A Novel Oral Proteasome Inhibitor for the Treatment of Multiple Myeloma

With Great Inhibitory Activity Against Proteasome

Overview

Drug Name	FHND91
Description	FHND91 is a novel N-capped dipeptidyl boronic acid proteasome inhibitor that is entirely converted into active form under physiological conditions. The proteasome is a key component of the ubiquitin-proteasome pathway (UPP) and has emerged as a validated target of multiple myeloma therapeutics. FHND91 is a selective oral proteasome inhibitor that binds irreversibly to the β5 submit of the 20S proteasome to exert anti-cancer effects. FHND91 is under development in the phase I/II clinical trial for the treatment of patients with relapsed or refractory multiple myeloma.
Target	Proteasome
Drug Modality	Small molecule
Indication	Multiple myeloma
Product Category	Inhibitor
Mechanism of Action	Selective inhibition of proteasome catalytic subunits
Status	Phase I (NMPA)
Patent	Granted

Collaboration Opportunity

Protheragen Inc. is actively seeking partnership for FHND91. Potential collaboration can be strategic alliance, licensing, or marketing agreement.

Target

E-mail: inquiry@protheragen.com

www.protheragen.com

101-4 Colin Dr, Holbrook, NY 11741, USA

Proteasome

Proteasome is a multicatalytic protease complex that widely exists in the nucleus and cytoplasm of all eukaryotic cells. The proteasome functions as an ATP-dependent degradation of intracellular proteins, and its specificity depends on interactions only with the proteins that are labelled by polyubiquitin chain or contain a specific amino acid sequence. Human 26S proteasome consists of 20S proteolytic core region and 19S regulatory particle. The 20S proteasome is an abundant, barrel-shaped molecule consisting of four highly homologous rings that enclose a central catalytic chamber with proteolytic active sites. Each ring contains seven subunits α and β. The two outer α-rings surround a small opening that only the denatured polypeptide substrate can pass through, while the two middle β-rings contain multiple proteolytic sites that function together to degrade the protein.

The proteasome plays an important role in the ubiquitin-protein pathway (UPP), which is a key pathway for intracellular protein degradation, regulation of antigen presentation, cell cycle, NF-kB metabolism, etc. The process of ubiquitination is divided into three steps regulated by ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2) and ubiquitin ligase (E3), in which E1 activates ubiquitin, E2 accepts the transfer of activated ubiquitin, and finally E3 selectively recognizes the substrate protein. Abnormal UPP is closely related to many diseases, such as autoimmune diseases, inflammation, and tumors. In malignant cells, UPP is often overexpressed due to excessive degradation needs caused by too many misfolded proteins. Previous studies have indicated that cancer cells rely heavily on proteasomes to meet the demand for turnover and are therefore more sensitive to proteasomal inhibition than normal cells. Therefore, the proteasome become a promising target for the treatment of many types of cancer.

Drug Modality

Small Molecule

FHND91 is a novel N-capped dipeptidyl boronic acid proteasome inhibitor with high selectivity and irreversibility against β5 of 20S proteasome. FHND91 is 100% converted in aqueous solution to active molecules and results in tumor cell death through endoplasmic reticulum stress-dependent and mitochondria-mediated pathways.

Indication

Multiple Myeloma

Multiple myeloma is a B-cell-dependent hematological malignancy caused by excessive clonal proliferation of terminally differentiated plasma cells in bone marrow. Abnormal myeloma cells produce a mutated form of immunoglobulin protein called M-protein, which accumulates in tissues and blood vessels. The characteristic features of myeloma include increased plasma cells in the bone marrow and extramedullary sites, elevated monoclonal M-protein in serum and urine, osteolytic bone lesions, renal insufficiency, anemia, and immunodeficiency. Multiple myeloma is the third most common hematologic malignancy among all hematologic malignancies diagnosed worldwide. According to global cancer registry data, there were approximately 176,400 new cases of multiple myeloma worldwide in 2020, with an age-standardized incidence rate of 1.78 cases per 100,000 population.

