Friday April 12, 2019
CHUV, César Roux Auditorium, BH 08
Rue du Bugnon 46, CH-1011 Lausanne

12th LIMNA Symposium

Organizing committee: Prof. Francesca Amati, Dr. Carles Canto, Prof. Roberto Coppari, Prof. Bart Deplancke, Prof. Lluis Fajas, Prof. Nelly Pitteloud, Prof. Bernard Thorens, Prof. Kei Sakamoto and Prof. Kristina Schoonjans.

Local organizers: Giorgia Benegiamo (EPFL), Gabriella Fernandes- Piras (CHUV), Eric Aria Fernandez (UNIL), Mukul Girotra (UNIL), Mario Romani (EPFL), Miriam Valera Alberni (Nestlé), Laura Velazquez Villegas (EPFL)

Invited Speakers

- **Prof. Mirko Trajkovski,** Laboratory of metabolic health, Centre Médical Universitaire (CMU), UNIGE, Geneva
- **Dr. Julijana Ivanisevic**, Metabolomic Unit, UNIL, Lausanne

Agenda

8h30-9h00 Welcome and distribution of badges

Opening

9h05
Welcome

Morning session 1

Chairman: Mario Romani

9h15 **Mirko Trajkovski**
Laboratory of metabolic health, Centre Médical Universitaire (CMU), UniGE, Geneva
Gut microbiota in improving metabolic health

9h55 **Fanny Langlet**
Lecturer Ambizione SNSF, Laboratory of Prof. Bernard Thorens, CIG, UNIL
Tancyte glucokinase regulates feeding behavior by modulating hypotalamic neuronal activity

10h15 **Eric Aria Fernandez**
PhD, Laboratory of Prof. Lluis Fajas, CIG, UNIL
Role of the SR proteins Srsf1 and Srsf2 in the integration of gene expression in adipose tissue during metabolic syndrome

10h35 Coffee Break

Morning session 2

Chairman: Miriam Valera Alberni

11h00 **Hao Li**
PhD, Laboratory of Prof. Johan Auwerx, Laboratory of Integrative Systems Physiology, EPFL
Identifying gene function and module connections by the integration of multi-species expression compendia

11h20 **Yi-Ru Yu**
Post-Doc, Laboratory of Prof. Ping-Chih Ho, Department of fundamental oncology, UNIL
Impaired mutochondrial fitness orchestrates T cell dysfunction in the tumor microenvironment

11h40 **Mukul Girotra**
Post-Doc, Laboratory of Prof. George Coukos, Ludwig Institute for Cancer Research, UNIL
Reprogramming hematopoietic stem cell function via modulation of mitochondrial activity

12h05 Lunch

Afternoon session

13h00 Poster session

Chairman: Mukul Girotra

14h25 **Julijana Ivanisevic**
Metabolomic Unit, UNIL, Lausanne
Revisiting metabolism with metabolomics: From model systems to human population studies

15h05 **Margherita Springer**
PhD, Laboratory of Prof. Jörg Hager, Metabolic phenotyping team, Nestlé Research
Using transcriptomics to decipher the role of sulfotransferase 1A1 in human adipocytes

15h20 **Giovanni Sorrentino**
Post-Doc, Laboratory of Prof. Kristina Schoonjans, Laboratory of Metabolic Signaling, EPFL
A bioinspired synthetic niche enables culture of liver organoids suitable for cinical application

15h40 **Elena Katsyuba**
Post-Doc, Laboratory of Prof. Johan Auwerx, Laboratory of Integrative Systems Physiology, EPFL
NAD+ boosting via its de novo biosynthesis can prevent kidney and liver injury and restore mitochondrial biogenesis

16h05 Coffee break

16h25 Concluding remarks and prizes distribution

TALK ABSTRACTS (in order of presentation)

Trajkovski, Mirko

Affiliation: Laboratory of metabolic health, Centre Médical Universitaire (CMU), UniGE, Geneva

