient data from national health registries were retrieved. Multivariate regression models and selected prognostic factors were used to analyze predictors of a poor outcome. N= 794. Following 1- year, 7.6% had died, 5.7 % had a recurrent stroke and 22.4% were functionally dependent. Our analysis revealed that age, stroke characteristics, comorbidity burden, hypertension and coronary heart disease were associated with mortality. For stroke recurrence, comorbidity burden was the only independent predictor. Age, pre-stroke function and stroke severity as well as etiology increased risk of disability. Stroke prognosis is dependent on age, pre-stroke function, comorbidity burden, stroke severity, hypertension and coronary heart disease.

How sustainable is your project?

As this is a large multicenter observational study including approximately 800 study participants. Reusing the extensive data collection for several research projects would be sustainable in terms limiting the use of materials, cost of personell for patient follow-up and time.

Designing an exercise program for people receiving opioid agonist therapy: Preliminary results from a qualitative study

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Opioid use disorder patients receiving opioid agonist therapy suffer from high morbidity and reduced quality of life. Physical exercise can help patients with substance use disorders to reduce their burden of substance use and improve their health. Despite this, compliance with exercise programs is inadequate in substance use treatment. Interestingly no large randomized controlled trials with physical exercise have been developed and tested in an opioid agonist therapy setting. This study aimed to examine how an exercise program should be developed and implemented in opioid agonist therapy clinics from a patient perspective. Qualitative data (N=14) were gathered in several outpatient clinics providing opioid agonist therapy in Western Norway. Using a semi-structured interview guide with pre-determined themes and systematic text condensation to analyse the results. The CapabilityOpportunity-Motivation to Behaviour (COM-B) theory was the underlying theoretical perspective. The preliminary results address COM-B's capability, opportunity, and reflective motivation as vital elements to start exercising. These findings may help future research address low compliance in exercise interventions and perform a large randomised controlled trial in opioid agonist therapy clinics.

How sustainable is your project?

People who take part in regular physical activities have been proven to benefit their physical, mental, and social wellbeing. The Sustainable Development Plan 2030 is acknowledged exercise as "an important and cost-effective enabler" for the achievement of SDGs globally.

Synergistic effect of surface etching and inner design of 3D printed scaffolds for bone tissue engineering

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Polycaprolactone (PCL), a biocompatible thermoplastic with strong mechanical properties, offers wide possibilities for the biofabrication of bone scaffolds. Its low melting point is very interesting for 3D printing, as it allows the engineering of defect-specific scaffolds with different inner patterns. Such scaffold can act as a skeleton on which cells can attach, and proliferate, while its inner pattern impacts the cell seeding efficiency. However, PCL has hydrophobic properties, resulting in poor cell attachment. To tackle this problem, methods have been developed to increase hydrophilicity of PCL, among which, chemical etching. In this study, we investigated the synergistic effect of different inner pattern of 3D printed PCL scaffolds and a chemical etching, on cell colonization. The scaffolds were characterized by stereo and scanning electron microscopy, and mechanical testing machine. The response of human bone mesenchymal stromal cells to these scaffolds was evaluated in terms of cell viability and morphology. Etching of PCL scaffolds induced homogeneous micrometre roughness. Tensile strength tests showed that, scaffolds with the less compactness gave higher results of modulus of elasticity. Regardless of the inner pattern, all scaffolds supported cell adhesion with high cell viability after 7 days. In conclusion, the combination of surface modification and inner pattern design has a promising potential to enhance cell attachment on 3D printed PCL scaffolds.

Developing a supervised machine learning model for predicting perioperative acute kidney injury in arthroplasty patients

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A shortened version of an original article abstract published in Computers in Biology and Medicine 2022:144 by Nikkinen O, Kolehmainen T et al., under CC-BY 4.0 license.
Perioperative acute kidney injury (AKI) is a common complication of lower limb arthroplasties. Our aim was to create a machine learning (ML) model to predict AKI defined by both serum creatinine (sCr) levels and urine output (UOP).
Retrospective, register-based study assessed 648 patients who underwent primary knee or hip replacement at Oulu University Hospital, Finland, between Jan. 2016 and Feb. 2017. The RUSBoost algorithm was used. Models were trained and validated using a five-fold cross-validation. External test set was not available at the time of the study. The performance of both the sCr level- and UOP-based AKI models improved when pre-, intra-, and postoperative features were used together. The best sCr level-based AKI model performed as follows: AUROC of 0.91, area under precision-recall (AUPR) of 0.35, sens. of 0.88, spec. of 0.87, and precision of 0.22. This model correctly classified 22 out of 25 patients with AKI. The best UOP-based AKI model performed as follows: AUROC of 0.98, AUPR of 0.48, sens. of 0.88, spec. of 0.93, and precision of 0.34. This model correctly classified 23 out of 26 patients with AKI.
The results of our study are not generalizable, and larger studies are needed. The best ML method for this kind of data remains uncertain.