Multiple myeloma is a highly treatable but ultimately incurable neoplastic disorder. In patients who are eligible for autologous stem cell transplantation (ASCT), drugs are administered as induction and maintenance therapy. In those who are not eligible for ASCT, drug therapy constitutes the backbone of treatment. The availability of proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, and histone deacetylase inhibitors has greatly advanced the treatment and improved the survival of patients with multiple myeloma. Proteasome inhibition is a crucial therapeutic strategy in the treatment of multiple myeloma.

Mechanism of Action

Selective Inhibition of Proteasome Catalytic Subunits

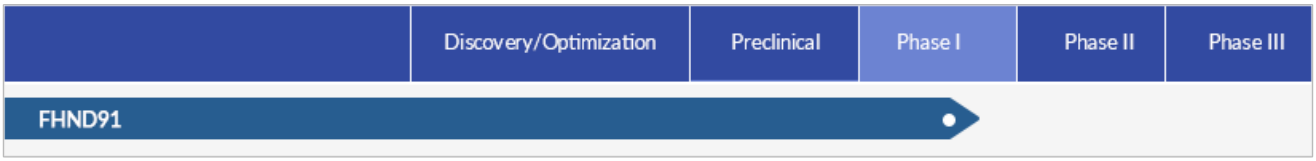
The proteasome is an enzyme complex within the cell responsible for breaking down proteins that have been marked for removal by the attachment of a tag called ubiquitin. The ubiquitin-proteasome pathway (UPP) plays an essential role in regulating the concentration of specific proteins inside the cell, thereby maintaining homeostasis, the natural tendency of the cell to remain stable. In multiple myeloma cells, large amounts of monoclonal proteins are produced and secreted. By inhibiting proteasome function, misfolded or unfolded proteins are accumulated in the endoplasmic reticulum (ER), which is known as ER stress. ER stress leads to activate pro- and anti-proliferative signals, disrupts cell cycle regulation, activates apoptotic pathways, and

ultimately results in cancer cell death. In addition, proteasome inhibitors inhibit the binding to stromal cells and the production of growth and survival factors by multiple myeloma cells in the bone marrow.
FHND91 is a selective oral proteasome inhibitor that binds irreversibly to the β5 submission of the 20S proteasome to exert anti-cancer effects. FHND91 leads to the accumulation of ubiquitination proteins, resulting in G2/M phase arrest, down-regulation of NF-κB expression, and tumor cell apoptosis through ER stress-dependent and mitochondria-mediated pathways, and ultimately tumor cell death. Compared with Bortezomib, FHND91 showed stronger selective inhibition of proteasome catalytic subunits and fewer off-target effect *in vitro*.

Status

The Status of FHND91

Patents for the compound have been approved in China, United States, Australia, and have been applied in Europe, Japan, South Korea, and Canada.



Data

***In Vitro* and *In Vivo* Activity**	*In vitro*, FHND91 showed potent inhibitory activity against proteasomes and cell lines at the nanomolar level. Compared with Ixazomib, FHND91 showed better antitumor activity and lower application dose. FHND91 exhibited significant *in vivo* antitumor activity in RPMI8226 PDX model and protected bone parenchyma from invasion and destruction by multiple myeloma cells in the rabbit bone mouse model inoculated with myeloma cells from multiple myeloma patients.

Clinical Safety	In the clinical trial, 14 subjects have been enrolled (0.4 mg/1, 0.8 mg/3, 1.4 mg/3, 2.0 mg/5, 2.8 mg/2, 3. 6 mg/0). No dose limiting toxicities (DLT) or drug related serious adverse events (SAE) were observed in the subjects. FHND91 exhibited a larger safety window compared with Ixazomib. The expansion trial is being performed at a dose of 2.0 mg.