Title of presentation: Gut microbiota in improving metabolic health

Abstract: Food intake, energy expenditure and body adiposity are homeostatically regulated, and malfunctions of this balance can cause obesity. Brown adipose tissue (BAT) catabolises calories to produce heat, and its function can be induced by prolonged cold exposure and beta-adrenergic stimulation. BAT is present at distinct anatomical sites, including the interscapular, perirenal, and axillary depots. In response to cold or caloric restriction, brown fat cells also emerge in subcutaneous white fat (known as "beige" cells), a process referred to as WAT browning. Increased beige and brown fat development promote energy expenditure and improve insulin sensitivity, suggesting the manipulation of the fat stores as an anti-obesity therapeutic perspective.
The intestinal microbiota co-develops with the host, and its composition is influenced by several physiological, pathological and environmental factors. The microbiota influences the whole-body metabolism by affecting the energy balance on multiple levels. Cold exposure and caloric restriction lead to marked shift of the microbiota composition, and transplantation of this altered microbiota to germ-free mice is sufficient to improve the metabolic status of the host and increase its insulin sensitivity. This is concomitant with the enhanced fat browning, contributing to increased energy expenditure and fat loss. I will discuss our recent findings that suggest molecular explanation of the microbiota-host signalling axis in regulating the energy homeostasis.

Langlet, Fanny

Affiliation: CIG-UNIL

Title of presentation: Tanycyte glucokinase regulates feeding behavior by modulating hypothalamic neuronal activity.

Authors list: Antoine Rohrbach, Roxane Pasquettaz and Fanny Langlet

Abstract: The brain senses glucose and regulates glucose metabolism using integrated glucose-sensing units composed of neurons and glial cells. Among glial cells, specific hypothalamic ependymoglial cells called tanycytes are henceforth known as “sensors” of peripheral glucose levels, and consequently as "regulators" of energy balance. In this study, we investigate the impact of tanycyte glucose-sensing on neuronal activity and the latter's regulation of energy balance. By injecting TAT-CRE in the third ventricle of adult Glucokinase (Gck)-floxed mice, we deleted Gck in tanycytes in order to abrogate Gck-dependant glucose sensing. Our physiological results indicate that tanycyte Gck deletion has limited impact on glucose homeostasis, but modulates feeding behavior. In particular, mice with Gck deletion display a lower food intake during refeeding. This effect is associated with a decrease in neuronal activation in the arcuate nucleus visualized by cfos immunostaining, as well as changes in the expression of key hypothalamic neuronal genes. These results show the pivotal role of tanycytes in the glucostatic regulation of food intake by modulating neuronal function. The elucidation of underlying mechanisms could allow the development of new therapeutic strategies for obesity and associated metabolic syndromes.

Fernandez, Eric Aria

Affiliation: CIG-UNIL

Title of presentation: Role of the SR proteins Srsf1 and Srsf2 in the integration of gene expression in adipose tissue during metabolic syndrome.

Authors list: Eric A Fernandez, Judit Castillo-Armengol, Tiziana Caputo, Beatrice Desvergne, Lluis Fajas, Isabel C Lopez-Mejia

Abstract: The serine- and arginine-rich (SR) family of RNA binding proteins is composed of 12 members in humans. Two of those members: SRSF1, formerly known as ASF/SF2, and SRSF2, formerly known as SC35, play roles in splicing and transcription. A respectable amount of studies have been carried out to understand and reveal their implication in various types of cancer, HIV, as well as rare diseases like the Hutchinson-Gilford Progeria Syndrome. However, the same cannot be said regarding the role of SR proteins in metabolic syndrome, especially in adipose tissue. Thus, we set out to determine the role of the SR proteins, specifically SRSF1 and SRSF2 during metabolic syndrome in adipose tissue. Preliminary results of in vitro models show changes in Srsf1 and Srsf2 protein expression during the differentiation of white and brown adipocytes. Also, Srsf2 was increased with insulin stimulation of mature white adipocytes. However, there was no significant difference in the expression of Srsf2 between insulin resistant conditions (TNFα, IL-6 and Palmitate) and normal condition. In Srsf1 adipose tissue-specific knockout mice (Srsf1 ATKO), the perigonadal (pg), subcutaneous (sc), and retroperitoneal (rp) white adipose tissue (WAT) depots were significantly smaller compared to ones of the control group. But, the brown adipose tissue (BAT) was bigger in the Srsf1 ATKO than those of the control group. On the other hand, Srsf2 adipose tissue-specific knockout mice (Srsf2 ATKO) showed impaired insulin sensitivity, lower fat mass, as well as decreased size in pg, sc, and rpWAT as well as BAT depots. These phenotypes were exacerbated under high-fat diet. Moreover, Srsf2 ATKO mice exhibit higher metabolic rates. Using the ENCODE project database, we were able to find interactions between Srsf1 and mitochondrial function genes, including Sirt1, Tfam, Atp5a1, Acadm, and Acadl. Also, we found interactions between Srsf2 and lipid metabolism genes, including Cers2, Cers5, Fasn, and Pgam1. These results suggest SRSF1 and SRSF2 are affecting the development and function of both white and brown adipose tissue. Overall, this study could contribute to the understanding of the etiology of the metabolic syndrome, thus to the development of potential novel therapies.

