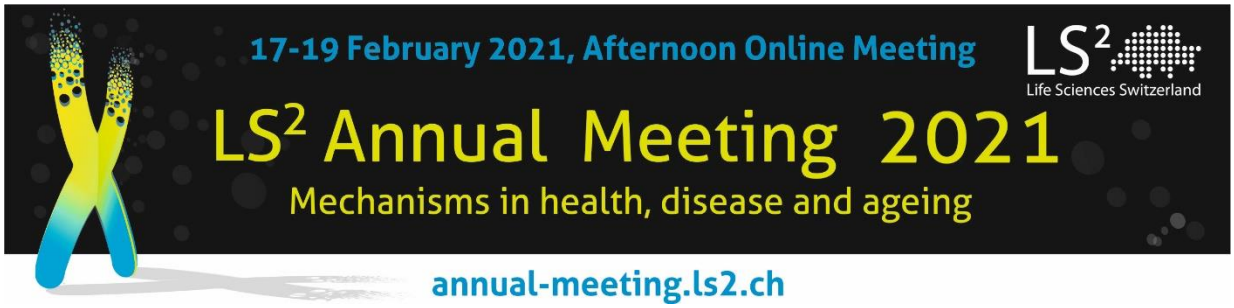

Abstracts of invited and sponsored speakers of
Scientific e-Symposia
LS² Annual e-Meeting

Thursday 18 February 2021 (15:35 – 17:20 CET):

Friday 19 February 2021 (16:00 – 17:45 CET):

iPSC derived Cardiomyocytes and Cardiac Microtissues

This symposium is organized by **Gabriela Kania (UZH)** and **Marie-Noëlle Giraud (UNIFR)** as part of our LS² Cardiovascular Intersection

- **Christine MUMMERY**
  Leiden University Medical Center (NL)

Cardiovascular diseases and drugs: where are we with hiPSC models?

Derivation of cardiovascular cell types from human pluripotent stem cells derived from patients or introducing targeted mutations is an area of growing interest as a platform for disease modelling, drug discovery and toxicity. Our lab has been investigating microtissue solutions in which cardiomyocytes and cardiac vascular and stromal cells are present. This promotes cardiomyocyte maturation and in combination with new methods for functional phenotyping, we have been able to quantify the outcomes of drug and disease mutation responses in situ. The use of isogenic pairs of hiPSC lines with and without mutations has proven very important since variability between "healthy control" hiPSC lines is often greater than the difference between diseased cells and its isogenic control. Examples of studies using disease and drug responses in cardiac microtissues will be shown.

- **Christian ZUPPINGER**
  University of Bern (CH)

3D cardiac cell culture: prospects and limitations of cardiac spheroids

Cellular aggregates, scaffold-free micro-tissues, or spheroids have been used almost since the very beginning of cell culture models, and they belong to the most frequently used 3D cell culture types for drug development and safety testing. This type of in vitro model owns much of its popularity to the comparably simple and rapid production and semi-automatic analysis methods available today. Also, a smaller number of costly or rare cells per micro-tissue is needed, which is especially welcome with human, stem cell-derived cardiovascular cells, and as the spheroids are floating, they can be cultured in formats that are compatible with already available instruments such as multi-well plate readers. Recently, more sophisticated culture and analysis options for cardiac spheroids have been developed, including co-culturing with other cell types, continuous perfusion, and electrical stimulation. Although many publications, including our own, have demonstrated several tissue-like features, and more relevant responses of cardiac spheroids in comparison to standard 2D cultures of the same cells, this type of 3D culture comes with limitations regarding the measurement of cell-physiological properties of cardiac muscle. Those measurements have traditionally been performed using animal models or with freshly isolated cardiomyocytes. Hydrogel-based cardiac 3D cultures or similar, larger tissue formats may offer more complex read-outs at the price of a more demanding and costlier production and slower throughput. Finally, there is still much more work to do for establishing 3D cell culture as a widespread and validated tool in cardiovascular research and life science in general.

