

opn2EXPERTS – Stabilization of protein-protein interactions for cancer treatment

Which protein-protein interaction would you propose to stabilize to target cancer cells?

Answers to this [question](#) including a proposal for collaboration can only be considered if they arrive no later than May 11, 2023, 11:59 pm PST.

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

It has recently been discovered that some clinically successful drugs, such as lenalidomide and trametinib, work by stabilizing protein-protein interactions (PPIs). These kinds of drugs have been called “molecular glues”. In many cases, they induce interactions with ubiquitin E3 ligases and lead to protein degradation, but there is no reason to believe that the effects of glues should be limited to that. Indeed, trametinib stabilizes an interaction of a kinase and a pseudokinase, and SHP2 inhibitors stabilize an intramolecular interaction. This raises the question: Could this mode of action be more widely applicable in drug discovery? If so, which PPIs would drive anti-tumor effects upon stabilization?

With these questions in mind, we would like to reach out to the scientific community to collect proposals for PPIs which, when stabilized, could have a beneficial effect for cancer patients. The focus would be on effects within the cancer cells, be they strongly antiproliferative or immune stimulating (see also “in scope” below). Which pathways are affected and how the effects are brought about would be of secondary importance.

Which PPIs lend themselves to stabilization by small molecules? This question is not the primary focus of this call. We would hope to begin addressing this question by elucidating the molecular and structural details of the interaction. Reconstitution of the interaction in fully defined biochemical assays would provide the basis for the identification of small molecules that enhance it. Most assays that measure PPI can be readily tuned to allow screening for enhancers of the interaction, providing an in-route for drug discovery.

It is the intention of this call to arrive at a concept that supports the search for small molecule PPI enhancers with a potential of being developed into cancer drugs.

Briefly put, we invite research collaboration proposals that focus on PPIs with evidence of being of potential therapeutic value when stabilized.

What potential solutions could be in scope?

In this opnMe call, we would like to support research that focusses on a PPI with potential of being of therapeutic value when stabilized. The proposed PPIs must meet several criteria, and these will also be applied by our scientific review team during its evaluation process: There has to be convincing evidence that a stabilization of the PPI can have therapeutic benefit. This can be one of the following two effects:

- a. A strong antiproliferative and/or pro-apoptotic effect on cancer cells, with no comparable effect on non-cancerous cells or
- b. Enhancement of the immune attack on the cancer cells

Additional MUSTs:

- Both binding partners must be known

- The PPI must be direct
- There must be a clear rationale for the expected effect of strengthening the PPI to be cancer cell-specific with significantly weaker effects on non-cancerous tissues
- The expected beneficial effect must occur in monotherapy
- At least one binding partner must be a folded protein domain

SHOULDs:

- The concept should be applicable to solid tumors with a high unmet medical need
- There should be an initial understanding of the molecular basis of the PPI, such that fully defined assays for enhancers of the interaction can be developed
- The interaction should be sufficiently weak to leave room for enhancement by small molecules

INCLUDED

- Inter- and intramolecular interactions

What potential solutions would be out of scope?

- Indirect PPIs
- Protein-DNA or Protein-RNA interactions
- Interactions involving two unstructured binding partners
- Concepts relying on phase transitions
- Interactions that impact cancer cells and healthy cells equally
- Concepts that would lead to general cytotoxicity (i.e., not tumor selective)
- Concepts that target the immune system only
- Predicted PPIs without supporting experimental evidence
- Purely computational approaches
- Methods to identify PPIs
- PPIs that only affect hematological cancers
- PPIs that only work in combination with another therapy
- PPIs that only limit cancer cell spreading (metastasis preventing concepts)

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 respective Cancer Research team of Boehringer Ingelheim. In addition, we offer research funding of up to 500,000 € for an in-depth characterization of the PPI as part of a collaboration. This can include, but does not have to be limited to, research that:

- Confirms the potential therapeutic benefit of PPI enhancement, e.g., using mutant proteins with enhanced affinity
- Characterizes the molecular details of the interaction, such as sequence requirements and dependence on post-translational modifications

- Elucidates the 3D-structure of the protein complex
- Tests the effect of strengthening the interaction in mouse models
- Develops methods that quantify the PPI in a fully defined biochemical system

Note that part of the work could be done in collaboration with Boehringer Ingelheim.

Your 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 500,000 € per submitted project in total. Please note that the full budget can only be requested that meet all criteria outlines in our “in scope” section.

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 for a PPI that has an effect on cancer cell viability or immunogenicity upon stabilization.
- A synopsis that outlines which characteristics outlined in the “in scope section” are met with the proposed PPI.
- Outlining potentially existing data or previous publications that support the hypothesis, based on existing techniques and established assays.
- A research plan outlining further validation and characterization of the interaction towards its exploitation for the development of therapeutics.
- 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 500,000 euros per submitted project in total. The full amount can only be requested if the proposed solution fulfills all “in scope” considerations (please see above).
- 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 May 11, 2023, 11:59 pm PST at the very latest
Phase 2	Our review of all proposals will be completed by end of June 2023 and scientists will be informed after that.
Phase 3	Potential collaboration starting date in Q3-4/2023

Submitting a collaboration proposal

- Check the outline of the opn2EXPERTS “[Stabilization of protein-protein interactions for cancer treatment](#)” question 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.