Li, Hao

Affiliation: EPFL

Title of presentation: Identifying gene function and module connections by the integration of multi-species expression compendia

Authors list: Hao Li, Johan Auwerx

Abstract: The functions of many eukaryotic genes are still poorly understood. We developed and validated a new method, termed GeneBridge, which is based on two linked approaches to impute gene function and bridge genes with biological processes. First, Gene-Module Association Determination (G-MAD) allows the annotation of gene function. Second, Module-Module Association Determination (M-MAD) allows predicting connectivity among modules. We applied the GeneBridge tools to large-scale multi-species expression compendia—1,700 datasets with over 300,000 samples from human, mouse, rat, fly, worm, and yeast—collected in this study. Unlike most existing bioinformatics tools, GeneBridge exploits both positive and negative gene/module-module associations. We constructed association networks, such as those bridging mitochondria and proteasome, mitochondria and histone demethylation, as well as ribosomes and lipid biosynthesis. The GeneBridge tools together with the expression compendia are available at systems-genetics.org, to facilitate the identification of connections linking genes, modules, phenotypes, and diseases.

Yu, Yi-Ru

Affiliation: Department of Fundamental Oncology, University of Lausanne

Title of presentation: Impaired mitochondrial fitness orchestrates T cell dysfunction in the tumor microenvironment

Authors list: Yi-Ru Yu, Haiping Wang, Tung Chao, Fabien Franco, Yao-Chen Tsui, Ping-Chih Ho

Abstract: Cancer immunotherapy, including checkpoint blockade and adoptive transfer of tumor-reactive T cells, represents a paradigm shift in the treatment of malignancies in recent years, and yields remarkable responses by reawakening anti-tumor immunity in established tumors. Nevertheless, a significant portion of patients are refractory to cancer immunotherapies, which may be in part due to the persistent impairment of anti-tumor effector functions in T cells, a phenomenon referred to as T cell exhaustion. Emerging evidence reveal that alterations in global chromatin accessibility and de novo DNA methylation patterns are keys events to drive development of T cell exhaustion under chronic antigenic stresses. However, it remains elusive how T cells engage epigenetic reprogramming to orchestrate exhausted state. Here, we found that tumor-infiltrating tumor-reactive T cells with accumulation of damaged mitochondria, characterized by increased mitochondrial mass but reduced mitochondrial membrane potential and cristae, display more severe exhausted phenotypes, including decreased proliferation capacity, reduced cytokine production and up-regulation of co-inhibitory receptors. The accumulation of damaged mitochondria is in part due to the deficiency of mitophagy machinery. Importantly, we found that the accumulation of dysfunctional mitochondria is corelated to the specificity and affinity of antigen, and also supported by the PD-1 expression. Ultimately, the combination of glucose deprivation, hypoxia and TCR signaling in vitro can drastically weaken T cell immunity with the accumulation of dysfunctional mitochondria as seen in TILs previously. Taken together, our study suggests that mitochondrial fitness is pivotal for T cell-mediated immunity and the accumulation of dysfunctional mitochondria could result in exhaustion phenotypes in T cells. This further provides pillars for better harnessing T cell immune responses with metabolic regulations for immunotherapy.

