opn2EXPERTS - Deciphering molecular targets of human Myeloid-Derived Growth Factor (MYDGF)

How do you propose deciphering the molecular targets of human Myeloid-Derived Growth Factor (MYDGF)?

Answers to this question including a proposal for collaboration can only be considered if they arrive no later than December 17, 2020 11:59 pm PST.

Transparency disclaimer: The submitted solutions will be reviewed first by a Boehringer Ingelheim biologist expert team and the final review of the best proposals would be performed in conjunction with an existing external advisor, an internationally-recognized expert in the field of MYDGF.

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

Human Myeloid-Derived Growth Factor (MYDGF) is a 142 amino acid-long protein with incompletely understood (patho)physiological functions. It was initially found to be secreted from bone marrow-derived monocytes and macrophages (1, 2). Subsequently, others described MYDGF to also be an endoplasmatic reticulum-resident protein, with broad expression across several tissues, fluids, and in various cell lines (3-5).

MYDGF has been implicated in cardiac repair after myocardial infarction by inhibiting ischemia-reperfusion-associated cardiomyocyte apoptosis and by promoting angiogenesis in the infarct border (1, 6). Further studies suggest diverse (patho)physiological functions that may be context-dependent. For instance, a role in glucose homeostasis has been postulated through MYDGF's induction of glucagon-like peptide-1 (GLP-1) secretion from

intestinal epithelial endocrine L-cells. MYDGF has additionally been identified in the secretome of cancer cell lines (7).

Although MYDGF's structure and functionally important moieties have been defined (4, 8), the molecular mechanisms underpinning its biological effects need further elucidation. In the context of cardiac repair, MYDGF is thought to function as a secreted protein and to activate down-stream signaling pathways in target cells, i.e. cardiomyocytes and endothelial cells (1). The primary molecular MYDGF targets, however, are yet to be discovered. Identification of MYDGF interactors would improve our mechanistic understanding of MYDGF's functional effects and would deliver valuable insights on the full therapeutic potential of this exciting protein. We invite you to propose unconventional strategies how to identify molecular MYDGF targets.

What potential solutions could be in scope?

Any unconventional but feasible approach that allows identifying and verifying MYDGF interactors from biological matrices such as primary cells, cell lines, fluids, or tissues. The proposal needs to be highly feasible, should be based on existing assays and involve tools / reagents that are either available or which can be easily produced. We expect that the project will be executed in your laboratory and takes advantage of existing technologies and assays. We will only consider project proposals which can be completed within 18 months or less. Within this period, you should be able to generate confirmation of your hypothesis based on predefined experimental milestones.

What potential solutions would be out of scope?

Please note that any proposals referring to IL-25 and IL-27 will not be considered (previous annotation error for C19orf10 as described in detail in reference 1).

Proposals that allow identifying MYDGF downstream signaling pathways but are not suited to identify the primary molecular targets of MYDGF.

Projects that are based on technologies that require substantial establishment and validation (no previous hands-on experience) will be deprioritized.

Approaches that use technologies other than classical pull-down methods will be favored.

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

We are open to all proposals that can fully or partially meet the indicated requirements.

For this call, we commit to a review turn-around until end of January 2021. If your project is selected, you will have the opportunity to directly collaborate with the Research Beyond Borders (RBB) team of Boehringer Ingelheim. You can expect an initial funding of up to 200,000 euros for the prospective collaboration period (maximum 18 months in total). Please note that additional budget would become available, if experimental milestones and Go decision confirmed your hypothesis within the 18 months period.

In addition, Boehringer Ingelheim will provide qualified custom-made biological tools such as human MYDGF as well as mutants with reduced functionality (as exemplified in reference 8) as untagged or tagged versions. Antibodies for MYDGF detection (e.g. Western Blot and ELISA) can be provided as well as MYDGF-expressing or -deficient (knockout) cells.

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) publically 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 to identify and validate MYDGF's molecular target(s)/ interactor(s).

