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Project Title:

Diethylsuccinate as a novel therapeutic for Idiopathic pulmonary fibrosis

Background: Idiopathic pulmonary fibrosis (IPF) is a chronic progressive disease with a median survival of only 3-4 years, significantly shorter than many types of cancer. It is characterized by exaggerated extracellular matrix (ECM) deposition in the lungs, loss of alveolar tissue and disrupted gas exchange. Currently, there are only two therapeutic options for the treatment of IPF, pirfenidone and nintedanib. While these drugs slow disease progression and might prolong survival, they are neither curative, nor do they entirely stop loss of lung function. Furthermore, a significant proportion of patients discontinue anti-fibrotic therapy due to side effects. Therefore, other therapeutic options are urgently needed.

Diethyl succinate (DES) is a cell-permeable modification of succinate, a citric acid cycle metabolite. Of note, this metabolic pathway is dysregulated in IPF and can influence ECM-deposition and cell survival. We found that DES improves bleomycin-induced pulmonary fibrosis (PF) in a mouse model and reduces ECM-related genes/proteins (e.g. collagen 1) in fibroblasts and PCLS from IPF patients.

Hypothesis and Objectives: Due to our preliminary data, we know that DES exerts antifibrotic effects and thus hypothesize that it may be a novel therapeutic agent in IPF. We want to assess whether (I) DES has therapeutic potential in PF of different etiologies (II) which mechanisms and cells mediate these effects and (III) whether DES is able to revert fibrosis.

Methodology: We will use bleomycin and TGF-beta transgenic mouse models of PF to test different delivery routes for DES (intraperitoneal, inhalative, per oral) and assess fibrosis using hydroxyproline test, Ashcroft scoring, and lung function test. Fibroblasts and alveolar epithelial cells will be used for cell culture experiments, followed by ELISA, qPCR and WB to detect DES effects on for example ECM production, lipofibroblast differentiation or survival associated

pathways. We will investigate proliferation/apoptosis via EDU/Ki67 and AnnexinV/PI/activated caspase3 staining respectively, cell counts and caspase 3/7 activity. Precision cut lung slices (PCLS) from PF patients of different etiology and healthy controls will be treated with DES. Readouts will include safety and pharmacokinetics (mouse models), respective pathways/affected cells (RNASeq, sc/sn-RNASeq) including validation and morphometry (microscopy/immunofluorescence).

References:

Rajesh, R; Mooslechner, AA; Schweighofer, H; Pahernik, S; Lanz, I; Atallah, R; Platzer, W; Aigner, C; Benazzo, A; Angiari, S; Marsh, L; Kwapiszewska, G; Heinemann, A; Bärnthaler, T; Succinate aggravates pulmonary fibrosis through the succinate/SUCNR1 axis.

Am J Physiol Lung Cell Mol Physiol. 2025;

Rajesh, R; Atallah, R; Bärnthaler; Dysregulation of metabolic pathways in pulmonary fibrosis T, Pharmacology and Therapeutics 2023; 246: 108436

Michael DENGLER, PhD

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



Project Title: **Harnessing Immunogenic Cell Death for Improved Lung Cancer Therapy**

Background:

Non-small cell lung cancer (NSCLC) is often considered the poster child of genomic medicine, with its genetic alterations being increasingly well-characterized (1). However, this leap in molecular understanding has yet to deliver substantial clinical benefit for the majority of NSCLC patients, and NSCLC remains the deadliest cancer worldwide (2).

Despite the use of targeted drugs, most patients with common oncogenic driver mutations such as in EGFR or KRAS relapse after approximately 19 months (3). Even more dismal is the outcome of patients without oncogenic driver mutations. Depending on their PD-L1 expression level, high-expressor patients under single-agent immunotherapy progress after only 9 months on treatment (4), whereas low-expressor patients require additional toxic chemotherapy to reach this goal (5). These data provide striking evidence that an unmet medical need in treatment options for NSCLC patients exists.

The primary challenge for long-term survival of NSCLC patients is the high relapse rate, largely driven by immune evasion that prevents the sustained immune recognition of NSCLC cells (6). This is curious, as NSCLC harbors a high number of potentially immunogenic alterations, essentially placing it within the most mutated cancer entities (7). It is therefore of utmost importance to improve immune recognition and facilitate immune control of NSCLC.

Evasion of programmed cell death and avoiding immune destruction are key hallmarks of cancer (8). Immunogenic cell death (ICD), a form of programmed cell death that promotes inflammation, plays a vital role in stimulating the immune system's response against cancer cells. Activation of ICD pathways such as necroptosis and pyroptosis trigger active plasma membrane pore formation and the release of cellular contents (damaged associated molecular patterns, DAMPs) and cytokines into the intercellular space. This attracts and activates immune cells (9). In many cancer types, the key regulators of the necroptotic and pyroptotic pathway are generally downregulated, suggesting that cancer cells survive by escaping ICD (10, 11).

