opn2EXPERTS - Targeting senescence in chronic liver disease

Using novel targeted approaches, how would you propose to address cellular senescence to treat chronic liver disease?

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

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

Senescence refers to a cellular state that is characterized by an irreversible cell cycle arrest and apoptosis resistance. This phenotype can be triggered by a number of stressors, including oxidative stress, telomere shortening/dysfunction, or oncogenic signaling involving the DNA-damage response. Senescent cells undergo numerous phenotypic alterations including chromatin rearrangement, autophagy dysregulation, metabolic dysfunction and increased secretion of a broad repertoire of pro-inflammatory and pro-fibrotic factors, collectively known as the senescence associated secretory phenotype (SASP). Senescent cells have been shown to accumulate in aging and a plethora of age-related and chronic disorders in many different tissues. Pre-clinical studies not only indicate their accumulation but also a causal contribution to disease progression driven by their altered phenotype.

In chronic liver disease (CLD) senescent cells have been demonstrated to accumulate in the liver and their numbers are increasing in parallel to disease severity. For example, this has been shown in human steatosis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), as well as HBV and HCV-related fibrosis and cirrhosis. While

hepatocytes have been identified to be one of the major cell types acquiring a senescent phenotype under these circumstances, fractions of hepatic stellate cells, cholangiocytes, and liver endothelial cells can undergo these phenotypic alterations as well.

In parallel to the human system, disease related accumulation of senescent cells was observed in different preclinical models of CLD. Genetic or pharmacological removal of senescent cells in those models let to the reduction of steatosis, inflammation and fibrosis and improved liver regeneration, indicating their causal contribution to the respective pathology.

In line with that, anti-senescence or senotherapy has been identified as a promising therapeutic approach for the treatment of age-related and chronic diseases. In this regard, the removal of senescent cells (senolysis) or the reversal of the senescent phenotype (senomorphics) have been identified as valuable mechanisms of action for therapeutic intervention.

Initially, compounds with senolytic activity have been identified in an opportunistic approach by repurposing anti-cancer drugs that primarily target apoptosis resistance pathways. For example, the combination of dasatinib and quercetin was able to reduce the senescent cell burden and to improve the disease phenotype in a variety of preclinical models of age-related and chronic disorders. In addition, initial clinical studies applying these so-called 1st generation senolytics have provided evidence that such approaches have the capacity to decrease the number of senescent cells also in human disease.

Due to the missing selectivity for senescent cells, such compounds and approaches are prone for unwanted side effects especially when applied systemically. To circumvent this, approaches that selectively act on senescent cells are explored – as part of our opn2EXPERTS question in the context of CLD.

Currently, the contribution of the different hepatic cell types to the senescent cell pool in the diseased liver as well as their impact on disease progression has not been precisely characterized. In line with that, the relevance and therapeutic potential of targeted anti-senescence therapy in CLD in general and with regard to specific cell types in particular, has not been deciphered in detail so far.

We are looking for proposals to address these open questions. Of interest are novel senescent cell-specific or senescent cell-targeted approaches that eliminate senescent cells or that reverse their phenotype. Additionally, liver-cell type related screening platforms delivering novel senolytic targets or agents are of high interest.

What potential solutions could be in scope?

- Novel targeted senolytic approaches with relevance in CLD including:
    - Senescent cell specific targets / target pathways
    - Concepts that specifically target senescent cells, such as hepatocytes, stellate cells, etc.
- Screening platforms/assays to identify novel senolytic targets in cell types or systems relevant for chronic liver disease

Submitted hypotheses that could be substantiated based on preliminary experimental data in the context of CLD will be preferred as part of the review process.

What potential solutions would be out of scope?

- Untargeted/ first generation senolytics
- Non-senescence specific targets / target concepts
- Senolytic approaches with no relevance for CLD
- Screening platforms utilizing cell types that are not relevant for CLD
- Screening platforms based on non-mammalian cells

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 Discovery Research team of Boehringer Ingelheim and tap into their experience in the field of senescence. As an incentive specific to this opn2EXPERTS call, we offer an exclusive access to first generation pre-clinical senolytic tool compounds to validate your submitted hypotheses, should your proposal have been selected by our scientific review team. In addition, 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.

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.

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 **September 22, 2022, 11:59 pm PST at** the very latest
Phase 2	Our review of all proposals will be completed towards the end of October 2022 and scientists will be informed through November 2022.
Phase 3	Potential collaboration starting date in Q4/2022

Submitting a collaboration proposal

- Check the outline of the opn2EXPERTS "Targeting senescence in chronic liver disease" 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.