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Application deadline: March 21, 2025

Nerea Alonso Lopez

Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz

Project Title: BAMBinO: bile acids as metabolic regulators in osteoporosis

Background:

Osteoporosis is a common metabolic disease, causing high morbidity and major economic costs. Obesity is often linked to bone deterioration leading to a greater risk of peripheral fragility fractures and clinical complications in these patients. The association between obesity and osteoporosis is complex and usually the fracture risk is underestimated in obese patients. Thus, understanding this relationship could improve the diagnosis and treatment of susceptible individuals and provide insights into the mechanisms involved in bone loss. Our preliminary data suggest that diet-induced changes in bile acid metabolism could be related to poor bone health, possibly via changes in the farnesoid X receptor (FXR)-driven metabolic pathways.

Hypothesis and Objectives:

We aim to investigate the mechanisms underlying bile acid-induced metabolic rewiring in bone, especially focusing on changes in carnitine and amino acid pathways. We also aim to uncover novel metabolic biomarkers for bone loss that could be used to better predict fracture risk and provide stratified clinical care as well as to identify therapeutic targets with potential interest for personalised treatments in osteoporosis, including obesity-related bone loss.

Approaches and methods:

Bile acid-related metabolic alterations in carnitines and amino acids will be assessed in bone cells and biofluids of a diet-induced rat model for obesity and further investigated in an Fxr-/- murine model treated with rescue diets. Associated molecular, metabolic, and microbiome-related biomarkers will be identified in both models and osteoporotic patients via comprehensive quantitative panels and untargeted -omics methods. Validation of common targets will be carried out in primary human osteoblasts and osteoclasts. A separate analysis of markers for obesity-related bone loss will be performed.

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Medical University of Graz

PhD Program MOLMED

Nina Dalkner

Clinical Department of Psychiatry and Psychotherapeutic Medicine, Medical University of Graz

Project Title: XR2ESILIENCE: Pioneering XR technology for the promotion of resilience and mental health of the healthcare workforce

Background:

The health care system is in an existential crisis threatening public trust, community engagement, and worsening outcomes. The declining availability of health care staff and the increased workload have had profound effects on societies, placing considerable pressures on health care services and their staff. A recent scoping review demonstrated that nurses worldwide encountered significant mental health challenges, including depression, cognitive impairment, anxiety, trauma/post-traumatic stress disorder, burnout, and sleep disorder [1-3]. Promoting resilience in times of crisis appears to be a promising goal for supporting their well-being and enhancing their capacity to provide effective care.

The use of extended reality (XR) technologies has the potential to enhance mental health and resilience among healthcare workers, given that XR applications are immersive, interactive, and appealing [4,5]. However, while most resilience training programs have been proven to be scientifically effective, they are often not implemented in healthcare institutions. This presents a significant challenge for XR2RESILIENCE. Together with stakeholders and future users, we aim to develop a training program through co-creation that will not only be applied in practice but will also lead to measurable improvements.

Additional information:

- ⇨ XR2ESILIENCE addresses the entire scope of the call HORIZON-HLTH-2023-CARE-04: Resilience and mental wellbeing of the health and care workforce and is funded by Horizon Europe.
- ⇨ XR2ESILIENCE includes research expertise and knowledge in the areas of psychology, medical science, nursing, health services research, bio-sensors and wearable technologies, human factors research, social sciences, psychophysiological research, technology, and user research.
- ⇨ XR2ESILIENCE runs for 4 years and started in August 2024. Countries involved are Austria, Germany, Spain, Portugal, and Croatia.

Hypothesis and Objectives:

Objective 1: Developing a pioneering XR-supported resilience training approach for healthcare workers.

Objective 2: Ensure high acceptance based on a stakeholder informed integration of the XR2ESILIENCE solution into existing organizational training and work practices.

Objective 3: Test the effectiveness of the XR-supported resilience training solution at the individual, organizational, and system levels.

Objective 4: Develop an upscaling strategy to bring XR2ESILIENCE training solutions to other target groups in the European Union.