Harnessing ICD pathways has therefore emerged as a promising strategy to develop new treatment approaches to shape the tumor immune microenvironment and to enhance existing therapies, particularly immunotherapy (9).

Hypothesis and Objectives:

Our preliminary work provides evidence that the deregulation/repression of ICD also contributes to NSCLC development. We hypothesize that re-activating ICD in tumor cells will improve immune recognition of NSCLC. However, our current understanding of ICD in NSCLC remains limited. Thus, this PhD project will apply comprehensive *in vitro* and *in vivo* approaches, combined with cutting-edge technologies, to systematically investigate the functional role and regulation of key necroptosis and pyroptosis genes in NSCLC. Furthermore, it will explore novel strategies to restore and activate ICD, promote an inflamed tumor microenvironment, and enhance tumor control.

Methodology:

This PhD project will utilize a wide array of technologies and model systems ranging from primary human NSCLC patient samples and *in vivo* mouse model systems to CRISPR-Cas9-based *in vitro* and *in vivo* screening tools. For example, we have established a state-of-the-art mutant Kras-driven genetically engineered mouse model which allows tumor-specific rapid CRISPR/Cas9-mediated target gene knockout (CRISPRko) or activation (CRISPRa) *in vivo*. This model will be used to modulate the expression of key necroptosis and pyroptosis genes and explore the impact on lung cancer development/progression and on the composition of the tumor immune microenvironment.

Furthermore, whole-genome CRISPR functional genomics screening will be performed to identify the regulatory networks controlling expression of key regulators of pyroptosis and necroptosis. For this, *in vitro* CRISPR screens will be combined with endogenous gene expression reporter systems and fluorescent biosensors of necroptosis and pyroptosis induction to monitor for changes in the ICD pathways.

The project will be conducted in close collaboration with a multidisciplinary team, including physician-scientists, bioinformaticians, and industry partners.

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Johannes FESSLER, PhD

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Project Title: Evaluating immunological aging as a driver of immune dysfunction

Background:

Autoimmunity is a major health burden affecting roughly 5% of the world's population and recent evidence suggests that premature immune cell aging is a key characteristic of autoimmune patients.(1) Immune aging refers to changes that affect the ability of the immune system to respond effectively to infections, vaccines, and other challenges and is associated with a spectrum of morbidities and mortality.(2) Importantly, there is no cure for autoimmunity to date. Therefore, achieving tight control over disease progression as early as possible has been shown to lead to improved outcomes and thus represent the gold standard for current clinical practice.

Hypothesis and Objectives:

The proposed work aims to think outside the box and investigate if premature immunosenescence is associated with facets of autoimmunity including but not limited to auto-antibody presence. Specifically, we hypothesize that premature immune cell aging is a pivotal driver of autoimmunity. Autoimmunity is considered to result from a combination of underlying reasons. In this context, immunosenescence might be representative for several of these reasons as it is considered to be the consequence of chronic infections, a pro-inflammatory milieu as well as an unfavorable metabolic and nutritive environment.

Methodology:

For this project we will use sophisticated ex vivo as well as in vitro approaches to study immunological aging of human subjects. Cell culture, cytokine-multiplexing and flow cytometry techniques in combination with RNA sequencing and Metabolomics will be used to determine aging characteristics of immune cells and the use of anti-aging drugs will help to determine the potential to regulate immune cell phenotype, differentiation and function. To validate the findings, we will use appropriate human cohorts or mouse models that will allow us to explore potential mechanisms of action.

References:

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Martin GAUSTER, PhD

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Project Title:

Maternal obesity and its impact on the placental extracellular matrix composition

Background:

Obesity among women of reproductive age has increased globally, resulting in a higher prevalence of obesity among delivering mothers and contributing to a rise in pregnancy complications and adverse outcomes for both mothers and their children. Maternal obesity is associated with significant changes in placental structure and function, including altered lipid metabolism, increased inflammation, and oxidative stress, which can impact fetal growth and long-term health [1–5]. While these metabolic and inflammatory changes are well documented, direct evidence linking maternal obesity to specific alterations in the extracellular matrix (ECM) composition of the placenta is still limited. However, the placenta's ability to adapt to maternal metabolic stress suggests that extracellular matrix (ECM) remodeling may be one aspect of broader placental adjustments, potentially affecting nutrient transport, tissue structure, and fetal development [4–6]. Overall, the rising rates of maternal obesity highlights the urgent need for further research into its effects on placental ECM and the development of targeted interventions to improve pregnancy outcomes.