Girotra, Mukul

Affiliation: LICR (UNIL)/ SV EPFL

Title of presentation: Reprogramming hematopoietic stem cell function via modulation of mitochondrial activity

Authors list: Mukul Girotra, Marcela Rincon-Restrepo, Aurelien Oggier, George Coukos, Olaia Naveiras, Serge Rezzi and Nicola Vannini

Abstract: A fine balance of quiescence, self-renewal and differentiation is key to preserve the hematopoietic stem cell (HSC) pool, and maintain lifelong production of all mature blood cells. In recent years cellular metabolism has emerged as a crucial regulator of HSC fate. HSCs differ from their committed progeny by relying primarily on anaerobic glycolysis rather than mitochondrial oxidative phosphorylation for energy production. However, whether this change in the metabolic program is the cause or a consequence of the unique function of HSCs remains unknown. We previously demonstrated that modulation of mitochondrial metabolism influences HSC fate, by chemically uncoupling the electron transport chain we were able to maintain HSC function in culture conditions that normally induce rapid differentiation (Vannini N*, Girotra M*. et al., 2016, Nature Communication). Moreover, we demonstrated that modulation of mitochondrial activity in ex-vivo cultured human HSCs, via NAD+ boosting agent Nicotinamide Riboside (NR), results in better long-term blood production in serially transplanted humanized mice. Strikingly, in vivo administration of NR dramatically improves survival and accelerates blood recovery in HSC-transplanted mice (in press, Cell Stem Cell). Here we proceeded to carry out a screen, using mitochondrial activity as readout, to identify metabolic modulators that enhance HSC activity and function. We found two novel candidates, a natural compound and a vitamin precursor, that modulate mitochondrial activity in both mouse and human HSCs, and resulted in enhanced HSC function post bone-marrow transplantation. Interestingly, we found that these candidates mediate their effects partially via inducing mitophagy, supporting recent studies highlighting the role of mitophagy as a key driver of HSC function. Moreover, our preliminary analysis reveals that they mediate similar effects in aged human HSCs, making them ideal candidates to revert age-associated myeloid bias in human patients. Our data thus reveal a causal relationship between mitochondrial metabolism, mitophagy and fate choice in HSCs, and also provide a valuable tool to identify optimal ex vivo conditions for HSC expansion and improve the outcome for patients suffering from bone marrow insufficiency.

Ivanisevic, Julijana

Affiliation: Metabolomic Unit, UNIL, Lausanne

Title of presentation: Revisiting metabolism with metabolomics: From model systems to human population studies

Abstract: In this post-genomic era of biology, metabolomics' greatest strength is its comprehensive and high-throughput nature as a phenotyping technology that allows for the cost-effective measurement of a massive panel of metabolites from diverse biological matrices. Due to significant advancements in technology and bioinformatics, metabolomics has evolved as a next generation metabolic profiling to provide an integrated look at the metabolism as a whole. The aim of this seminar is to provide an overview of analytical approaches and concepts to facilitate the investigation and prospective modulation of deregulated metabolism that underlines complex metabolic diseases.

Springer, Margherita

Affiliation: Nestle Research

Title of presentation: Using transcriptomics to decipher the role of sulfotransferase 1A1 in human adipocytes

Authors list: Margherita Springer, Sylviane Métairon, Frédéric Raymond, Prasad Chaskar, Christian Chabert & Jörg Hager

Abstract: Constitutional thinness is a unique human phenotype of resistance to weight gain. To understand this phenotype, we collected subcutaneous adipose tissue samples from the constitutionally thin and normal weight controls and performed transcriptomics. Transcriptomics on the adipose tissue samples revealed striking differences in the transcriptome. The most significant change was in the expression of sulfotransferase 1A1 (SULT1A1) which was decreased in the adipose tissue of the constitutionally thin. SULT1A1 is an enzyme which conjugates sulfate to exogenous compounds. Previous reports have not cited a function for SULT1A1 in adipose tissue. To investigate the role of SULT1A1 in adipose tissue, we used the SGBS cell line which is a model for human adipocytes. In SGBS cells, we observed that siRNA mediated knockdown of SULT1A1 decreased the release of lipids from adipocytes suggesting that loss of SULT1A1 alters an important function of the adipocyte. To decipher the role SULT1A1 in adipose tissue, we performed transcriptomics on human adipocytes transfected with siRNA targeting SULT1A1 or transfected with a scrambled siRNA. Knockdown of SULT1A1 resulted in differential expression of 296 probes, of which 204 were upregulated and 92 were downregulated. Pathway analysis indicated an enrichment of genes annotated to glucocorticoid receptor signaling and liver receptor X signaling. We hypothesized that knockdown of SULT1A1 reduced sulfate conjugation of ligands responsible for activation of these signaling pathways. To validate this hypothesis, we used a computational approach to predict the affinity of the purported ligands to SULT1A1. We then corroborated our observations with cellular experiments. This is the first study to investigate the function of SULT1A1 in adipose tissue. In a future study, we plan to characterize how complete loss of SULT1A1 influences whole body metabolism in Sult1a1 knockout mice.