- **Przemyslaw BLYSZCZUK**
  University Hospital Zurich (CH)

Human cardiac microtissues as a model to study myocardial fibrosis

Fibrotic changes in the myocardium represent a common pathology in heart disease. Understanding pathogenesis of fibrotic processes in the human heart is essential for development of effective therapies. However, availability of fresh patients' cardiac samples for experimental research is limited, therefore there is a need for development of alternative models. Self-aggregating, scaffold-free cardiac microtissues comprising of human iPSCs-derived cardiomyocytes together with human primary cardiac fibroblasts represent such alternative in vitro model of human cardiac tissue. By using profibrotic cytokine TGF-β, we induced profibrotic changes in these microtissues. TGF-β-treated cardiac microtissues increased in size, upregulated fibrotic markers on transcript and protein levels and showed altered spontaneous contraction rate and contraction pattern. Our results pointed to active role of cardiac fibroblasts in regulating contraction of fibrotic cardiac microtissues. Furthermore, we showed that our model can be successfully used to test anti-fibrotic pharmacological compounds. In conclusion, fibrotic cardiac microtissues can be used as a high-throughput model for drug testing and to study cellular and molecular mechanisms of cardiac fibrosis.

Precision Medicine and Biomarkers: The Quest for Gold

This symposium is organized by **Mark Ibberson (SIB)** and **Alan Bridge (SIB)** as part of our LS² Bioinformatics Intersection - Swiss Institute of Bioinformatics (SIB).

- **Ewan PEARSON**
  University of Dundee (UK)

Precision medicine in Diabetes

People are all different, and this is no different when we consider people with diabetes, yet the current approaches to management of diabetes tend to treat everyone the same. The field of precision medicine aims to recognise these differences – whether at the level of their phenotype or at the molecular level. Faced with multiple, and increasing, treatment options for diabetes as well as increasing healthcare costs there is a clear need to target therapy to maximise benefit and reduce harm for every patient with diabetes.

This talk will discuss advances in precision medicine and pharmacogenetics in diabetes over the last decade. I will initially outline striking examples seen in monogenic diabetes: subtypes of Maturity Onset Diabetes of the Young and for Neonatal Diabetes caused by potassium channel gene mutations, where patients are often able to transfer off insulin injections onto oral treatment. However, patients with monogenic forms of diabetes are rare, and this lecture will move on to how we might begin to tailor treatment in more common forms of diabetes – such as type 2 diabetes. I will then provide an overview of our latest understanding of the genetics of type 2 diabetes, where >400 variants have been identified and where extremes of the polygenic risk score are associated with considerable differences in diabetes risk. Partitioning genetic risk into component pathophysiological processes also allows us to start to predict progression of diabetes or drug response based upon the individual underlying diabetes aetiology.

There is increasing evidence that genetic and other molecular and clinical characteristics will impact on treatment outcomes. The exciting challenge now is how we incorporate this information into clinical care and establish that this improves patient outcomes.

- **Maria GÓMEZ**
  Lund University

BEAt-DKD (Biomarker Enterprise to Attack DKD) and the power of public private partnerships in diabetes research

Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease and a debilitating disease with patients facing mortalities exceeding most cancers. Despite the recent introduction of novel drugs (endothelin receptor antagonists and sodium glucose cotransporter 2 -SGLT2 inhibitors) that have shown renal and cardiovascular protection, DKD remains a large unmet medical need and DKD treatment development should abandon the idea of “one size fits all” to take into account disease heterogeneity and drug response variability of individual patients.

BEAt-DKD (www.beat-dkd.eu) is a unique public-private partnership committed to deliver better stratification of patients and more effective tools for use in innovative clinical trials, with the aim to improve prevention and management of DKD and establish a new paradigm for precision medicine in

DKD. This is a 5-year project that started October 2016, engages 29 partners in 11 countries and has already generated new important insights in the pathogenesis, heterogeneity and treatment response in DKD.

The overall aims of the consortium are 1) to provide a holistic systems medicine view of the pathogenesis of DKD with the aim to identify targetable mechanisms and pathways underlying initiation and progression of DKD, applying a novel sub-classification of diabetes, and 2) to identify and validate biomarkers of disease progression and treatment responses.

