FARZI Aitak, MD, PhD

Division of Pharmacology, Otto Loewi Research Center for Vascular Biology, Immunology and Inflammation, Medical University of Graz

Project Title:

Polyamines in microbiota-gut-brain signaling and psychiatric disorders

Background:

Polyamines such as spermidine affect several aspects of gut microbiota-brain communication. At the intestinal level, polyamines affect the microbiome, enhance intestinal barrier and improve metabolic dysfunction in response to diet-induced obesity (1). Furthermore, several intestinal bacteria are able to synthesize or metabolize polyamines. Centrally, spermidine improves cognitive function by inducing mitophagy and increasing mitochondrial respiration (2). Both the gut microbiome and impaired mitochondrial function have also been implicated in psychiatric disorders and preclinical models of psychiatric disorders exhibit alterations of both systems. Dysfunction of both systems could further affect mood by inducing neuroinflammation and an imbalance of neurotransmitters and neurotrophic factors. However, the impact of polyamines on microbiota-gut-brain signaling has not been investigated in the context of psychiatric disorders.

Hypothesis and Objectives:

We hypothesize that dietary or bacteria derived polyamines ameliorate changes in affective behavior (e.g. anxiety and sociability) in preclinical models of psychiatric disorders induced by high-fat diet or stress. Our objectives include investigating: (i) the impact of dietary or bacteria-derived polyamines on emotional behavior in preclinical models of anxiety and depression; (ii) the contribution of the intestinal microbiome; and (iii) the effects on glial and neuronal autophagy / mitophagy and mitochondrial function.

Methodology:

The recruited PhD student will use established mouse models of depression and anxiety induced by high fat diet or stress in combination with behavioral test batteries assessing

emotional behavior, stress coping, sociability and cognition (3). The involvement of the intestinal microbiota will be investigated by fecal microbiota transfer experiments, bacterial community profiling (16S and/or metagenomics) and analysis of (bacterial) metabolites by metabolomics approaches. Brain autophagy / mitophagy and mitochondrial function will be assessed by assessing protein levels of mitophagy and autophagy markers in relevant brain areas, visualizing the cellular (co-)localization and distribution of neuronal, glial, mitochondrial and autophagy markers by immunofluorescence and visualization of autophagosomes and mitochondria by transmission electron microscopy. The selected PhD candidate will collaborate closely with the interdisciplinary research team within the Cluster of Excellence “Metabolic Control of Aging and Disease (MetAGE)”, spanning three prominent Austrian Universities.

References:

1. Hofer SJ, Simon AK, Bergmann M, Eisenberg T, Kroemer G, Madeo F. Mechanisms of spermidine-induced autophagy and geroprotection. Nat Aging. 2022;2(12):1112-29.
2. Schroeder S, Hofer SJ, Zimmermann A, Pechlaner R, Dammbrueck C, Pendl T, et al. Dietary spermidine improves cognitive function. Cell Rep. 2021;35(2):108985.
3. Hassan AM, Mancano G, Kashofer K, Liebisch G, Farzi A, Zenz G, et al. Anhedonia induced by high-fat diet in mice depends on gut microbiota and leptin. Nutr Neurosci. 2020:1-14.

FARZI Aitak, MD, PhD

Division of Pharmacology, Otto Loewi Research Center for Vascular Biology, Immunology and Inflammation, Medical University of Graz

Project Title:

Brain-organ crosstalk in stress-induced depression and associated metabolic changes

Background:

Stressful life events increase the risk for mental disorders, such as depression, as well as metabolic disorders including cardiovascular disease, obesity, diabetes mellitus and liver disease (1). The biological pathways underlying the association between mental health issues and metabolic disorders include dysfunction of the neuroendocrine system and brain circuitries integrating homeostatic and mood regulatory responses. In addition, various metabolic and inflammatory signals (derived from the intestinal microbiome, adipose tissue or liver) contribute to both metabolic and mood disorders. Among others, behavioral changes in response to chronic stress are induced by hypoactivity of a neuronal population of the hypothamalus expressing the neuropeptides AgRP and NPY (2). These neurons are well known to be stimulated by hunger signals and to be involved in feeding and energy metabolism (3). It is however not understood in detail which mechanisms lead to hypoactivity of AgRP neurons in response to stress and how hypoactivity of this neuronal population affects metabolism and behavior.

Hypothesis and Objectives:

We hypothesize that peripheral metabolic signals (e.g. insulin, leptin, PYY, glucose, fatty acids) and pro-inflammatory cytokines (e.g. Il-1b, Tnf-a) affect the activity of hypothalamic neuronal populations in response to stress and thereby modulate feeding, metabolism and affective behavior. Our objectives include investigating: (i) the impact of different types of stressors on peripheral metabolic and immune signals; (ii) their effects on the activity of neuronal populations of the hypothalamus; and (iii) the effects of these neuronal populations on feeding and affective behavior.

Methodology:

The recruited PhD student will use established mouse models of depression induced by chronic social defeat or chronic unpredictable mild stress. Behavioral effects will be assessed by established behavioral test batteries assessing emotional behavior, stress coping, sociability and cognition. Pro-inflammatory cytokine and metabolic hormone levels will be assessed by magnetic bead-based immunoassays. Neuronal activation will be assessed by immunofluorescence co-staining for c-fos and other hypothalamic neuropeptides. Metabolic and behavioral effects of these neurons can be analyzed by combining activity-dependent cell labeling (FosTRAP) and stimulatory DREADD receptors.

References:

1. Kivimaki M, Bartolomucci A, Kawachi I. The multiple roles of life stress in metabolic disorders. Nat Rev Endocrinol. 2023;19(1):10-27.
2. Fang X, Jiang S, Wang J, Bai Y, Kim CS, Blake D, et al. Chronic unpredictable stress induces depression-related behaviors by suppressing AgRP neuron activity. Mol Psychiatry. 2021;26(6):2299-315.
3. Ip CK, Zhang L, Farzi A, Qi Y, Clarke I, Reed F, et al. Amygdala NPY Circuits Promote the Development of Accelerated Obesity under Chronic Stress Conditions. Cell Metab. 2019;30(1):111-28 e6.