Hypothesis and Objectives:

This project will address the hypothesis that maternal obesity alters the composition of the placental ECM. Special emphasis will be placed on hyaluronic acid (HA) and its synthesizing enzymes (hyaluronic acid synthases), which are hypothesized to undergo changes in both expression and enzymatic function in response to an obese microenvironment, resulting in aberrant glycan chain length. These alterations are proposed to result from the chronic low-grade inflammation associated with the placental environment in maternal obesity.

Methodology:

Light- and confocal laser scanning microscopy, as well as atomic force microscopy will be employed, alongside nanopore measurements of hyaluronic acid (HA). Quantification of ECM components will be performed via ELISA. OMICs approaches will be applied for spatial transcriptional profiling and expression analysis of ECM proteins, including collagens, metalloproteases, and indirect ECM proteins such as hyaluronic acid synthases. Additionally, standard molecular biology techniques, such as qPCR and Western blot analyses, will be conducted. Primary placental cells will be isolated, and 3D cell culture experiments will be carried out in the presence and absence of obesity-associated stimulators.

References:

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Gernot GRABNER, PhD
Dagmar KRATKY, PhD (Co-PI)

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Project Title:

Characterization of PNPLA3 enzyme function via small-molecule inhibitors

Background:

Metabolic dysfunction-associated steatotic liver disease (MASLD) is an emerging public health concern, currently affecting roughly one quarter of the global population¹. MASLD is the predominant chronic liver disease in Western countries with increasing prevalence alongside obesity and type 2 diabetes. With steatosis as a generally observed underlying hallmark, some patients advance to steatohepatitis, liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC)². Currently, 20% of HCC cases in the Western world originate from MASLD and it is estimated to become the predominant cause of HCC globally by 2030³. The major genetic risk factor for the development and progression of MASLD is a single-nucleotide polymorphism (SNP) in the gene encoding for patatin-like phospholipase domain-containing protein 3 (PNPLA3), also known as adiponutrin (ADPN)². This SNP (rs738409 C>G) leads to an amino acid exchange in the PNPLA3 protein from isoleucine at position 148 to methionine (I148M). While numerous studies demonstrate that PNPLA3 I148M correlates with MASLD development and progression, the underlying molecular mechanism is currently still a matter of intense debate⁴. PNPLA3 has been ascribed various enzymatic activities, which of these activities are physiologically relevant and how they are affected in the I148M variant remains, however, controversial⁵

Objective:

We will use **(I)** computational modeling, **(II)** direct biochemical assays utilizing our established lipid screening platform and **(III)** small-molecule inhibitors for detailed characterization of PNPLA3 enzymatic activity. We consider this as key prerequisite to unravel the distinct contribution of PNPLA3 and PNPLA3 I148M to lipid metabolism and MASLD development and progression.

Methodology:

(I) For computational modeling, the active sites of PNPLA3s will be represented by three-dimensional point clouds annotated with different physico-chemical properties using the Innophore Catalophore™ platform. In the absence of experimental structures of PNPLA3, we will start with modeled structures generated using AlphaFold. The PhD candidate will improve Catalophore models with molecular dynamics (MD) simulations and integrate experimental data generated in experimental approach **(II)** in an iterative process. These analyses will be conducted in collaboration with Prof. Karl Gruber (Institute of Molecular Biosciences, University of Graz).

(II) The PhD candidate will express and purify PNPLA3 variants and perform in vitro screening of an established lipid substrate library. The candidate will optimize reaction conditions and compare v_{max}/K_m values for different substrates. Furthermore, potential substrates and catalyzed reactions unveiled by in silico prediction in experimental approach **(I)** will be analyzed experimentally by in vitro assays using human and mouse PNPLA3 WT and PNPLA3 I148M.

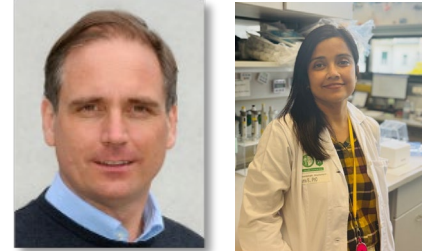
(III) The PhD candidate will be closely involved in the development of PNPLA3 inhibitors in collaboration with Prof. Rolf Breinbauer (Institute of Organic Chemistry, Graz University of Technology).

References:

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Sayantane DUTTA, PhD (Co-PI)

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**Project Title: Dissecting Cytokine Signaling for Precision
Targeting of Therapy-Resistant Leukemic Stem Cells in AML**

Background:

Acute myeloid leukemia (AML) is an aggressive blood cancer affecting both children and adults, characterized by high relapse rates and poor long-term survival. A major challenge in treating AML is the persistence of leukemic stem cells (LSCs), which evade conventional therapies due to their quiescence, enhanced DNA repair capacity, and intrinsic drug resistance. While standard treatments often induce remission, residual LSCs can reinitiate disease, underscoring the urgent need for innovative strategies that specifically target this critical cell population.

