opnMe by Boehringer Ingelheim

ALPK1 inhibitor BI-4286

Using suitable model systems, how would you propose to demonstrate and validate the role of ALPK1 in defined disease indications?

Answers to this question including a proposal for collaboration can only be considered if they arrive no later than March 10, 2026, 11:59 pm PST.

Boehringer Ingelheim

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Summary

With the goal to better understand the mechanistic role of ALPK1 signaling in disease pathology outside of infectious diseases, we now share a well-characterized small molecule inhibitor of ALPK1, BI-4286 to stimulate novel disease hypotheses.

Successful applicants will receive the previously unpublished and highly potent and selective ALPK1 inhibitor BI-4286 free of charge in the amount required for *in vitro* and *in vivo* experiments together with comprehensive information on the molecule. Funding of up to 300,000 euros is available for selected proposals that would be jointly pursued as part of a partnership with scientists from Boehringer Ingelheim.

We look forward to receiving your innovative research proposals in alignment with our collaborative discovery research priorities. To have a chance to collaborate on groundbreaking research, submit your proposals no later than **March 10, 2026, 11:59 pm PST.**

Background

ALPK1 is a cytoplasmic pattern recognition receptor expressed across various cell types. It is believed to play a role in the pathology of several diseases with high unmet medical need, but mechanistically, its function is best described in the context of infectious diseases. Exactly those are not in scope of the current opnMe call.

It is well established that ALPK1 is activated by the gram-negative bacterial metabolite ADP-heptose. Mechanistically, ADP-heptose binds to the N-terminus of ALPK1, liberating the C-terminal kinase domain and enabling downstream signaling. Once activated, ALPK1 phosphorylates TIFA, leading to the formation of the TIFAsome and activation of the NF-κB pathway.

Recent findings indicate that ALPK1 can also be activated by alternative nucleotide-diphosphate (NDP)-heptoses, such as CDP-heptose and UDP-heptose. These molecules are thought to be produced by a variety of organisms, including archaea, viruses, and even eukaryotes. Additionally, mutations in ALPK1 have been shown to trigger its activity, potentially leading to aberrant activation by mammalian nucleotide sugars such as UDP-mannose. Notably, mutations in ALPK1 have been implicated in the rare disease ROSAH syndrome (Retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, and headache), suggesting that ALPK1 activity may play a role in a broader range of diseases.

However, the role of ALPK1 in disease pathology beyond ROSAH and infectious diseases is poorly understood. Therefore, we invite collaborative research proposals to investigate and validate the role of ALPK1 in defined human diseases caused by aberrant activation. Very important will be to show target engagement activity and provide biomarker read-outs in the context of the proposed disease model.

To validate and strengthen disease links, we offer access to our ALPK1 inhibitor, BI-4286, for use in disease-relevant cell-based assays and *in vivo* models, in the amounts required for a proof of concept of the suggested research hypothesis.

In vitro activity

BI-4286 is a non-covalent, allosteric ALPK1 inhibitor. In a biochemical assay using recombinant full-length ALPK1 protein, it potently inhibits both human and mouse ALPK1 activity with IC_{50} values of 5 nM and 18 nM, respectively. The cellular activity of BI-4286 has been demonstrated in several rodent and human cell-based assays, including the THP-1 NFkB reporter gene assay (IC_{50} = 0.174 µM) and the inhibition of IL-8 secretion in primary human macrophages stimulated with the ALPK1 agonist ADP-heptose (IC_{50} = 1.2 µM). In addition, BI-4286 inhibits IP-10 secretion in mouse bone marrow-derived macrophages stimulated with ADP-heptose (IC_{50} of 2.6 µM). Furthermore, BI-4286 inhibits IL-8 secretion in peripheral human whole blood stimulated with ADP-heptose (IC_{50} of 3.2 µM).

Please see the *in vitro* activity table below for the key features for BI-4286.

	BI-4286
hum / mou ALPK1 ADP Glo IC_{50} [µM] @1 mM ATP	0.005 / 0.018
THP-1 NFkB 10% hum serum IC_{50} [µM]	0.174
hum macr. IC_{50} [µM]	1.2
hum WB IL-8 IC_{50} [µM]	3.2

In vitro DMPK and CMC parameters

BI-4286 has good metabolic stability in mouse, rat, human liver microsomes and hepatocytes and shows good cellular permeability in a Caco-2 assay (see table below). In addition, BI-4286 has good solubility in water at acidic or neutral pH.

	BI-4286
Microsomes MetStab m/r/h [% Q_H]	55 / 33 / 66
Hepatocytes MetStab m/r/h [% Q_H] w. 50% plasma	22 / 16 / 20
Caco2 $P_{app\text{-}intr}$ [10^{-6} cm/s] / efflux ratio	5 / 6

PPB m/r/h [%]	93 / 86 / 93
SolScreen @ pH 4.5 / 6.8 [µg/ml]	83 / 73

In vivo DMPK

BI-4286 shows favorable pharmacokinetic (PK) properties in mice and rats, using a standard Natrolsol formulation. In an acute ADP-heptose mouse challenge model full efficacy (inhibition of IP-10 secretion) was demonstrated at a dose of 20 mg/kg.

