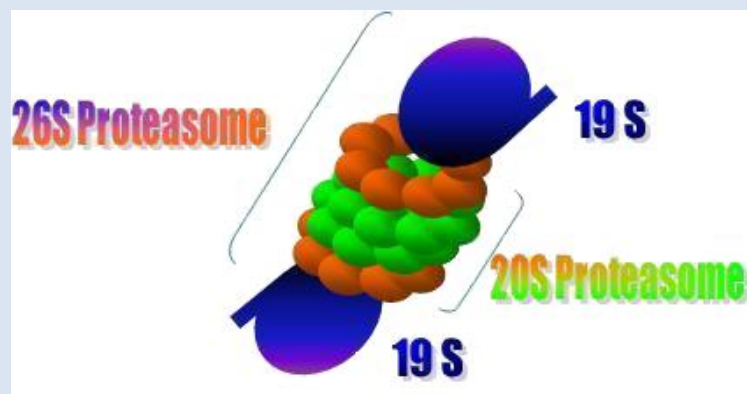


Proteasome Inhibitors, Novel Therapeutic Drugs for Cancer and Immune Disorders



APPLICATIONS

- To inhibit malignant cell proliferation.
- To repress undesirable overactive immune responses.

ADVANTAGES

- LGP07154 is a small synthetic molecule.
- Velcade, a proteasome inhibitor, has been validated and approved by the FDA for treatment by i.v. admin. of multiple myeloma and mantle cell lymphoma.
- LGP07154 is available in both oral and i.v. formulations, offering a new mode of administration.

INTELLECTUAL PROPERTY

US patent filed
Q3 2009

BACKGROUND Proteasomes are essential for intracellular protein degradation. For fast growing cells and activated lymphocytes, proteasome inhibition results in growth inhibition and apoptosis. Resting cells are much less sensitive to proteasome inhibition via apoptosis induction. This differential cell susceptibility provides a therapeutic window to kill fast growing cells, such as tumor cells and lymphoblasts, without harming most somatic cells. Proteasome inhibitors can be used to treat cancers and immune disorders.

TECHNOLOGY Dr. Wu and the Chinese National Center for Drug Screening (CNCDS) in Shanghai, have screened 45,000 small molecule compounds to identify novel proteasome inhibitors. The screening and subsequent functional studies resulted in 9 lead compounds. Further lead optimization by medicinal chemistry led to the synthesis of a novel compound, LGP07154, which has an

enzymatic IC₅₀ of 16 nM. This molecule has a low molecular weight (500 Daltons) and its structure is resistant to degradation by digestive tract enzymes, thus it can be administered orally.

RESULTS Lead compounds were identified using enzymatic assays and in vitro biological assays. Their acute toxicity was assessed using unstimulated mouse thymocytes. Among the compounds tested, 4 drugs induced substantial cell death at a concentration 2-3 fold above the IC₅₀ of T-cell proliferation. Twenty derivatives were synthesized based on the structure of the best lead and a compound with superior IC₅₀ was identified and further characterized.

In comparison with Velcade™, a competitive inhibitor of proteasome proteases, the novel proteasome inhibitors have similar but not identical activities.