In this presentation we will provide a summary of achievements so far, and we will highlight activities which benefitted from working in synergy with other IMI consortia (i.e. effective data federation for the combination of existing and novel data sets and overcoming data sharing issues; discovery from a data-driven analysis revealing 5 novel subgroups of adult-onset diabetes, of a severe insulin-resistant group having higher risk to develop DKD). We will also exemplify how integration of multi-omics data from cell, animal and human studies can be used to identify molecular pathways and biomarkers associated with treatment response.

- **Gema Fuerte Hortigón** – industry talk
  Bucher biotec AG & Mission Bio Inc

High-throughput single-cell DNA-sequencing and protein analysis reveals CRISPR-editing efficiency as well as clonal evolution in cancer

Cancer is a clonal disease developing from a single cell, however, because of its inherent genetic instability cancer cell populations tend to evolve to be genetically heterogeneous. Finding the best treatment option requires a multi-omics understanding of the disease state at the single-cell level.
In addition to genetic mutations often caused by single nucleotide variants (SNVs), gene copy number variants (CNVs) play a large role in driving cancer progression and evolution making some clonal populations more virulent and drug-resistant than others. Using acute myeloid leukemia (AML) as an example we show here that the Tapestri Platform enables comprehensive identification of those cell populations through combining single-cell DNA sequencing with cell surface protein detection, thereby accurately defining clonal populations and reconstructing clonal phylogenies. In a second step, this information can be used in precision medicine to ultimately find the best treatment options for each patient. Genome-editing systems are increasingly used to advance such cell therapies, but edited cellular systems need to be thoroughly characterized to fully understand the exact nature of induced mutations. Both on and off-target effects and the complexities of mutation zygosity and co-occurrence must be determined. Single-cell DNA-sequencing data reveals all these combinations at multiple sites and is therefore an ideal tool for quality control as well as improvement and should be a priority for those looking to bring exciting ex vivo and in vivo therapeutics to the clinic.

- **David Benz** – industry talk
  Bucher biotec AG

Exosomes as Novel Multicomponent Biomarkers: Challenges and Opportunities

Exosomes are 40-150 nm-sized extracellular vesicles released by all cell types, including tumor cells, and are widely distributed in body fluids, such as blood, bile, urine and saliva. Interest in these vesicles has exploded in recent years as they carry a large variety of DNA, RNA, proteins and lipids. Thus, they have been implicated as key mediators of non-contact intercellular communication and have been identified as candidates for early-stage diagnostics as well as therapeutic delivery vectors, e.g. in the treatment of cancer or Alzheimer's disease (Song et al., 2020). We will give an overview on the opportunities and challenges ahead to streamline the research in this promising field.

Autophagy and Ageing – implications for age-related diseases

This symposium is organized by **Alexander Eggel (UNIBE)** and **Jörn Dengjel (UNIFR)**, as part of the LS² Autophagy Section.

- **Katja SIMON**
  Kennedy Institute of Rheumatology (UK)

Autophagy in Immune Senescence

With increasing life expectancy, the number of people over 60 years is expected to double by 2050, reaching 2.1 billion worldwide. The severity of many infections increases substantially with age, and the success of childhood vaccination is widely recognized but the importance of vaccination of the elderly population is frequently underestimated. Vaccines are known to be particularly ineffective in the elderly, yet some vaccines such as influenza are primarily given to that age group. Immune senescence is characterized by a decline in innate and adaptive immunity together with an increase in low-grade chronic inflammation contributing to age-related diseases such as osteoarthritis, cardiovascular and neurodegenerative diseases. Reversing or halting immune ageing would open opportunities to improve management of age-related morbidities and have a major impact on the health of our society. The discovery of autophagy-related proteins greatly advanced the mechanistic understanding of autophagy. We showed that autophagy prevents immune aging. In this lecture, I will present our most recent data of a novel pathway relying on autophagy's potential to improve human vaccination of the elderly. I will discuss the translational regulation of autophagy that controls proteostasis in long- lived T and B lymphocytes and novel ways to reverse immune senescence