How sustainable is your project?

In Nordic healthcare a vast amount of patient related data accumulates and is stored. The same trend is to be expected in low/middle income countries. Machine learning methods should be studied and used to interpret the data in a way which could prevent adverse outcomes and improve cost-effectiveness.

Birthweight and cardiometabolic risk profile during mid-adolescence: findings from a rural birth cohort in Bangladesh

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We investigated the association of birthweight (BW) with markers of cardiometabolic risk in a rural birth cohort. MINIMat (Maternal and Infant Nutrition Interventions in Matlab)–a community-based, randomized trial–examined the effect of prenatal food and micronutrient supplementation on maternal and birth outcomes from 2002–2004. The children born to the participating mothers formed the MINIMat cohort. BW was recorded with an electronic scale (precision ±10 g). During the 15-year follow-up, we measured fasting plasma triglyceride (TG), total cholesterol (TC), low-density (LDL) and high-density (HDL) lipoproteins, glucose and insulin. Systolic blood pressure (SBP), body mass index and waist circumference (WC) were also measured. We calculated insulin resistance (IR) using the Homeostatic Model Assessment equation. The sample comprised 2252 adolescents (52.1% girls). The mean BW was 2690 g (standard deviation (SD) 392). The prevalence of low BW (<2500 g) was 30.6% (28.7–32.5). At 15 years, 7.1% (6.0–8.2) were overweight/obese. With each SD higher BW, the WC increased by 1.3% [95% confidence interval (CI): 0.9–1.8%; p<0.001]. One SD higher BW resulted in 1.5% higher HDL level (0.6–2.4%; p<0.001). Only among the boys, the TG level decreased by 2.9% with each SD increase in BW (0.6–5.2%; p=0.013). BW was not associated with SBP, TC, LDL or IR. The magnitude of the associations appeared small. Further research is needed to explore the lifecourse implication of these findings.

Improving anti-Yo diagnostics in paraneoplastic cerebellar degeneration

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Paraneoplastic cerebellar degeneration (PCD) is a severe autoimmune disease, where the immune system attacks the purkinje neurons of the cerebellum. This is due to a failure in the body's immune tolerance, as the immune system targets a neoplasm. With PCD the most common associated cancers are overian and breast cancer, and to aid diagnosis one look for an antibody in the sera of the patients, anti-yo. CDR2 is a protein which was long thought to be the main target of anti-Yo, and therefore most laboratory tests are targeted at CDR2. The cell-based assays used in laboratories today use CDR2 as the main antigen for anti-Yo but has a low specificity of 8%. Recent studies show that CDR2L seems to be the major target of anti-Yo. The objective of the project is to show that CDR2L is a more precise antigen for anti-Yo, than CDR2.
We analyzed sera and CSF from 44 anti-Yo PCD positive patients in our biobank and 30 blinded PCD patients from a partner in France, where 15 have anti-Yo PCD. In addition, we performed the analysis on 50 control sera from the blood bank at HUH, and 20 women with ovarian cancer but no neurological symptoms. The samples were analyzed on the most common tests used in laboratories today. All anti-Yo PCD patients tested positive on a CDR2L Cell-based assay and negative on the controls.
Conclusion: CDR2L should be included in the diagnostic workup of PCD.

Studies on pathogenic mechanisms of non-albicans Candida derived from oral cancer patients

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Mouth is a primary source of infections and Candida infections are associated with mortality. Oral Candida infections can be life threatening in medically compromised patients. The present study aims were to investigate differences in proteolytic activity of Candida strains and examine the prevalence of Candida strains in oral cancer patients of the Helsinki University Hospital. One hundred patients with squamous cell carcinoma of oral cavity were recruited to the study. Saliva samples were collected and cultivated on CHROMagar Candida medium. The API ID 32C yeast identification kit and Bichro-Dubli Fumouze latex agglutination test were used. Candida proteinase activity was analyzed using MDPF-gelatin zymography, fluorometric assays and degradation assays were performed using claudin-4 and human plasma fibronectin. The levels of IL-1β, IL-10, and TNF-α were measured using ELISA. These studies showed that C. albicans was the most common species in oral cavity of oral carcinoma patients. Differences existed in the proteolytic activity of non-albicans Candida (NAC) and C. albicans strains. The Candida strains degraded fibronectin and CLDN-4 and the degradation ability varied among the strains. C. tropicalis showed higher proteolytic activity compared with the other strains. The results showed a significant increase in IL-1β levels in subjects with NAC compared to Candida-negative saliva samples. NAC may play a role in tissue inflammatory response by inducing cytokine response.