GRAIER Wolfgang, PhD

Molecular Biology & Biochemistry, Gottfried Schatz Research Center
Medical University of Graz

Project Title:

Metabolic rewiring as a new therapeutic approach against aging

Background:

Mitochondria, the powerhouses of cells, play a crucial role in energy metabolism. However, their function declines with age, contributing to various age-related diseases. So far, poorly understood aging-associated processes impair the organelle's ability to generate ATP and cause oxidative stress that damages mitochondrial proteins and lipids, further compromising their function[1]. We have described aging-related changes in the inter-organelle tethering and Ca^{2+} communications making senescent cells more vulnerable to mitochondrial Ca^{2+}-overload[2]. Such settings bear danger for an increased generation of reactive oxygen species (ROS). However, senescent cells protect themselves by desensitization of the mitochondrial Ca^{2+} uptake machinery[3] and the engagement of hexokinase 1 as an energy stress sensor that regulates the shape, connectivity, and metabolic activity of this organelle[4].

Hypothesis and Objectives:

We hypothesize that by specifically manipulating mitochondrial bioenergetics, we selectively induce cell death in senescent cells (AIM 1). This will liberate the growth and differentiation of tissue-presented progenitor cells (AIM 2), ultimately leading to tissue repair (AIM 3).

Methodology:

Human cell and non-mammalian animal models of aging will be used. Besides state-of-the-art biochemical and molecular biology techniques, we will employ biosensor-based multi-channel (sub-)cellular recordings of, e.g., cell function, metabolism, transcription, and signaling using super-/high-resolution microscopes (SIM, LSM, LS). Hence, electrophysiological recordings of mitochondria, FACS, and multicell analysis recordings will be performed.

References:

1. Amorim, J. A. *et al.* Mitochondrial and metabolic dysfunction in ageing and age-related diseases. *Nat Rev Endocrinol* 1–16 (2022) doi:10.1038/s41574-021-00626-7.
2. Madreiter-Sokolowski, C. T. *et al.* Enhanced inter-compartmental Ca^{2+} flux modulates mitochondrial metabolism and apoptotic threshold during aging. *Redox biology* **20**, (2018). doi: 10.1016/j.redox.2018.11.003
3. Madreiter-Sokolowski, C. T. *et al.* PRMT1-mediated methylation of MICU1 determines the UCP2/3 dependency of mitochondrial Ca^{2+} uptake in immortalized cells. *Nat Commun* **7**, 12897 (2016). doi:10.1038/ncomms12897
4. Pilic, J. *et al.* Hexokinase 1 forms rings that regulate mitochondrial fission during energy stress. *Mol. Cell* (2024) doi:10.1016/j.molcel.2024.06.009.

MADL Tobias, PhD

Medicinal Chemistry, Otto Loewi Research Center for Vascular Biology, Immunology and Inflammation, Medical University of Graz

Project Title:

Uncovering methlation dynamics in ageing and age-related diseases (MetAGE Cluster of Excellence)

Background:

Methylation of proteins, nucleic acids, and metabolites plays a critical role in numerous physiological and pathophysiological processes. While it is known that these molecules are regulated by methylation, the comprehensive mechanisms driving the global dynamics of methylation remain poorly understood. Specifically, the coupling of protein, nucleic acid, and metabolite methylation with metabolism, and the implications of methylation in ageing and lifespan-modulating interventions are controversial. Our recent development of a novel NMR-based method for quantifying global protein arginine methylation has revealed that a significant proportion of arginines in cells and tissues are methylated. Additionally, we have identified significant variations in arginine methylation levels in cancers, neurodegenerative diseases, and ageing, suggesting a pivotal role in age-related diseases.[1-5] Here, we offer a PhD project to investigate the regulation and dynamics of global protein, nucleic acid, and metabolite methylation, and its coupling to metabolism in the context of ageing and age-related diseases.

Hypothesis and Objectives:

We hypothesize that the levels of and dynamics of protein, nucleic acid, and metabolite methylation are intertwined with metabolism, and that dispruptions of methylation dynamics are indicative in aging and age-related diseases. The objectives of this project are to:

- reveal the (sub)cellular dynamics of protein, nucleic acid, and metabolite methylation
- uncover the coupling between methylation processes and cellular metabolism
- identify differences in (sub)cellular dynamics of methylation in aging and age-related diseases in cells and *in vivo*

Methodology:

To address these objectives, the PhD candidate will develop and apply a NMR-based quantification protocol to study (sub)cellular dynamics of methylation and employ (selectively)

isotope-labeled metabolites in combination with genetic and pharmacological modifiers of methylation. The PhD candidate will reveal the interplay between methylation and metabolism using advanced metabolomics techniques and use *in vivo* model systems provided by the *MetAGE* consortium to explore the modulation of methylation in response to key ageing modulators. Furthermore, the PhD candidate will work closely with the *MetAGE* consortium to integrate findings from proteomics, epigenetic analyses, and functional assays, and study clinical samples to validate the relevance of methylation dynamics in ageing and age-related diseases.

Despite the recognized importance of methylation in regulating physiological processes, the detailed mechanisms governing methylation levels and dynamics are not fully elucidated. This PhD project aims to uncover the unknown links and interactions between methylation, metabolism, and ageing, providing new insights into the role of methylation in age-related diseases.

We invite motivated and talented candidates to apply for this exciting PhD project, which offers the opportunity to work at the forefront of research on methylation dynamics and ageing. This project will provide comprehensive training in state-of-the-art techniques and foster collaboration within a dynamic research consortium.