Research questions:

Q1: Which resilience factors and mechanisms have the greatest influence on mental health in healthcare workers and thus are the best candidates for implementing a XR-supported training approach? (Objective 1)

Q2: What are barriers and facilitators to the implementation of XR-supported resilience training and the application of a prevention programme in healthcare organisations? (Objective 2)

Q3: How effective is XR-supported resilience training for nursing personnel on a personal, organisational, and system levels? (Objective 3)

Q4: What recommendations for healthcare organisations can be derived from the project's results? (Objective 4)

Approaches and methods:

XR2ESILIENCE will develop a resilience assessment tool and an innovative training framework that can be supported by XR technology. This framework uses the individual resilience profiles to create personalized training programs for nurses. The individualized training integrates empirical findings on resilience factors and mechanisms (meta-analysis of existing data and evidence from literature as well as a longitudinal study). XR2ESILIENCE deploys an Inductive Research-through-Design, Agile and Stakeholder centric development (iRAScD) methodology. The user-centred-design (UCD) approach guarantees that the final XR2ESILIENCE training solution is easy-to-use and achieves high acceptance in the workforce as well as an excellent user experience.

The core of the project is data collection and analysis from a randomised controlled trial (in 5 European countries) investigating the effects of the developed XR2ESILIENCE intervention on stress levels (including digital biomarkers), psychological and mental health parameters and acceptance factors. This approach is designed to be effective not only at the individual level but also at the organizational level. Thus, the project aims to identify both barriers and facilitators for the XR2ESILIENCE intervention, and to conduct analyses on its impact and cost-effectiveness.

The research methodological approach used in XR2ESILIENCE will allow to guide the application of research findings in the real world and provide recommendations to stakeholders, healthcare organisations, and policy makers.

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Christian Diener

Diagnostic & Research Institute for Hygiene, Microbiology and Environmental Medicine, Medical University of Graz

Project Title: Designing the niche space of the human gut microbiome

Background:

Virtually every surface of our planet is colonized by microbes and the human body is no exception. The 38 trillion microbes living in our gut metabolize a large fraction of the dietary metabolites, pharmaceutical drugs, and xenobiotics we consume1 and thus provide an important interface between the environment and our blood stream2.

Whereas many of the species forming the human gut microbiome have been well-characterized by now, **we still know very little about the factors that determine which microbial species can coexist in any given individual**. This currently limits our understanding regarding engraftment of pathogens and probiotics and how those will interact with other microbes and host tissues in the human gut3.

Hypothesis and Objectives:

Metabolic interactions between microbes in complex microbial communities and their host are a complex ballet of metabolic exchanges and the resulting ecology. The research project will aim to chip away at this complexity using a combination of wet lab and computational techniques with the goal to **quantify and predict the nutrient uptake patterns** of individual microbial strains and species **embedded in complex communities** and varying environments. By studying uptake fluxes and the resulting species phenotypes *in silico*, *in vitro*, *ex vivo*, and in vivo we aim to provide a resource map for important microbial species in the human gut that will make nutrient uptake and the resulting microbial phenotypes predictable. Those patterns will then be used to **match next generation probiotics to individual microbiomes** by **orthogonal niche engraftment** or to **design specific synbiotics** to enable engraftment in resistant donor microbiomes.

Approaches and methods:

Our research combines a variety of techniques ranging from high throughput wet lab approaches including metagenomics, metabolomics, and single-cell culturing to computational methods such as metabolic modeling, functional association analysis, and machine learning and thus **provides a large degree of flexibility** for the applicants background and role within the project[4,5].

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Senka Holzer

Department of Cardiology and Gottfried Schatz Research Center, Medical University of Graz

Project Titel: Communicating stress to cell nuclei in cardiomyocytes

Background:

The cardiomyocyte nucleus houses gene transcription machinery vital for the heart's adaptation to stress and changes in hemodynamic demand. However, there is a fundamental, open gap in our understanding of how stress signals travel from the cellular environment to the nucleus, and how the transcriptome adapts to enhance contractility upon physiological stress such as exercise, or, conversely, how it may compromise contractile function in pathophysiological conditions and cardiac disease.