- **Linda PARTRIDGE**
  Max Planck Institute for Biology of Ageing (DE) & Institute of Healthy Ageing and GEE at UCL (UK)

Ageing: a gut feeling

The loss of function and pathology caused by ageing can be ameliorated by genetic and pharmacological interventions in laboratory animals. Inhibition of the mTOR network has evolutionarily conserved effects on lifespan and ageing. We have found that the gut is a key target tissue for the mTORC1 inhibitor rapamycin, with benefits to both the health of the gut itself and to lifespan. Intestinal health during ageing is thus an important determinant of the health of the whole organism.

This Symposium is supported by the Swiss Society for Aging Research (SSFAR).

Multiparametric Microscopy in Basic and Translational Research

This symposium is organized by **Urs Ziegler (UZH**) and **Joana Delgado Martins (UZH)** as part of our LS^2 Microscopy Intersection

- **Lucas PELKMANS**
  University of Zurich

Cellular state determines the multimodal signaling response of single cells

A fundamental property of cells is that they make decisions adapted to their internal state and surrounding. This context-aware behaviour requires the processing of large amounts of information, but it is unclear how cells can reliably achieve this using heterogeneous signaling responses. Here we apply brief epidermal growth factor stimulation of human epithelial cells grown in culture, combined with multiplexed quantification of signaling responses and pre-existing cellular state markers across multiple spatial scales. We find that heterogeneous growth factor responses of signaling nodes in a network reflect adaptive information processing, each carrying partially non-redundant information about the cellular state. Collectively, as a multimodal response, this provides individual cells with a large amount of information to accurately place growth factor concentration within the context of their cellular state. We propose that heterogeneity and complexity in signaling networks have co-evolved to enable specific and context-aware cellular decision making in a multicellular setting.

- **Christian HOLZ**
  Molecular Devices

New 3D applications on Molecular Devices intelligent automated imaging solutions.

Trends continue towards the development of more sophisticated and physiologically relevant in vitro assays such as stem cell-derived models, 3D assays and organoid cultures, organ-on-a-chip technology, and tissue modelling. In parallel, fully automated imaging solutions now enable an ever-deeper insight into cell compartments while intelligent software tools are turning the high information content of 3D images into meaningful results. We discuss how the ImageXpress Micro Confocal High-Content Imaging System and the ImageXpress Pico Automated Cell Imager offer advanced solutions for scaling up research and identifying new drug candidates in the fight against cancer, diabetes, brain disorders, and chronic heart disease.

Mitochondria in Health, Disease and Ageing

This symposium is organized by **Torsten Ochsenreiter** (UNIBE) as part of the LS^2 MCB Section

- **Anna WREDENBERG**
  Karolinska Institutet

The role of mitochondrial SAM in health and disease

Production of the methyl-group donor S-adenosylmethionine (SAM) depends on one-carbon metabolism, with vital intermediary steps being localised to mitochondria. It remains uncertain how one-carbon availability connects to mitochondrial function. By generating knockout mice as well as patient-specific Drosophila melanogaster models for the mitochondrial SAM carrier, we show that gradual decline of mitochondrial SAM (mitoSAM) import causes hierarchical defects in fly and mouse, comprising loss of metabolites and OXPHOS assembly. Complex I stability and iron-sulfur cluster biosynthesis are directly controlled by mitoSAM levels, while other protein targets are predominantly methylated outside of the organelle prior to import. Interestingly, methylation modifications on mitochondrial RNAs seem to be least affected by a diminishing mitoSAM pool. Further, our data establishes that the mitoSAM pool follows cytosolic production, forming a feedback loop and identifying mitochondria as responsive receivers of one-carbon units. Thus, we demonstrate that cellular methylation potential is connected to energy metabolism, with direct relevance aging and disease.

