Oral SOS1::KRAS inhibitor | BI-3406

Overview

For a short period of time, we share the unprecedented, potent and selective, orally bioavailable SOS1::KRAS inhibitor BI-3406 which is suited for both *in vitro* and *in vivo* experiments for collaborative research on novel disease indications. BI-3406 inhibits the protein interaction between Son of Sevenless 1 (SOS1) and Kirsten rat sarcoma viral oncogene (KRAS) leading to a disruption of downstream signaling resulting in an anti-proliferative cytostatic effect. Funding of up to 200.000 € will be available upon request and shall be outlined in the application.

We invite scientists to submit proposals containing an *in vivo* testable disease hypothesis that can be addressed using our oral SOS1::KRAS inhibitor no later than December 13, 2019, 23.59 pm PST.

Proposals detailing new therapeutic thinking for diseases with high medical need or are aligned to the collaborative priorities for Boehringer Ingelheim's therapeutic areas (see below) have the greatest chance for selection.

Summary

BI-3406 is a protein- protein interaction (PPI) inhibitor which binds to SOS1 and inhibits its protein interaction with its downstream signaling partner KRAS. In the following we refer to it as our SOS1::KRAS inhibitor. With this molecule, we share an unprecedented, highly potent and selective tool, non-covalent and orally bioavailable compound for collaborative research on novel disease indications.

BI-3406 potently inhibits the interaction of SOS1 with RAS-GDP (IC_{50} of 5 nM). This significantly reduces formation of GTP-loaded activated KRAS. In KRAS mutant NCI-H358 cells the small molecule SOS1::KRAS inhibitor reduces pERK formation with an IC50 of 4 nM

and cellular proliferation with an IC_{50} of 24 nM in 3D assays. Our SOS1 inhibitor was found to be potent and efficacious *in vitro* in a larger number of KRASmutant tumor cell lines and patient derived tumor models where it generated a cytostatic effect. BI-3406 is well tolerated and suitable for oral *in vivo* testing in several animal species. The compound will be provided free of charge in the amount required for the experiments.

Background

Mitogen-activated protein kinase (MAPK) pathways are kinase modules that link extracellular signals to the machinery, which controls fundamental cellular processes such as growth, proliferation, differentiation, migration and apoptosis. The pathway's general structure includes a small G protein (RAS) and three protein kinases (RAF, MEK, ERK). KRAS belongs to the RAS-family of GTPases and plays a major role as the major form of RAS in human cancer.

KRAS functions as a molecular switch cycling between the GTP-bound representing the (active or "on") state and the GDP-bound- (inactive or "off") state. All RAS family members, such as KRAS, have a weak intrinsic GTPase activity and slow nucleotide exchange rates. Two classes of enzymes have evolved to facilitate cycling between the active GTP-bound state and the inactive GDP-bound form. GTPase Activating Proteins (GAPs) increase the intrinsic GTPase activity of RAS family proteins, leading to the formation of GDP bound RAS (e.g. NF1; GTP→GDP), whereas guanine nucleotide exchange factors (GEFs), such as Son of Sevenless 1 (SOS1), directly interact with KRAS and release GDP, enabling GTP binding and re-activation (GDP→GTP).

In the active or GTP-bound state, KRAS binds to its effector proteins thereby activating downstream signaling cascades such as MAPK pathway (1). In normal cells, RAS signaling is crucial for proliferation, differentiation and survival. Mutated RAS oncoproteins differ functionally from their normal counterparts resulting in hyper activation of RAS signaling.
Cancer-associated mutations in KRAS further suppress the intrinsic and GAP-induced GTPase activity leading to an increased population of signaling competent GTP loaded KRAS molecules [3, 4, 5, 6]. Tumor cells can be dependent on KRAS signaling carrying a KRAS mutation or amplification, an NF1 deletion or an upstream RTK mutation.