	BI-4286
Mouse *p.o.* PK @ 28 mg/kg AUC [µM*h/l] / F [%] / MRT [h]	15.1 / 100 / 1.9
Rat *p.o.* PK @ 5 mg/kg AUC [µM*h/l] / F [%] / MRT [h]	5.7 / 100 / 2.9

Selectivity

BI-4286 shows no activity in a panel of 384 kinase (no off-target hits at a concentration of 10 µM) and in a panel of 44 GPCR receptors, nuclear hormone receptors, transporters, or ion channels (no off-target hits at 10 µM).

In vitro cytotoxicity and phospholipidosis

BI-4286 shows no cytotoxicity in HepG2-MTT-Cytotox assay (EC_{50} >200 µM) and has very low phospholipidogenic potential (PL FEC > 50 µM).

What potential solutions could be in scope?

Any unconventional but feasible approach for the identification and validation of a role of ALPK1 signaling in disease. The approach should provide evidence for target engagement activity and provide a biomarker enabled read-out. The following indications are part of our current discovery research priorities:

- Cardiomyopathy, acute myocardial infarction
- MASH and cirrhosis
- Chronic kidney disease
- Neurodegenerative diseases
- Schizoaffective disorder and paranoid schizophrenia

- Myositis, sarcoidosis, coeliac disease, Sjorgren's, and inflammatory bowel syndrome
- Retinal diseases and glaucoma
- Endometriosis

When submitting a proposal, please select one specific indication that your hypothesis should focus on.

What potential solutions would be out of scope?

Projects that are based on hypotheses requiring first substantial establishment and validation (no previous hands-on experience) will be deprioritized

Any solutions that would require an ALPK1 activator

Proposals focusing exclusively on infectious disease indications

Cancer indications including immuno-oncology

Proposals focusing on ROSAH syndrome

Approaches that are using model systems other than rodent or human

Purely computational approaches without lab-environment to validate the hypothesis

Any research proposals covering more than one indication

What benefits do we offer to you in exchange for having submitted a solution?

If your project is selected, you will have the opportunity to directly collaborate with relevant disease experts of our Discovery Research Teams of Boehringer Ingelheim. You can expect appropriate funding for the prospective collaboration period. Your exact funding request should be outlined in your proposal. As a framework, we suggest that your initial funding request is structured in milestone and does not exceed 300,000 Euros per submitted project in total (including direct, indirect, overhead costs).

Our collaboration agreement will provide full transparency about each partner's rights & obligations (including intellectual property rights). As part of the agreement, you will be encouraged to publish following the collaboration agreement (to be negotiated in good faith).

What are the key success criteria on which we base our selection for the best answer?

The proposal needs to be highly feasible, should be based on established and existing methods, assays and involve tools / reagents that are either available or which can be easily produced. We expect that the project will be executed in your laboratory and takes advantage of existing technologies and assays.

In addition, we are seeking research collaboration proposals that contain:

A well-structured proposal outlining a new and compelling scientific approach using BI-4286 in the context of a defined disease that matches with our in scope criteria.

The working hypothesis must be testable and distinct from those previously published. It should aim at validating the role of ALPK1 in the context of the chosen disease indication and provides a proof for target engagement that could be measured through the use of disease specific biomarkers.

Your exact funding request should be outlined in your proposal based on a well-thought-through project. The project should be structured in milestones and planned with key decision points (clear Go/No-Go criteria). The funding request for the initial milestones resulting in a Go/No-Go decision should not exceed 300,000 Euros for a maximum period of two years.

Proven track record in the required field of expertise.

Ability to implement the outlined solution as part of a scientific collaboration project with Boehringer Ingelheim including access to a wet laboratory and/or suitable animal facility.

Proposals with a realistic chance to generate tangible results within 2 years will be prioritized.

Confidential information

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.

Anticipated Project Phases or Project Plan

Phase 1	Please complete your submission by **March 10, 2026, 11:59 pm PST** at the very latest.
Phase 2	Our review of all proposals will be completed by end of May 2026, and scientists will be informed after that.
Phase 3	Start of discussions for the collaboration agreement in Q3/2026.

Submitting a collaboration proposal

Check the profile on opnMe or alternatively,

Download your submission template from the site.

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.

References

1. Hu X., Yang C., Wang P. G., Zhang G-L. ADP-heptose: A new innate immune modulator *Carbohydr Res*. **2019**, 473:123-128. DOI: 10.1016/j.carres.2018.12.011, PubMed.
2. Maubach G., Lim M. C. C., Naumann M. Discovery of biosynthetic enzymes for β -D-manno-heptoses across kingdoms: novel agonists for ALPK1/NF- κ B-dependent immune response *Signal Transduct Target Ther*. **2024**, 9(1):277. DOI: 10.1038/s41392-024-02003-y, PubMed.
3. Snelling T., Saalfrank A., Wood N. T., Cohen P. ALPK1 mutants causing ROSAH syndrome or Spiradenoma are activated by human nucleotide sugars *Proc Natl Acad Sci U S A*. **2023**, 120(50):e2313148120. DOI: 10.1073/pnas.2313148120, PubMed.