Complex I ROS Modulator

Highlights

We share an unprecedented, potent and selective NADH:ubiquinone oxidoreductase (Complex I) ROS modulator for collaborative research on novel disease indications. This tool compound lowers oxidative stress by inhibiting the generation of reactive oxygen species (ROS), derived from mitochondrial Complex I, while leaving the NADH:ubiquinone oxidoreductase activity unaffected. The compound is brain penetrant and shows pharmacokinetic (PK) properties that are suitable for *in vivo* testing in rodents.
We invite scientists to submit proposals containing a testable hypothesis using our Complex I ROS modulator no later than **September 15, 2018 23.59 pm PST**. Funding of up to 200.000 € will be available upon request and shall be outlined in the application.

Overview

Boehringer Ingelheim invites scientists to submit their proposals for novel indications or diseases for its potent and selective NADH:ubiquinone oxidoreductase (Complex I) ROS modulator. This tool compound lowers oxidative stress by inhibiting the generation of reactive oxygen species (ROS), derived from mitochondrial Complex I, while leaving the NADH:ubiquinone oxidoreductase activity unaffected. The compound is brain penetrant and shows pharmacokinetic (PK) properties that are suitable for *in vivo* testing in animal species
Collaboration partners would work with Boehringer Ingelheim scientists and benefit from direct access to their drug discovery and validation capabilities.

The partnership will include privileged access to an unprecedented, potent and selective Complex I ROS modulator compound which has not been published so far. Additional compounds having differentiated properties and pharmacological profiles may also be available for sharing on request.
The opportunity bears the potential for cutting edge publication of the research at conferences and in refereed journals.

Submissions for collaborations can only be considered if they arrive no later than September 15, 2018, 23.59 pm PST and must be submitted on opnMe.com.

Summary

Boehringer Ingelheim invites proposals for novel disease hypotheses for a NADH:ubiquinone oxidoreductase (Complex I) ROS modulator. This tool compound lowers oxidative stress by inhibiting the generation of reactive oxygen species (ROS), derived from mitochondrial Complex I, while leaving the NADH:ubiquinone oxidoreductase activity unaffected. The compound is brain penetrant and shows pharmacokinetic (PK) properties that are suitable for *in vivo* testing in several animal species. Scientists will collaborate with Boehringer Ingelheim and be given access to an unique Complex I ROS modulator compound to conduct experiments to test their hypotheses and identify novel diseases, indications or pathways linked to Complex I ROS modulation. We invite scientists to submit proposals containing a testable hypothesis using our Complex I ROS modulators. Funding of up to 200.000 € will be available upon request and shall be outlined in the submission proposal.

Background

Due to its relative slow turnover rate for ubiquinone reduction NADH:ubiquinone oxidoreductase (Complex I) is the rate-limiting enzyme in the mitochondrial electron transfer chain (respiratory chain). Genetic and functional evidence indicates that Complex I is a major source of mitochondrial ROS-formation [1] and thus a major contributor to oxidative stress, a pathological hallmark in neurodegenerative and other diseases [2-5]. Hence, a Complex I ROS modulator which lowers ROS-production while leaving the ubiquinone reduction mechanism unaffected is expected to reduce oxidative stress in a more targeted (i.e. intra-mitochondrial) and more specific manner (i.e. non-stoichiometric scavenging) than other antioxidants that failed in clinical trials.

Boehringer Ingelheim has created a unique preclinical Complex I ROS modulator tool compound that lowers oxidative stress by inhibiting the generation of ROS, derived from mitochondrial Complex I, while leaving the NADH:ubiquinone oxidoreductase activity unaffected. Complex I ROS modulators with this mechanism of action are unprecedented in literature. The compound will be provided free of charge in the amount required for the experiments.

The novel Boehringer Ingelheim small molecule inhibits purified bovine Complex I mediated ROS-formation with an IC_{50} of 80 nM. Compounds from this series have been shown to have no species selectivity. The Complex I ROS modulator was also shown to be selective versus other ROS-generating enzymes (e.g. xanthine oxidase, monoamine oxidase and NO-synthases all >10µM) and does not show cytotoxicity at 30 µM in neuroblastoma cells, indicating that mitochondrial respiration is unaffected (modulation concept). Furthermore the small molecule shows protects glutathione-depleted neuroblastoma cells in a model of oxidative stress (HT_{22} cells, EC_{50} = 80 nM)

and dopaminergic neurons in the MPTP-model, a neurotoxin inhibiting mitochondrial Complex I resulting in diminished Ubiquinone -reduction and ATP synthesis as well as stimulated ROS-formation.

Assay	IC_{50} [nM]
Complex I IC_{50} (bovine)	80 nM
Xanthinoxidase IC_{50} (ROS generation)	>10000
HT_{22} cell protection EC_{50}	80 nM

The Boehringer Ingelheim Complex I ROS modulator has acceptable solubility in water at neutral pH and high permeability in Caco2 and MDCK assays. PK properties in several animal species are suitable for once or twice daily oral dosing in acute or sub-chronic *in vivo* experiments. The small molecule shows high selectivity at 10 µM concentration versus a panel of 68 receptors (no inhibition), 25 Kinases (IKKβ and VEGFR2 >75% inhibition) and 17 other enzymes (15-LO, 5-LO and LPO >75% inhibition). Initial safety studies in rats showed no cardiovascular effects up to a 50 mg/kg dose.

The front-runner Complex I ROS modulator is a member of a family of compounds generated in our Complex I modulator 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. Murphy, *Biochem. J.* (2009) 417(1) 1-13, DOI: 10.1042/BJ20081386 https://www.ncbi.nlm.nih.gov/pubmed/19061483
2. Janssen et al., *J. Inherit. Metab. Dis.* (2006) 29(4) 499-515, DOI: 10.1007/s10545-006-0362-4 https://www.ncbi.nlm.nih.gov/pubmed/16838076
3. Koilkonda et al., *J. Ophtalmol.* (2011) 179412, DOI: 10.1155/2011/179412 https://www.ncbi.nlm.nih.gov/pubmed/21253496
4. Piccoli et al., *J. Med. Genet.* (2008) 45(9) e5508, DOI:10.1136/jmg.2008.058628 https://www.ncbi.nlm.nih.gov/pubmed/18524835
5. SanGiovanni et al., *PLoS One.* (2009) 4(5) 197-201, DOI:10.1371/journal.pone.0005508 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2677106/

Key Success Criteria

Boehringer Ingelheim is seeking proposals that have:

- A strong scientific proposal with a new and compelling scientific idea for Complex I ROS modulators 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 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

Boehringer Ingelheim is open to all proposals that can fully or partially meet their requirements. Funding of up to 200.000 € will be available upon request and shall be outlined in the submission 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 by end of October 2018
Phase 2 – Collaborations starting Q4 2018 / Q1 2019

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"