Hypothesis and Objectives:

Here, we will follow the hypothesis that cardiomyocyte nuclei are highly responsive to environmental stress driven by neurohormonal, metabolic and mechanical triggers, and that (peri)nuclear Ca^{2+} signaling dynamics plays a major role in environment-transcription communication. Our recent, unexpected data revealed a new sequence of events in conveying stress to cardiomyocyte nuclei. We showed that under stress—characterized by increased (peri)nuclear Ca^{2+} levels—the cell nucleus undergoes stronger contraction during each heartbeat; it moves toward the cell periphery; and it shows clear signs of heterochromatin clumping and formation of contact sites between euchromatin and the nuclear envelope. Therefore, we will (1) systematically characterize how physiological and pathophysiological stress affect nuclear contractility, positioning, and motility in ventricular cardiomyocytes, (2) match the effects of nuclear mechanics and repositioning to changes in the local signaling milieu, especially the (peri)nuclear Ca^{2+} concentrations, (3) address the subsequent effects on chromatin reorganization, and (4) provide comprehensive analyses of the resulting alterations in the cellular transcriptome.

Methodology:

We will first combine cellular assays and cutting-edge visualization techniques to characterize nuclear mechanics and motility under physiological stress due to regular exercise and pathophysiological stress induced by pressure overload. Next, we will match nuclear motions with the local Ca^{2+} levels and Ca^{2+}-mediated signaling environment quantified using ultra-fast confocal imaging. Finally, we will combine advanced imaging, chromatin accessibility assays and RNA sequencing to decipher subsequent alterations in the transcriptomic landscape, which may be the key to identifying beneficial effects of exercise on the heart, and elucidating early, treatable mechanisms in adverse cardiac remodeling and associated conditions.

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Julia Mader

Division of Endocrionolgy and Diabetology, Department of Internal Medicine, Medical University of Graz

Project Titel: The role of automated insulin delivery in diabetes care

Background:

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia due to insulin deficiency or resistance. The management of insulin-treated diabetes requires (continuous) glucose monitoring and adequate insulin administration to maintain optimal glycemic control and reduce complications. Traditional insulin therapy often relies on multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII), which can be challenging for people with diabetes in terms of adherence and finding the correct dose. Automated insulin delivery (AID) systems, which integrate continuous glucose monitors (CGM) with insulin pumps through advanced algorithms, offer a promising solution to optimize glycemic control while reducing patient burden. Several studies have demonstrated that AID systems can improve time-inrange (TIR), reduce hypoglycemic episodes, and enhance overall quality of life for individuals with type 1 and type 2 diabetes. Despite these advancements, there remain gaps in understanding the long-term efficacy, user acceptance, and potential limitations of these systems in real-world settings. The proposed research topic aims to provide insights into the efficacy, usability, and future potential of AID systems in diabetes care, paving the way for broader implementation and policy recommendations.

Hypothesis and Objectives:

Automated insulin delivery systems improve glycemic outcomes, reduce complications, and enhance quality of life compared to conventional insulin therapy in diabetes management.

- To evaluate the effectiveness of AID systems in improving glycemic control (HbA1c levels, TIR, frequency of hypoglycemia/hyperglycemia episodes) in the outpatient setting.
- To evaluate the effectiveness of AID systems in improving glycemic control (HbA1c levels, TIR, frequency of hypoglycemia/hyperglycemia episodes) in the inpatient setting.
- To assess patient-reported outcomes, including quality of life, treatment satisfaction, and adherence to AID therapy.
- To investigate the long-term sustainability, safety, and potential risks associated with AID usage incl. skin reactions towards the adhesives used.
- To analyze real-world data on the use of AID systems across diverse populations and healthcare settings.

Methodology:

Retrospective analysis:

Analysis of real-world data on the use of AID systems across diverse populations and healthcare settings.

Retrospective analysis:

a) A prospective, randomized controlled trial (RCT) comparing a novel AID system with conventional insulin therapy over a period of 3-6 months in type 1 diabetes in the outpatient setting.

b) A prospective, randomized controlled trial (RCT) comparing a novel AID systems with conventional insulin therapy over a period of 3-6 months in type 2 diabetes in the outpatient setting.

c) A short-term randomized controlled trial (RCT) comparing an AID system with conventional insulin therapy during inpatient stay.

