opnMe by Boehringer Ingelheim

# opn2EXPERTS – Characterize human hepatocyte response to NASH/fibrotic ECM

## Using novel cellular systems, how would you characterize the phenotypic and functional response of human hepatocytes to pathological shifts in ECM composition in the context of NASH and liver fibrosis?

Answers to this question including a proposal for collaboration can only be considered if they arrive no later than March 22, 2022 11:59 pm PST.

Boehringer Ingelheim

# Table of contents

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

Chronic liver damage in patients with nonalcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) leads to pathological accumulation of extracellular matrix (ECM) proteins and progressive liver fibrosis. The ECM plays a major role in modulating cellular function in liver disease, not only by providing structure and support for the cells, but also by influencing cell behavior through mechanical and biochemical signals. Several studies have investigated the changes in ECM composition and structural organization, as well as biomechanical properties, in fibrotic tissues. However, the impact of these changes in human hepatocytes has not been addressed.

Hepatocytes comprise ~80% of liver cells and perform vital functions, including protein secretion, detoxification, and metabolic functions. Hepatocyte lipid accumulation is a hallmark of early NAFLD, while later stages of NASH are characterized by massive hepatocyte loss, hepatocyte regeneration, and phenotypic changes. These include EMT-like alterations, senescence, and secretion of profibrotic factors that activate other cell types, such as hepatic stellate cells (HSC) and macrophages. Understanding the impact of diseased ECM in hepatocyte physiology is crucial for the development of novel therapies for NASH that promote hepatocyte survival and prevent pathological alterations.

Current studies are limited by the lack of human NASH ECM *in vitro* or *ex vivo* models, as well as comprehensive readouts that capture the complexity of hepatocyte physiology and crosstalk with other human liver cells in NASH. We are looking for proposals that address these limitations and deliver new potential therapeutic targets (genes, proteins, pathways) for late-stage NASH (F3, F4) and/or novel *in vitro* assays for screening such targets.

## What potential solutions could be in scope?

- Studies that characterize healthy and/or NASH-derived primary human hepatocytes grown in human healthy and/or NASH-derived ECM and identify new genes, proteins or pathways that are deregulated in late-stage NASH (F3, F4) and could be targeted to develop new therapies.
- Development and validation of novel assays using primary human hepatocytes and native human ECM, with relevant phenotypic or functional readouts, that can be used for screening or studying novel antifibrotic therapies.
- Proposals using multicellular models (e.g., Hepatocytes / Kupffer cells / HSC, organoids, organ-on-a-chip) and studies of hepatocyte interactions with other liver cells are welcome as long as they center around human hepatocyte function.

## What potential solutions would be out of scope?

The following will be considered out of scope:

- Proposals focusing on models that utilize cells or matrix components that are from non-human species
- Proposals for cell systems lacking applications to the disease setting of liver fibrosis
- Proposals that address liver fibrosis from a hepatocarcinoma (oncology) perspective
- Proposals focused on liver fibrosis caused by viral infection (HBV, HCV).
- Proposals focused on drug metabolism or drug-induced liver injury (DILI).
- Proposals that focus solely on earlier stages of NASH (e.g., hepatocyte lipid accumulation)
- Proposals that focus on single components of ECM rather than complex native matrix, e.g., collagen-coated plates

## 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 Cardiometabolic 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 of transparency 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 has 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 **May 15, 2024, 11:59 pm PST at** the very latest. |
| Phase 2 | Our review of all proposals will be completed by end June 2024 and scientists will be informed after that. |
| Phase 3 | Start of discussions for the collaboration agreement in Q3/2024. |

## Submitting a collaboration proposal

- Check the outline of the opn2EXPERTS "Characterize human hepatocyte response to NASH/fibrotic ECM" 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.