A First-in-class Molecular Glue Degrader for the Treatment of Cancers

Overview

Drug Name	PPM-100
Description	PPM-100 is a molecular glue degrader specifically engineered to degrade DNA-binding protein Ikaros (IKZF1) and zinc finger protein Aiolos (IKZF3). It is being developed in preclinical studies for the treatment of blood cancers and solid tumors.
Target	IKZF1/3
Drug Modality	Molecular glue degrader
Indication	Blood cancers and solid tumors
Product Category	Signal transduction modulators
Mechanism of Action	Degradation of IKZF1 and IKZF3
Status	Preclinical
Patent	Granted

Collaboration Opportunity

Protheragen Inc. is actively seeking partnership for PPM-100. Potential collaboration can be strategic alliance, licensing, or marketing agreement.We look forward to hearing from you.

Target

IKZF1

Introduction	DNA-binding protein Ikaros, also known as IKAROS family zinc finger 1 (IKZF1), is a protein encoded by the IKZF1 gene in humans. IKZF1 is a member of the lymphoid-restricted zinc finger transcription factor family that regulates lymphocyte differentiation and proliferation. It regulates transcription through chromatin

	remodeling and epigenetic modification, and affects signaling pathways critical for lymphocyte differentiation, such as PI3K/AKT, IL-7 signaling, and integrin-dependent cell survival.
Approved Name	IKAROS family zinc finger 1
Official Symbol	IKZF1
Gene Type	Gene with protein product
Synonyms	hlk-1; LyF-1; Hs.54452; IKAROS; PPP1R92
Ensembl	ENST00000331340.8
Gene ID	10320
mRNA Refseq	NM_006060
Protein Refseq	NP_006051.1
OMIM	603023
UniProt ID	Q13422
Chromosome Location	7p12.2

IKZF3

Introduction	IKAROS family zinc finger 3 (IKZF3), also known as Aiolos, is also a member of the lymphoid-restricted zinc finger transcription factor family that is involved in the regulation of lymphocyte development. IKZF3 is important in the regulation of B lymphocyte proliferation and differentiation. IKZF3 participates in chromatin remodeling. Regulation of gene expression in B lymphocytes by IKZF3 is complex as it appears to require the sequential formation of IKZF1 homodimers, IKZF1/3 heterodimers, and IKZF3 homodimers.
Approved Name	IKAROS family zinc finger 3
Official Symbol	IKZF3
Gene Type	Gene with protein product
Synonyms	Aiolos
Ensembl	ENST00000346872.8
Gene ID	22806
mRNA Refseq	NM_012481
Protein Refseq	NP_036613.2
OMIM	606221
UniProt ID	Q9UKT9
Chromosome Location	17q12-q21.1

Drug Modality

Molecular Glue Degrader

PPM-100 is a unique molecular glue that is expected to possess superior pharmacological properties comparing to PROTACs with smaller molecule weight, better oral bioavailability, higher membrane permeability and better cellular uptake. PPM-100 is one of PPM molecular glue degraders with pleiotropic activities that are proved to selectively kill several types of cancer cells, stimulate T and NK cell activation, and downregulate synthesis of inflammatory mediators. These PPM molecular glue degraders have great potentials for immunotherapy of cancers, chronic inflammation, and other conditions as a monotherapy or in combinations with other agents.

Advantages of PPM Molecular Glue Degraders

	PROTACs	Molecular glues	PPM Molecular glues
Features	bivalent	monovalent	monovalent
Links	yes	no	no
MW (Dalton)	700-1000	<500	<500
Lipinski's rule of five	defy	within	within
Target protein	predictable	to be determined	**clear enzymes**
Degradation of target protein	yes	yes	yes
Inhibition of target protein activity	unclear	unclear	**yes**
Binding pocket	required	not required	required
Binding affinity	strong affinity to E3 ligase and the target protein; two ligands are connected by a linker	weak affinity for either E3 ligase or target protein is needed; display an event driven	weak affinity for either E3 ligase or target protein is needed; display an event driven

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		catalytic MoA	catalytic MoA
Potential for solid tumors	yes/no	yes/no	**yes**
Immunomodulation	unclear	unclear	**yes**
Anti-inflammation	unclear	unclear	**yes**