Inflammation is a well-established hallmark of cancer and plays a pivotal role in shaping both normal and malignant hematopoiesis. Acute and chronic inflammatory signals influence hematopoietic stem cell (HSC) function, clonal evolution, and aging. TNF receptor (TNFR) signaling, a central pathway in inflammation, is crucial for maintaining healthy hematopoiesis. RIPK3 (Receptor-Interacting Serine/Threonine-Protein Kinase 3) is a downstream effector of TNFR1 that plays a central role in a form of programmed cell death called necroptosis(1, 2). Our lab has uncovered a tumor-suppressive role for RIPK3 signaling in AML(3-5), opening up new therapeutic possibilities. Building on these insights, this PhD project will investigate how upstream activation of the inflammatory TNFR1-RIPK3 signaling axis contributes to AML pathogenesis and LSC biology. By combining molecular biology, in vitro models, and in vivo validation, the candidate will explore how cytokine-based interventions can be leveraged to selectively eliminate LSCs.

Hypothesis and Objectives:

Our previous work has shown that activating pro-inflammatory TNFR1 signaling in primary AML blasts induces both cell death and differentiation. Remarkably, the same treatment enhances the proliferation of healthy hematopoietic stem and progenitor cells (HSPCs),

revealing a promising therapeutic window to target leukemic cells while sparing normal hematopoiesis.

This PhD project aims to:

- Elucidate how inflammatory signals impact healthy and leukemic hematopoiesis.
- Dissect the tumor-suppressive mechanisms of TNFR signaling in AML.
- Identify actionable molecular pathways that could contribute to precision treatment strategies targeting leukemic stem cells with minimal toxicity.

This project lies at the interface of molecular oncology and precision medicine, aiming to uncover mechanistic insights that can inform the development of patient-tailored therapies for high-risk AML. The successful candidate will join a multidisciplinary international team in a vibrant and collaborative research environment, with access to cutting-edge technologies and opportunities for international networking.

Methodology:

The project will leverage a combination of molecular, cellular, and in vivo approaches to address the proposed questions.

Key experimental systems and techniques include:

- **Genetic engineering using CRISPR-Cas9** in a panel of AML cell lines to investigate TNFR superfamily members and their downstream signaling complexes.
- **Ex vivo culture models** using both healthy human HSPCs and patient-derived AML progenitor cells to study cytokine signaling in a controlled setting.
- **In vivo models**, including:
 - Syngeneic murine bone marrow transplantation using gene-targeted mouse strains.
 - Patient-derived xenograft (PDX) models to evaluate the role of TNFR signaling in AML cell death and differentiation in a human-relevant context.

The host lab offers extensive expertise in hematologic malignancy models, functional genomics, and translational research, providing a stimulating environment for career development in oncology.

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Zhanat KOSHENOV, PhD

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Project Title: Investigation of activity dependent synaptic bioenergetics

Background:

The brain, arguably the most important organ in our bodies, is also the most energetically expensive one. Our brains consume about 20% of the body's fuel, while comprising only 2% of its weight. Most of the energy in the brain is spent by neurons on processes associated with neurotransmission, or passage of a signal from one neuron to the next that happens at specialized compartments called synapses¹. Synaptic transmission requires precise coordination between neuronal activity and metabolic support^{2,3}. Thus, the concept of activity-dependent synaptic bioenergetics explores how energy production and utilization are dynamically regulated in response to neuronal firing and synaptic signaling.

Recently, we have uncovered one of the mechanisms of such activity dependent metabolic control that depends on a protein called SLC13A5, a sodium citrate transporter⁴. SLC13A5 boosts presynaptic glycolysis by clearing cytosolic citrate during neuronal activity, thus disinhibiting synaptic glycolysis⁵. Disruptions in such bioenergetic processes have been implicated in various neurodegenerative diseases, where they contribute to synaptic dysfunction and cognitive decline^{1,5}. Investigating the molecular and cellular mechanisms underlying activity-dependent energy regulation at synapses is crucial for understanding brain function and developing therapeutic strategies for neurological disorders.

Hypothesis and Objectives:

Most of our understanding of cellular energy metabolism comes from studies done in liver, muscle, or cancer cells, none of which resemble the specialized morphology of neurons.

Given the morphological and functional differences between neurons and most other cell types, we hypothesize that neurons, especially at synaptic compartments, have evolved unique bioenergetic control mechanisms in accordance with their specialized needs.

Understanding these mechanisms will help us better understand brain metabolism and allow us to develop therapies for healthy brain aging and combat neurodegeneration.

Some of the main objectives of this project is to identify novel mechanisms and players in synaptic activity dependent bioenergetics and find ways to leverage gained knowledge to better understand brain function in health and disease.

