Dual Vanin inhibitor | BI-4122

Overview

In humans, the Vanin 1 and 2 genes encode secreted and membrane-bound ectoenzymes that convert pantetheine into pantothenic acid and cysteamine. We share for collaboration a highly potent and selective dual Vanin inhibitor that blocks the enzymatic activity of Vanin 1 and 2, suitable for investigations *in vitro* and *in vivo*. Interested scientists are invited to submit testable research proposals that demonstrate utility of Vanin enzymatic activity inhibition in novel disease indications with high unmet medical need.

All incoming proposals will be evaluated by a scientific jury comprising of Boehringer Ingelheim scientists, and, upon selection, chosen proposals would be pursued through joint collaborations with the successful applicants. Funding of up to 200,000 euros will be available for each selected proposal.

Submissions for collaborations can only be considered if they arrive no later than November 24, 2021, 11:59 pm PST.

Summary

BI-4122 is an orally available small molecule inhibitor that blocks in a reversible, competitive manner the enzymatic activity of Vanin 1 and 2, and therefore potently inhibits the conversion of pantetheine into pantothenic acid and cysteamine. Interested scientists are invited to submit testable research proposals that demonstrate utility of Vanin enzymatic activity inhibition in novel disease indications with high unmet medical need. This dual inhibitor will be provided free of charge in the amount required for *in vitro* and *in vivo* experiments together with in depth information on the compound to successful applicants.

Background

Vanin-1 and -2 are single-domain enzymes tethered to the extracellular surface by a glycosylphosphatidylinositol (GPI)-linker but is also shed in from the cell surface into the extracellular milieu. The Vanin enzymes function to convert pantetheine into pantothenic acid and cystamine, which is then reduced to cysteamine. Vanin-1 is expressed in immune-competent tissues as well as in intestine, liver, and kidney. Vanin 2 expression is detectable in most tissues with highest expression in spleen, kidney, and blood (1).

The Vanin enzymes regulate cellular redox homeostasis, as its reaction products are capable of interfering with glutathione biosynthesis. Studies in Vanin-1 knockout mice have shown that the knockout animals were more resistant to oxidative stress and showed a lower inflammatory response compared with their wild-type littermates following challenge with different injury triggers (2). In addition, Vanin-1 knockout mice are resistant to inflammatory bowel disease (3) and the Vanins have been implicated in other disorders including malaria susceptibility, psoriasis, carcinogenesis, and cardiovascular disease (4-6).
BI-4122 is a small molecule compound that potently inhibits Vanin enzymatic activity in mice and humans with nanomolar potency. It possesses a very favorable selectivity profile and DMPK properties, allowing standard oral application in dose response *in vivo* studies.

We are very interested to obtain proposals with a specific disease focus which would provide us with a scientific rationale to demonstrate the therapeutic potential of BI-4122 in suitable assays.

In vitro activity

The orally bioavailable small molecule BI-4122 inhibits the enzymatic activity of Vanin 1 and 2 with IC_{50} of 0.3 and 1.5 nM biochemical potency and 2nM in a human whole blood assay. The compound is also potently inhibiting Vanin enzymatic activity of mouse and rat, making it a suitable tool for model investigations in these species.

Assay	IC_{50} [nM]
Human VNN 1 IC_{50}	0.3
Human VNN 2 IC_{50}	1.5
Human Whole Blood IC_{50}	2

In vitro DMPK and CMC parameters

BI-4122 has good solubility in water at all pH values. It shows high permeability in Caco-2 assay but significant efflux in the MDCK permeability assay.

In vivo DMPK parameters

Pharmacokinetic (PK) properties in rodent animal species are suitable for once or twice daily oral dosing in acute or sub-chronic *in vivo* experiments.

Selectivity

BI-4122 shows no significant activity in a panel of 268 kinases and 68 enzymes/receptors tested at 10 µM.

References

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Key Success Criteria for the selection of proposals

Boehringer Ingelheim is seeking research collaboration proposals that have:

- A strong scientific proposal with a new and compelling scientific idea for a dual Vanin inhibitor in a novel human disease indication
- A novel, testable working hypothesis distinct from those previously published

Proposals which include primary (disease) tissues, or a humanized model would provide additional attractiveness.

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

The collaborative priorities for Boehringer Ingelheim's therapeutic areas are shown in the following table:

Oncology and Immuno-Oncology	The primary focus is on solid tumors that have a high unmet medical need. In addition, orphan indications (e.g. RASopathies) and hematological indications are also of interest.
Cardiometabolic diseases	Liver diseases • Non-alcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis, portal hypertension Retinopathies • Geographic atrophy/dry and wet AMD • Diabetic retinopathy/DME and related retinal diseases Novel obesity treatments achieving weight loss > 10% CKD and heart failure Breakthrough treatments for type 2 diabetes, such as pancreas regeneration options
CNS diseases	Novel treatment options for neuropsychiatric diseases such as: • Schizophrenia: Cognitive Impairment, Negative Symptoms, (Relapse Prevention) • Major Depression • Cognition: Reward, Motivation & Emotion, Disease Progression • Borderline Personality Disorder
Immunology & Respiratory	Systemic sclerosis-scleroderma (SSc) SSc-Interstitial Lung Disease (ILD) Inflammatory bowel diseases such as Crohn's disease including specific approaches for fistulizing and refractory ileal Crohn's disease and ulcerative colitis Interstitial pulmonary fibrosis (IPF)/PF-ILD: Block of pro-fibrotic signaling beyond standard of care Disease-modifying therapies for respiratory indications Approaches to induce lung regeneration and repair mechanisms Aberrant epithelial sensing

	Epithelial-fibroblast interactions Macrophage repair function
Research Beyond Borders	Gene Therapy: Novel therapeutic concepts/targets, which are amenable to AAV-based gene therapy. Technology advancement in the field of tissue selective AAV capsid variants with translational potential to man; innovative technology, which allows spatio-temporal control of cargo expression, increased cargo size or modulation of immune response to AAV capsids and/or DNA cassettes; human tissue/organ models for translational screening or characterization of AAVs. Regenerative Medicine: Focus on biology underlying endogenous mechanisms & master switches to regenerate tissues. The proposed therapeutic concept should be supported by preclinical in vivo data with a clear translational path to patients. Therapeutic fields of interest include, but are not limited to, tissue such as bone, cartilage, spinal cord and thymus. Emerging Therapeutic Concepts: Open to new and disruptive ideas in uncharted therapeutic spaces to treat diseases for which there are no effective therapies, including rare diseases. New Therapeutic Technologies: Capture emerging technologies/modalities that will change medical practice e.g. exosomes and extracellular vesicles.

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 its requirements. Funding of up to 200,000 euros 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 towards the end of November after the deadline and we aim to finalize our review by end of January 2022.
Phase 2 – The earliest potential collaboration starting date would be in Q2/2022

Submitting a collaboration proposal

- Check the dual Vanin inhibitor profile on opnMe or alternatively,
- Click the “Download your submission template” banner to access the collaboration submission template (requires login or registration).
- 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.