A Non-covalent BTK Inhibitor for the Treatment of B-Cell Lymphomas

Overcoming Acquired Resistance Mutation

Overview

Drug Name	BioLink2018
Description	BioLink2018 is a non-covalent, reversible Bruton tyrosine kinase (BTK) inhibitor in early clinical development for the oral treatment of B-cell lymphomas. BioLink2018 non-covalently binds to BTK to inhibit the BTK activity and is not affected by the C481S mutation. In clinical studies, BioLink2018 showed higher potency and better kinase selectivity for BTK over EGFR and other Tec family kinases than peer non-covalent reversible BTK inhibitor, indicating it may have fewer off-target side effects and a better safety profile.
Target	Bruton tyrosine kinase (BTK)
Drug Modality	Small molecule
Indication	B-cell lymphomas
Product Category	Inhibitor
Mechanism of Action	Inhibition of BTK activity by non-covalent binding
Status	Phase I
Patent	Granted

Collaboration Opportunity

Protheragen Inc. is actively seeking partnership for BioLink2018. Potential collaboration can be strategic alliance, licensing, or marketing agreement.
We look forward to hearing from you.

Target

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Bruton Tyrosine Kinase (BTK)

Introduction	Bruton tyrosine kinase (BTK) is a Tec family cytoplasmic tyrosine kinase. BTK is a protein of 659 amino acid and contains a single kinase domain and multiple protein-protein interaction domains: an NH2-terminal pleckstrin homology (PH) domain, which binds to phosphatidylinositols during the process of membrane localization, is followed by Src homology 2 (SH2), Src homology 3 (SH3), and proline-rich domains that regulate binding to other cellular signaling molecules. BTK is a key component of the B cell receptor (BCR) signaling pathway and is critical for normal B cell development, differentiation, proliferation, and survival. BCR signaling pathway genes have been shown to be constitutively increased in B cell malignancies including chronic lymphocytic leukemia, and these diseases have been shown to be highly sensitive to therapeutics targeting BTK.

Approved Name	Bruton tyrosine kinase
Official Symbol	BTK
Gene Type	Protein coding
Synonyms	Bruton's tyrosine kinase; AGMX1; IMD1; ATK; XLA; PSCTK1
Ensembl	ENSG00000010671
Gene ID	695
mRNA Refseq	NM_000061
Protein Refseq	NP_000052
OMIM	300300
UniProt ID	Q06187
Chromosome Location	Xq22.1

Clinical Resources

Gene Function	The protein encoded by this gene plays a crucial role in B-cell development. Mutations in this gene cause X-linked agammaglobulinemia (XLA) type 1, which is an immunodeficiency characterized by the failure to produce mature B lymphocytes, and associated with a failure of Ig heavy chain rearrangement. Alternative splicing results in multiple transcript variants encoding different isoforms.
Major Conditions	Cancer

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Drug Modality

Small Molecule

BioLink2018 is an orally bioavailable reversible BTK inhibitor that is expected to overcome acquired resistance developed from marketed covalent BTK inhibitors in various B-cell lymphomas. In preclinical studies, BioLink2018 showed potential advantages such as overcoming drug resistance, improved target selectivity, strong anti-tumor efficacy, and favorable safety.

Indication

B-cell Lymphomas

B cells are one of two major types of lymphocytes that develop in adult bone marrow and in the fetal liver of mammals. B cells express surface immunoglobulins, which act as specific antigen receptors. B cell activation is dependent on both recognition of a specific antigen and T cell help. Activated B cells divide and differentiate into either memory cells or plasma cells. B-cell lymphomas are malignant neoplasms that arise by different stages of B-cell differentiation, with a broad spectrum from small- to large- cell types and from low to high clinical behavior. Precursor B-cell lymphomas, including lymphoblastic lymphomas and leukemia, derive from progenitor cells that have not been activated and are still in the undifferentiated stage. All other lymphomas representing different stages of differentiation are included in the category of mature B-cell lymphomas.
B-cell lymphomas are the main type of non-Hodgkin lymphoma (NHL) and can be classified according to their rate of growth as low grade (indolent) or high grade (aggressive). Indolent NHLs include follicular lymphoma, marginal zone lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma, and lymphoplasmacytic lymphoma. Aggressive forms include diffuse large B-cell lymphoma (DLBCL), transformed follicular lymphoma, Burkitt lymphoma, and lymphoblastic lymphoma. Mantle cell lymphoma originating in naive B-cell is unique in that it has features of both indolent and aggressive disease. In general, indolent forms are highly treatable, while some aggressive forms such as DLBCL are potentially curable.

Mechanism of Action

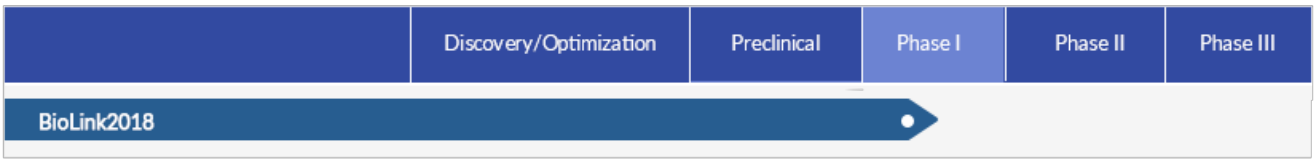
Inhibition of BTK Activity by Non-covalent Binding

The development, differentiation, proliferation, and survival of B lymphocytes are controlled by biochemical signals transmitted by the B-cell antigen receptor (BCR). BTK is commonly overexpressed in various B-cell lymphomas and is a key signaling molecule in BCR signal transduction. In addition, it is also identified as a dual-function regulator of apoptosis. Inhibition of the BTK activity can prevent B-cell activation and B-cell-mediated signaling, thereby inhibiting the growth of malignant B cells in a number of blood malignancies.
BioLink2018 is an oral inhibitor that binds noncovalently to BTK, including the C481S mutant form. C481S mutation is a acquired mutation in the BTK active site in which cysteine is substituted for serine at residue 481. This mutation is the most common resistance mechanism in patients whose disease progresses on covalent BTK inhibitors. BioLink2018 is not affected by the C481S mutation.

Status

The Status of BioLink2018

BioLink2018 is under phase I clinical evaluation for the treatment of various B-cell lymphomas such as mantle cell lymphoma, lymphoplasmacytic lymphoma, follicular lymphoma, and diffuse large B-cell lymphoma.



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