IL1RAP antibody | BI-5041

Overview

We share a highly potent and selective human IL1RAP mAb (IL1-receptor associated protein monoclonal antibody) for collaboration. Interested scientists from around the world are invited to submit testable research proposals that demonstrate that this molecule has utility in novel disease indications. We seek novel biology hypotheses for the in vitro use of our IL1RAP mAb for a human disease condition with high unmet medical need. Proposals which include primary (disease) tissues or a humanized model would provide additional attractiveness.

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 Euro will be available for each selected proposal.

Submissions for collaborations can only be considered if they arrive no later than April 8, 2020, 23.59 pm PST.

Summary

BI-5041 is a humanized monoclonal IL1RAP antibody that blocks IL1RAP interaction with the associated primary receptors, and therefore potently inhibiting signaling of IL1 family cytokines. We share this unprecedented, highly potent and selective antibody for collaborative research on novel disease indications. A negative control antibody can also be provided. Interested scientists from around the World are invited to submit testable research proposals with this molecule in novel disease indications. The compound will be provided free of charge in the amount required for the experiments and is suitable for in vitro assays and in humanized in vivo models. Based on a human efficacious dose PK/PD modeling it was calculated that BI-5041 could be considered for an i.v. schedule as part of in vivo studies.
Background

The IL1-receptor accessory protein, IL1RAP, is the co-receptor for IL1R1 (IL1R1), IL33R (IL1R4, ST2), and IL36R (IL1R6, IL1Rrp2) required for signaling of the cognate IL1 family cytokines such as, IL1 (α, β), IL33 and IL36 (α, β, γ).

The importance of IL1RAP in the signaling of the IL1 family of alarmins has been confirmed by genetic deletion of the co-receptor IL1RAP that led to a complete loss of signaling for IL1 (IL1 i.p. injection (1)); and IL33 (mast cells, (2)) as well as by transfection studies/pharmacological intervention for IL36 (3). In published literature, only a handful of IL1RAP antibodies have been described. Of note, each of these antibodies delivered only some level of bioactivity against some of the ligands, and none reached exquisite potency against all of the potential ligands IL1α, IL1β, IL33 and IL36 suggesting that the IL1RAP binding interface may differ between the different co-receptors.

IL1RAP is expected to be expressed in tissues where IL1-, IL33-, or IL36-receptors are present, such as lymph nodes (thymus, tonsil), bone marrow, brain, lung, skin, gut, liver and placenta. Myeloid leukemia stem cells in CML reportedly also express IL1RAP (4).

BI-5041 is a humanized IL1RAP antibody derived from a WT mouse immunization campaign and B cell sorting. It targets a unique epitope on IL1RAP that blocks IL1, IL33 and IL36 signaling. Inhibition of each of the cytokines that signal through IL1RAP is currently explored in clinical studies using either antibodies to the individual cytokines or to the cognate receptors, demonstrating the attractiveness of this pathway family. This antibody is not cross reactive to mouse, rat or rabbit IL1RAP. Hence, humanized models are required for in vivo studies.

BI-5041 also binds with similar affinity to the soluble ILRAP, a spliced form that may act as a natural signaling inhibitor by forming unproductive complexes with the individual primary receptors for IL1, IL33 and IL36.

Our extensive in vitro studies have demonstrated that BI-5041 exhibits cell-type specific inhibition. A summary of the cellular molecular profile of BI-5041 is presented below.
<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Cytokine Stimulation</th>
<th>Blockade by BI-5041?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Epithelium</td>
<td>IL1, IL33, IL36</td>
<td>Yes</td>
</tr>
<tr>
<td>Macrophages</td>
<td>IL1 IL36 Combination</td>
<td>Partial / Experiment Dependent</td>
</tr>
<tr>
<td>T Cells</td>
<td>IL4 IL36 Combination</td>
<td>Partial / Experiment Dependent</td>
</tr>
</tbody>
</table>

We are very interested to obtain proposals with a specific disease focus which would provide us with a scientific rationale for this cell-type specific inhibition and demonstrate the therapeutic potential of BI-5041 in human patient derived test systems.

References

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 IL1RAP antibody 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
- 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:

<table>
<thead>
<tr>
<th>Oncology and Immuno-Oncology</th>
<th>The primary focus is on solid tumors that have a high unmet medical need. In addition, orphan indications and hematological indications are also of interest.</th>
</tr>
</thead>
</table>
| 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    | 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

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 its 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 during the second half of April 2020 and we aim to finalize our review by end of May 2020.
Phase 2 – Potential collaboration starting date Q3/Q4 2020
Submitting a collaboration proposal

- Check the [IL1RAP Antibody](#) 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.