- **Pierre MAECHLER**
  University of Geneva

Short or long mitochondria, a dilemma for glucose homeostasis

Mitochondria are dynamic organelles subjected to continuous length adaptation through fusion and fission events, in particular in response to energy homeostasis. Glucose is the primary energy fuel for cells in our body and its levels are essentially controlled by the pancreatic beta-cells and the liver; the former secreting insulin that promotes glucose clearance and the latter being in charge of hepatic glucose production. Mitochondria play an important role in beta-cells for the coupling of glucose metabolism to insulin secretion and in the liver for gluconeogenesis.

Mitochondrial fusion and fission events are controlled by a set of proteins. Among them, prohibitins are located in the mitochondrial inner membrane and form ring-shaped complexes. Prohibitin-deficient cells show fragmented mitochondria, defective cristae and excessive proteolytic cleavage of OPA1. The long form of OPA1 (L-OPA1) is essential for fusion, whereas the short form of OPA1 (S-OPA1) is associated with fission. In mice, knockout of prohibitins specifically in hepatocytes or ß-cells alter cellular functions with severe specific phenotypes, respectively glucose shortage or excess, namely diabetes. Stabilization of L-OPA1 protects against tissue damage, leading to the amelioration of the mitochondrial function. Overall, it remains controversial whether altered mitochondrial morphology is the cause or the consequence of mitochondrial dysfunction.

- **Stephen HELLIWELL –** industry talk
  Rejuveron Life Sciences AG

rejuveron

Ageing and mitochondria

A seminal paper published in 2013 defined the "Nine Hallmarks of Aging"; key aspects of our biology that alter as we age, and ultimately act in concert to prevent us from aging more healthily. These hallmarks are divided into 3 groups defining the foundational, antagonistic, and integrative hallmarks, reflecting the causes of, the initial response to, and the cells and processes that succumb to this damage, respectively (López-Otín, Cell, 2013).

Mitochondrial dysfunction is an antagonistic hallmark of aging, and, as such, much effort has been directed towards understanding how and why mitochondria become dysfunctional with age. This in turn lead to increased efforts by both Academia and Industry to delineate druggable mechanisms, and therapies, that will improve mitochondrial function in the elderly population, or perhaps even prevent this dysfunction before it happens. In this way many deleterious phenotypes associated with aging could be limited – allowing for healthier, better aging. I will summarize some of those efforts in this presentation.

Rejuveron is an integrated biotechnology platform company that develops and improves therapies and technologies to promote healthy aging and prolong lifespan. We create and support start-up companies by providing coaching, infrastructure, and full funding to entrepreneurial scientists to co-create therapies that benefit our aging population

Chemical Biology and Drug Discovery

This symposium was planned by Philip Skaanderup (Novartis) and is organized by **Christian Heinis (EPFL)** as part of our partner society, the DMCCB, a division of the Swiss Chemical Society

- **Nina HARTRAMPF**
  University of Zurich (CH)

Flow-based Synthesis of Chemically Modified Peptides and Proteins

The field of biopharmaceuticals is rapidly expanding, requiring new methods for on-demand production of chemically modified peptides and proteins. This chemical synthesis involves iterative formation of amide bonds on an immobilized solid phase and requires high yields for efficient incorporation of each individual amino acid. Flow-based synthesis methods are used to accomplish rapid synthesis of tailored peptides and proteins with the advantage of automated in-line data collection. This analytical data can be used to further optimize and predict chemical synthesis outcome, including sequence-dependent events such as aggregation. By optimizing this method with respect to minimized time and by-product formation, flow-based synthesis now routinely delivers proteins exceeding 100 amino acids in length. Complete control of every incorporated amino acid is opening the chemical space to a theoretically unlimited amount of modifications, such as incorporation of functional handles, glycoproteins, post-translational modifications and the synthesis of D-proteins.