References:

1. Zhang F, Bischof H, Burgstaller S, Bourgeois BMR, Malli R, Madl T (2024) Genetically encoded fluorescent sensor to monitor intracellular arginine methylation. J Photochem Photobiol B 252:112867. doi:10.1016/j.jphotobiol.2024.112867
2. Usluer S, Galhuber M, Khanna Y, Bourgeois B, Spreitzer E, Michenthaler H, Prokesch A, Madl T (2024) Disordered regions mediate the interaction of p53 and MRE11. Biochim Biophys Acta Mol Cell Res 1871 (2):119654. doi:10.1016/j.bbamcr.2023.119654
3. Karner C, Anders I, Vejzovic D, Szkandera J, Scheipl S, Deutsch AJA, Weiss L, Vierlinger K, Kolb D, Kuhberger S, Heitzer E, Habisch H, Zhang F, Madl T, Reininger-Gutmann B, Liegl-Atzwanger B, Rinner B (2023) Targeting epigenetic features in clear cell sarcomas based on patient-derived cell lines. J Transl Med 21 (1):54. doi:10.1186/s12967-022-03843-4
4. Zhang F, Rakhimbekova A, Lashley T, Madl T (2023) Brain regions show different metabolic and protein arginine methylation phenotypes in frontotemporal dementias and Alzheimer's disease. Prog Neurobiol 221:102400. doi:10.1016/j.pneurobio.2022.102400
5. Zhang F, Kerbl-Knapp J, Rodriguez Colman MJ, Meinitzer A, Macher T, Vujic N, Fasching S, Jany-Luig E, Korbelius M, Kuentzel KB, Mack M, Akhmetshina A, Pirchheim A, Paar M, Rinner B, Horl G, Steyrer E, Stelzl U, Burgering B, Eisenberg T, Pertschy B, Kratky D, Madl T (2021) Global analysis of protein arginine methylation. Cell Rep Methods 1 (2):100016. doi:10.1016/j.crmeth.2021.100016

STROBL Herbert, MD

Division of Immunology, Otto Loewi Research Center for Vascular Biology, Immunology and Inflammation, Medical University Graz

Project Title:

Mechanism underlying the age-related decline in tolerogenic DC subsets.

Background:

Aging is accompanied by a loss of immune system function, potentially resulting in age-related changes such as diminishment of vaccination efficacy, the re-activation of latent viruses and in an increase in severe pulmonary infections. Additionally, aging is associated with a gradual loss of self-tolerance. Dendritic cells (DCs) represent a heterogeneous class of leukocytes comprising tolerogenic and immunogenic cell subsets. DCs take up and process foreign and self-antigens in the periphery and migrate to lymph nodes, where they stimulate antigen-specific T cells. Additionally, they maintain the pool of regulatory T cells in peripheral tissues. Previous studies revealed changes in the composition of DC subsets during aging. However, the molecular mechanism underlying these changes remained poorly understood. Tolerogenic DCs reside in peripheral barrier tissues such as skin, lung and intestine, and are capable of instructing regulatory T cells. They arise from peripheral blood DC precursor cells and blood monocytes. Tolerogenic DCs in skin known as epidermal/mucosal Langerhans cells (LCs) and intestine i.e. $CD103^{+}CD11b^{+}$DCs arise via blood monocytes and/or conventional DC2s via TGF-beta receptor signaling, while monocyte-derived DCs populate inflammatory lesions independently of TGF-beta. These processes can be modeled in vitro using cytokine supplemented short term culture systems. We and others previously described switch factors that induce tolerogenic at expense of pro-inflammatory DC subsets, and vica versa [1] [2].

Hypothesis and Objectives:

We here hypothesize that DC instructive signaling processes change during aging resulting in the attrition of tolerogenic in favour of pro-inflammatory DC subset differentiation of monocytes and DC precursors. We previously established several cytokine-dependent differentiation culture models that allow the generation of TGF-beta1-dependent LCs and intestinal DCs from

blood cDC2s and monocytes [3] [4]. These models will be employed for identifying age-related changes in DC subset differentiation.

Methodology:

The PhD student will purify cDC2s and monocytes from healthy young (20-25 years) vs older (55-60 years) adults, and study their differentiation capacity in response to TGF-beta1 supplemented LC and intestinal $CD103^+$ intestinal DC differentiation cultures. Additionally, non-LC monocyte-derived DC and macrophages will be generated in parallel in response to combinations of cytokines in the absence of exogenous TGF-beta1. Differences between young vs old will be monitored. Subsequently the underlying molecular mechanism will be studied. In a parallel effort and to obtain *in vivo* data, immunophenotyping of human DC subsets will be performed in patient samples; moreover age-related changes in DC subsets from murine disease models, such as pulmonary infection and fibrosis will be studied. The PhD student will culture human DC subsets, perform flow cytometry, RNA seq, and will perform gene perturbation studies using lentiviral vectors and gene editing. Additionally, the student will analyze DC subsets and immune responses in mice.

References:

1. Strobl, H., Krump, C., and Borek, I. (2019). Micro-environmental signals directing human epidermal Langerhans cell differentiation. Semin Cell Dev Biol *86*, 36-43. 10.1016/j.semcdb.2018.02.016.
2. Jurkin, J., Krump, C., Koffel, R., Fieber, C., Schuster, C., Brunner, P.M., Borek, I., Eisenwort, G., Lim, C., Mages, J., et al. (2017). Human skin dendritic cell fate is differentially regulated by the monocyte identity factor Kruppel-like factor 4 during steady state and inflammation. J Allergy Clin Immunol *139*, 1873-1884 e1810. 10.1016/j.jaci.2016.09.018.
3. Bauer, T., Zagorska, A., Jurkin, J., Yasmin, N., Koffel, R., Richter, S., Gesslbauer, B., Lemke, G., and Strobl, H. (2012). Identification of Axl as a downstream effector of TGF-beta1 during Langerhans cell differentiation and epidermal homeostasis. J Exp Med *209*, 2033-2047. 10.1084/jem.20120493.
4. Yasmin, N., Bauer, T., Modak, M., Wagner, K., Schuster, C., Koffel, R., Seyerl, M., Stockl, J., Elbe-Burger, A., Graf, D., and Strobl, H. (2013). Identification of bone morphogenetic protein 7 (BMP7) as an instructive factor for human epidermal Langerhans cell differentiation. J Exp Med *210*, 2597-2610. 10.1084/jem.20130275.