Sorrentino, Giovanni

Affiliation: Laboratory of Metabolic Signaling

Title of presentation: A bioinspired synthetic niche enables culture of liver organoids suitable for clinical application

Authors list: Giovanni Sorrentino, Saba Rezakhani, Ece Yildiz, Sandro Nuciforo, Markus H. Heim, Matthias P. Lutolf, Kristina Schoonjans.

Abstract: Non-alcoholic fatty liver disease (NAFLD) is a degenerative disorder and has become the most common liver disease worldwide. The recent demonstration that primary cells from the liver can be expanded in vitro as organoids holds enormous promise for regenerative medicine1–5. The use of three-dimensional (3D) cultures based on ill-defined and potentially immunogenic matrices, however, significantly compromises the establishment of liver organoid-derived cells for translational purposes6. To overcome this limitation, we here adopted chemically defined hydrogels7 as mechanically tunable synthetic niches for mouse and human hepatic organoids. Derivation of liver organoids within these minimal 3D environments was found to be highly sensitive to matrix stiffness, requiring activation of the Src family of kinases (SFKs)/Yes-associated protein (YAP) axis independent of acto-myosin contractility. The use of synthetic matrices allowed for the unprecedented establishment of biopsy-derived human liver organoids without the requirement of animal-derived components at any step of the process, thus making this protocol fully compatible with clinical applications.

Katsyuba, Elena

Affiliation: IBI SV EPFL

Title of presentation: NAD+ boosting via its de novo biosynthesis can prevent kidney and liver injury and restore mitochondrial biogenesis.

Authors list: Elena Katsyuba, Adrienne Mottis, Marika Zietak, Francesca De Franco, Vera van der Velpen, Karim Gariani, Lucia Cialabrini, Olli Matilainen, Paride Liscio, Julijana Ivanisevic, Nadia Raffaelli, Kristina Schoonjans, Roberto Pellicciari, Johan Auwerx

Abstract: Nicotinamide adenine dinucleotide (NAD+) is a cosubstrate for several enzymes, including the sirtuin family of NAD+-dependent protein deacylases. Beneficial effects of increased NAD+ levels and sirtuin activation on mitochondrial homeostasis, organismal metabolism and lifespan have been established across different species. It is therefore not surprising that in recent years the rapt attention of the scientific community has been focused on multiple strategies aiming to boost NAD+ content. We present here an innovative way to increase NAD+ levels by stimulating its de novo synthesis from tryptophan. We show that α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (ACMSD), the enzyme that limits the proportion of ACMS able to undergo spontaneous cyclisation in the de novo NAD+ synthesis pathway, controls cellular NAD+ levels via a mechanism that is conserved from C. elegans to the mouse. Genetic and pharmacological loss of function of ACMSD boosts de novo NAD+ synthesis and SIRT1 activity, ultimately enhancing mitochondrial function. We furthermore characterised a series of potent and selective ACMSD inhibitors, which, given the restricted expression of ACMSD in kidney and liver, are of high therapeutic interest to protect these tissues from injury. As such these inhibitors were able to protect mice against non-alcoholic fatty liver disease and acute kidney injury. ACMSD hence is a key modulator of cellular NAD+ levels, sirtuin activity, and mitochondrial homeostasis in kidney and liver.

POSTERS (in alphabetical order)

