Leveraging Liver Thermogenesis in the context of health and disease

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Liver thermogenesis refers to the process by which the liver generates heat, playing a crucial role in maintaining the body's core temperature and overall energy homeostasis. This physiological phenomenon is part of the broader field of thermoregulation, where various organs and tissues contribute to sustaining a stable internal environment despite external temperature fluctuations. The liver, being a highly metabolically active organ, contributes significantly to basal metabolic rate through the heat produced during metabolic processes such as gluconeogenesis, glycogenolysis, and the urea cycle.

Understanding liver thermogenesis involves exploring the complex biochemical pathways and molecular mechanisms that govern heat production. Key players include mitochondrial activity, uncoupling proteins, and various hormones and signaling molecules that regulate metabolic rate and energy expenditure. Additionally, liver thermogenesis is influenced by nutritional status, physical activity, and environmental conditions, highlighting its adaptive nature.

Research into liver thermogenesis not only provides insights into basic physiological processes but also has significant implications for addressing metabolic disorders. Conditions such as obesity, diabetes, and thyroid dysfunctions often involve dysregulation of energy balance and thermogenesis. Targeting liver thermogenesis presents a promising therapeutic strategy for these health issues. For instance, enhancing liver thermogenesis could help increase energy expenditure, thereby reducing excess fat storage and improving insulin sensitivity in obese and diabetic patients. Moreover, modulating this process could aid in the management of thyroid disorders, where metabolic rate is often disrupted.

Pharmacological interventions or lifestyle modifications that boost liver thermogenesis could offer a novel approach to restoring metabolic health. By leveraging the liver's role in energy expenditure, it may be possible to develop treatments that specifically enhance metabolic rates and correct imbalances associated with various metabolic diseases.

In summary, liver thermogenesis is a vital component of the body's energy regulation system, intertwining with various metabolic processes and adaptive responses. By delving into its mechanisms and regulatory factors, we can better understand how to maintain metabolic balance and address related health issues. Targeting liver thermogenesis holds potential as a therapeutic avenue for combating obesity, diabetes, and other metabolic disorders, paving the way for innovative treatments that enhance overall metabolic health.

Here we will discuss the current knowledge on the molecular and physiological determinants of liver thermogenesis, with a strong focus on mitochondrial homeostasis, which emerges as a valuable target. The goal of your project is to design a strategy to: (1) use modulators of important mitochondrial-related pathways in the

context of liver thermogenesis, and (2) identify new compounds/drugs that improve clinical outcomes by targeting metabolic pathways. You will hence design a collaborative team strategy to screen for small synthetic molecules acting on selected pathways and plan the preclinical development of such candidate drugs to target liver thermogenesis. This will include *in-silico*, *in-vitro* and *in-vivo* strategies for rigorous testing, to reduce the list of candidate molecules to only a few validated targets for clinical trials. Whereas the *in-vitro* and *in-vivo* proposed strategies will only by developed theoretically, a practical *in-silico* screening strategy can be implemented and tested. You will work in close collaboration with scientists that are engaged in a similar project in “real” life. The following items will have to be addressed in your research project:

1. Defining a product profile: Define the targeted disease and expected treatment outcome.

2. Target ID: Why mitochondria are a good target and what is the best specific molecular target? What kind of inhibition/activation do you want to achieve? Provide background and rationale why you have chosen this target.
Literature, licensing

3. Target validation: How to make sure acting on the target will have the expected outcome without causing side effects?
- literature
- biochemistry
- cell based studies
- animal models
- human genetics
- gene networks
- in-silico modelling
- pharmacology

4. Screening: How to design and execute a cost effective and instructive screen which will provide hits?
- compound libraries: natural, semi-synthetic, NCEs
- virtual screening
- high throughput/low content vs low throughput/high content,
- biochemical vs cell-based screen
- hit ID

5. Hit to Lead:
- understanding lead quality
- potency
- selectivity (off target effects)
- alerting structures (toxicophores)
- synthetic accessibility
- SAR using in vitro assays

6. Lead optimization: Getting all the desired properties in 1 compound = DC
- in vitro biochemical and cellular assays

- understanding properties (potency, selectivity, toxicology)
- pharmacokinetics, pharmacodynamics

7. Preclinical proof of concept (PCC):
- cell based assays
- animal models (preclinical POC)
- pharmacology
- toxicology

General and Practical information

(A) Work will be planned, discussed, and evaluated during office hours. If not during regular course time, you should make an appointment by e-mail with the TAs (see below) or at admin.auwerx@epfl.ch

(B) The teaching assistants (TAs) that will help you are Giacomo, Adrien and Wenyu. Their e-mails are:
- giacomo.vonalvensleben@epfl.ch
- adrien.faure@epfl.ch
- w.liu@epfl.ch

(C) You will be evaluated on: (1) participation in discussions during the group sessions; (2) group report (<25 A4 pages in MS Word) to be handled by week ~9-10 (to be defined); (3) group presentation (20 minutes – max 25 slides in MS ppt); and (4) an individual exam on your project and the general subject of translational research. The exam is scheduled for December 2024. The exact date will be communicated in due course.

(D) Plagiarism, as well as AI-written text, will not be tolerated. Any infringement to the rules will cause the disqualification of the report with an “NA” as a score for the whole group. All statements in your report/presentation will have to be properly referenced.

(E) Background reading. The following papers/books are considered background and should be read before the first session of office hours, when we will test your knowledge about them. Some of these papers can be found on Moodle.