Orally bioavailable BCL6 degrader

(BCL6 degrader BI-1136)

Overview

For a short period of time, we share the unprecedented, potent and selective orally bioavailable BCL6 degrader BI-1136 which is suited for both *in vitro* and *in vivo* experiments for collaborative research on novel disease indications. BI-1136 potently degrades human and mouse BCL6 (DC_{50} = 63 nM in SU-DHL-4 cells). Funding of up to 200.000 € will be available upon request and shall be outlined in the application.

The main difference of this oral BCL6 degrader BI-1136 in comparison to the other BCL6 degrader BI-3802 on opnMe.com is its suitability for *in vivo* experiments in animals.

We invite scientists to submit proposals containing an *in vivo* testable hypothesis using our oral BCL6 degrader no later than **July 31, 2019, 23.59 pm PST.**

Summary

With BI-1136 we share an unprecedented, potent and selective orally bioavailable BCL6 degrader for collaborative research on novel disease indications. This tool compound potently inhibits the interaction of the BTB/POZ domain of BCL6 with several co-repressors *in vitro* (IC_{50} ≤ 50 nM). In a cellular context, the BCL6 degrader inhibits the BCL6::Co-repressor complex formation with an IC_{50} of 210 nM. Moreover, our BCL6 degrader was found to be a potent and efficacious degrader of the BCL6 protein in mouse and human diffuse large B-cell lymphoma (DLBCL) cell lines (DC_{50} = 63 nM in SU-DHL-4 cells) as well as in other BCL6 expressing cells tested (macrophages, NSCLC, Burkitt and breast cancer cell lines). The BCL6 degrader shows pharmacokinetic (PK) properties that are suitable for *in vivo* testing in several animal species and is well tolerated. The compound will be provided free of charge in the amount required for the experiments, and is provided under an existing collaboration agreement with FORMA Therapeutics, Inc. (Watertown, MA).

Background

The transcriptional regulator BCL6 represses genes required for the differentiation of B-cells in germinal centers (GC). Errors in the GC reaction can give rise to mutated B cells that maintain an elevated proliferation and fail to differentiate, contributing to the genesis of DLBCL. BCL6 is an oncogenic driver for DLBCL (Basso and Dalla-Favera, 2012; Hatzi and Melnick, 2014; Pasqualucci, 2013) and its expression is frequently elevated by mutations in DLBCL. However, despite significant research efforts, the clinical relevance of targeting BCL6 in DLBCL remains to be proven.

The *in vitro* profile of our orally bioavailable BCL6 degrader is very comparable to our molecular probe BI-3802 (Kerres, 2107) on opnMe.com. The differentiating aspect is the oral bioavailability. A negative control (distomer) having a differentiated pharmacological profile may also be available for sharing on request. BI-1136 has acceptable solubility in water at neutral pH, high permeability in Caco2 and MDCK assays and medium plasma protein binding and stability in mouse liver microsomes. PK properties in several animal species are suitable for once or twice daily oral dosing in acute or sub-chronic *in vivo* experiments, resulting in significant but not complete degradation of BCL6 in SU-DHL-4 xenografts.

BI-1136 shows high selectivity at 10 µM concentration versus a panel of 44 receptors (no inhibition) and 42 Kinases (no inhibition). The compound is well tolerated in mice up to 1g/kg daily dose in mice.

References

1. Basso and Dalla-Favera, *Immunol. Rev.* (2012) 247, 172–183, DOI: 10.1111/j.1600-065X.2012.01112.x. https://www.ncbi.nlm.nih.gov/pubmed/22500840
2. Hatzi and Melnick, *Trends Mol. Med.* (2014) 20, 343–352 DOI: 10.1016/j.molmed.2014.03.001 https://www.ncbi.nlm.nih.gov/pubmed/24698494
3. Kerres et al., *Cell Reports* (2017) 20, 2860–2875, DOI: 10.1016/j.celrep.2017.08.081. https://www.ncbi.nlm.nih.gov/pubmed/28930682
4. Pasqualucci et al., *Nature* (2011) 471, 189–195, DOI: 10.1038/nature09730. https://www.ncbi.nlm.nih.gov/pubmed/21390126

Key Success Criteria

Boehringer Ingelheim is seeking proposals that have:

- A strong scientific proposal with a new and compelling scientific idea for a BCL6 degrader in a novel disease indication or pathway
- A novel, testable working hypothesis distinct from those previously published
- Research plan detailing an *in vivo* proof of concept (PoC) study in rodents.

Additional key success criteria are:

- The quality and feasibility of the existing data and/or the experimental plan that will be used to test the hypothesis
- The experimental endpoints and how well these can be translated to human disease

If confidential data exists that would strengthen the proposal, the solution provider may indicate that confidential information is available to share under a Confidential Disclosure Agreement (CDA). If Boehringer Ingelheim finds the non-confidential concept proposal sufficiently interesting, they will execute a CDA for confidential discussions.

Possible Approaches

Our Boehringer Ingelheim team is open to all proposals that can fully or partially meet their requirements. Funding of up to €200.000 may be available for selected projects upon request and support requirements should be outlined in the submitted proposal. Collaborating scientists will benefit from direct access to Boehringer Ingelheim's drug discovery and validation capabilities.

Anticipated Project Phases or Project Plan

Phase 1 – Review of Proposals will start at the beginning of August 2019 and we aim to finalize our review by end of September 2019.
Phase 2 – Potential collaboration starting date Q4 2019 / Q1 2020

Submitting a collaboration proposal

- Click the “download your submission template or upload your proposal today” banner to access the collaboration submission template.
- Log in, or register for *opnMe.com* (you will be prompted).
- Follow the instructions to download the template or upload your submission document
- 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 Molecules for Collaboration program.