- **Stefan KNAPP**
  Goethe University Frankfurt (DE)

Targeting protein scaffolding function in kinases

In living cells, proteins are organized in large complexes comprising adapter proteins, enzymes and regulatory proteins. The roles of the protein components of such large multifunctional complexes are usually assigned based on simplistic models and the complexity of regulation of multiprotein complexes is neglected in the development of inhibitors and drugs targeting classical enzymes. However, studies on the dynamics of protein interactions and signalling networks have demonstrated that scaffolding is not only an important function of structural and non-enzymatically active proteins, but it is also a feature of most classical enzymes that should not be neglected during drug development. In this talk, I will exemplify the implications of altering protein interactions by allosteric small molecules as well as canonical ATP competitive inhibitors using protein kinases as an example. I will demonstrate how different binding modes that alter protein conformation and dynamics may result in diverse effects on cellular signalling as well as on phenotypic responses. Targeting scaffolding roles will also enable new target classes such as catalytically inactive pseudokinases, that represent a considerable number of largely unexplored targets which have been linked to the development of many diseases.

- **Vanessa PIERROZ - industry talk**
  Promega

Promega's 3-in-one assay to study autophagy: Autophagy LC3 HiBiT Reporter Assay System

Autophagy is a key process in health and a variety of diseases. Aging is also signed by a dwindling of the autophagic activity. Promega offers many assay technologies to interrogate cellular functions, including bioluminescent reporters, fluorescence imaging capabilities, and antibody-free protein blotting. Delivering all these assay modalities with a single reporter module, HiBiT-HaloTag, is a unique Promega capability. The Autophagy LC3 HiBiT Reporter, a tandem reporter system, allows researchers to perform plate reader assays, HiBiT protein blotting, and HaloTag imaging using a single reporter cell line. The versatile autophagy reporter provides a powerful tool for the quantitative study of the autophagy pathway, identifying novel modulators of autophagic flux, and the efficient confirmation of mechanism of action. Dr. Vanessa Pierroz, Scientific Product Manager, will present the technology, and she will be available throughout the meeting for interaction in one-to-one virtual rooms. You can also come and visit our virtual booth to get more information about Promega's offering.

TOR Signalling in Health, Disease and Ageing

This symposium is organized by **Robbie Joséph Loewith (UNIGE)** and **Claudio De Virgilio (UNIFR)** as part of the LS^2 MCB Section

- **Estela JACINTO**
  Rutgers University (USA)

mTORC2 and the hexosamine pathway in T cell development and lymphoma

Highly proliferating cells reprogram their metabolism in order to meet the increasing demand for nutrients that are necessary for energy and macromolecule synthesis. A key signaling molecule that orchestrates metabolic reprogramming is mTOR. mTOR is part of two protein complexes, mTORC1 and mTORC2. Numerous studies have unraveled how mTORC1 is activated in highly proliferating cells in the presence of growth signals but how mTORC2 is activated and its role in metabolism is poorly understood. Using cell culture and in vivo mouse models, we found that mTORC2 activation increases as demand for nutrients escalates. During the highly proliferative phases of T cell development in the thymus and during lymphoma development, mTORC2 activation increases to promote de novo hexosamine biosynthesis (dn-HBP). mTORC2 modulates the rate-limiting enzyme of dn-HBP, GFAT1, and maintains flux through the HBP to ensure survival during nutrient shortage. We will discuss how mTORC2 and dn-HBP are critical during the highly proliferative phases of T cell development and how they are essential for ab- but not gd-T cell development. We will also discuss how the HBP is reprogrammed by mTORC2 during lymphomagenesis and how we can exploit the dependency of T cell malignancies on dn-HBP for more effective cancer therapy.

- **Joseph BAUR**
  University of Pensylvannia (USA)