STROBL Herbert, MD

Division of Immunology, Otto Loewi Research Center for Vascular Biology, Immunology and Inflammation, Medical University Graz

Project Title:

Mechanism underlying forced myelopoiesis during aging

Background:

Hematopooetic stem cells (HSC) undergo self-renewal and differentiate into various blood and leukocyte lineages throughout life. All HSC and progenitor cell subsets are included in a minor fraction of bone marrow and blood cells expressing CD34, constituting ca 1 and 0.1% of mononuclear cells in bone marrow and blood, respectively. These $CD34^+$ cells include various hierarchical cell stages from HSCs to uni-lineage committed progenitor cells; thus hematopoietic/immune cell lineage commitment largely occur within this cell fraction[1]. While frequencies of total $CD34^+$ cells undergo only minor changes in younger vs older adults, phenotypically defined progenitor cells included in this cell fraction exhibit marked age-related functional changes, including loss in proliferative capacity and a bias towards myeloid cell differentiation. Forced myelopoiesis is accompanied by enhanced production of inflammatory cytokines, known as “inflammaging”, promoting a variety of age-related diseases[2]. Furthermore, the pool of myeloid progenitor cell-derived blood monocytes is regulated by nutritive signals, potentially contributing to the fasting-dependent anti-inflammatory effects[3]. A better understanding of the mechanism underlying hematopoietic stem cell aging and inflammaging may lead to new strategies to interfere with age-related diseases, and may also lead to improved procedures for HSC -based cell and gene therapy.

Hypothesis and Objectives:

This project aims to dissect the age-related changes in phenotypically defined HSC and progenitor cell stages included within the $CD34^+$ bone marrow and peripheral blood cell fraction. Subsequent mechanistic studies will aim to functionally implicate defined molecular pathways in HSC cell aging and age-associated myelopoiesis.

Med Uni Graz

MetAGE

Methodology:

The PhD student will perform single cell RNA sequencing of purified $CD34^+$ cells from cohorts of healthy young (20-25 years) vs older (55-60 years) adults. Changes in gene expression among phenotypically defined progenitor cell subsets in young vs old adults will then be identified. Differentially expressed genes will be validated at the protein level. Subsequently, gain and loss of function analyses of candidate genes will be performed using expansion and lineage differentiation cultures of human $CD34^+$ cord blood progenitor/stem cells. Interaction among genes will be analyzed using combined strategies of lentiviral gene transduction and CRISPR/Cas9 gene editing in cord blood $CD34^+$ cells.

References:

1. Dzierzak, E., and Bigas, A. (2018). Blood Development: Hematopoietic Stem Cell Dependence and Independence. Cell Stem Cell *22*, 639-651. 10.1016/j.stem.2018.04.015.
2. Fulop, T., Larbi, A., Pawelec, G., Khalil, A., Cohen, A.A., Hirokawa, K., Witkowski, J.M., and Franceschi, C. (2023). Immunology of Aging: the Birth of Inflammaging. Clin Rev Allergy Immunol *64*, 109-122. 10.1007/s12016-021-08899-6.
3. Janssen, H., Kahles, F., Liu, D., Downey, J., Koekkoek, L.L., Roudko, V., D'Souza, D., McAlpine, C.S., Halle, L., Poller, W.C., et al. (2023). Monocytes re-enter the bone marrow during fasting and alter the host response to infection. Immunity *56*, 783-796 e787. 10.1016/j.immuni.2023.01.024.

KAUTZKY-WILLER Alexandra, MD

Department of Medicine III, Division of Endocrinology and Metabolism,
Medical University of Vienna

Project Title:

Identify sex/gender-related similarities and differences in response to aging and dietary and pharmacological interventions

Background:

We and others have shown important differences between men and women in glucose and lipid metabolism, cardiovascular health and inflammation. In general, women live longer than men and have younger **biological ages** as assessed by molecular biomarkers [1]. Various health determinants, such as individual lifestyle, the socio-economic environment, preventable risk factors, as well as differences in use of health services contribute to the premature death in men (gender component). Women also have better **cardiometabolic health** than men, at least up to **menopause** [2], and despite higher fat mass for a given body mass index (BMI). This difference can be in part explained by estrogen-mediated protection against stress-induced cardiac inflammation and remodeling in premenopausal women [3]. There are major differences in the development and occurrence of cardiometabolic diseases. Hence women have a lower risk of NAFLD and of developing T2DM, especially in young and middle-aged populations. The protective role of estrogen in females plays a major role and decreases in the menopause. However also testosterone levels impact cardiometabolic health and aging in both sexes. Moreover, women have higher risk of mental health disorders that further increase in the presence of metabolic disorders. Caloric restriction may have stronger effects on metabolic health in females compared to males, however the underlying pathophysiological mechanisms are not known so far.

Hypothesis and Objectives:

We aim to disentangle the complex interaction between healthy aging and sexual dimorphism by performing nutritional intervention studies proposed in MetAGE in both male and female mice and humans and by analyzing human and murine samples of both sexes for (i) sex specific- and (ii) gender specific effects of dietary interventions and pharmacological therapies on healthy aging, and (iii) time restricted eating and metabolic control in sex specific high-risk

groups as well as possible effects of hormone replacement therapies. In addition, we will investigate the effect of sex hormones and lipid-lowering drugs on healthy aging in men and women.

Methodology:

We will explore mechanisms underlying sex differences in preclinical models undergoing dietary as well as pharmacological interventions. With support from animal research, we will study the influence of sex hormones on metabolic health in the different phases of the life cycle and aging by comparing pre- and postmenopausal women and groups of men at comparable age as well as specific vulnerable groups of women and men at high cardiometabolic risk. Finally, we will attempt to better understand how gender-specific age-related changes determine the patients´ perception of disease, help-seeking behavior, access to and individual use of health care, and communication between patients and health care workers.

References:

1. Mauvais-Jarvis F et al. (2020). Sex and gender: modifiers of health, disease, and medicine. The Lancet. 396(10250): 565–582. doi: 10.1016/S0140-6736(20)31561-0.
2. Goossens GH et al. (2021). Sexual dimorphism in cardiometabolic health: the role of adipose tissue, muscle and liver. Nat Rev Endocrinol. 17(1): 47–66. doi: 10.1038/s41574-020-00431-8.
3. Barcena de Arellano ML et al. (2019). Sex differences in the aging human heart: decreased sirtuins, proinflammatory shift and reduced anti-oxidative defense. Aging (Albany NY). 11(7): 1918–1933. doi: 10.18632/aging.101881.

