opn2EXPERTS - Decipher interactors and structure of non-canonical EZH2

How would you propose to decipher and validate the non-canonical EZH2 structure and its interacting partners in the context of lung fibrosis?

Answers to this question including a proposal for collaboration can only be considered if they arrive no later than October 20, 2022, 11:59 pm PST.

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

The enhancer of zeste homolog 2 (EZH2) is known as a histone methyltransferase enzyme that functions canonically as a catalytic subunit of the polycomb repressive complex 2 (PRC2) to tri-methylate histone 3 on Lysine 27 (H3K27me3), resulting in gene silencing and chromatin compaction. EZH2 overexpression, hyperactivation, and mutations have been implicated in the pathogenesis of several cancers, showing a positive correlation with disease progression and poor patient outcomes[1]. However, pharmacological inhibition of canonical EZH2-PRC2 methyltransferase activity often showed variable effects in clinical studies[2].

Importantly, beside the canonical function which mediates gene silencing, EZH2 can also activate gene expression independently of PRC2 and plays a critical role in disease initiation and progression. Recent studies have suggested that the transition to non-canonical EZH2 is mediated by a hidden, partially disordered transactivation domain on EZH2 which can be unlocked by certain phosphorylation events, leading to structural transitions which enable the transcriptional activation role of EZH2[2,3].

Pulmonary fibrosis (PF) is a chronic respiratory disease characterized by progressive fibrotic lung remodeling and respiratory failure. The disease is ultimately fatal, despite the

emerging therapeutics. We recently discovered non-canonical EZH2 as a key transcriptional activator/coactivator in driving aberrant repair in lung fibrosis. Non-canonical EZH2 forms a fibrotic complex with RNA Polymerase 2 which activates a fibrotic crosstalk between epithelium and mesenchyme upon injury[4]. These data suggest that targeting the non-canonical EZH2 represents a promising therapeutic strategy in PF. However, it remains conceptually challenging to develop a strategy that specifically suppresses the non-canonical EZH2 function. We therefore look for proposals that aim to decipher novel binding partners of the non-canonical EZH2 including a validation based on structural analysis. The ideal solution should deliver a potential starting point for novel therapeutic interventions against the non-canonical EZH2-driven lung fibrosis.

What potential solutions could be in scope?

The following approaches to answer our question include, but are not limited to:

1. Any unconventional, but feasible scientific idea that allows identifying and validating novel non-canonical EZH2 interacting partner(s) in the context of lung fibrosis.
2. In our opinion, a thorough validation will include an in-depth analysis package consisting of biochemical, biophysical, and structural analyses.
3. Relevant to human disease.
4. Any unconventional but feasible approach should be based on existing assays and available tools in your laboratory or can be easily produced.

What potential solutions would be out of scope?

1. Proposals that allow identifying non-canonical EZH2 downstream signaling pathways but are not suited to identify the primary binding partners of non-canonical EZH2.
2. Proposals lacking applications to the disease setting.
3. Proposals that are based on standard biochemical assays and/or no previous hands-on experience will be deprioritized
4. Proposals that are considered primarily as fee for service.

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

Selected scientists will have the opportunity to directly collaborate with Boehringer Ingelheim's drug discovery research team.

An appropriate funding for the prospective collaboration period is available. The exact funding request should be outlined in the submitted proposal. As a framework, we suggest that the initial funding request is structured in milestone and does not exceed 200,000 euros per submitted proposal. Please note that additional budget would become available, if experimental milestones and Go decision confirmed your hypothesis within the 24 months period.

Furthermore, 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).

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. 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 including an experimental plan that will be used to test your hypothesis.
- A novel, testable working hypothesis distinct from those previously published.
- Outline 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.
- Accompanied by a thorough validation package consisting of biochemical, biophysical, and structural analyses.

- Potentially includes (non-confidential) existing data and results.
- Framing the questions and the innovation aspects which includes a well thought-through project plan with key decision points (e.g. clear Go/No-Go criteria).
- Contain a defined funding request. The project should be structured in milestones and planned with key decision points. 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.
- An initial hypothesis that can be validated within a maximum time frame of about 24 months. Please note that additional budget would become available, if experimental milestones and Go decision confirmed your hypothesis within the 24 months period.
- Proven track record in the required field of expertise.
- Ability to implement the outlined solution as part of a scientific collaboration project 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 **Oct 20, 2022, 11:59 pm PST** at the very latest
Phase 2	Our review of all proposals will be completed by mid of December and we will start to reach out to all applicants shortly after beginning of January 2023.
Phase 3	Potential collaboration starting date in Q1-2/2023

Submitting a collaboration proposal

- Check the outline of the opn2EXPERTS "Decipher molecular binding partners of non-canonical EZH2" 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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2. Wang J., Yu X., Gong W., Liu X., Park K-S., Ma A., Tsai Y-H., Shen Y., Onikubo T., Pi W-C., Allison D. F., Liu J., Chen W-Y., Cai L., Roeder R. G., Jin J., Wang G. G. EZH2 noncanonically binds cMyc and p300 through a cryptic transactivation domain to mediate gene activation and promote oncogenesis *Nat Cell Biol* **2022**, 24(3):384-399. DOI: 10.1038/s41556-022-00850-x, PubMed.
3. Jiao L., Shubbar M., Yang X., Zhang Q., Chen S., Wu Q., Chen Z., Rizo J., Liu X. A partially disordered region connects gene repression and activation functions of EZH2 *Proc National Acad Sci* **2020**, 117(29):16992-17002. DOI: 10.1073/pnas.1914866117, PubMed.
4. Le H. Q., Hill M. A., Kollak I., Keck M., Schroeder V., Wirth J., Skronska-Wasek W., Schruf E., Strobel B., Stahl H., Herrmann F. E., Campos A. R., Li J., Quast K., Knebel D., Viollet C., Thomas M. J., Lamb D., Garnett J. P. An EZH2-dependent transcriptional complex promotes aberrant epithelial remodelling after injury. *Embo Rep* **2021**, 22(8):e52785. DOI: 10.15252/embr.202152785, PubMed.