Participants:

Individuals diagnosed with type 1 and type 2 diabetes who meet the inclusion and none of the exclusion criteria for the three respective trials.

Intervention: Participants in the intervention group will use an AID system consisting of a CGM, insulin pump, and automated algorithm. The control group will continue on standard insulin therapy (MDI or CSII).

Data Collection:

Primary outcomes: HbA1c levels, percentage of TIR/TAR/TBR, and incidence of (severe) hypoglycemia.

Secondary outcomes: Quality of life (measured through validated questionnaires), treatment adherence, and device usability.

Safety outcomes: Incidence of device malfunctions, diabetic ketoacidosis (DKA), and any adverse events.

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Christine Moissl-Eichinger

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Project Titel: Exploring the Immunomodulatory Role of Archaeal Extracellular Vesicles in Macrophage Function and Host Immunity

Background:

Within the special research program SFB Immunometabolism (https://www.immunometabolism.at/), we investigate how macrophages maintain tissue integrity metabolically. At the Medical University of Graz, we specialize in the role of the human microbiome, with a focus on archaea[1] such as *Methanobrevibacter*. Recently, we discovered that human-associated archaea release extracellular vesicles (AEVs), which can elicit cytokine responses in human cell lines[2]. These findings open a previously underexplored research path for understanding archaeal interactions with the immune system.

Hypothesis and Objectives:

This project aims to elucidate the biological significance of archaeal vesicles in the host. Based on evidence that bacterial extracellular vesicles (EVs) cross intestinal barriers, disseminate throughout the body, and modulate immune responses, we hypothesize that AEVs similarly function as effector vehicles. These vesicles may influence systemic and tissue-resident macrophages, including Kupffer cells, by modulating immune responses. The ultimate objective is to uncover the immunomodulatory potential of AEVs and their components, and opening the way for novel, archaea-based therapeutic strategies.

Methodology:

Human macrophages will be derived from CD14-positive monocytes, and murine bone-marrow-derived macrophages will be generated in-house. Kupffer cells will be included in the experiments. AEVs will be produced from *Methanobrevibacter* species and *Methanosphaera stadtmanae* using an established protocol, and bacterial EVs will serve as a control for comparison. Macrophages will be exposed to AEVs, and changes in functionality will be assessed using RNA-seq after total RNA extraction. Uptake of fluorescently labeled AEVs will be monitored using live-cell imaging techniques. To identify immunomodulatory components, individual AEV fractions will be generated through density centrifugation or size exclusion chromatography and tested in cell culture assays. *In vivo* experiments (performed in collaboration) will involve injecting AEVs into healthy animal models to monitor systemic immune responses and assess macrophage functionality ex vivo. Additional experiments using a murine infection model will evaluate the effects of AEVs under inflammatory conditions.

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Thomas Pieber

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Project Title: Novel metabolic biomarkers of aging and age-related diseases

Background:

Biological aging is enormously complex and is thought to be driven by the interplay of numerous dysregulated cellular and biochemical processes (1). State-of-the-art mass spectrometry and NMR spectroscopy methods can identify hundreds to thousands of metabolites and lipoprotein-related species in human plasma, and numerous studies have attempted to understand how they relate to the aging process (2, 3). Recent studies show that obesity is associated with accelerated metabolic aging, cardiovascular risk factors, cardiovascular disease risk and all-cause mortality risk (4, 5).

Hypothesis and Objectives:

We hypothesize that metabolomic biomarkers will allow to differentiate biological metabolomic age from chronological age. We will develop a metabolomic clock from reliably measurable metabolites/lipoproteins in plasma and evaluate relationships between the metabolomic age gap, cardiovascular phenotypes and mortality. For this PhD project, we will utilize the novel metabolomic prospective cohort Pro-MetAGE within the MetAGE Clinical Trial Programme (6) and a large existing human cohort (BioPersMed) (7).

