Novel NLRP3 Inhibitor for the Treatment of Inflammatory Diseases

With Potency and High Selectivity

Overview

Drug Name	BioLink2024
Description	Among inflammasome family members, the nucleotide-binding domain leucine-rich repeats family protein 3 (NLRP3) is a prime target for a variety of inflammatory diseases. BioLink2024 is a highly potent and selective oral NLRP3 inhibitor, which showed good dose-dependent anti-inflammatory response in mouse acute peritonitis model induced by lipopolysaccharide (LPS) and adenosine triphosphate (ATP). In addition, BioLink2024 demonstrated significant anti-inflammatory activity in a 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis animal model.
Target	NLRP3
Drug Modality	Small molecule
Indication	Inflammatory diseases
Product Category	Inhibitor
Mechanism of Action	Inhibition of NLRP3 inflammasome activity
Status	Preclinical
Patent	PCT filed

Collaboration Opportunity

Protheragen Inc. is actively seeking partnership for BioLink2024. Potential collaboration can be strategic alliance, licensing, or marketing agreement.
We look forward to hearing from you.

Target

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NLRP3

Introduction	Recognition of pro-inflammatory stimuli by pattern recognition receptors (PRRs) plays a key role in initiating the innate immune response. NLRP3 is a 118 kDa cytoplasmic PRR protein expressed by a variety of cells such as neutrophils, macrophages, lymphocytes, epithelial cells, and dendritic cells. The NLRP3 inflammasome complex consists of NLRP3 protein as a sensor, apoptosis-associated speck-like protein (ASC) as an adaptor, and caspase-1 as an effector. The NLRP3 inflammasome complex functions as an upstream activator of nuclear factor kappa B (NF-κB) signaling, and plays a role in the regulation of inflammation, immune response, and apoptosis.
Approved Name	NLR family pyrin domain containing 3
Official Symbol	NLRP3
Gene Type	Protein coding
Synonyms	AGTAVPRL; AVP; FCAS; FCU; NALP3; PYPAF1; MWS; CLR1.1
Ensembl	ENSG00000162711
Gene ID	114548
mRNA Refseq	NM_004895
Protein Refseq	NP_004886
OMIM	606416
UniProt ID	Q96P20
Chromosome Location	1q44

Clinical Resources

Gene Function	The NLRP3 gene encodes a pyrin-like protein containing a pyrin domain, a nucleotide-binding site (NBS) domain, and a leucine-rich repeat (LRR) motif. Mutations in this gene are associated with familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), chronic infantile neurological cutaneous and articular (CINCA) syndrome, neonatal-onset multisystem inflammatory disease (NOMID), keratoendotheliitis fugax hereditarian, and deafness, autosomal dominant 34, with or without inflammation.
Pathway	NF-κB signaling
Major Conditions	Inflammatory diseases

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Drug Modality

Small Molecule

BioLink2024 is a potent and selective NLRP3 inhibitor with a non-sulfonylurea analogue that binds directly to NLRP3 in cells. Both *in vitro* and *in vivo* experiments showed that BioLink2024 had highly specific inhibition effects against NLRP3 activation and IL-1β production.

Indication

Inflammatory Diseases

The NLRP3 inflammasome is a key component of the innate immune system and plays an important role in inflammation-related diseases such as atherosclerosis, Alzheimer's disease (AD), rheumatoid arthritis (RA), and inflammatory bowel disease (IBD) by promoting the release of IL-1β and IL-18. Activation of NLRP3 inflammasome aggravates oxidative stress and vascular endothelial dysfunction, and accelerates the pathological process of cardiovascular diseases. In RA, the deletion of NLRP3 and its downstream components significantly attenuates inflammation and cartilage destruction. In addition, in microglia of the nervous system, NLRP3 inflammasome can be activated by protein misfolding deposition or amyloid β (Aβ) aggregation to promote the occurrence and progression of neurodegenerative diseases. IBD is an idiopathic intestinal disease characterized by chronic, recurrent inflammation. Activation of NLRP3 inflammasome further enhances the inflammatory response, resulting in aggravation of colonic damage.
According to the analysis by Data Bridge Market Research, the expected CAGR of the global anti-inflammatory therapeutics market tends to be around 6.50% in the forecast period 2022-2029. The market was valued at USD 79.75 billion in 2021 and will grow to USD 132 billion by 2029. The increasing awareness of inflammatory diseases, rising prevalence of chronic diseases, and increasing aging population will lead to the growth of the market.

Mechanism of Action

Inhibition of NLRP3 Inflammasome Activity

The NLRP3 inflammasome is composed of the NLRP3 protein, procaspase-1, and the adaptor protein ASC. It plays a vital role in regulating inflammation and its aberrant activation promotes various inflammatory disorders. The activation of the NLRP3 inflammasome is a two-stage process. The first stage is the priming stage, which begins with the recognition of pathogen/damage-associated molecular patterns (PAMPs/DAMPs) by Toll-like receptors (TLRs). During this stage, TLRs recognize various stress factors and activate NF-κB signaling, leading to increased production of precursor proteins, including the NLRP3 protein, pro-IL-1β, and pro-IL-18. The second stage is the assembly stage, which begins with the assembly of the NLRP3 inflammasome. The NLRP3 protein, ASC, and procaspase-1 assemble into the mature complex, which then transforms the immature IL-1β and IL-18 into their mature forms.

NLRP3 inflammasome inhibitors are developed to suppress the activation of NLRP3 inflammasome by targeting the complex signaling pathways, including priming or assembly stage of NLRP3 inflammasome activation, and the content of K+, Ca2+, Cl- and ROS in the microenvironment, and gasdermin D (GSDMD) cleavage by activated caspase-1. Inflammasome inhibitors containing the sulfonylurea and sulfonamide moieties have been developed, most of which have a core scaffold similar to MCC950, and these inhibitors may have similar hepatotoxicity.

BioLink2024 is a non-sulfonylurea NLRP3 inflammasome inhibitor that specifically inhibits NLRP3 activation. Due to its potent biological activity and high selectivity in *in vivo* studies, BioLink2024 has potential as a therapeutic agent for inflammatory bowel disease and other NLRP3-driven diseases.

Status

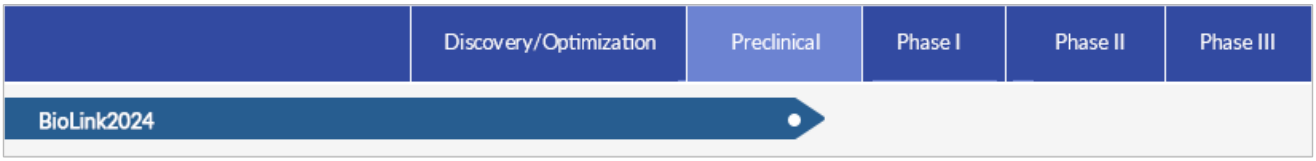
The Status of BioLink2024

Exploratory studies on a variety of disease indications are ongoing, and IND enabling studies are planned.

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