Position: PhD – Medical University of Vienna

Requirements: MD degree or eligibility for the MUW MD/PhD Program (https://www.meduniwien.ac.at/web/studierende/mein-studium/diplomstudium-humanmedizin/exzellenzprogramm-mdphd/)

Language skills: fluent English, basic or fluent German of Advantage since the student will work and engage with mainly german speaking human subj

MADEO Frank, PhD

Institute of Molecular Biosciences, University of Graz

Project Title:

Metabolic regulation of spermidine-mediated hypusination

Background:

The polyamine spermidine is a ubiquitous molecule linked to multiple health benefits. It exists in free and bound (e.g., to DNA/RNA) forms, but both the subcellular and intercellular distribution are poorly understood. Free spermidine partly acts via the hypusination of eIF5A, but the relationship between hypusinated eIF5A and different metabolic pathways has not been addressed. Overall, it remains unclear whether aging or nutritional cues affect hypusination differently.

Hypothesis and Objectives:

We hypothesize that eIF5A hypusination and other downstream effectors of spermidine respond differently to specific metabolic pathways. Our objectives are to (i) explore differences in spermidine within different metabolic scenarios by employing a newly developed reporter system in Drosophila (ii) determine polyamine profiles under different nutritional cues and (iii) establish a link between the metabolic status and eIF5A hypusination. Mouse models will also be investigated.

Methodology:

We will use biochemical and cell-biological approaches to assess tissue- and cell-specific metabolite/polyamine profiles during aging and investigate physiological, pharmacological and genetic perturbations of hypusination. To achieve the latter, we plan to develop novel ELISA- and MS-based methods to detect this rare posttranslational modification, in order to overcome laborious, immunoblot-based methods.

References:

1. Madeo, F., Eisenberg, T., Pietrocola, F. & Kroemer, G. Spermidine in health and disease. *Science* **359**, eaan2788 (2018).

2. Eisenberg, T. *et al.* Cardioprotection and lifespan extension by the natural polyamine spermidine. *Nat Med* **22**, 1428–1438 (2016).

3. Hofer, S. et al. Spermidine is essential for fasting-mediated autophagy and longevity. *Nat Cell Biol* accepted (2024)

PHILIPPE Cecile, PhD

Department of Biomedical Imaging and Image-guided Therapy, Division of Nuclear Medicine, Medical University of Vienna

Project Title:

Metabolic control of aging and disease – preclinical imaging investigations

Background:

As the continuous increase in human life expectancy is resulting in a larger elderly population with multiple health conditions, promoting healthy aging has become a pressing societal challenge, emphasizing the need for validated strategies to extend the disease-free phase of life, known as the health span.

Our preclinical study aims to investigate metabolic aging under disease and stress conditions using advanced imaging techniques. Positron emission tomography (PET) will be employed for non-invasive in vivo imaging of metabolic functions within the whole body.

Hypothesis and Objectives:

We aim to identify changes in energy metabolism during aging in both healthy and obese animal subjects of both sexes, especially under stress conditions, pharmacological interventions, or dietary measures. Specifically, we will explore how these factors affect metabolic aging and disease progression.

Methodology:

The study will involve animal monitoring via metabolic cages, interventions (diatry measures or drug treatment), longitudinal PET imaging of different animal cohorts using specific radiotracers for energy metabolism and post-processing of the imaging data.

References:

1. López-Otín, C., Galluzzi, L., Freije, J.M.P., Madeo, F., Kroemer, G., 2016. Metabolic Control of Longevity. Cell 166(4):802-821.
2. Wirth, A., Wolf, B., Huang, C.K., Glage, S., Hofer, S.J., Bankstahl, M., Bär, C., Thum, T., Kahl, K.G., Sigrist, S.J., Madeo, F., Bankstahl, J.P., Ponimaskin, E., 2021. Novel aspects

of age-protection by spermidine supplementation are associated with preserved telomere length. Geroscience 43(2):673-690.

3. Subtirelu, R.C., Teichner, E.M., Su, Y., Al-Daoud, O., Patel, M., Patil, S., Writer, M., Werner, T., Revheim, M.E., Høilund-Carlsen, P.F., Alavi, A., 2023. Aging and Cerebral Glucose Metabolism: 18F-FDG-PET/CT Reveals Distinct Global and Regional Metabolic Changes in Healthy Patients. Life 13(10):2044.
4. Ustsinau, U., Ehret, V., Fürnsinn, C., Scherer, T., Helbich, T.H., Hacker, M., Kršśák, M., Philippe, C., 2023. Novel approach using [18F]FTHA-PET and de novo synthesized VLDL for assessment of FFA metabolism in a rat model of diet induced NAFLD. Clinical Nutrition 42 (10): 1839-1848.

Position: PhD – Medical University of Vienna

Requirements: Master degree in a relevant discipline (e.g. biology, pharmacy, nutrition science, veterinary medicine, etc.)

Willingness to carry out preclinical experiments.

Knowledge of imaging devices, especially PET, is preferential.

Motivation to work in an interdisciplinary team.

Excellent communication and teamwork skills.

Language skills: fluent English

PHILIPPE Cecile, PhD

Department of Biomedical Imaging and Image-guided Therapy, Division of Nuclear Medicine, Medical University of Vienna

Project Title:

Metabolic control of aging and disease – Kinetic modeling in preclinical metabolic imaging

Background:

As the continuous increase in human life expectancy is resulting in a larger elderly population with multiple health conditions, promoting healthy aging has become a pressing societal challenge, emphasizing the need for validated strategies to extend the disease-free phase of life, known as the health span.

Our preclinical study aims to investigate metabolic aging under disease and stress conditions using advanced imaging techniques. Positron emission tomography (PET) will be employed for non-invasive in vivo imaging of metabolic functions within the whole body.

Hypothesis and Objectives:

We aim to identify changes in energy metabolism during aging in both healthy and obese animal subjects of both sexes, especially under stress conditions, pharmacological interventions, or dietary measures. Specifically, we will explore how these factors affect metabolic aging and disease progression.

Methodology:

The study will involve longitudinal dynamic PET imaging of different animal cohorts using specific radiotracers for energy metabolism and post-processing of the imaging data including kinetic modeling to comprehensively evaluate the underlying metabolic processes.

References:

1. López-Otín, C., Galluzzi, L., Freije, J.M.P., Madeo, F., Kroemer, G., 2016. Metabolic Control of Longevity. Cell 166(4):802-821.
2. Wirth, A., Wolf, B., Huang, C.K., Glage, S., Hofer, S.J., Bankstahl, M., Bär, C., Thum, T., Kahl, K.G., Sigrist, S.J., Madeo, F., Bankstahl, J.P., Ponimaskin, E., 2021. Novel aspects

of age-protection by spermidine supplementation are associated with preserved telomere length. Geroscience 43(2):673-690.

