Modulating Hepatic Lipid Metabolism in NAFLD

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Non-alcoholic fatty liver disease (NAFLD), characterized by the excessive accumulation of triglycerides in hepatocytes, is one of the most prevalent chronic liver diseases globally. The progression of NAFLD, which can lead to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, or hepatocellular carcinoma, reflects a disruption in the balance between hepatic lipid input—mainly from dietary sources and de-novo lipogenesis (DNL)—and lipid clearance via β-oxidation and lipid export. Despite its high prevalence and serious clinical implications, pharmacological options for NAFLD remain limited and often focus on alleviating symptoms rather than addressing the underlying metabolic dysregulation.

Recent studies have underscored the importance of targeting hepatic lipid metabolism and mitochondrial function to reverse steatosis and restore metabolic health. Particular attention has been paid to pathways regulating fatty acid synthesis and oxidation, redox homeostasis, and cellular energy sensing. Key regulatory systems include the control of malonyl-CoA synthesis and utilization, activation of transcriptional networks governing β-oxidation, modulation of fatty acid synthase activity, and manipulation of AMP-activated kinase signaling. Understanding and intervening in these networks presents a promising strategy for therapeutic innovation.

In this course, you will explore hepatic metabolic pathways and mitochondrial signaling circuits to identify a therapeutic leverage point—an enzyme, transporter, cofactor cycle, or signaling node—whose modulation could restore lipid homeostasis and reduce liver fat accumulation. The course encourages you to independently analyze metabolic networks and define the most promising intervention point based on evidence from the literature, structural biology, gene expression, and disease models.

You will be guided through a complete drug-discovery strategy aimed at developing a small-molecule compound to modulate your selected target. This includes identifying and validating the molecular target, defining the mode of action, designing an in-silico screening pipeline, evaluating structure–activity relationships, and proposing in-vitro and in-vivo proof-of-concept studies. Whereas the in-vitro and in-vivo steps will be theoretical, a practical in-silico screening component will be implemented. Your research project will conclude with the formulation of a clinical translation roadmap, culminating in a proposed Target Product Profile (TPP) and early-phase development strategy.

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

2. Target ID: Analyze hepatic lipid and energy networks to identify a strong molecular target. What kind of inhibition or activation do you want to achieve? Provide background and rationale.

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 assistant (TA) that will help you is Wenyu LIU. His e-mail is:
- 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 2025. 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.