PARTNERING OPPORTUNITY

NOVEL CANCER THERAPIES: HIGHLY SENSITIVE SCREENING TOOL FOR POLYCOMB REPRESSIVE COMPLEX INHIBITORS

PARTNERING PROPOSAL

Aberrant **epigenetic chromatin modifications are key drivers behind deregulation of gene expression and development of disease.** Chromatin-based repression of master regulatory genes is controlled by **Polycomb Repressive Complexes (PRC1 and PRC2).** Altered expression of PRC1 and PRC2 subunits are directly linked to tumorigenesis and therefore present potential targets for cancer therapies. IMBA scientists have developed a **proprietary cellular screening tool for identifying inhibitors of the Polycomb Repressive Pathway.** This assay enables **unbiased investigation of PRC targets,** the **high-throughput screening** of numerous compounds and the **identification of a new class of cancer drugs. IMBA is actively seeking for licensing partners with business interests in the field of Polycomb-based cancer therapies.**

MEDICAL RELEVANCE

The **Polycomb Repressive Complexes (PRC)** are chromatin modifiers **responsible for silencing of key developmental and signaling genes.** Transcriptional repression involves epigenetic chromatin modifications that are critical for the maintenance of cellular identity. Not surprisingly, **deregulation of the family of Polycomb group proteins is directly linked to tumorigenesis.** Several PRC2 inhibitors in clinical development show promising efficacy for different types of cancer, including Non-Hodgkin Lymphoma and pediatric cancers characterized by the deletions of the SWI/SNF complex component SMARCB1 (also known as SNF5). Hence, there is an **opportunity for therapeutic intervention with PRC1 and PRC2 inhibitors and the need for a highly sensitive assay system** that allows for screening of new compounds targeting the Polycomb Pathway.

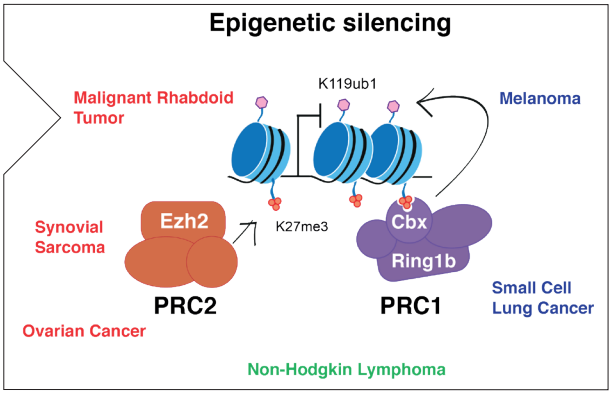

Figure 1. Opportunities for therapeutic intervention with inhibitors of PRC1 and PRC2.

SCIENTIFIC BACKGROUND

Polycomb Repressive Complexes 1 and 2 form a large family of multi-subunit complexes with divergent catalytic and non-catalytic subunits responsible for chromatin modifications and control of heritable gene silencing. While catalytic PRC2 subunit Ezh2 or PRC1 core components Bmi1 and Cbx7 can act as oncogenes, recent studies also reveal the potential tumor-suppressor function of PcG proteins suggesting that the role of these regulators may be context dependent.

IMBA scientists have developed an **in vivo cellular assay system** to **screen for novel small molecules specifically antagonizing oncogenic Polycomb activity.** The assay consists of a cell line which enables targeting of selective PRC1 or PRC2 to a reporter gene in the context of native chromatin structure. Selective nucleation of functional PRC can be achieved by fusing a DNA binding domain to specific PRC1 or PRC2 core subunits (eg. Cbx7). Upon recruitment to the reporter gene, distinct PRCs are nucleated forming repressive chromatin which ultimately leads to reporter gene silencing.

The addition of a PRC inhibitor to the cellular assay system results in impairment of the repressive chromatin-modifying activity which is indicated by activation of reporter gene expression. In Figure 2, the **Polycomb assay demonstrates cellular activity of known Cbx7 antagonist UNC3866** and **shows enhanced inhibition by a novel Cbx7 inhibitor.**

DR. BOHR-GASSE 3 | 1030 VIENNA, AUSTRIA | T: +43 1 79044-DW | F: +43 1 79044-100
IBAN: AT22 1100 0012 7034 1900 | BIC: BKAUATWW

APPLICATION IN DRUG DISCOVERY

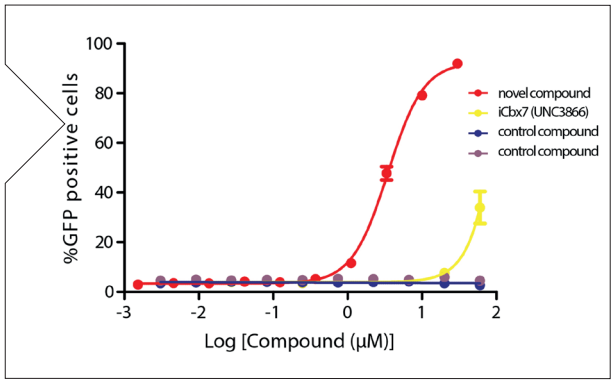

Figure 2. Dose response data from reporter mouse ES cells with canonical PRC1-dependent GFP repression for selected UNC CBX ligands, reported small molecule weak CBX ligand and negative control.

IMBA's **cellular PRC screening assay** can be used to **identify novel inhibitors of PRC1 and PCR2 for cancer therapy** and **evaluate the potency and specificity of inhibition.**

The **assay** is conducted in living cells thus **producing in vivo results.** The design of the assay is advantageous due to the positive signal achieved as a result of inhibiting Polycomb activity **with high sensitivity.** In addition, PRC1 as well as PRC2 can be tested and for each protein, diverse subunits can be analyzed. Consequently, **numerous inhibitors can be screened for each subunit on a high throughput basis.**

STAGE OF DEVELOPMENT

Proof-of-concept for the cellular screening tool was achieved with a PRC1 inhibitor UNC3866 published in the literature. Functionality of the assay was further confirmed with a known PRC2 inhibitor. Furthermore, an unknown **very potent PRC1 inhibitor** was identified using the test system. The novel compound has more than **20-fold enhanced potency over published PRC1 inhibitors** and efficient PRC1 eviction from validated in vivo Polycomb target genes was confirmed by Chromatin Immunoprecipitation and Next-Gen Sequencing. This is remarkable because so far only few compounds could be identified as PRC1 inhibitors. For further development of the cellular screening tool, IMBA is collaborating with the University of North Carolina (UNC) to screen a library for potential new drugs.

The test system is available for licensing. In addition, the novel PRC1 inhibitor can be provided as a positive control together with the assay. IMBA is also interested in collaborations to screen for potential new drugs and offers screening activities as a service.

PATENT SITUATION

IMBA filed a European Patent application in 2017 and a PCT application in 2018. The invention relates to the screening of chemical agents for their ability to interfere in catalytic activity, protein-protein or protein-DNA interaction.

REFERENCES

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CONTACT PERSON

BUSINESS
Petra Köhler, PhD
Ascenion GmbH*
Technology Manager
Phone: +49 531 6181-2091
E-Mail: koehler@ascenion.de

SCIENCE
Oliver Bell, PhD
Junior Group Leader, IMBA
Phone: +43-1-79044-4320
E-Mail: oliver.bell@imba.oeaw.ac.at
www.imba.oeaw.ac.at/research/oliver-bell/

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