Methodology:

The PhD candidate will learn to isolate and culture primary rat and mouse neurons. The student will be trained in using high-, and super-resolution fluorescence microscopy techniques to image live and fixed neurons and measure synaptic metabolite fluxes as well as synaptic vesicle recycling. The candidate will be supported in using standard methods in molecular biology and biochemistry, including, but not limited to cloning, PCR, Western blot, DNA isolation.

References:

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Project Title: Translational Test Models for Functional Assessment of Bioactive Wound Dressings in Chronic Wound Environments

Background:

Chronic wounds, such as diabetic ulcers, venous leg ulcers, and pressure sores, represent a significant global healthcare burden. These wounds fail to progress through the normal stages of healing due to persistent inflammation, infection, oxidative stress, and impaired cellular responses. Current treatment options are limited and often ineffective, leading to prolonged patient suffering, increased healthcare costs, and risk of severe complications including amputation.

A major barrier in developing effective therapies is the lack of reliable, translational in vivo models that accurately mimic the complex pathophysiology of non-healing wounds. Most existing animal models heal too efficiently, limiting their utility for testing advanced bioactive dressings and regenerative treatments intended for chronic wound scenarios.

Hypothesis and Objectives:

A refined porcine wound model that integrates key features of chronic wounds—persistent inflammation, bacterial colonization, and oxidative stress—will more accurately replicate the human chronic wound environment and provide a robust platform for testing bioactive wound therapies.

Key objectives:

- To refine an existing porcine model of non-healing wounds by incorporating bacterial components (e.g., LPS, alpha-toxin from *Staphylococcus aureus*) and oxidative stress inducers to better mimic the chronic wound microenvironment.
- To characterize wound healing kinetics in the refined model using macroscopic, histological, and molecular analyses.
- To validate translational relevance by comparing the refined porcine model with human chronic wound biopsies.
- To functionally assess novel bioactive wound dressings in both the refined non-healing model and standard models to determine their regenerative potential.

Methodology:

Model Refinement: Non-healing wounds will be induced in pigs using an inflammatory stimulus, bacterial components (LPS and *S. aureus* alpha-toxin), and oxidative stress factors.

In Vivo Assessment: Wound area, perfusion, and healing progression will be monitored over time using imaging and scoring systems until full closure is observed.

Histological & Molecular Characterization:

- **Tissue Analysis:** Histology and immunohistochemistry (IHC) will assess re-epithelialization (e.g., Ki67 staining), immune cell infiltration, and tissue remodeling.
- **Gene Expression:** Quantitative PCR will be used to evaluate the expression of key inflammatory (e.g., IL-6, TNF- α), regenerative (e.g., FGF2), and remodeling markers (e.g., ACTA2).

Human Comparison: Porcine wound tissue will be directly compared to human chronic wound biopsies using IHC and gene expression profiling.

Functional Testing: Experimental bioactive wound dressings will be applied in both standard and refined wound models to evaluate their therapeutic efficacy.

References:

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Project Title:

Decoding and Targeting Mitochondria–ER Crosstalk in Cellular and Organismal Aging

Background:

Previous findings in an *in vitro* aging model using endothelial cells revealed an enhanced interaction between mitochondria and the endoplasmic reticulum (ER) in aged cells. This appears to serve as an adaptive mechanism to mitigate cellular dysfunction but may also increase the risk of mitochondrial Ca²⁺ overload.

Hypothesis and Objectives:

We hypothesize that similar alterations in mitochondria–ER contact sites occur during *in vivo* aging and may serve as targets for novel anti-aging compounds. This Ph.D. project aims to investigate structural and functional changes in these contact sites in *Caenorhabditis elegans* (*C. elegans*) during aging. Additionally, we seek to identify key proteins involved in regulating mitochondria–ER interactions in both *in vitro* and *in vivo* aging. In parallel, candidate compounds targeting mitochondria–ER interplay – identified through a screen conducted by the Austrian Science Fund-funded SENIOPROM consortium – will be tested in *C. elegans* and various cellular aging models.

Methodology:

Aging will be modeled using replicative, stress-induced, and oncogene-driven senescence as well as *C. elegans*. The project will employ standard molecular biology techniques alongside live-cell fluorescence microscopy using organelle-targeted biosensors and marker proteins. Novel *C. elegans* strains expressing these fluorescent tools will be generated for *in vivo* imaging.

Candidate Profile:

We are looking for a highly motivated Ph.D. candidate with experience in cell culture, *C. elegans* maintenance, and fluorescence microscopy. A strong interest in experimental



research, a meticulous and independent working style, and a genuine enthusiasm for contributing to a collaborative international research team are essential.

References:

Please familiarize yourself with our publications via [PubMed Madreiter-Sokolowski](#).