Methodology:

For the prospective cohort Pro-MetAGE young (18-35 years) and older (over 60 years) subjects with normal and obesity will be recruited, and the clinical, anthropometric and metabolic phenotype will be assessed. Plasma samples from the Pro-MetAGE cohort will be analysed using proton nuclear magnetic resonance spectroscopy (NMR) and liquid chromatography–mass spectrometry (LC-MS) platforms. Statistical models will be applied to generate metabolomic clocks from plasma metabolome and compared against epigenetic clocks, e.g., PhenoAge or GrimAge, and clocks based on inflammatory cytokine levels (iAGE). Novel metabolic aging biomarkers will be validated with plasma sample of the prospective long-term BioPersMed cohort.

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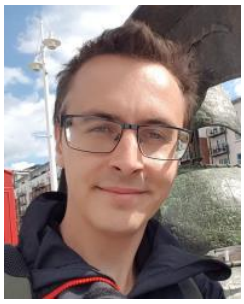

Project Title: Identification and characterization of novel gene candidates regulating aggression

Background:

Aggression is an innate behaviour expressed throughout the animal kingdom for various reasons including foraging, fighting for territories or defending offspring. However, in humans, excessive aggression has been found as part of many major neuropsychiatric disorders such as attention deficit hyperactivity disorder, schizophrenia or dementia.

Hypothesis and Objectives:

Across species, genetic factors are important players for the development of excessive aggression. A number of risk genes for heightened aggression have been studied using candidate gene approaches, but this has not led to new aggression-reducing treatments yet. Zebrafish are an emerging model organism in the research field, given the availability of well-established behavioural assays to study aggression, platforms for high throughput drug screening, a growing toolbox for genome editing such as CRISPR/Cas9 and transgenic lines permitting the investigation of neural activity and manipulation of neural circuits *in vivo* (1,2). Based on our previous work (3,4), we hypothesize that detailed gene expression studies of fighting zebrafish will reveal novel gene candidates regulating aggression. Within this project the function of selected genes will be studied in detail at the behavioural and neurobiological level.

Methodology:

The recruited PhD student will use zebrafish as a model system to indentify and characterize novel genes regulating aggression. For this, the student will use zebrafish aggression assays in combination with RNAseq of brain tissues to identify novel genes relevant for the behavior. CRISPR/Cas9 will be used to manipulate target genes followed by behavioural phenotyping of the novel transgenic lines. Neurobiological readouts include the regional and cellular expression pattern across the brain as well as neuronal activation measurements by immunohistochemical rpS6 staining. In addition, the student will study effects of the gene knockout on the major neurotransmitter systems using qPCR, ELISA and/or HPLC. In collaboration with Prof. Winter (University of Exeter) and Dr. Magnes (Joanneum research) we will also study *in vivo* neural activity in larval transgenic zebrafish and brain metabolomic changes during aggression, respectively.

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Margret Paar & Pedro Sánchez Murcia

Ottp Loewi Research Center (Medicinal Chemistry), Laboratory of Computer-Aided Molecular Design, Medical University of Graz

Project Title: Controlled degradation of nanorobots via computationally-engineered biocatalysts

Background:

Small-scale robotics, ranging from just a few nanometers to sub-millimeters, has made remarkable strides in healthcare and environmental applications. These tiny marvels offer innovative solutions to some of society's most pressing challenges. However, a critical roadblock remains: enhancing energy efficiency and ensuring sustainable materials throughout their life cycle.

Currently, most materials used in micro/nanorobotics are neither sourced nor produced in Europe, highlighting the urgent need for greener alternatives. Addressing this, the **GREENS Initiative**, a cutting-edge project funded by the European Commission under the prestigious Marie Skłodowska-Curie Actions (MSCA) Doctoral Network, is forging interdisciplinary connections between small-scale robotics and fields like green chemistry, sustainability, and the circular economy.

A standout objective of the GREENS program is to **explore how biocatalysts can extend the life cycle and improve the degradation processes of micro/nanorobots**. Here, computational methods are playing a transformative role, especially in the realm of enzyme engineering. These advanced tools are paving the way for more efficient, eco-friendly robotic designs, bringing us closer to a sustainable future.