Hyper activation of RAS leads to oncogenic transformation of cells and is described as a driver in tumorigenesis as observed for cancers with activating KRAS mutations (2). The majority of KRAS mutant cancers are dependent on RAS/MAPK signaling (3, 4 and 5). Developing molecularly driven therapeutics to directly or indirectly block KRAS activity has proven extremely challenging due to the picomolar affinity of GDP/GTP-binding site, very slow off-rates and the lack of well-defined pockets on a flat protein::protein interaction surfaces of RAS with GEFs or GAPs. Mutations of KRAS occur in 1 out of 7 cancers reaching up to 30% in lung adenocarcinoma cases, 40% in colorectal cancer and 90% in pancreatic cancer patients (6, 7).

Selective inhibition of SOS1 significantly reduces formation of activated (GTP-loaded) KRAS and thereby inhibits downstream MAPK signaling. SOS1 needs to be recruited to the membrane where it binds to Shp2 and Grb2 to act as GEF. The inhibition led to a decreased survival rate of tumor cells carrying a KRAS mutation or amplification whereas, no effect was observed in KRAS non addicted wild-type cells [7].

BI-3406 is a small molecule that inhibits SOS1 interaction with RAS-GDP and thereby reducing formation of GTP-loaded active KRAS. Reduced amounts of KRAS-GTP levels result in reduced downstream MAPK signaling. Modulation of the conversion of inactive RAS-GDP to active RAS-GTP leads to cytostasis in cancer cells (*in vitro* and *in vivo*) carrying an activating KRAS mutation. The compound is well tolerated in mice. Twice daily oral treatment results in monotherapy in a tumor growth inhibition of approximately 60-90%. BI-3406 will have no effect on cells not addicted to RTK-RAS-MAPK signaling.

Besides KRAS mutations or amplifications several other aberrations in GTPase activating proteins (e.g. NF1) are known. Our SOS1 inhibitor has the potential to work in those areas as well (e.g. RASopathies).

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 an oral SOS1::KRAS inhibitor in a novel disease indication or beyond KRAS mutation positive tumors
- Novel innovative combination approaches for SOS1::KRAS inhibitors
- 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
- Medical need and/or alignment with the collaborative priorities for Boehringer Ingelheim's therapeutic areas

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 and show strong sensitivity following treatment with BI-3406 either in monotherapy or in combination. In addition, orphan indications 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% Breakthrough treatments for type 2 diabetes, such as pancreas recovery options
CNS diseases	Novel treatment options for neuropsychiatric diseases such as Neuropsychiatric diseases including Alzheimer's disease (e.g. cognitive impairment; non-cognitive symptoms) Schizophrenia (e.g. negative symptoms and/or cognitive impairment) Depression (e.g. treatment-resistant depression) Impulsivity disorders (e.g. substance use disorder; obsessive-compulsive disorder; borderline personality disorder).
Immunology & Respiratory	Understanding the role of KRAS signaling on immune cells (e.g. Tfh) and non-immune cells (e.g. fibroblasts) with respect to aberrant tissue remodeling (fibrosis) in indications such as. 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
Research Beyond Borders	Gene Therapy: Tissue selective AAV capsid variants (focus on eye-and liver-specificity); technology and/or AAV capsid variants which evade pre-existing immunity; expression control systems with ligands suitable for chronic administration; research and early development gene therapy projects with in vivo pre-clinical proof of concept. Regenerative Medicine: Drug-based modulation of pathways/targets involved in the stimulation of human endogenous cells for tissue regeneration to ultimately restore organ physiological functions (i.e. beta cell regeneration for T2D; hair cell regeneration for age-related hearing loss). Other diseases of interest are sarcopenia, dry AMD and osteoarthritis) Infectious Diseases: Novel approaches addressing antimicrobial resistance in bacterial and invasive fungal infections (i.e. S. aureus, A. baumannii, P. aeruginosa, M. tuberculosis and Candida spp.).Viral diseases currently lacking cure (i.e. chronic hepatitis B).

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 January 2020 and we aim to finalize our review by end of February 2020.
Phase 2 – Potential collaboration starting date Q2/Q3 2020

Submitting a collaboration proposal

- Check the SOS1::KRAS 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.