- 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.
- We will only consider project proposals which can be completed within 18 months or less. Within this period, you should be able to generate confirmation about your hypothesis based on predefined experimental milestones.
- 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 confidential 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 **December 17, 2020 11:59 pm PST** the very latest
Phase 2	Our review of Proposals will be finished by end of January 2021
Phase 3	Potential collaboration starting date late Q1/2021

Submitting a collaboration proposal

- Check the outline of the opn2EXPERTS MYDGF question on opnMe or alternatively,

- Click the “Download your answer submission template” banner to access the collaboration submission template.
- Follow the instructions upload your submission document (requires login or registration).
- The upload allows you to attach additional application files if you want to.
- 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.

References

1. Korf-Klingebiel M., Reboll M. R., Klede S., Brod T., Pich A., Polten F., Napp L. C., Bauersachs J, Ganser A., Brinkmann E., Reimann I., Kempf T., Niessen H. W., Mizrahi J., Schönfeld H. J., Iglesias A., Bobadilla M., Wang Y., Wollert K. C. Myeloid-derived growth factor (C19orf10) mediates cardiac repair following myocardial infarction *Nature Medicine* **2015**, 21, 140–149. DOI: 10.1038/nm.3778, PubMed.
2. Wang L., Li Y., Guo B., Zhang J., Zhu B., Li H., Ding Y., Meng B., Zhao H., Xiang L., Dong J., Liu M., Zhang J., Xiang L., Xiang G. Myeloid-Derived Growth Factor Promotes Intestinal Glucagon-Like Peptide-1 Production in Male Mice With Type 2 Diabetes *Endocrinology* **2020**, 161(2) :bqaa003. DOI: 10.1210/endocr/bqaa003, PubMed.
3. Bortnov V., Annis D. S., Fogerty F.J., Barretto K. T., Turton K. B., Mosher D. F. Myeloid-derived growth factor is a resident endoplasmic reticulum protein J. Bio. Chem. 2018, 293(34):13166-13175. DOI: 10.1074/jbc.AC118.002052, PubMed.
4. Bortnov V., Tonelli M., Lee W., Lin Z., Annis D. S., Demerdash O. N., Bateman A., Mitchell J. C., Ge Y., Markley J. L., Mosher D. F. Solution structure of human myeloid-derived growth factor suggests a conserved function in the endoplasmic reticulum *Nat. Commun.* **2019**, 10(1):5612. DOI: 10.1038/s41467-019-13577-5, PubMed.
5. Polten F., Reboll M. R., Widera C., Kempf T., Bethmann K., Gupta P., Miglietta J., Pekcec A., Tillmanns J., Bauersachs J., Giannitsis E., Pich A., Wollert K. C. Plasma Concentrations of Myeloid-Derived Growth Factor in Healthy Individuals and Patients with Acute Myocardial Infarction as Assessed by Multiple Reaction Monitoring-Mass Spectrometry *Anal Chem.* **2019**, 91(2):1302-1308. DOI: 10.1021/acs.analchem.8b03041, PubMed.
6. Yuan Z., Tsou Y., Zhang X., Huang S., Yang Y., Gao M., Ho W., Zhao Q., Ye X., Xu X. Injectable Citrate-Based Hydrogel as an Angiogenic Biomaterial Improves Cardiac

Repair after Myocardial Infarction *ACS Appl Mater Interfaces* **2019**, 11(42):38429-38439. DOI: 10.1021/acsami.9b12043, PubMed.

7. Sunagozaka H., Honda M., Yamashita T., Nishino R., Takatori H., Arai K., Yamashita T., Sakai Y., Kaneko S. Identification of a secretory protein c19orf10 activated in hepatocellular carcinoma *Int J Cancer*. **2011**, 129(7):1576-85. DOI: 10.1002/ijc.25830, PubMed.
8. Ebenhoch R., Akhdar A., Reboll M. R., Korf-Klingebiel M., Gupta P., Armstrong J., Huang Y., Frego L., Rybina I., Miglietta J., Pekcec A., Wollert K. C., Nar H. Crystal structure and receptor-interacting residues of MYDGF – a protein mediating ischemic tissue repair *Nat Commun*. **2019**, 10(1):5379. DOI: 10.1038/s41467-019-13343-7, PubMed.