3. Subtirelu, R.C., Teichner, E.M., Su, Y., Al-Daoud, O., Patel, M., Patil, S., Writer, M., Werner, T., Revheim, M.E., Høilund-Carlsen, P.F., Alavi, A., 2023. Aging and Cerebral Glucose Metabolism: 18F-FDG-PET/CT Reveals Distinct Global and Regional Metabolic Changes in Healthy Patients. Life 13(10):2044.
4. Ustsinau, U., Ehret, V., Fürnsinn, C., Scherer, T., Helbich, T.H., Hacker, M., Kršśák, M., Philippe, C., 2023. Novel approach using [18F]FTHA-PET and de novo synthesized VLDL for assessment of FFA metabolism in a rat model of diet induced NAFLD. Clinical Nutrition 42 (10): 1839-1848.
5. Huang, S.C., 2008. Role of Kinetic Modeling in Biomedical Imaging. J Med Sci. 28(2):57-63.

Position: PhD – Medical University of Vienna

Requirements: Master degree in a relevant discipline (e.g. biomedical engenieering, physics, etc.).

Strong background and experience in image post-processing (e.g. PMOD)

Knowledge of imaging devices, especially PET.

Willingness to carry out preclinical experiments.

Motivation to work in an interdisciplinary team.

Excellent communication and teamwork skills.

Language skills: fluent English

SCHERER Thomas, MD

Department of Medicine III, Division of Endocrinology and Metabolism,
Medical University of Vienna

Project Title:

Aging-related loss of metabolic flexibility and control on brain interorgan crosstalk

Background:

The brain processes and integrates endocrine and nutritional information from the whole body and partakes in a complex interorgan communication via the autonomic nervous system to control nutrient partitioning and fat mass. At the same time, peripheral endocrine and nutritional signals are able to affect brain function, and metabolic diseases are linked to neuropsychiatric disorders including depression. Embedded into the broader context of the Metage Cluster of Excellence, we here focus on deciphering the role of the brain in maintaining metabolic flexibility in aging human subjects.

Hypothesis and Objectives:

We and others showed that the brain controls whole body glucose and lipid metabolism via the autonomic nervous system. In this project we want to test the influence of aging and diet on peripheral metabolism and brain nutrient handling. We hope to thereby provide new insights into brain-interorgan crosstalk and novel disease mechanisms to combat aging-related metabolic disease and associated comorbidities.

Methodology:

We want to combine deep-metabolic phenotyping using standard endocrine/metabolic test and stable isotopes in conjunction with non-invasive metabolic imaging, using cutting edge magnetic resonance imaging and spectroscopy in humans. We will apply different calorie interventions such as alternate day fasting, very low-calorie diets and overfeeding challenges in small cohorts of lean/obese and old/young individuals to characterize the role of the brain in maintaining metabolic control.

References:

4. Leptin increases hepatic triglyceride export via a vagal mechanism in humans. Metz M, Beghini M, Wolf P, Pfleger L, Hackl M, Bastian M, Freudenthaler A, Harreiter J, Zeyda M, Baumgartner-Parzer S, Marculescu R, Marella N, Hannich T, Györi G, Berlakovich G, Roden M, Krebs M, Risti R, Lookene A, Trauner M, Kautzky-Willer A, Krssak M, Stangl H, Fürnsinn C, Scherer T* Cell Metab 2022 Nov 1;34(11):1719-1731.e5. doi: 10.1016/j.cmet.2022.09.020
5. Bednarik P, Goranovic D, Svátková A, Niess F, Hingerl L, Strasser B, Deelchand D, Spurny-Dworak B, Krssak M, Trattnig S, Hangel G, Scherer T, Lanzenberger R, Bogner W ^{1}H magnetic resonance spectroscopic imaging of deuterated glucose and of neurotransmitter metabolism at 7 T in the human brain. *2022 Nat Biomed Eng. 2023 Apr 27. doi: 10.1038/s41551-023-01035-z.*
6. M Metz, C Baumgartner, H Stangl, T Scherer Measuring VLDL1 secretion in humans with an intravenous fat emulsion test. Star Protocols Feb 9, 2023 https://doi.org/10.1016/j.xpro.2023.102089

Position: PhD – Medical University of Vienna

Requirements: MD degree or eligibility for the MUW MD/PhD Program (https://www.meduniwien.ac.at/web/studierende/mein-studium/diplomstudium-humanmedizin/exzellenzprogramm-mdphd/)

Language skills: fluent English, basic or fluent German of Advantage since the student will work and engage with mainly German speaking human subjects

SCHREIBER Renate, PhD

Institute of Molecular Biosciences, University of Graz

Project: Adipocyte lipolysis upon aging and dietary interventions

Background:

Adipocytes within adipose tissue play a key role in controlling energy homeostasis. During overnutrition, adipocytes store energy as triacylglycerol (TG) in cytosolic lipid droplets. Upon energy need, TGs are mobilized by hydrolases primarily adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) in a process termed lipolysis to supply the body with fatty acids (FA) for fuel, signaling molecules, and building blocks for cellular membrances (i.e. autophagy)[1,2]. However, how adipocyte lipolysis is affected by aging and dietary intervention(s) remain insufficiently understood and controversial[3,4].

Hypothesis and Objectives:

We hypothesize that nutrional interventions improve aging-associated alterations in adipocyte lipolysis in mice and men. In this project, the PhD candidate will investigate the kinetics of lipid metabolism (i.e. lipolysis and lipid synthesis) on organismal and molecular level.

Methodology:

To address this question, explorative studies will be performed in mice during circadian cycles of fasting and refeeding and upon dietary intervention. Flux analyses using stable isotopes will allow to quantify lipid metabolism in vivo. State-of-the art whole-body phenotyping will be applied to assess energy and lipid metabolism (i.e., indirect calorimetry, glucose/insulin tolerance tests). Adipocyte lipolysis will also be determined on a functional, molecular, and biochemical level in mouse tissues, human biopsies, and isolated adipocytes.