Hypothesis and Objectives:

The primary aim of this PhD position is to design and develop innovative enzyme scaffolds with precisely tailored properties, enabling the efficient degradation of materials used in micro/nanorobots.

Methodology:

The PhD project focuses on identifying and designing enzyme activities *à-la-carte* (i.e., lipases, esterases, ferritin, and silicases) to achieve controlled degradation of materials used in micro/nanorobots. Cutting-edge approaches, including *de-novo* design, computer-aided enzyme redesign using classical and quantum mechanics, and machine learning, will be employed alongside the development of precise enzymatic assays and high-throughput robotic platforms to deliver novel

enzyme activities. The selected enzymes will be heterologously expressed and meticulously tested for their efficiency in breaking down various robotic chassis materials, including iron-based structures, silica biotemplates, polysaccharides, vegetable oils, and polycaprolactone (PCL). Additionally, these biocatalysts will be integrated into the robotic structures to enhance their life cycle and sustainability.

The successful PhD candidate will have the exceptional opportunity to join a multinational, interdisciplinary scientific network while collaborating closely with an innovative enterprise specializing in bioprocess development, bridging academia and industry.

Specific MSCA Doctoral Network requirements: the PhD candidate needs to fulfill all eligibility criteria (carrier stage, mobility rule) for recruited researchers specificed by the European Commission for the MSCA Doctoral Networks (Horizon Europe).

Simon Sedej

Division of Cardiology, Department of Internal Medicine, Medical University of Graz

Project Title: Targeting the fat-heart axis to promote healthy cardiac aging

Background:

Obesity is a leading risk factor that exacerbates aging and contributes to the increasing prevalence of heart failure with preserved ejection fraction (HFpEF), a systemic and age-related metabolic syndrome with few specific therapies available (1). We discovered that selected caloric restriction mimetics (CRMs) reduce obesity, restore metabolic perturbations, and improve cardiac function in aging and HFpEF (2,3). However, how CRMs target maladaptive communication between the heart and adipose tissue is largely unknown.

Hypothesis and Objectives:

We hypothesize that reduced mobilization of fatty acids mitigates the development and progression of HFpEF by suppressing adipose tissue maladaptive signals to the heart. Our aims are to (i) determine age-related changes in the crosstalk between adipose tissue and cardiac muscle in HFpEF at the molecular, cellular and tissue to organismal levels, and (ii) elucidate the mechanisms underlying salutary effects of selected CRMs on the maladaptive fat-heart crosstalk in age-related HFpEF Our objective is to identify CRMs as novel therapies that extend health span through improving adipose tissue function and delaying cardiac aging.

Methodology:

The PhD student will employ a clinically-relevant HFpEF animal model in combination with genetically-modified mice. S/he will learn and apply state-of-the-art *in vivo* cardiac and metabolic phenotyping, ranging from cardiac function evaluation using echocardiography and intra-cardiac catheterization as well as serial insulin and glucose tolerance testing, indirect calorimetry to exercise tolerance testing. These experiments will be coupled to mass spectrometry-based metabolome and lipidome analysis of the myocardium, adipose tissue and plasma of young and old animals. Confocal microscopy-based analysis and biochemical and molecular biology assays, such as determination of autophagic flux, mitochondrial respiration, and inflammatory markers will provide key insights into the processes by which reduced mobilization of fatty acids mitigates the development and progression of HFpEF in aging. The PhD student will work in close collaboration with renowned research groups within the Cluster of Excellence “Metabolic control of aging and disease – from models to humans”, and benefit from structured PhD training and career development programs.

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Harald Sourij

Division of Endocrionolgy and Diabetology, Department of Internal Medicine, Medical University of Graz

Project Title: Novel biomarker and statistical approaches for prediction of recurrent cardiovascular events

Background:

People surviving myocardial infarction are exposed to a high and persistent risk of future recurrent cardiovascular (CV) events. More than 15% of subjects suffer from myocardial reinfarction, stroke, and/or CV death within four years of the index event [1].