1. Angeles Martinez, Liliana

Affiliation: EPFL

Title of presentation: Crowding conditions in the modeling of microbial systems

Authors list: Liliana Angeles-Martinez, Vassily Hatzimanikatis

Abstract: Microbial activity can be detected almost everywhere: skin, gut, the houses we live, hospitals, soil, rocks, riverbeds, etc. Many of these microbial communities grow in constrained spaces, such as biofilms, characterizes by the close proximity of cells, and the crowded and inhomogeneous conditions. The modeling of microbial communities have attracted the attention of researchers as a way to understand and manipulate the possible interactions among the microorganisms in order to improve the yield of a microbial process or control a disease In biofilms, and other clustered microbial systems, the individual cells are organized in multilayer structures, which offer protection to the community against environmental stresses and perturbations. Under such conditions, the motion of chemical components may be affected by the presence of solids components, reducing in this way the diffusion of the nutrients (Minton, 2001). The aim of this work is to analyze how the crowding conditions could modify the dynamics of a microbial system growing in a biofilm, as well as the spatial distribution of the phenotypes in the system. The modeling of these type of system requires integrating different layers of information such as (i) nutrient diffusion, (ii) cell metabolism, (iii) metabolic fluxes, (iv) reaction thermodynamics, and (iii) cell division. For this purpose, we developed an individual based approach that combines computational techniques such as Thermodynamics-based Flux Analysis (Henry et al. 2007), and Cellular Automata (CA) to solve this multi-scale problem. The growth of Escherichia coli in biofilms is provided as an illustrative example. The spatial distribution and the phenotypic composition of the system is strongly affected by the crowding conditions. Therefore, time-delay in the appearence of phenotypes could modify the possible cross-feeding interactions in a multi-species community. This framework provides a deeper insight of the spatio-temporal dynamics of biofilms, and it can be used to design and control of clustered microbial communities. References 1. Henry, C.S., Broadbelt, L.J., and Hatzimanikatis, V. 2007. Biophys. J. 92:1792-1805. 2. Minton, A.P. 2001. J. Biol. Chem. 276:10577–80.

2. Ghosal, Sriparna

Affiliation: EPFL

Title of presentation: Implication of the Mitochondrial Fusion Protein Mitofusin 1 in the Nucleus Accumbens in Anxiety-and Depression-Like Behaviors

Authors list: Sriparna Ghosal, Meltem Weger, Jocelyn Grosse, Isabelle-Marie Guillot de Suduiraut, and Carmen Sandi

Abstract: Mitochondrial function in the nucleus accumbens (NAc) has been recently implicated in the regulation of complex social behaviors, and impairment in mitochondrial functions in the NAc is observed in highly anxious rats. Mitofusin 1 (Mfn1) is a mitochondrial fusion protein, and its mutation has been shown to cause mitochondrial fragmentation and defects in mitochondrial motility. Here, we investigated the role of accumbal Mfn1, a major modulator of mitochondrial dynamics, for the regulation of anxiety and depression-like behaviors. We demonstrate that neuronal loss of Mfn1 in the NAc increases anxiety- and depression-like behaviors. Specifically, we show that Mfn1 floxed mice injected with AAV-Synapsin-Cre into the NAc spent less time in the open arms of the elevated plus maze (EPM) and in the lit part of the light-dark box than controls (littermate Mfn1 floxed mice receiving AAV-GFP virus into the NAc). In addition, Mfn1 NAc knockdown (KD) mice displayed less time interacting with an unfamiliar CD1 mouse in a social interaction test. In the forced swim test, Mfn1 NAc KD mice exhibited a lower latency to immobility than controls. Notably, Mfn1 NAc KD mice did not differ from controls in measures of locomotion in the open field test or distance traveled in the EPM. Collectively, these results identify a protective role for Mfn1 in the NAc against anxiety-and depression-like behaviors, and suggest that targeting mitochondrial function may be an important avenue for developing new mood stabilizing agents.

3. Haiping, Wang

Affiliation: Ludwig Cancer Centre at University of Lausanne

Title of presentation: CD36-mediated metabolic adaptation guides regulatory T cells in tumors

Authors list: Haiping Wang, Florence Picard, Marcel Philipp Trefny, Roy Silverstein, Ira Goldberg, Alfred Zippelius, Ping-Chih Ho