Adipocyte mTORC1 maintains systemic lipid homeostasis

Pharmacological agents targeting the mTOR complexes are used clinically as immunosuppressants and anticancer agents and can extend the lifespans of model organisms. An undesirable side effect of these drugs is hyperlipidemia. Although multiple roles have been described for mTOR complex 1 (mTORC1) in lipid metabolism, the etiology of hyperlipidemia in vivo remains incompletely understood. The objective of this study was to determine the influence of adipocyte mTORC1 signaling in systemic lipid homeostasis. Mice lacking the mTORC1 subunit Raptor in their adipocytes failed to completely suppress lipolysis in the fed state and displayed prominent hypertriglyceridemia and hypercholesterolemia. Blocking lipolysis in their adipose tissue by deleting the key lipolytic enzyme ATGL restored normal levels of triglycerides and cholesterol in the fed state as well as the ability to clear triglycerides in an oral fat tolerance test. These findings suggest that unsuppressed adipose lipolysis in the fed state interferes with triglyceride clearance and contributes to hyperlipidemia and that adipocyte mTORC1 activity is necessary for appropriate suppression of lipolysis. Thus, adipocyte mTORC1 is necessary for the maintenance of systemic lipid homeostasis.

➢ **Matthias WYMANN** – sponsored talk
Department of Biomedicine, University of Basel

Targeting the phosphoinositide 3-kinase / target of rapamycin pathway in cancer, immunity, metabolism and neurodegenerative disease

The phosphoinositide 3-kinase (PI3K) – mechanistic target of rapamycin (mTOR) pathway is key to cancer progression, regulates inflammatory, allergic and metabolic events and plays a role in neurodegenerative disease. The four class I PI3Ks are the only PI3K family members to produce the plasma membrane lipid PtdIns(3,4,5)P3. This acts as a docking site for effector proteins with phosphoinositide-binding domains such as protein kinase B (PKB/Akt). PKB and PtdIns(3,4,5)P3 branch off to activate the mTOR complexes 1 (TORC1) and 2 (TORC2) respectively.[1] Class I PI3K control glucose uptake (PI3Ka and PI3Kb) and PI3Kg affects thermogenesis and insulin resistance in adiposity.[2, 3] In cancer the pathway is deregulated by mutations of growth factor receptors, Ras, PI3K and more, while in patients with Tuberous sclerosis complex (TSC) mutated overactivation of TORC1 triggers morbidities such as epilepsy (>90%), subependymal nodules (SENs >90%), subependymal giant cell astrocytomas (SEGAs <20%), mental impairment and more.

In collaboration with PIQUR Therapeutics AG, Basel, we have developed pan-class I PI3K inhibitors (PI3Ki; PQR309,[4] PQR514[5]), highly selective mTOR kinase inhibitors (TORKi; PQR620,[6] PQR626[7], conformationally restricted TORKi[8]) and dual PI3Ki/TORKi (PQR530).[9] PQR309 advanced to phase II clinical trials in solid tumors and lymphoma, and was also formulated for topical application in cutaneous T-cell lymphoma (CTCL) and plaque psoriasis.

All the above molecules were extensively tested in mouse cancer models[10, 11] and preclinically developed. A distinct feature of PQR309, PQR530, PQR620, and PQR626 is excellent brain penetration, which allowed their assessment in neurodegenerative disease such as TSC. While PQR309 and PQR530 showed some efficacity to suppress spontaneous epileptic seizures in a TSC-induced (GFAP-Cre x $Tsc1^{flox/flox}$) mouse model, these compounds also triggered an increase glucose and insulin levels due to pan-PI3K inhibition. The TORKi PQR620 [6, 12] and its more stable analogue PQR626[7, 13] did not elevate insulin levels and clearly demonstrated the efficacy of TORKi action in the CNS.

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Endocrine Interactions

This symposium is organized by **Thomas Lutz (UZH)**, as part of the LS² Physiology Section.

- **Hans Rudolf BERTHOUD**
  Pennington Biomedical Research Center (USA)

Gut-Brain Communication and Bariatric Surgery

Identification of the molecular mechanisms responsible for the remarkable health benefits of bariatric surgeries in patients with severe obesity would go a long way in developing more efficient behavioral and pharmacological treatment options without the invasive surgery. In both humans and rodents, bariatric surgeries, Roux-en-Y gastric bypass (RYGB) in particular, reduce body weight/adiposity through a combination of reduced energy intake and efficiency, and increased energy expenditure, to achieve a new energy balance set point. Various hormonal and neural signaling pathways constituting the gut-brain axis are prime candidates for these effects, but a "smoking gun" has not yet been found. I will summarize findings by us and others in transgenic mouse models with deletions of various hormone and neural signaling pathways. The theoretical requirements for gastric bypass surgery to be effective in changing long-term energy balance or, in other words, resetting the defended level of body weight/adiposity will also be discussed.