Blood-based biomarkers have been studied as key predictors of cardiovascular risk and mortality in people with cardiovascular disease, including markers that indicate cardiac damage. Beyond traditional risk factors such as LDL-cholesterol, HbA1c or lipoprotein (a), a residual CV risk is defined as the remaining risk of CV events or progression of CV disease that persists despite treatment according to evidence-based guideline recommendations. Analyses of various cohorts showed that high-sensitivity CRP (hsCRP) indicating residual inflammatory risk, predicts CV events independently from LDL-cholesterol, and that the contribution of LDL and hsCRP to CV risk is additive [2]. HsCRP as well as NTproBNP (a biomarker used to indicate heart failure) have demonstrated beneficial effects in risk re-classification and establishing risk scores in selected populations; However they are not yet recommended for usage in routine clinical practice [3-5]. The BIO-RISK-EVENT trial is an integral part of the Horizon Europe project PoCCardio, a project that aims to develop a point of care biomarker measurement device that once properly validated, could help to identify people with extremely high-CV-risk patients in routine care. The randomized, controlled, multinational, multicenter clinical trial aims to investigate the effects of an intensified residual risk management including the administration of an SGLT2 inhibitor, the omega 3-fatty acid eicosapent-ethyl and the anti-inflammatory drug colchicine on cardiovascular outcomes in subjects with recent myocardial infarction.

Besides traditional biomarkers including serum lipids, HbA1c, eGFR, and BMI, alterations in metabolites related to ceramides, cholines, acylcarnitines, and other fatty acids and amino acids in response to intensified CV risk management therapy using colchicine, icosapent ethyl, and empagliflozin compared to standard risk management therapy will be explored in the Bio-Risk-Event cohort. The metabolites will be identified and validated using e.g. NMR platforms. Novel longitudinal modeling and machine learning approaches have shown better CVD risk stratification and prediction ability than traditional survival models because of their ability to incorporate repeated measurements of risk factors, statistical robustness, and better handling of interactions among variables.

Hypothesis and Objectives:

The objectives of the proposed PhD project will be:

to validate, developed from the BIO-RISK-EVENT trial, the biomarker-based CV risk-stratification tool for people with acute myocardial infarction in a large myocardial infarction cohort.

to evaluate and compare the performance of novel statistical models with an emphasis on joint and random forest survival models using longitudinal information of both classical and novel biomarkers for estimating and predicting the risk of CVD events in the Bio-Risk-Event cohort.

Methodology:

Validation of an existing risk prediction tool in a large (n>10.000) local cohort of people with acute myocardial infarction. Applying various statistical models to the data of the BIO-RISK-EVENT trials using various sets of clinical and biomarker data to predict CV outcomes and to identify serum biomarker-based predictors or predictor pannels for treatment response to SGLT2 inhibitors, icosapent-ethyl or colchicine in the BIO-RISK-EVENT trial.

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Martin Stradner

Division of Rheumatology and Immunology, Medical University of Graz

Project Title: Pre-Sjögren Syndrome targeted immunology evaluation

Background:

Primary Sjögren's Syndrome (pSS) is a systemic autoimmune disease leading to inflammation and destruction of the exocrine glands (1). Due to its subtile onset it is often misdiagnosed or overlooked leading to a significant delay of diagnosis (2). Therefore, most of the current knowledge on the pathophysiology of pSS is derived from patients with long-standing disease (3). Patient symptoms, immune phenotype and glandular infiltrates at the onset of pSS are unknown and biomarkers for early diagnosis have not been evaluated so far. The "Pre-Sjögren Syndrome Targeted Immunology Evaluation (preSStige)" represents a pioneering effort aimed at uncovering the initial immunological dysregulations in pSS (4). Spearheaded by collaborative efforts between the Universities of Graz, Austria, and Brest, France, this interdisciplinary research initiative seeks to revolutionize the understanding and early detection of pSS.

Hypothesis and Objectives:

The overarching goal of the research is to discern whether identified immune system changes are root causes of pSS or mere consequences of persistent inflammation. Structured as a longitudinal cohort study, the project identifies individuals at risk for pSS (pre-Sjogren patients) and follows their progression until the development of pSS or other systemic autoimmune diseases. Presently, the study has enrolled 41 individuals, some of whom have already manifested pSS or other autoimmune diseases. Early analyses have unearthed compelling pathogenic indicators, including alterations in the naïve CD4+ T cell pool and lymphoepithelial lesions.

