opn2EXPERTS – Propose novel approaches to degrade ECM in fibrotic livers

How would you propose to enhance extracellular matrix degradation in the liver of NASH patients using innovative *in vitro* assay systems, or *in vivo* models?

Answers to this question including a proposal for collaboration can only be considered if they arrive no later than June 2, 2022 11:59 pm PST.

What is the context of the problem that we would like to solve?

NASH (nonalcoholic steatohepatitis) is a chronic liver disease characterized by liver inflammation, steatosis, and hepatocellular injury leading to development of fibrosis. Despite liver fibrosis progressively becoming a global public health problem, currently there are no effective FDA approved anti-fibrotic treatments. The progressive accumulation of extracellular matrix (ECM) subverts the normal histological architecture, which eventually leads to impaired hepatic function and ultimately causes liver failure. While most studies aiming to treat liver fibrosis focus on inhibiting hepatic stellate cell activation, thereby decreasing ECM deposition, ECM degradation and resolution of fibrosis ("fibrolysis") may offer an interventional opportunity that has not been fully explored.

In the healthy liver, ECM components are continuously synthesized and degraded to maintain ECM homeostasis. Hepatocytes, hepatic stellate cells, Kupffer cells, and liver sinusoidal endothelial cells contribute to matrix turnover by secreting ECM proteins, matrix metalloproteinases, or tissue inhibitors of metalloproteinases. Disruption of the balance between matrix production and degradation can be the basis of the excessive ECM accumulation and subsequent fibrosis development.

Understanding the molecular mechanisms, pathways, and cell types that drive ECM remodeling towards fibrosis resolution is crucial to the development of novel therapies that would ameliorate liver fibrosis. Therefore, we are looking for innovative models 1) to validate therapeutic targets (genes, proteins, pathways) that may directly enhance ECM turnover or 2) that aim to identify novel therapeutic targets for enhancing ECM turnover.

What potential solutions could be in scope?

- Innovative *in vitro* assay systems, or *in vivo* models that allow the identification and validation of protein targets that enhance ECM degradation, thereby attenuating liver fibrosis.
- Covering, but not limited to the following ideas:
    - Screening assays, including CRISPR/Cas9-based screens, in relevant cellular systems, to identify potential modulators of enhanced ECM degradation that can be developed into novel antifibrotic therapies.
    - Mammalian cell culture models (primary human liver cells, precision cut liver slices) as well as non-mammalian model organisms (Zebrafish, *Drosophila*, or *C. elegans)* to identify protein targets that enhance ECM degradation.
    - *In vivo* screens using an *in vivo* model of ECM turnover.
- Studies aimed to elucidate how cellular and molecular mechanisms that promote ECM degradation can be manipulated.

What potential solutions would be out of scope?

The following will be considered out of scope:

- Cell systems lacking applications to the disease setting of liver fibrosis.
- Liver fibrosis associated with hepatocarcinoma.

What benefits do we offer to you in exchange for having submitted a solution?

If your project is selected, you will have the opportunity to directly collaborate with the Cardio Metabolic Diseases Research team of Boehringer Ingelheim. You can expect

appropriate funding for the prospective collaboration period. The exact funding request should be outlined in your proposal. As a framework, we suggest that your initial funding request is structured in milestones and does not exceed 200,000 euros per submitted project in total.

The opportunity for a funded stay at Boehringer Ingelheim for technology exchange / training is potentially available, as is the availability of custom biological tools and reagents.

Our collaboration agreement will provide full transparency about each partner's rights & obligations (including intellectual property rights). As part of the agreement, you will be encouraged to publish following the collaboration agreement (to be negotiated in good faith).

To maintain the highest degree possible in an open innovation environment, we plan to announce the winner(s) publicly and feature them on opnMe.com and our social media channels. We would guide you through this process and as part of it we would kindly ask for your upfront consent, in case our scientific jury had selected your answer.

What are the key success criteria on which we base our selection for the best answer?

We are seeking research collaboration proposals that contain:

- A well-structured proposal outlining a new and compelling scientific approach.
- A novel, testable working hypothesis distinct from those previously published.
- Outlining of the technical feasibility, and potentially existing data or previous publications that support feasibility / experience with outlined technology, based on existing techniques and established assays.
- Your exact funding request should be outlined in your proposal based on a well-thought-through project. The project should be structured in milestones and planned with key decision points (clear Go/No-Go criteria). The funding request for the initial milestones resulting in a Go/No-Go decision should not exceed 200,000 euros per submitted project in total.
- Proven track record in the required field(s) of expertise.
- Ability to implement the outlined solution as part of a scientific collaboration project with Boehringer Ingelheim including access to a laboratory.

What information should be included in your answer submission?

Please use our answer submission template to provide a 2–3-page non-confidential proposal (available for download on the following site).

If confidential data exists that would strengthen the proposal, please indicate that information is available to share under a Confidential Disclosure Agreement (CDA). If we find the non-confidential concept proposal sufficiently interesting, we will execute a CDA for confidential discussions.

Anticipated Project Phases or Project Plan

Phase 1	Please complete your submission by **June 2, 2022 11:59 pm PST at** the very latest
Phase 2	Our review of all proposals will be completed by end of August 2022 and scientists will be informed beginning of September 2022.
Phase 3	Potential collaboration starting date in Q3/4-2022

Submitting a collaboration proposal

- Check the outline of the opn2EXPERTS "Propose novel approaches to degrade ECM in fibrotic livers" on opnMe.
- Alternatively, you may click the "Get Submission Template" banner to access the material transfer template.
- Follow the instructions to upload your submission document (requires login or registration).
- The upload allows you to attach additional application files if desired.
- You will be able to access your final submitted collaboration proposal in your personal dashboard and follow its review status.
- Please also visit the FAQ section on opnMe.com to learn more about our opn2EXPERTS program.