opnMe by Boehringer Ingelheim

opn2EXPERTS – Tumor-specific genetic dependencies

Which cancer cell-selective dependency, supported by experimental validation, would you propose to capitalize on to trigger regression in solid tumors?

Answers to this question including a proposal for collaboration can only be considered if they arrive no later than September 12, 2023, 11.59 pm PST.

Boehringer Ingelheim

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

Genetic networks are characterized by extensive functional redundancy, both between and within pathways. During tumorigenesis however, cancer cells can acquire mutations, copy number alterations (including loss of whole chromosomes), or epigenetic changes that inactivate genes, and inhibit protein function or potentially, entire pathways[1]. This may in turn render critical cellular functions dependent on just one protein or protein complex.

Such cancer cell-selective dependencies are more common than previously thought and several have already been experimentally validated: 20% of ovarian tumors feature amplification of G1/S-specific cyclin-E1 (CCNE1). These have been shown to depend on Myt1 kinase (PKMYT1), which negatively regulates CDK1, likely to prevent premature entry into mitosis[2]. Microsatellite instabilities (MSI), associated with a number of tumors but especially prevalent in colon cancers, confer a dependency on Werner syndrome helicase (WRN), deletion of which leads to severe genome integrity defects[3–4]. Loss of chromosome Y is a frequent event in male cancer patients, reported in ~93% of esophageal adenocarcinomas, ~12% of male breast cancers, and ~23% of urothelial bladder cancers. Cell lines derived from these patients are dependent on chrX-encoded genes[1].

Targeting such cancer cell-specific dependencies is an attractive therapeutic concept especially if, as in the examples listed above, a biomarker hypothesis exists. This enables the identification of patients who will likely respond to inhibition of the proposed target.

Through this opnMe call, we invite you to submit proposals for a research collaboration to fully characterize a new cancer-specific context dependency. This dependency should be a cell-intrinsic protein or protein complex and should be able to serve as a starting point for pharmacological intervention in primary solid tumors with the potential to trigger tumor regression *in vivo*.

What potential solutions could be in scope?

Novel, previously unpublished cancer cell-intrinsic dependencies with *in vitro* proof-of-concept data. If *in vivo* evidence is available, please include a brief description of the findings.

Additional MUSTs:

- A description of the terminal phenotype observed upon loss of the function of the target.
- Targets must be associated with a biomarker that predicts (or at least correlates with) a tumor cell's sensitivity to interference with the respective target. This biomarker must have the potential to serve as a patient selection biomarker in the future.
- Your proposal must be limited to cancer cell-intrinsic targets (e.g., cell surface molecules, signaling molecules, transcription factors; other enzymes) in solid tumors with high unmet medical need.

SHOULDs:

- A description of the biological function of the target, if known.
- Information about the structure (based on published structures or predictions, e.g., from AlphaFold), pocket size, pocket volume, protein-protein interactions and/or binding partners of the target, if known.
- A conceptual outline for targeting your proposed protein therapeutically using small molecules or other validated modalities. Note: Proof-of-concept data for druggability are not required as part of your proposal.

What potential solutions would be out of scope?

- Dependencies that are not sufficiently different in their impact on cancer cells vs healthy cells, i.e., could lead to off-tumor toxicity.
- Non-cancer cell autonomous targets.
- Targets with metastasis-only phenotypes.
- Weak genetic dependency defined as:
- <50% cell growth inhibition upon loss of target in vitro.
- Loss of target taking longer than 15 days to manifest phenotypically in vitro.
- Lack of suitable biomarker.
- Unstructured proteins or proteins that lack accessible pockets or epitopes.
- Targeting strategies centered around si/shRNA molecules.

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 Cancer 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 milestones and does not exceed 500,000 euros per submitted project in total.

If planned *in vivo* validation of the selected target has not yet been completed, Boehringer Ingelheim will fund this work, which can be carried out at your institution or via a contract research organization.

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 results 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.

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 describing a novel target in oncology including a description of the preliminary data supporting the proposed target. The proposed cancer cell-selective dependency should be supported by convincing evidence as outlined in the in-scope criteria above.
- A plan for in vivo target validation if this has not already been attempted.
- A research plan clearly outlining open questions regarding the suitability of the target, proposed experiments to address these and an assessment of technical feasibility of proposed work packages.
- Your exact funding request should be outlined in your proposal. 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.
- Ability to implement the outlined solution as part of a scientific collaboration project with Boehringer Ingelheim including access to a laboratory and the sufficient technical expertise and research environment to complete the project.

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 12, 11:59 pm PST at** the very latest
Phase 2	Our review of all proposals will be completed by end of October 2023 and scientists will be informed through November 2023.
Phase 3	Potential collaboration starting date in Q1 2024.

Submitting a collaboration proposal

- Check the outline of the opn2EXPERTS "Tumor-specific genetic dependencies" 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.

References

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