A TEAD-YAP Interaction Inhibitor for the Treatment of Advanced Solid Tumors

Overview

Drug Name	PKY001
Description	The small molecule compound PKY001 is a direct YAP-TEAD interaction inhibitor that acts on the Hippo signaling pathway. It is being developed to treat advanced solid tumors caused by abnormalities in the Hippo signaling pathway, such as NF2-deficient malignant pleural mesothelioma, Hippo mutation NSCLC, or tumors with YAP/TAZ fusion such as epithelioid hemangioendothelioma.
Target	TEAD/YAP transcription complex
Drug Modality	Small molecule
Indication	Advanced solid tumors with abnormal Hippo signaling pathway
Product Category	Oncology
Mechanism of Action	Blocking the interaction between TEAD and YAP
Status	IND (NMPA)
Patent	Granted or filed

Collaboration Opportunity

Protheragen Inc. is actively seeking partnership for PKY001. Potential collaboration can be strategic alliance, licensing, or marketing agreement.
We look forward to hearing from you.

Target

TEAD/YAP Transcription Complex

The Hippo pathway is a highly conserved signaling pathway, which plays an important role in regulating cell

proliferation and apoptosis, and it is dysregulated in a number of diseases such as tumors, fibrosis, and neurodegenerative diseases. In many solid tumors including lung cancer, breast cancer, etc., mutations in the Hippo signaling pathway of related proteins, such as NF2, LATS1/2, and FAT1, result in the blockage of the degradation pathway of YAP/TAZ through phosphorylation. Excess YAP/TAZ enters the nucleus from the cytoplasm to control the expression of the key genes related to the growth of the cells by binding to the TEAD proteins and thus promoting the proliferation of tumor cells.

Many solid tumors are characterized by high levels of expression of YAP/TAZ transcription factors. For example, YAP/TAZ is overexpressed in 19% of uterine squamous cell carcinomas and 15% of esophageal squamous cell carcinomas. In addition, abnormalities in the Hippo signaling pathway have been found in patients with tumors that have developed resistance to certain drug-targeted therapies, such as EGFR inhibitors or KRAS G12C inhibitors, suggesting that the abnormalities in the Hippo signaling pathway may be one of the mechanisms by which tumors develop resistance to targeted oncological therapies.

Drug Modality

Small Molecule

Hippo pathway is well known for its role in cancer development. PKY001 is a small molecule inhibitor that directly blocks YAP/TAZ-TEAD interaction to act on the Hippo signaling pathway. In preclinical studies, PKY001 showed good oral bioavailability and high target specificity. Dose-dependent anti-tumor growth inhibition was demonstrated in tumor models with Hippo dysregulation.

Indication

Solid Tumors

Aberration of the Hippo pathway is associated with the hallmarks of oncogenesis, including induction of excessive proliferation, cell invasion, and metastasis, as well as a role in mechanisms of cancer cell maintenance and chemotherapy resistance. Many cancers carry Hippo mutations such as FAT1 mutation,

LATS1 mutation, and NF-2 deficiency. For example, FAT1 mutations occur in about 29% and 57% of patients with head and neck squamous cell carcinoma (HNSCC) and non-small cell lung cancer (NSCLC), respectively. In NSCLC, Hippo mutations have also been found in patients with tumors that have developed resistance to certain drug-targeted therapies.

In vitro cell assays, PKY001 inhibited the growth of many NSCLC and HNSCC tumor cell lines. Studies in xenograft mouse tumor models showed that PKY001 could improve antitumor activity and mouse survival when combined with EFGR inhibitors. Therefore, PKY001 has the potential as a monotherapy or in combination with existing targeted therapies to treat patients refractory to current targeted therapies due to Hippo signaling abnormalities.

Mechanism of Action

Blocking the Interaction Between TEAD and YAP

The Hippo signaling pathway is a crucial regulatory pathway impacting diverse biological processes. Through a series of kinase cascade reactions, LATS1/2 kinases are activated, which phosphorylate YAP/TAZ. The binding of YAP/TAZ transcriptional co-activators to TEAD proteins represents the core mechanism by which the Hippo pathway regulates the expression of multiple genes mediating various cellular functions. When the Hippo pathway is inactivated or inhibited, YAP/TAZ remain unphosphorylated, translocate into the nucleus, and interact with TEAD to activate gene expression associated with cell proliferation, survival, and stemness, thereby promoting tumorigenesis and progression. Dysregulation of the Hippo pathway is frequently observed in solid tumors that exhibit hyperproliferation, drug resistance, or immune evasion. Consequently, blocking Hippo-mediated transcriptional activation, particularly the interaction between YAP/TAZ and TEAD, has emerged as an attractive therapeutic strategy for treating advanced solid tumors with Hippo pathway dysregulation. PKY001 binds to TEAD proteins and directly disrupts their interaction with YAP/TAZ, thereby preventing activation of downstream oncogene expression. By inhibiting oncogene expression, PKY001 reduces cancer cell proliferation rates while diminishing metastatic potential.

Status

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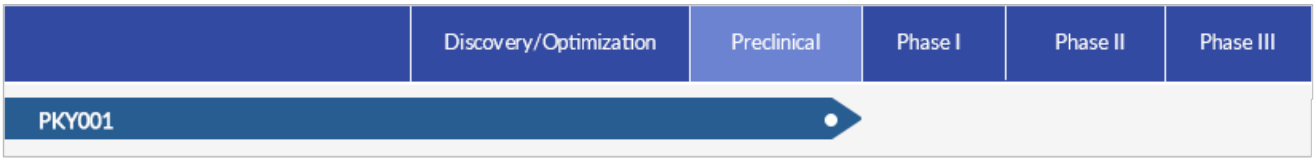
The Status of PKY001

PKY001 has obtained IND approval in China, and the IND application in the United States is currently underway.



Data

Preclinical Efficacy and Safety Studies	• PKY001 demonstrated dose-dependent inhibition of tumor growth in Hippo dysregulated tumor models. • PKY001 showed reasonable safety profiles in rats and beagle dogs with therapeutic window of about 7-fold. The estimated effective dose in humans ranges from a minimum of 50mg to a maximum of 450mg.
Key Findings and Conclusions	• PKY001 showed potential as a monotherapy in mesothelioma models. • Combining PKY001 with an EGFR inhibitor or a G12C inhibitor improved efficacy and prolonged antitumor activity in NSCLC tumor models.

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