SGLT6 (SLC5A11, SMIT2) inhibitor

Overview

We share an unprecedented, potent and selective SGLT6 inhibitor for collaborative research on novel disease indications. This tool compound is brain penetrant and shows pharmacokinetic (PK) properties that are suitable for in vivo testing in rodents. Additional compounds having differentiated properties and pharmacological profiles may also be available for sharing on request.

We invite scientists to submit proposals containing a testable hypothesis using our SGLT6 inhibitors.

Submissions for collaborations can only be considered if they arrive no later than February 28, 2018, 23.59 pm PST.

Summary

Boehringer Ingelheim invites proposals for novel disease hypotheses for SGLT6 (SLC5A11, SMIT2) antagonists. Scientists will collaborate with Boehringer Ingelheim and be given access to an unique SGLT6 antagonist compound to conduct experiments to test their hypotheses and identify novel diseases, indications or pathways linked to SGLT6. This tool compound is brain penetrant and shows pharmacokinetic (PK) properties that are suitable for in vivo testing in rodents. Additional compounds having differentiated properties and pharmacological profiles may also be available for sharing on request. We invite scientists to submit proposals containing a testable hypothesis using our SGLT6 inhibitors.

Background

Through their control of many essential physiological functions, such as nutrient uptake, solute carrier (SLC) proteins have been recognized as attractive drug targets. Nonetheless, the role(s) of many of these molecules remains unexplored [1]. Sodium glucose cotransporters (SGLT) typically facilitate monosaccharide transport across cellular membranes [2]. SGLT6 (SLC5A11) also known as SMIT2, has the lowest amino acid identity of the SGLTs with human SGLT1 (50%) and preferentially transports inositol over glucose in a Na+ dependent manor [3, 4]. In contrast with SMIT1 (SLC5A3), SLGT6 has a more limited tissue distribution in humans with expression in the CNS, small intestine and kidney being prominent. By influencing inositol concentrations in many various metabolic pathways, SMITs may represent promising targets for a number of diseases [5].

Boehringer Ingelheim has created a unique preclinical SGLT6 antagonist tool compound. SGLT6 antagonists are unprecedented in literature. The compound will be provided free of charge in the amount required for the experiments.

The small molecule SGLT6 inhibitor shows an IC50 of 1 nM on 14C-myo-inositol uptake in HEK293 cells overexpressing human SGLT6 [6].

ASSAY	IC50
hSGLT6, IC_{50}	~1 nM
hSGLT1, IC_{50}	700 nM
hSGLT2, IC_{50}	35 nM
dSMIT1, IC_{50}	1090 nM

The SGLT6 inhibitor has low solubility in water at neutral pH and high permeability in Caco2 and MDCK assays. PK properties in rodents are suitable for once or twice daily oral dosing in acute or

sub-chronic *in vivo* experiments. The SGLT6 inhibitor shows moderate selectivity versus human SGLT2 (~35 fold) but high selectivity versus human SGLT1 (~700fold) and dog SMIT1 (>1000fold). A modified IRWIN test in mice showed no side-effects up to a 30 mg/kg dose.

The front-runner SGLT6 antagonist is a member of a family of compounds generated in our SGLT6 program. Additional compounds have different properties and pharmacological profiles and may be available for sharing.

Boehringer Ingelheim believes that its unique preclinical tool compounds have a vast opportunity beyond the therapeutic settings that its scientists are currently focusing upon. For this reason Boehringer Ingelheim will provide access to some of its preclinical tool compounds with optimized pharmacological properties from current and past discovery research projects for scientists to probe novel disease biology.

References

1. Cesar-Razquin et al., *Cell* (2015) 162(3) 478-487, DOI: 10.1016/j.cell.2015.07.022 https://www.ncbi.nlm.nih.gov/pubmed/26232220
2. Grempler et al., *FEBS Lett.* (2012) 586(3) 248-53, DOI: 10.1016/j.febslet.2011.12.027 https://www.ncbi.nlm.nih.gov/pubmed/22212718
3. Wright, *Mol. Aspects Med.* (2013) 34(2-3) 183-196, DOI: 10.1016/j.mam.2012.11.002 https://www.ncbi.nlm.nih.gov/pubmed/23506865
4. Lin et al., *Arch. Biochem. Biophys.* (2009) 481(2) 197-201, DOI: 10.1016/j.abb.2008.11.008 https://www.ncbi.nlm.nih.gov/pubmed/19032932
5. Schneider, *FEBS Lett*. (2015) 589(10) 1049-1058, DOI: 10.1016/j.febslet.2015.03.012 https://www.ncbi.nlm.nih.gov/pubmed/25819438
6. Grempler et al., *Diabetes Obes. Metab.* (2012) 14(1) 83-90, DOI: 10.1111/j.1463-1326.2011.01517.x https://www.ncbi.nlm.nih.gov/pubmed/21985634

Key Success Criteria

Boehringer Ingelheim is seeking proposals that have:

- A strong scientific proposal with a new and compelling scientific idea for SGLT6 (SLC5A11, SMIT2) antagonists in a novel disease indication or pathway
- A novel, testable working hypothesis distinct from those previously published

Additional key success criteria are:

- The quality and feasibility of the 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 is open to all proposals that can fully or partially meet their requirements.

Anticipated Project Phases or Project Plan

Phase 1 – Review of Proposals by end April 2018
Phase 2 – Collaborations starting Q3 2018

Submitting a response

- Click the “Collaborate” button at the top of the page.
- Log in, or register for *opnMe.com* (you will be prompted).
- Download proposal template for collaboration (recommended)
- Upload your proposal and attach additional files of information if you want to.
- Click “Continue to next step”