- **Christina BOYLE**
  University of Zurich (CH)

Influence of obesity during pregnancy on the mother's mental and metabolic health

Paralleling the global rise in obesity, it is estimated that up to 30% of pregnant women worldwide are obese, which increases the risk of short- and long-term adverse health outcome for both the mother and child. While numerous studies have used rodent models of maternal obesity to better understand its pathophysiological consequences on long-term health, almost all have done so with the primary goal of assessing the intergenerational effects on the offspring, and characterization of changes in the dams are sparse. Women who are overweight or obese during pregnancy are at a higher risk for developing both metabolic and mental disorders, like gestational diabetes and postpartum depression. In order to investigate the relationships between maternal obesity and the mother's health, we are characterizing a rat model of maternal obesity that is based on a polygenic predisposition for obesity, which is exacerbated by access to a sweetened, high fat diet. I will present data from ongoing studies characterizing the metabolic and behavioral phenotypes of obesity-prone and obesity-resistant rat dams. I will conclude by discussing further development and future applications of this model. For example, in a translational study, we are using gene expression data from the brains of lean and obese lactating rat dams to generate novel gene networks. The gene networks are then used to create brain-specific polygenic risk scores (PRS), and we will test if these PRS moderate the association between maternal obesity and postpartum depression in the mothers of human birth cohort datasets.

Systems Biology and Molecular Medicine

This symposium is organized by **Attila Becskei (UNIBAS)** and **Yolanda Schaerli (UNIL)** as part of the LS² Systems Biology section

- **Michael KNOP**
  University of Heidelberg (DE)

Applications of Multiplexed AnchorSeq insertion site sequencing: from functional genomics to Covid-19 diagnostics

Abstract not available

- **Mihaela ZAVOLAN**
  Biozentrum - University of Basel (CH)

Modulation of protein synthesis during cellular and organismal life

The synthesis of proteins is a core, energetically-costly cellular activity. With the availability of techniques for quantifying translation transcriptome-wide and with sub-codon resolution, novel aspects of the process have come to light. In this talk I will present our efforts to uncover how the protein output of individual transcripts changes during the life of individual cells and entire organisms. In particular, I will present our results that identified mTORC1 signaling as an important driver of aging-related muscle loss.

Precision Pharmacology: Translating Today's Discoveries into Tomorrow's Therapies

This symposium is organized by **Gabriele Weitz-Schmidt (UNIBAS)** as part of our partner society Swiss Society for Experimental Pharmacology - SSEP

- **Sonja KLEINLOGEL**
  Department of Physiology, University of Bern (CH)

Precision pharmacology in ocular diseases (gene therapy)
Abstract not available

- **Carole BOURQUIN**
  School of Pharmaceutical Sciences, University of Geneva (CH)

Precision pharmacology in cancer immunotherapy
Abstract not available

- **Christoph HANDSCHIN**
  Biozentrum, University of Basel (CH)

Engaging skeletal muscle for healthy aging: lifestyle and pharmacological interventions

The aging process is intrinsically linked to a massive remodeling of cells, tissues and organs, leading to a deterioration of pleiotropic morphological and functional properties. The etiology of these changes, including causative events and factors, resulting pathological cascades and epiphenomena, is still enigmatic. Hence, the increase in lifespan globally, but mostly in Western societies, is largely attributed to general societal improvements such as sanitation, health care or food supply, but only minimally by new specific insights into the aging process. Nevertheless, various pathways and pharmacological compounds have been proposed to provide leverage to mitigate age-linked deteriorations, health- and lifespan in recent years. In this talk, I will discuss some of these advances, and compare these claims to the much more established effects of lifestyle-based interventions, in particular those elicited by physical activity and exercise training.