Abstract: Regulatory T cells (Tregs) play an indispensable role in maintaining peripheral tolerance and preventing autoimmune disease. In addition to modulating tissue homeostasis, the suppressive properties of Tregs can also be harnessed by cancers to evade immunosurveillance. Therefore, depleting Tregs has been shown to unleash antitumor immunity and interrupt formation of an immunosuppressive tumor microenvironment (TME). However, systemic loss of Tregs due to Treg depletion also leads to severe autoimmunity. Therefore, the identification of novel approaches that specifically target intratumoral Tregs is direly needed for unleashing antitumor immunity and cancer immunotherapy. Here we show that intratumoral Tregs increase lipid uptake and content and elevated expression of CD36, a fatty acid translocase, as compared to Tregs in circulation and other normal tissues, in several cancer types. By using the transgenic mice model, we found that Treg-specific ablation of CD36 reduces accumulation of intratumoral Treg and suppresses tumor growth. Importantly, Treg-specific CD36 deficiency does not lead to autoimmunity in aged mice and CD36-deficient Tregs remain their suppressive activity on restraining CD4 T cell-induced inflammatory bowl disease. Mechanistically, CD36 expression supports survival of intratumoral Tregs by fine-tuning their mitochondrial fitness via PPAR signaling. Thus, high expression of CD36 in intratumoral Tregs orchestrates Treg metabolic adaptation in tumors by intervening metabolic regulations, further promotes tumor growth by suppressing the anti-tumor immune responses. Ultimately, anti-PD-1 blockade treatment elicits therapeutic benefits in mice with Treg-specific ablation of CD36. Altogether, our study suggests that CD36 might be a potential target for specifically waning down intratumoral Tregs and provide proof-of-concept evidence that targeting CD36 in tumors could unleash anti-tumor immunity and synergize with checkpoint blockade treatment.

4. Lee, Umji

Affiliation: EPFL/NIHS

Title of presentation: Apelin promotes capillary remodeling during muscle regeneration via Tead1 transcription factor

Authors list: Umji Lee, Sonia Karaz, Julie Russeil, Maria Deak, Pascal Stuelsatz, Bart Deplancke and Jerome N. Feige

Abstract: Aging is a complex and multifactorial process leading to numerous health-related diseases. Sarcopenia, a gradual loss of skeletal muscle mass and function, is an inevitable process associated with the loss of life quality while increasing the risk of mortality in elderly individuals. Currently-available treatments, however, only include a moderate amount of exercise and nutritional management without any specific biological diagnosis or medical treatment. Apelin (APLN) is an endogenous peptide released by myofibers in response to muscle contraction during exercise and exerts paracrine and systemic effects. Apelin level declines with age while its restoration reverses loss of muscle function. However, much remains to be learnt about how aging influences the molecular regulation of the apelin promoter, and characterized the mechanisms of how apelin enhances muscle regeneration. This study, therefore, aims to explore transcriptional regulation of apelin by transcription factors and their functional role in muscle physiology. Using a novel TF screening method, a yeast one hybrid (Y1H), we discovered a new transcriptional mechanism through which the Tead1 transcription factor regulates apelin production. The six transcription factors (Tead1, Zic3, Zfp319, Zdhhc9, Gcm2 and Barx1) that bind to the cis-regulatory elements of the apelin precursor gene, located in the 200bp upstream region of the transcription start site. Importantly, we uncovered a novel role of the Tead1/apelin axis in myogenesis and vascular repatterning during muscle regeneration in vivo. Our data reveal a direct link between Tead1 and apelin, and provide a possible mechanism how apelin contributes to form muscular hypertrophy systematically.

5. **Mohammadi Peyhani, Homa**

Affiliation: Chemical engineering

Title of presentation: Assigning enzyme sequences to orphan and novel reactions using knowledge of substrate reactive sites

Authors list: Homa MohammadiPeyhani, Noushin Hadadi, Miskovic Ljubisa, Vassily Hatzimanikatis

Abstract: Recent advances in synthetic biochemistry have resulted in a wealth of de novo hypothetical enzymatic reactions that are not matched to protein-encoding genes, deeming them “orphan”. Nearly half of known metabolic enzymes are also orphan, leaving important gaps in metabolic network maps. Proposing genes for the catalysis of orphan reactions is critical for applications ranging from biotechnology to medicine. In this work, a novel computational method, BridgIT, assigned a potential enzyme sequence to orphan reactions and nearly all theoretically possible biochemical transformations, providing candidate genes to catalyze these reactions to the research community. BridgIT introduces, for the first time, information about the enzyme binding pocket into reaction similarity comparisons and it assesses the similarity of two reactions, one orphan and one non-orphan, using the reactive sites of their substrates and their surrounding structures, along with the structures of the generated products, and then suggests protein sequences and genes of the most similar non-orphan reactions as candidates for catalyzing the orphan ones. We performed two large-scale validation studies to test BridgIT predictions against experimental biochemical evidence. For the 234 orphan reactions from KEGG 2011 that became non-orphan in KEGG 2018, BridgIT predicted the exact or a highly related enzyme for 211 of them. Moreover, for 334 out of 379 novel reactions in 2014 that were later catalogued in KEGG 2018, BridgIT predicted the exact or highly similar enzyme sequences. BridgIT requires knowledge about only four connecting bonds around the atoms of the reactive sites to correctly identify protein sequences for 93% of analyzed enzymatic reactions. The proposed candidate enzymes by BridgIT, are either capable of catalyzing these reactions or they can serve as good initial sequences for the enzyme engineering. BridgIT online tool is freely available on the web (http://lcsb-databases.epfl.ch/) for academia upon registration.