The selected PhD candidate will work in a vital research environment and participate in a doctoral program led by a multidisciplinary team within the Cluster of Excellence “MetAGE”. The PhD candidate will work in close collaboration with F. Madeo, T. Eisenberg, M. Trauner, and T. Pieber. and will have the opportunity to perform part of the project in a host laboratory abroad.

References:

1. Zechner, R., Madeo, F. & Kratky, D. Cytosolic lipolysis and lipophagy: Two sides of the same coin. *Nat. Rev. Mol. Cell Biol.* **18**, 671–684 (2017).
2. Schreiber, R., Xie, H. & Schweiger, M. Of mice and men: The physiological role of adipose triglyceride lipase (ATGL). *Biochim. Biophys. Acta - Mol. Cell Biol. Lipids* **1864**, 880–899 (2019).
3. Klein, S., Young, V. R., Blackburn, G. L., Bistrian, B. R. & Wolfe, R. R. Palmitate and glycerol kinetics during brief starvation in normal weight young adult and elderly subjects. *J. Clin. Invest.* **78**, 928–933 (1986).
4. Gao, H. *et al.* Age-Induced Reduction in Human Lipolysis: A Potential Role for Adipocyte Noradrenaline Degradation. *Cell Metab.* **32**, 1–3 (2020).

SCHREIBER Renate, PhD

Institute of Molecular Biosciences, University of Graz

Project: How does alterd adipocyte lipolysis impact healthy aging?

Background:

Energy is stored primarily in adipocytes in intracellular lipid droplets as triacylglycerol and is mobilized upon need in a process termed lipolysis catalyzed by two major enzymes: adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL)[1]. Increased adipocyte lipolysis is associated with detrimental effects causing cellular and subsequent tissue dysfunction. In contrast, decreased lipolysis is implicated to be a key driver for unhealthy aging. Remarkably, in mouse models, both low and high adipocyte lipolysis have shown beneficial metabolic effects[2,3].

Hypothesis and Objectives:

We propose that altered adipocyte lipolysis will improve metabolic health during aging. To explore the role of adipocyte lipolysis upon aging, the PhD candidate will study genetically modified mouse models.

Methodology:

The PhD student will study mouse models upon genetic and pharmacological inhibition of lipases (i.e., ATGL and/or HSL) upon high caloric diet feeding and aging. To genetically mimic caloric restriction, a transgenic mouse line transiently overexpressing ATGL will be generated and studied. The metabolic effects of fasting regimen(s) in these transgenic lines will be investigated including food intake, energy expenditure, body composition, glucose metabolism, and thermoregulation. To gain mechanistic insights, omics (transcript, protein, lipid) together with biochemical and functional analyses will be performed on total adipose tissue and isolated adipocytes. Plasma and biopsies will be studied from a young/aged human subpopulation upon pharmacological inhibition of lipolysis and dietary intervention.

The selected PhD candidate will work in a vital research environment and will participate in a doctoral program led by a multidisciplinary team within the Cluster of Excellence “MetAGE”. The PhD candidate will work in close collaboration with M. Schweiger, S. Sedej, T. Eisenberg,

U. Stelzl, and M. Trauner and will have the opportunity to perform part of the project in a host laboratory abroad.

References:

1. Schweiger, M. *et al.* Adipose triglyceride lipase and hormone-sensitive lipase are the major enzymes in adipose tissue triacylglycerol catabolism. *J. Biol. Chem.* **281**, 40236–40241 (2006).
2. Schreiber, R. *et al.* Hypophagia and metabolic adaptations in mice with defective ATGL-mediated lipolysis cause resistance to HFD-induced obesity. *Proc. Natl. Acad. Sci. U. S. A.* **112**, 13850–13855 (2015).
3. Ahmadian, M. *et al.* Adipose overexpression of desnutrin promotes fatty acid use and attenuates diet-induced obesity. *Diabetes* **58**, 855–866 (2009).

SCHWEIGER Martina, PhD

Institute of Molecular Biosciences, University of Graz

Project Title:

The role of macrophages in sustaining adipose tissue function with age

Background:

Metabolic flexibility, the body's capacity to adapt fuel oxidation to fuel availability, ensures survival amid varying nutrient supply and is lost with age[1]. Adipose tissue (AT) is the body's larges energy store, as such controlling systemic energy homeostasis. AT displays species-conserved changes with aging, including redistribution from peripheral to visceral depots and chronic inflammation, that is also characterized by an altered AT macrophage (ATM) profile[2]. Caloric restriction not only decreases total AT mass but also reduces AT inflammation, which is associated with restored metabolic flexibility and healthspan extension[3]. While the impact of nutritional interventions on immune changes and metabolic flexibility is unclear, targeting age-related AT dysfunction could extend health span

Hypothesis and Objectives:

We propose that age-related changes in AT distribution and immune cell function largely contributes to reduced metabolic flexibility and disease upon aging. We want to investigate whether **changes in adipocyte metabolism modify the immune phenotype of visceral and subcutaneous AT** thereby contributing to the detrimental effects of aging. By lipolysis inhibition, targeting cytokine signaling, fasting mimetics, and different feeding/fasting regimens we aim to **transform the inflamed dysfunctional AT into a healthy tissue** with restored metabolic flexibility and capacity to take up nutrient lipids.

Methodology:

The research will employ studies in adipocyte and macrophage specific lipase-deficient mice followed by a comprehensive array of **cutting-edge techniques**, ecompassing flow cytometry, immunofluorescence, RNA-sequencing, metabolomic, lipidomic, and proteomic analyses which will be combined with 2D- or 3D cultures of primary cells and cell lines followed by secretome- and functional analyses to investigate metabolism (*e.g.,* lipolysis, lipid uptake and -oxidation).

The selected PhD student will attend a **doctoral training program** linked to the research activity of MetAGE, a unique and **highly interdisciplinary team**, collaborate closely with fellows in the groups of R. Schreiber, T. Scherer, H. Strobl, and U. Stelzl and will have the opportunity to perform part of the project in a host laboratory abroad.

