opnMe by Boehringer Ingelheim

Targeting the gut-liver axis in cirrhosis

How would you propose to improve gut hyperpermeability by targeting the intestinal barrier with the goal to ameliorate the outcome of liver disease?

Answers to this question including a proposal for collaboration can only be considered if they arrive no later than March 26, 2025, 11:59 pm PST.

Boehringer Ingelheim

Table of contents

What is the context of the problem that we would like to solve? 2
What potential solutions could be in scope? 2
What potential solutions would be out of scope? 3
What benefits do we offer to you in exchange for having submitted a solution? 3
What are the key success criteria on which we base our selection for the best answer? 3
What information should be included in your answer submission? 4
Anticipated Project Phases or Project Plan 4
Submitting a collaboration proposal 4

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

Chronic liver damage in patients with cirrhosis is accompanied by increased intestinal hyperpermeability. Through the portal circulation, the gut and the liver are connected, forming the gut-liver axis. Therefore, everything that crosses the intestinal barrier reaches the liver, where it can be metabolized or interact with the immune and resident cells. Increased translocation of bacteria and bacterial products and other pathogenic substances from the intestine to the liver can trigger systemic inflammatory responses and recruitment of systemic leukocytes, resulting in hepatocyte apoptosis/necrosis as well as activation of hepatic stellate cells that can promote fibrosis. This is a self-perpetuating spiral ultimately promoting decompensation events and worse outcomes in patients. Throughout progression of liver disease, the intestine is subjected to subclinical inflammation, leading to impaired dendritic cell activity, expansion of pro-inflammatory lymphocytes and depletion of anti-inflammatory T helper cells, thereby further increasing the permeability of the gut barrier, leading to more inflammation to the liver and subsequently also to the gut.

As part of this opnMe call, we are exploring targeting the intestinal hyperpermeability to reduce inflammation as a driver of liver cirrhosis.

Hence, we are inviting scientists to submit research proposals that showcase novel ways to address this problem and deliver new potential therapeutic targets (genes, proteins, pathways) for restoring the gut barrier hereby using suitable cellular models or assays to show efficacy.

What potential solutions could be in scope?

- Mechanisms that aim to target the epithelial barrier, either by regenerating/protecting intestinal epithelial cells (IECs), improving tight junction function, and/or improving goblet cell function and mucus layer integrity.
- Mechanism that indirectly affect gut hyperpermeability e.g., improving liver sinusoidal endothelial cells (LSEC) function
- Preliminary data showing that the proposed mechanism of action/target is supported by *in vitro* and/or *in vivo* genetic or pharmacological data, and the presence of human disease link (human genetic and/or altered target in patient tissues) would strengthen the proposal.
- Innovative methods to measure gut hyperpermeability metabolites and gut derived products.
- Innovative validated preclinical models (*in vitro/ex vivo/in vivo)* that could serve for target identification and validation.

What potential solutions would be out of scope?

- Proposals that solely target the microbiome, virome, or mycobiome
- Proposals including Fecal microbiota transplantation (FMT), antibiotics, probiotics, or dietary interventions
- Proposals that solely target cholangiocytes, bile-acid, or farsenoid X receptor (FxR) signaling
- Proposals focused on exosomes approaches
- Proposals that solely focus on IBD induced gut barrier damage
- Proposals addressing early steatotic liver disease
- Proposals that focus on incretin approaches
- Proposal lacking translatability to human

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 Cardiovascular-Renal-Metabolic Diseases Research team of Boehringer Ingelheim. You can expect appropriate funding for the prospective collaboration period. Your exact funding request should be outlined in your proposal. As a framework, we suggest that your initial funding request is structured in milestone 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).

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.
- 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 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 **March 26, 2025, 11:59 pm PST** at the very latest.
Phase 2	Our review of all proposals will be completed by mid-May 2025 and scientists will be informed after that.
Phase 3	Start of discussions for the collaboration agreement in Q3-4/2025.

Submitting a collaboration proposal

- Check the outline of the opn2EXPERTS "Targeting the gut-liver axis in cirrhosis " 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.

Reference

1. Rodrigues S. G., van der Merwe S., Krag A., Wiest R. Gut-liver axis: Pathophysiological concepts and medical perspective in chronic liver diseases *Semin Immunol*. **2024**, 71:101859. DOI: 10.1016/j.smim.2023.101859, PubMed.