Indication

Blood Cancers and Solid Tumors

Molecular glues are a unique type of small molecular compounds that degrade, stabilize, or activate target proteins upon binding, thereby altering protein-protein interactions. Small-molecule molecular glues have great potential applications in the treatment of human diseases, including cancers. Molecular glue can target essentially any protein that plays a key role in the etiology of cancers, and among these protein targets there are many that were previously considered undruggable. Molecular glue recruits the target protein to an enzyme that for proteasomal degradation and they may be a viable therapeutic alternative for many cancer-related proteins that are not well targeted by conventional small molecules.Cancers are divided into solid tumors and blood cancers and most of them are lethal. Solid tumors appear to be more biologically complex than blood cancers, with redundant pathways and drug-delivery challenges. Solid tumors are formed by the accumulation of abnormal tissues that do not contain any fluid or cysts and are classified as benign or malignant. The solid tumor market was valued at USD 209.61 billion in 2021 and is expected to reach USD 901.27 billion by 2029, registering a CAGR of 20.0% during the forecast period from 2022 to 2029. Unlike solid tumors that arise from organs or tissues, blood cancers (also known as hematologic tumors) originate from blood cells. It is predicted that there will be about 1.85 million new cases of hematological cancers worldwide in 2040, including 918,872 cases of lymphoma, 656,345 cases of leukemia, and 275,047 cases of myeloma. The blood cancer market was valued at USD 43.71 billion in 2021 and is expected to reach USD 89.68 billion by 2029, registering a CAGR of 9.40% during the forecast period 2022-2029.

Mechanism of Action

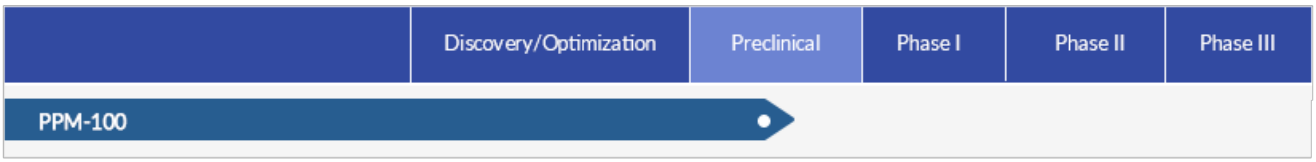
Degradation of IKZF1 and IKZF3

KZF1 and IKZF3 are lymphocyte transcription factors that are key regulators of malignant plasma cell survival in multiple myeloma. In addition, they are of great importance in the occurrence, metastasis, and prognosis of other hematological malignancies and solid tumors. Since IKZF1 and IKZF3 lack druggable binding pockets, they are considered as undruggable target proteins. Acting as molecular glue, PPM-100 can promote ubiquitination and degradation of IKZF1 and IKZF3. PPM-100 is expected to possess superior pharmacological properties comparing to PROTACs with smaller molecule weight, better oral bioavailability, higher membrane permeability, and better cellular uptake.

Status

The Status of PPM-100

PPM-100 is under preclinical development. In vitro, PPM-100 showed cytotoxicity on a variety of cancer cells including human myeloma cells, prostate cancer cells, breast cancer cells, renal cancer cells, and colorectal cancer cells, as well as caused the degradation of c-MYC in cancer cells, the decrease of proinflammatory cytokines, the increase of T cells activation and so on.



Data

Disruption of Cell Cycle Progression in OCI-Ly3 Human Lymphoma Cells

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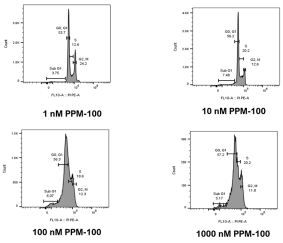
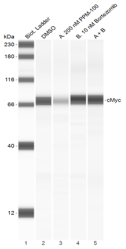


OCI-Ly3 non-Hodgkin's lymphoma cells were treated with PPM-100 for 24 hours. The results showed the cell cycle progression was disrupted.



Degradation of c-MYC in SKBR3 Human Breast Cancer Cells

SKBR3 breast cancer cells were treated with PPM-100 overnight. As shown, PPM-100 caused the degradation of c-MYC (a master regulator of cancer cell metabolism) in the SKBR3 cells.

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