References:

1. Bret H. Goodpaster and Lauren M. Sparks, 'Metabolic Flexibility in Health and Disease', Cell Metabolism, 25.5 (2017), 1027–36 https://doi.org/10.1016/j.cmet.2017.04.015.
2. Tammy T. Nguyen and Silvia Corvera, 'Adipose Tissue as a Linchpin of Organismal Ageing', Nature Metabolism, 6.5 (2024), 793–807 https://doi.org/10.1038/s42255-024-01046-3.
3. Min-Yi Ou and others, 'Adipose Tissue Aging: Mechanisms and Therapeutic Implications', Cell Death & Disease, 13.4 (2022), 300 https://doi.org/10.1038/s41419-022-04752-6.

STELZL Ulrich, PhD

Institute of Pharmaceutical Sciences, University of Graz

Project Title:

Cellular proteome and phosphorylation dynamics in aging

Background:

The group is focusing on the analysis of molecular interaction networks with the aim to understand the dynamics of molecular networks underlying cellular processes related to human disease. Experimental functional genomics techniques, e.g. HTP Y2H screening and mass spectrometry, are utilized in combination with biochemical, cell biological and computational methods.

Current DNA sequencing approaches and mass spectrometry-based proteomics technologies allow the simultaneous measurements of gene/protein variants for series of cell types, conditions or disease states. The question arises how to determine the impact of combined small changes for cellular function, disease development and drug action? In our work we focus on the systematic analyses of the functional impact of genetic variation and post-translational protein modification on protein-protein interaction and underlying cellular phenotypes. Using deep scanning mutagenesis approaches we bridge the knowledge gap between nucleotide resolution genomics and protein resolution proteomics.

Hypothesis and Objectives:

Here we plan to investigate the crosstalk of lipid- and polyamine metabolism to other cellular process through assessing proteome wide alterations in models of ageing. Through combined genetic (ko-strategies) and environmental / drug perturbation / aging intervention, quantitative proteomics/phospho-proteomics will help elucidating mechanistic links of aging processes in particular to autophagy, ribosome biogenesis and lipid metabolism. In collaboration with the MetAGE aeras polyamines, proteostasis and the data science platform, this systems biology approach will specifically elucidate the role of kinase activities for aging processes.

Methodology:

Genomics, cell biology, protein interaction analysis, mass spectrometry-based proteomics and integrative bioinformatic data analysis.

References:

1. Kohlmayr JM, et al. (2024); Mutational scanning pinpoints distinct binding sites of key ATGL regulators in lipolysis; Nat Commun 15, 2516; doi: 10.1038/s41467-024-46937-x [OA]
2. Moesslacher CS, et al. (2023); Missense variant interaction scanning reveals a critical role of the FERM domain for tumor suppressor protein NF2 conformation and function; Life Sci Alliance 6: 202302043; doi: 10.26508/lsa.202302043 [OA]
3. Jehle S, et al. (2022); A human kinase yeast array for the identification of kinases modulating phosphorylation-dependent protein-protein interactions; Mol Syst Biol 18, e10820; doi: 10.15252/msb.202110820 [OA]
4. Kunowska N, Stelzl U (2022); Decoding the cellular effects of genetic variation through interaction proteomics; Curr Opin Chem Biol 66: 102100; doi: 10.1016/j.cbpa.2021.102100

https://europepmc.org/search?query=%28AUTH%3A%22stelzl%20u%22%29

TRAUNER Michael, MD

Hans Popper Laboratory for Molecular Hepatology, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna

Project Title:

Role of bile acids in lipostasis and aging-associated decline of metabolic control

Background:

In addition to their digestive functions, bile acids (BAs) act as signaling molecules efficiently regulating their own metabolism and transport as well as key aspects of lipid and glucose homeostasis in mutual interaction with gut microbiota (1). Changes in BA homeostasis contribute to the pathogenesis of a metabolic disorders including metabolic dysfunction-associated steatotic liver disease (MASLD) (2,3). During overnutrition, adipose tissue (AT) buffers excess energy in form of triacylglycerols. In times of increased energy need, these stores are mobilized by hydrolases (in a process termed lipolysis) to supply the body with fatty acids (FA) as both fuel and signaling molecules and building blocks for cellular membranes (4). Deregulated lipolysis causes FA spillover, leading to ectopic lipid deposition with so-called lipotoxic effects and subsequent tissue dysfunction in MASLD (2). The latter is also a driver of cardiometabolic morbidity, highlighting the vicious cycle induced by impaired AT function.

Hypothesis and Objectives:

We aim to explore the dynamics of host and microbial BA metabolism and its impact on lipostasis during dietary, BA-targeted pharmacological interventions and aging. Given the critical (patho)physiological potential of AT, we need to better understand its function during aging to address lipolytic flexibility in a time-resolved manner (i.e., examine the ability of cells to turn on/off lipolysis under changing nutrient conditions) and how it impacts the liver, skeletal muscle and the heart (lipostasis).

Methodology:

We will combine biochemical assays with lipid flux studies and whole-body metabolic holistic phenotyping, including advanced metabolic imaging to better understand the impact of aging and dietary interventions on AT and liver function. Genetic and pharmacological approaches to alter BA signaling, AT lipolysis as well as their intercations with immune cell function will

give mechanistic insights into if and how these processes promote metabolic reprogramming and healthy aging. Mouse/cell culture data will be corssvalidated and integrated with findings obtained in human/clinical samples.

References:

1. Fuchs CD, Trauner M. (2022). Role of bile acids and their receptors in gastrointestinal and hepatic pathophysiology. Nat Rev Gastroenterol Hepatol. 19(7):432-450. doi: 10.1038/s41575-021-00566-7.
2. Loomba R et al. (2021). Mechanisms and disease consequences of nonalcoholic fatty liver disease. Cell. 184(10): 2537–2564. doi: 10.1016/j.cell.2021.04.015.
3. Tincopa MA et al. (2024). New and emerging treatments for metabolic dysfunction-associated steatohepatitis. Cell Metab. 36(5):912-926. doi: 10.1016/j.cmet.2024.03.011.
4. Zechner R et al. (2017). Cytosolic lipolysis and lipophagy: two sides of the same coin. Nat Rev Mol Cell Biol. 18(11): 671–684. doi: 10.1038/nrm.2017.76.

Position: PhD Student – Medical University of Vienna

Requirements:

Language skills: fluent English

Experience with molecular and cell biology, interest in work with cell culture and organoids, as well transgenic/knockoutmouse studies. Enthusiasm for an integrated holistic approach to explore inter-organ crosstalk in metabolic disorders and aging.