Roland MALLI, PhD

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Project Title:

Development of Next-Generation Potassium Ion Biosensors

Background:

Dynamic monitoring of ion fluxes, particularly potassium ions (K^+), in living systems is critical to understanding fundamental physiological processes such as neuronal excitability, cardiac rhythm, immune responses, and metabolic regulation^{1,2}. Yet, conventional K^+ biosensors and imaging protocols often lack the resolution, specificity, and temporal fidelity required to dissect the nuanced roles of K^+ fluctuations in health and disease³. Our mission is to pioneer the next generation of genetically encoded K^+ biosensors, tailored also for in vivo imaging, unlocking new dimensions in the study of neurodegeneration, cancer metabolism, and electrolyte homeostasis. By integrating cutting-edge biosensor engineering with advanced imaging platforms, we aim to visualize and decode previously inaccessible subcellular K^+ dynamics in real-time, within intact biological systems.

Hypothesis and Objectives:

We hypothesize that newly designed K^+ biosensors, using optimized fluorescent proteins, split-holo scaffolds, and polycistronic expression strategies, can overcome current limitations in sensitivity, kinetics, and multiplexing attempts. The central objective of this PhD project is to design, engineer, and validate high-performance genetically encoded K^+ biosensors for imaging applications. These biosensors will be tailored for multiplexed detection of K^+ fluxes alongside other physiological signals. Emphasis will be placed on improving the dynamic range, response time, and biocompatibility of the sensors for both single-cell and whole-organism imaging contexts.

Methodology:

The PhD candidate will undergo rigorous training in biosensor engineering and fluorescence imaging. The project will begin with rational and directed evolution of K^+ -sensing domains, followed by integration into reporter architectures compatible with in vivo systems such as

zebrafish, drosophila, and eventually murine models in the labs of our collaboration partners. Advanced techniques of live-cell microscopy will be employed to characterize sensor performance. Moreover, the candidate will develop multiplexed imaging protocols to simultaneously monitor subcellular K⁺ dynamics alongside other cellular activities. Collaborations with partner labs in Munich will support the development of in vivo-optimized biosensor variants through iterative rounds of evolution and testing. Additionally, translational relevance will be explored through applications in drug screening and disease marker discovery.

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Project Title: Archaeal keystone species in host microbiomes: Understanding and controlling Methanobrevibacter for Environmental and Health Benefits

Background:

Archaea, the most ancient domain of life, play a crucial yet historically underappreciated role in Earth's nutrient cycles and in human-associated microbiomes. Among them, Methanobrevibacter species are especially important for their role in methane production in ruminants - contributing up to 6% of anthropogenic greenhouse gas emissions. Recent research from our group has demonstrated that distinct Methanobrevibacter species can profoundly shape the human gut microbial ecosystem by modulating the availability of essential vitamins and metabolites, thereby impacting host physiology. However, our mechanistic understanding of archaeal dynamics and their interactions within complex microbial communities remains limited, primarily due to technical challenges and a longstanding research bias toward bacteria. Notably, Methanobrevibacter never acts in isolation; it relies on intricate syntrophic and mutualistic interactions with bacteria, serving as a central hub in inter-domain networks. This unique position opens up exciting opportunities to strategically manipulate the human microbiome through targeted interventions focused on its archaeal members.

➡ In the framework of the newly funded ERC Advanced Grant ArchMeth, starting in early 2026, two fully funded PhD positions will be available. We are seeking highly motivated and curious PhD candidates who are eager to learn cutting-edge techniques, think beyond conventional boundaries, and collaborate closely with a dynamic team of technicians, students, and postdoctoral researchers. The Moissl-Eichinger Lab offers an inspiring and supportive research environment that values diversity and scientific excellence, driven by genuine curiosity and ambition.

Hypothesis and Objectives:

We hypothesize that Methanobrevibacter species serve as keystone organisms within the human gut microbiome by orchestrating metabolic networks and interspecies interactions that modulate host health. The detailed goals of the two PhD positions are:

1. To unravel the syntrophic and mutualistic interactions between *Methanobrevibacter* species and key bacterial partners in the gut.
2. To develop and validate robust synthetic archaeal-bacterial consortia with defined functions and therapeutic potential.
3. To strategically perturb archaeal-bacterial interactions by internal and external interventions, with the goal to apply these findings to complex microbiomes

Methodology:

The proposed research integrates computational, experimental and in vivo approaches. Computationally, we will perform analysis of multi-omics data and use models to predict syntrophic relationships and metabolic fluxes. Experimentally, we will establish co-culture systems of archaea with several key bacterial partners under controlled (stable, perturbed) laboratory conditions, and assess, via various omics techniques, the dynamics of interactions. Findings will be validated with computational and in vivo models. Key instrumentation and techniques: B.sight high-throughput cultivation, anaerobic cultivation, omics (metagenomics, genomics, metabolomics, proteomics, transcriptomics), electron microscopy, genetic engineering, application of in silico approaches (MICOM, PyCoMo), bioinformatics.

