A Potential Best-in-class pan-RAS(ON) Inhibitor

Overview

Drug Name	PTH-0317
Description	Mutations in RAS proteins (including KRAS, HRAS and NRAS) are common in solid tumors. These mutations prevent the hydrolysis of GTP, keeping RAS constantly in an active state mediated by GTP, thereby promoting uncontrolled cell proliferation and survival. PTH-0317 is a potent and orally bioavailable pan-RAS inhibitor that is being developed for the treatment of solid tumors. PTH-0317 targets the active GTP-bound (ON) state of RAS proteins and has potential to overcome limitations of KRAS inhibitors and broaden the therapeutic landscape.
Target	RAS proteins
Drug Modality	Small molecule
Indication	Solid tumors
Product Category	Signal transduction modulators
Mechanism of Action	Disrupting the interaction between RAS proteins and their effectors
Status	IND-enabling
Patent	Granted

Collaboration Opportunity

Protheragen Inc. is actively seeking partnership for PTH-0317. Potential collaboration can be strategic alliance, licensing, or marketing agreement.
We look forward to hearing from you.

Target

RAS Proteins

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RAS proteins belong to a subgroup of a large family of membrane-localized small GTPases. The Ras superfamily includes the Ras, Rho, Arf, Rab, and Ran families. These serve as molecular switches for a wide variety of signal pathways that control cytoskeletal integrity, proliferation, cell adhesion, apoptosis and cell migration via activation of several pathways such as mitogen-activated protein (MAP) kinases. RAS proteins are low-molecular-weight GDP/GTP-binding guanine triphosphatases. There are three main isoforms of RAS proteins, namely HRAS, NRAS, and KRAS, which are universally expressed in almost all types of cells.
In normal cells, a balanced cycle of GTP and GDP through the inherent GTPase activity of RAS controls RAS-mediated signal transduction. However, mutations in the RAS gene abrogate this GTPase activity and disrupt the cycle of GTP and GDP, causing the protein to remain in a continuous "on" state. This leads to excessive activation of RAS-driven signals in the cells, promoting cancer and developmental defects. Mutations in RAS make significant contributions to cancer. Therefore, effective pharmacological targeting of RAS(ON) should prove effective for anticancer treatment.

Drug Modality

Small Molecule

PTH-0317 is a potential best-in-class pan-RAS inhibitor with outstanding high and broad-spectrum in vitro potency. In cell lines with KRAS mutations, its inhibitory effect on cell growth was significantly stronger than that of another small molecule inhibitor under clinical development. In addition, PTH-0317 exhibited a very significant inhibitory effect on ERK phosphorylation.

Indication

Solid Tumors

RAS gene mutations are implicated in a variety of cancers, and the main types of cancer include pancreatic cancer, colorectal cancer, lung cancer, melanoma, etc. Among the three RAS genes, KRAS mutations are the most frequently mutated within the RAS family, and are considered to be the primary driving factor in many

types of cancers. These mutations are involved in tumor development, metastatic progression and drug resistance.

Pancreatic Cancer	Pancreatic cancer is one of the most lethal malignancies, with a five-year survival rate of less than 10%. The Global Cancer Observatory of the International Agency for Research in Cancer (IARC) forecasts that by 2040, a 61.7% increase is expected in the total number of pancreatic cancer cases globally. Mutated RAS oncogenes are frequently detected in pancreatic tumor cells. The KRAS oncogene pathway, which is upregulated in 80- 85% of pancreatic cancers, is one of the potential targets for the treatment of pancreatic cancer. At the molecular level, KRAS oncogene mutations are reported in approximately 93% of pancreatic ductal adenocarcinomas.
Colorectal Cancer	Colorectal cancers are highly heterogeneous with respect to their aggressiveness, rate of progression and malignant potential. Most of colorectal cancers are classified as adenocarcinomas, and other less common types of colorectal cancers include squamous cell carcinoma, adenosquamous carcinoma, spindle cell carcinoma, and undifferentiated carcinoma. The global prevalence of colorectal cancer in 2020 was estimated at over 5.25 million, according to Globocan, with 1.9 million new cases reported that year. Around 40-50% of colorectal cancers exhibit mutations in KRAS or NRAS, especially in advanced stages.
Lung Cancer	According to the IARC, lung cancer is the malignancy of highest impact among men and women globally, both in terms of the total number of individuals it affects and the total number of resulting deaths. Based on data from the Globocan 2008 database and assuming that incidence rates remain stable over time, by 2030 the rate could reach nearly 2.9 million per year due to population growth alone. Changes in the KRAS gene are found in approximately 27% of in smokers with adenocarcinoma, and the prevalence of these changes also varies across different countries.

Mechanism of Action

Disrupting the Interaction Between RAS Proteins and Their Effectors

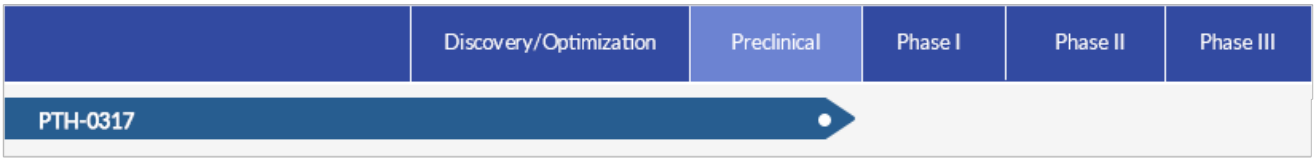
HRAS, KRAS, and NRAS genes encode small GTPases, which act as molecular switches and regulate cell

growth, differentiation, and survival through pathways such as MAPK/ERK and PI3K/AKT. RAS proteins toggle between active (GTP-bound) and inactive (GDP-bound) states to transmit signals from surface receptors. RAS mutations cause constitutive activation and oncogenic signaling. The most common missense mutations in cancer-related RAS genes are single amino-acid substitutions at three hotspots: glycine-12 (G12), glycine-12 (G13), and glutamine-61 (Q61). Mutation types and incidence vary from one cancer to another.
PTH-0317 is a potent and orally bioavailable small molecule inhibitor. This compound binds to the intracellular chaperone protein cyclosporin A (CypA) to form a binary complex with high affinity for active RAS proteins. The formation of the ternary complex disrupts the interaction between RAS and its effectors, thereby inhibiting downstream signaling. As a pan-RAS inhibitor, PTH-0317 targets different RAS isoforms and has potential to overcome certain limitations of KRAS inhibitors, thereby broadening the therapeutic landscape.

Status

The Status of PTH-0317

PTH-0317 demonstrated superior potency across various mutant KRAS cell lines and showed acceptable selectivity for wild-type KRAS cell lines. Moreover, in various CDX models, compared with other RAS inhibitors under development, lower doses of PTH-0317 achieved comparable tumor regression effects and showed higher exposure level, longer T1/2, and preferential distribution in tumor tissues.



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