Methodology:

The methodology blends clinical research with cutting-edge laboratory techniques to validate and comprehend the findings. Employing advanced tools, the study conducts in-depth profiling of T, B, and NK cells. Techniques like single-cell RNA sequencing, flow cytometry and deep learning for diagnosis prediction are integral components of the innovative research approach. What sets this study apart is its novelty as the first longitudinal investigation involving patients before or at the clinical onset of pSS. Instead of relying on data from long-term patients with established immune system dysregulation, this research ventures into uncharted territory, studying changes in individuals as they develop the autoimmune disease.

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Elisabeth Taucher

Division of Pulmonology, Department of Internal Medicine, Medical University of Graz

Project Title: Exercise as a tool to improve response to immumotherapy in lung cancer

Background:

Lung cancer is the number one cause of cancer-associated deaths worldwide. The five-year survival rate remains poor with only 22%, despite ever-evolving treatment options (1,2)

Tumor immunotherapy has significantly improved survival times among certain subgoups of patiens with cancer subtypes responding well to immunotherapy (3) Physical activity has been demonstrated to reduce the risk of at least 13 different cancer types, as shown by large epidemiologic studies (4,5). Exercise studies on rodents investigating wheel and treadmill running as well as swimming also showed a marked reduction of cancer incidence with physical activity in a broad range of tumor models (6,7). Immune function is significantly impacted by exercise, as physical activity leads to a better maintenance of T-cell repertoire, aiding in the direct elimination of cancer cells (8). Lower secenescent T-cell rates and higher rates of naïve T-cells have been found in individuals who are regularly active. Various subpopulations of senescent T-cells have been found to be significantly reduced in well-trained individuals, as measured by VO2max. This observation also translatedinto less defective T-cells being found in well-trained individuals as well as a predominance of T-cells mediating the antitumor response (9,10).

Mitochondria are double membrane cell organelles, their main function being the delivery of ATP to cells, needed to satisfy their energy demand (11,12). Another function of mitochondria is their constant crosstalk with the immune system (13). The immune system is affected by mitochondria by their production of reactive oxygen species, aiding as second messengers in signaling pathways closely linked to T-cell activation (14). Exercise leads to an increase of mitochondrial volume and density, and the function of mitochondria adpats through exercise as shown by an increased expression of mitochondrial enzymes facilitating aerobic capacity (15).

Hypothesis and Objectives:

With this FWF-funded research project we would like to investigate the link between training, mitochondrial function and ultimately, response to immunotherapy in lung cancer patients.

We hypothesize that an exactly defined training regimen can improve the response to immunotherapy in lung cancer patients, as compared to sedentary controls. We also hypothesize that mitochondrial function plays a crucial role in this context, improving the immune response through exercise.

Medical University of Graz

PhD Program MOLMED

Methodology:

In a first step we will investigate the effects of different training types and intensities in healthy individuals on their immune response. Second, we aim to enroll lung cancer patients at the Division of Pulmonology, University Hospital Graz, into our project who will take part in a 12-week training program. During the 12 weeks, lung cancer patients will receive immunotherapy as part of their routine antitumor therapy. Radiologic reduction in tumor size will be measured at the first restaging after the 12 week program, and compared to sedentary control patients receiving the same therapy regimen. The mitochondrial function will be analyzed using the patient's blood samples. Mitochondrial parameters will be evaluated in the healthy participants as well. Moreover, several immune system parameters (interleukins) will be measured in the blood samples, aiming to assess possible changes before and after exercise.

Thereby, we would like to outline a training regimen with optimum stimulation of the immune response, potentially improving therapy response as well. Moreover, we aim to outline at least one parameter of mitochondrial function especially suitable to determine the exercise level which is optimal to improve the outcome in cancer patients.

A main novelty aspect of this study is the exact definition of frequency, intensity, duration and timing of exercise in oncologic patients. We hope to outline an exercise schedule which may be given as general recommendation for future cancer patients as a routine part of antitumor therapy.

References:

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