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Susanne SATTLER, PhD

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Department of Cardiology, Gottfried Schatz Research Center,
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Project Title: Autoimmunity against non-protein targets in heart disease

Background:

Heart failure is a complex clinical syndrome marked by progressive structural remodeling and impaired cardiac function. While traditional risk factors such as hypertension and ischemic heart disease are well-characterized, emerging evidence suggests an autoimmune component may contribute to HF pathogenesis. Notably, auto-antibodies against lipid and other non-protein components have been detected in patients with cardiovascular disease, however the specific role of anti-lipid immune responses in the progression of heart failure remains poorly defined.

Hypothesis and Objectives:

Autoimmunity against non-protein targets (e.g. lipids) contributes to the progression of heart failure by promoting inflammatory processes in the myocardium.

Objectives:

- (1) To use publicly available omics datasets for the analysis of pathways involved in autoimmunity against non-protein targets and their implications in heart disease.
- (2) To establish in-house assays for the detection of a variety of non-protein auto-antibodies in human and mouse samples.
- (3) To characterize the profile and prevalence of autoantibodies in heart failure patients and evaluate their potential as biomarkers for heart failure progression and therapeutic response.
- (4) To determine the mechanistic role of auto-antibodies in cardiac inflammation and remodeling using in vitro and in vivo models.

(5) To determine the molecular mechanisms involved in the generation of auto-antibodies using in vitro and in vivo models.

Methodology:

We will make use of clinical cohorts and analyse serum from HF patients and matched controls for anti-lipid autoantibodies using ELISA and/or multiplex assays. Correlations with clinical data (ejection fraction, NT-proBNP, MRI findings) will be analyzed. For mechanistic studies, human cardiomyocytes and immune cells will be exposed to patient-derived auto-antibodies to assess pro-inflammatory and cytotoxic effects via cytokine profiling, apoptosis markers, and mitochondrial stress assays. A mouse model of ischaemic heart failure will be used to investigate the impact of passive transfer or depletion of anti-lipid auto-antibodies on cardiac function.

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Project Title: Monitoring and interfering with glioblastoma network formation with bioelectronic technologies

Background:

The ex-ovo chicken embryo model offers to monitor how individual tumor cells form a network, attract and contact blood vessels and form a solid tumor in real time. In this process, individual glioblastoma cells use electrical signals through cellular calcium (Ca^{2+}) rise that make the tumor growth faster and more resistant to chemotherapy (1-2).

Hypothesis and Objectives:

This tumor model is unique in several key aspects for the PhD project. The tumors grow on the surface of the breathing organ of a chicken embryo that is easily accessible for fluorescence microscopy and new bioelectronic setups. This PhD project offers the PhD student to

- 1) generate stable glioblastoma cell lines expressing a fluorescence reporter for regulatory transcriptional factor activation and cytosolic calcium signaling.
- 2) undertake long term fluorescence microscopy evaluating how cellular calcium signals and transcriptional programs are linked to vascularisation, proliferation and tumour formation in ex ovo CAM models of glioblastoma.
- 3) interfere in tumor treatment with electrical pulsing, local chemotherapy (3) and photo-uncaging compounds to control treatment over time, space and drug concentration.

Methodology:

Methods are based on monitoring and evaluation on the CAM chicken embryo tumor model, cell culture experiments, stable generation of glioblastoma cell lines, long-term fluorescence microscopy as well as immuno-histochemistry.

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Project Title: Targeting lipid and energy metabolism in beta cells to preserve beta cell function

Background:

Type 2 Diabetes is the fastest-growing chronic metabolic disease worldwide and contributes significantly to global morbidity and mortality. The pathogenesis of type 2 diabetes is strongly associated with excessive lipid accumulation in multiple insulin-sensitive tissues, leading to impaired peripheral insulin sensitivity. Furthermore, ectopic lipid deposition in beta cells disrupts beta cell function and ultimately promotes beta cell death. However, despite these adverse effects, lipids play a critical role in maintaining beta cell physiology. Adequate lipid availability and mobilization in beta cells is essential for sustaining insulin secretory function and beta cell health. A decline in exogenous fatty acid supply drastically impairs beta cell identity including glucose-stimulated insulin secretion and insulin storage capacity. However, the molecular mechanisms by which exogenous fatty acids modulate subcellular processes in beta cells to maintain or even promote their function and fitness remain incompletely elucidated. Understanding how lipids shape intracellular metabolic pathways may uncover novel targets for preserving beta cell integrity in the context of type 2 diabetes.