Formal and informal resource utilization among home-dwelling people with dementia during the COVID-19 lockdown

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COVID-19 isolated home-dwelling people with dementia (PwD) from home care services, respite care, and daytime activities. The study aimed to investigate the consequences of these restrictions on informal (family) and formal (homecare staff) resource utilization among co-residing and visiting caregivers. We included 105 PwD (≥65 years old) and their caregivers in the prospective PANdemic in DEMentia (PAN.DEM) study. Primary outcome was change in formal and informal resource utilization in pre- (12 Dec. 2019 to 11 Mar. 2020) and during the lockdown periods (20 April 2020 to 15 May 2020). We investigated the associations between informal and formal care utilization, sociodemographics, and clinical variables. The results showed that during the first two months of lockdown, PwD missed on average 20.5 hours of formal care in a month leading to an approximately 100% increase in informal care. Visiting caregivers increased by 1.9 days, but co-residing caregivers increased their number of days providing ADL by approximately 7 days per month after adjusting for PwD and caregiver demographics and clinical variables. Decrease in home nursing care was particularly visible for PwD living alone. The care situation for PwD changed dramatically in the early phase of the COVID-19 pandemic, especially for those living alone. For future crises and the forthcoming postpandemic period, health authorities must plan better and identify and prioritize those in greatest need.

Modulation of myeloperoxidase-derived damage on extracellular matrix by plasma ions

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Oxidants are generated during many physiologic and pathological processes. Over-production is associated with host tissue damage. Unlike cells, the extracellular matrix (ECM) is poorly protected against oxidation, and evidence has been presented significant ECM damage in atherosclerotic lesions. Activation of resident leukocytes results in $O_2^{\cdot -}$ and H_2O_2 formation and the release of myeloperoxidase (MPO). MPO catalyzes conversion of H_2O_2 and Cl^- to damaging oxidant HOCl, but it can also oxidize Br^-, I^-, SCN^-, NO_2^- and organic substrates. We *hypothesized* that these ions might modulate the damage induced by HOCl.

We have quantified chlorination and nitration damage to both isolated human plasma fibronectin and cell-derived ECM induced by a MPO-H_2O_2 system in the presence of Cl^-, Br^-, I^-, SCN^-, and also with or without NO_2^- via ELISA and LC-MS. Nitration levels increased with increasing amounts of NO_2^-, while the extent of HOCl-generated damage decreased on both targets, indicating that NO_2^- can inhibit chlorination induced by MPO-H_2O_2-Cl^-. Chlorination was also quantified for other anion combinations, and it has been shown that SCN^- also decreased the extent of damage.

These studies suggest that elevation of both NO_2^- and SCN^-, which can be readily achieved in humans, may modulate the extent of damage induced at sites of inflammation, including within the artery wall during atherosclerosis development.

Modulating pre-cardiac signalling to produce cell populations for regenerative medicine

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Cardiovascular diseases are one of the leading causes of death worldwide, demanding better treatment approaches. The adult heart is an organ characterized by an extremely limited self-regenerative capacity. Although cardiac cells have been successfully generated in vitro in many studies, integrating them into the living heart has been the main challenge for personalized medicine. Employing in vitro differentiation systems of human embryonic stem cells, we seek to derive a cell population that is safe to introduce to the damaged heart and helps its regeneration. For this, we focus on the early specification mechanisms during gastrulation and seek to understand the signalling interplay that governs the cardiac progenitor formation. By modulating signalling pathways, we have derived proepicardium, a precursor of the epicardium, an outer layer of the heart that acts as a signalling centre to support cardiomyocyte integrity and gives rise to non-cardiomyocyte lineages such as coronary vasculature. However, the reactivation of adult epicardium after infarction is known to cause fibrosis. Thus, we contemplate that its precursor, proepicardium, might constitute a better source of regenerative signalling that could promote the proliferation within the damaged cardiomyocyte layer. We are currently characterizing the in vitro-derived proepicardial population by RNAseq to understand its developmental stages.

How sustainable is your project?

This project aims to dissect the signalling pathways governing heart development, in order to derive developmentally matched cardiac cells for personalized medicine. This will enable a more sustainable recovery than conventional therapies, improving the life quality of patients in the long term.