6. Mottis, Adrienne

Affiliation: Laboratory of Integrative and Systems Physiology, EPFL

Title of presentation: Doxycycline-induced mitochondrial stress in germ-free mice reveals an organ-specific response and engages antiviral immunity

Authors list: Adrienne Mottis, Elena Katsyuba, Davide D'Amico, Evan G Williams, Pedro M Quiros, Virginija Jovaisaite, Nicola Harris, Ruedi Aebershold and Johan Auwerx

Abstract: Mitochondria play a crucial role in cellular and organismal homeostasis. Given their pleiotropic function, mitochondria are susceptible to multiple cellular stressors, ranging from protetoxic to oxidative stress, against which they have built a robust stress defense system. Our laboratory has an interest in understanding mitochondrial proteostatic stress signaling pathways. We used doxycycline (dox), an antibiotic that not only blocks bacterial, but also mitochondrial translation, to induce proteotoxic stress in the mitochondria. As the microbiome impacts multiple aspects of mammalian physiology, we analyzed the *in vivo* consequences of dox treatment in germ-free C57BL/6J mice, hence eliminating the potential confounding impact of dox on the microbiome. Here we show that dox elicits organ-specific responses to mitochondrial stress, as demonstrated by a multi-omics analytical approach. In the kidney, the response to mitochondrial stress is typified by the induction the ATF4-mediated integrated stress response and a blockade of cytosolic translation through eIF2α phosphorylation. Interestingly, in the liver the transcript levels of interferon-stimulated genes are induced upon treatment with dox. Furthermore, in bone-marrow-derived macrophages, dox and other mitochondrial stressors trigger antiviral immunity mechanism *in vitro*. A mitochondrial stress can therefore trigger a cellular response similar to that induced by a viral insult, suggesting that antiviral immunity signaling pathways can play a role of mitochondrial stress effectors.

7. Tsouka, Sophia

Affiliation: EPFL, Laboratory of Computational Systems Biotechnology

Title of presentation: A detailed lipids model tailored to the integration of omics data in yeast

Authors list: Sophia Tsouka, Vassily Hatzimanikatis

Abstract: Comprehensive lipid characterization has become essential, especially in modern day health related studies. Numerous links have been reported between lipid imbalances and various physiopathologies concerning membrane lipid homeostasis. The crucial need for lipidome characterization is accompanied by the development of appropriate tools for the analysis of the statistical inferences. While works on cellular lipid metabolism have been limited to the analysis of individual lipid species, swift progress in mass spectrometry based methodologies allows the analysis of the lipidome, the entirety of lipids in a cell. Computational metabolic models of various lipid pathways have emerged in an effort to evaluate the vast omics data available. We have created a comprehensive and concise metabolic model that can act as detailed repository of lipid metabolism. The model encompasses 1130 reactions and 800 metabolites across 7 cellular compartments (cytosol, mitochondria, peroxisomes, endoplasmic reticulum, Golgi apparatus, vacuole and nucleus – plus the extracellular domain), and includes the following lipid-related subsystems: biosynthesis, elongation, and degradation of fatty acids, biosynthesis and esterification of sterols, biosynthesis of phospholipids, sphingolipids, cardiolipin, and isoprenoids, triacylglyceride decomposition and the mevalonate pathway. It also includes several key parts of yeast metabolism such as glycolysis, citric acid cycle, oxidative phosphorylation etc. We have created a detailed thermodynamic database for all the metabolites of the network, and we performed a complete thermodynamic curation of the model. It can also be used as a scaffold for lipidomic measurement implementation, and we are currently extending it for human (and other) cell metabolism and physiologies, thus creating a platform to study lipid regulation for applications across organisms.