Hypothesis and Objectives:

We hypothesize that exogenous fatty acids play a critical role in cell signaling in beta cells, either by acting directly as lipid mediators or by serving as precursors for the formation of signaling lipids, thus maintaining beta cell function and health. We aim to better understand the underlying molecular mechanisms regulated by exogenous fatty acids in beta cells by:

- i) Investigating the impact of exogenous fatty acids on cellular processes that regulate mitochondrial bioenergetics and ER function.
- ii) Identifying signaling lipids that control these cellular processes.
- iii) Investigating the metabolic switch that transforms exogenous fatty acids from supportive metabolic factors to drivers of the pathogenesis of type 2 diabetes.

Methodology:

The PhD student will learn and apply cutting-edge and well-established molecular-biological techniques to investigate the impact of lipids on beta cell function and fitness at the (sub)cellular level. The project will involve the use of 2D and 3D cell culture techniques for established beta cell lines as well as primary pancreatic islets and beta cells. The PhD candidate will evaluate molecular and metabolic changes in beta cells by protein and gene expression analyses, including Western blot, immunohistochemistry, and qPCR. Alterations in mitochondrial and ER function will be further assessed by subcellular Ca^{2+} measurements and ATP levels as well as extracellular flux analyses. The metabolic activity of key enzymes regulated by exogenous fatty acids will be either modulated by pharmacological inhibition or by CRISPR/Cas9-mediated gene editing. Changes in the formation of biochemical intermediates will be investigated by metabolomic analysis and linked to the presence of specific signaling lipids by lipidomic analysis. Ultimately, the findings will be translated into human beta cells to ensure clinical relevance.

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Project Title:

Small *RAS*-mutated clones and the bone marrow microenvironment in myeloid neoplasms

Background:

Myeloid neoplasms (MN) are aggressive hematopoietic tumors often driven by *RAS* mutations (*RAS^{mut}*). *RAS^{mut}* in MN have long been classified simply as “present” or “absent”, but next-generation sequencing (NGS) has revealed varying clone sizes. Large *RAS^{mut}* clones are linked to poor outcomes, but **the impact of small *RAS^{mut}* clones is unclear. Analyzing NGS data from over 500 patients with chronic myelomonocytic leukemia, we found that both large and small *RAS^{mut}* clones are associated with adverse outcomes.**

Biologically, *RAS^{mut}* hematopoietic stem and progenitor cells (HSPCs) show increased proliferation and myelomonocytic bias, suggesting small *RAS^{mut}* clones may expand over time. However, **recent data indicate that clone sizes may also remain stable during progression, raising questions about how *RAS^{mut}* cells influence co-existing *RAS*-wildtype (*RAS^{wt}*) clones.**

Recently, *RAS^{mut}* have been implicated in altering the bone marrow microenvironment (BMME). While *RAS^{mut}* in BMME cells can increase leukemogenesis, studies of acute lymphoblastic leukemia suggest that *RAS^{mut}* leukemic cells can also modify the BMME itself.

Hypothesis and Objectives:

We hypothesize that **small *RAS^{mut}* clones significantly influence MN biology and disease progression**. Although they are only present in a small subset of leukemic cells only, **we propose that these clones modify the BMME, thereby promoting disease progression by impacting *RAS^{wt}* leukemic cells.**

Methodology:

We will first determine whether small and large RAS^{mut} clones affect the BMME. Using a murine RAS^{mut} leukemia model, we will perform bulk and single-cell RNA sequencing on BMME cells and compare the results to RAS^{wt} littermates to identify RAS -specific changes. Next, we will validate our findings in patient samples from our leukemia biobank. Mesenchymal stromal cells (MSCs) derived from cryopreserved bone marrow samples of MN patients with small and large RAS^{mut} clones will be compared to MSC from healthy donors to identify relevant candidate genes. Next, these candidate genes will be further investigated in vitro, where co-culture of MSCs from healthy donors with leukemic cell pools containing small and large fractions of RAS^{mut} cells will be established. For this, leukemic cell lines will be engineered via CRISPR/Cas9 to carry RAS^{mut} , then diluted with isogenic RAS^{wt} cells to achieve pre-defined RAS^{mut} variant allele frequencies (VAFs).

We will then assess whether the BMME of MN patients with small and large RAS^{mut} clones can indeed promote leukemogenesis in normal hematopoietic and leukemic RAS^{wt} cells. Therefore, we will co-culture normal hematopoietic cells and RAS^{wt} leukemic cells with MSCs derived from healthy donors and MN patients with small and large RAS^{mut} clones. In this model, we will then determine whether the MSC background influences the leukemogenic potential of the co-cultured hematopoietic cells.

Finally, we will use these MSC co-culture models to **investigate whether targeting selected candidate genes identified in our BMME transcriptomic analyses can reverse RAS^{mut} induced leukemogenic effects.** Potential therapeutic options arising from this will be further validated in patient-derived xenograft models using RAS^{mut} MN samples transplanted into immunocompromised mice.

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