Hyaluronic Acid Coating Encourages Macrophage Infiltration in Poly(Llactide-co-trimethylene carbonate) Scaffolds

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PLATMC comprise a promising material for applications in tissue engineering, however with the drawback of surface hydrophobicity and slow degradability. The aim of this study was to enhance the biological functionality of 3D porous PLATMC by functionalization with hyaluronic acid(HA). PLATMC scaffolds were prepared by salt leaching technique and assigned to HA coated and naïve control groups(n=36). Scaffolds were implanted in Lewis rats to investigate host response. Samples were kept in vivo for up to 6months. Bioplex cytokine assay for 23 protein markers were used. Macrophage infiltration was investigated by digitally quantified CD68 IHC staining. The image analysis data revealed a significant difference in macrophage infiltration between all timepoints with the highest number of macrophages at 8weeks. HA coating was found to promote macrophage infiltration at 4days($p=0.032$) and 30days($p=0.012$). However, after 180days we found no difference. In line with these findings, the multiplex protein analysis revealed a significantly higher concentration of: IL-1a, IL-1b, IL-6, GRO/KC, MIP-1a and MIP3A($p<0.001$) as well as VEGF($p=0.004$) and MCP-1($p=0.007$). The findings show that HA coating encourages macrophage infiltration by enhancing the expression of macrophage chemoattractant molecules, MCP-1 and GRO-KC. In addition, higher expression of, IL-1a, IL-1b, MIP-1a, MIP3A and VEGF advocates investigations into the effect of HA coating on other immune subtypes as well as angiogenesis.

Identification of Novel PLOD3 Variants in Patients and Characterization of the Recombinant Mutant Proteins

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Lysyl hydroxylase 3 (LH3) is one of the isoforms of lysyl hydroxylases (LHs) which catalyzes the hydroxylation and glycosylation of lysine and hydroxylysine residues, respectively during collagen biosynthesis. LH3 is encoded by the PLOD3 gene. To date, there are only a few reports which suggest that mutations in the PLOD3 gene cause severe connective tissue disorders. In the present study, we have identified more families with PLOD3 mutations. The main objective of this study is to produce and purify recombinant LH3-mutant proteins, measure lysyl hydroxylase (LH) and glucosyltransferase (GGT) activities, and assess the molecular mechanisms of the disease. Methods All the PLOD3/LH3 mutations were introduced into the baculovirus transfer vector system using a Site-Directed mutagenesis kit. Recombinant proteins were produced using High Five insect cells. Enzyme activities and the biophysical characteristics of the purified proteins were analyzed. Results We show that a PLOD3 disease can arise from GGT function-blocking mutations in both LH and GT domains of LH3. PLOD3 mutations in the GT domain causes reduced GGT activity via different mechanisms viz. reduced specific activity with or without reduced protein stability or dimerization. LH domain mutations affect the whole enzyme stability or dimerization and consequently, both LH and GGT activities are potentially reduced in vivo.

How sustainable is your project?

My current project which is mainly aimed at understanding the characterization of PLOD3 mutations will uncover a pathogenic mechanism for various PLOD3 mutated connective tissue disorders and will ultimately help diagnose the PLOD3 associated lifethreatening collagenopathies.

Long-term Cardiovascular Outcomes in Five-year Cancer Survivors: a Nationwide Cohort Study

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To investigate the long-term rates of cardiovascular outcome in five-year survivors of cancer, overall and according to age. Using Danish nationwide registries, five-year survivors of 20 cancers were matched with four controls from the background population by age and sex. Rates of outcomes in the cancer and non-cancer group were compared with Cox regression models, overall and according to age (i.e., 15-39, 40-59, and >60 years).

In total, 167,215 five-year cancer survivors were age- and sex-matched with 668,860 non-cancer controls. Five-year survivors had higher associated rates of cardiovascular outcomes, irrespective of age, and the incidence rates per 1,000 person-years of cardiovascular outcomes for cancer survivors and non-cancer controls were: HF: 6.2 (95% CI: 6.1-6.4) and 5.2 (5.1-5.3), respectively; atrial fibrillation: 11.1 (10.9-11.3) and 9.3 (9.3-9.4), respectively; venous thromboembolism: 5.1 (5.0-5.2) and 2.8 (2.8-2.9), respectively; ischemic stroke: 5.8 (5.6-5.9) and 5.4 (5.4-5.5), respectively; and myocardial infarction: 3.6 (3.5-3.7) and 3.4 (3.3-3.4), respectively. The absolute rates of cardiovascular outcomes were highest in the oldest group, whereas the relative rates were more pronounced in the youngest cancer group compared with matched controls. Compared with the general population, five-year cancer survivors had higher associated rates of cardiovascular outcomes across the spectrum of age.

How sustainable is your research?

The first draft was finished. The study found that five-year cancer survivors had higher associated rates of cardiovascular outcomes across the spectrum of age. These data underline the importance of risk assessment and prevention of cardiovascular diseases in five-year cancer survivors.