Aspartic Proteases Inhibitors: Implications in Drug Development

Human immunodeficiency virus (HIV), the causative agent of the acquired immunodeficiency syndrome (AIDS), infects a human cell and uses proteins and chemicals inside that cell to multiply. HIV-1 Protease is an enzyme that HIV needs to make new viruses. Protease inhibitors (PIs) block the protease enzyme. When protease is blocked, the production of immature non-infectious viral particles is formed demonstrating the function of this enzyme is essential for proper virion assembly and maturation. HIV-1 protease belongs to a group of proteases termed as aspartic proteases. Aspartic proteases are involved in a great variety of physiological and pathophysiological functions and include the mammalian pepsins, chymosins, cathepsins and renins. They have evoked tremendous attention because of their significant role in human diseases like Alzheimer’s disease, malaria, and candidal infections. In recent years, the introduction of highly active antiretroviral therapy (HAART) has dramatically decreased the mortality due to HIV. The HAART regimen combines three or more different drugs including a protease inhibitor. Presence of protease inhibitors in HAART reduced viral load in HIV patients. There are very few approved protease inhibitors and challenge lies in identifying more protease inhibitors that can be combined with drugs.

Dr. Mala Rao and her research team at National Chemical Laboratory (NCL), Pune have isolated a bacterium (Bacillus sp.) that lives under extreme environmental condition and produces an aspartic protease inhibitor (ATBI). ATBI has been characterized for its inhibition against HIV-1 protease, pepsin, and the protease from the fungus Aspergillus saitoi. The inhibitor is found to be a hydrophilic peptide with a molecular mass of 1147 Da. Sequence homology exhibited no similarity with the known peptidic inhibitors of HIV-1 protease. Investigation of the kinetics of the enzyme-inhibitor interactions revealed that ATBI is a non-competitive and tight binding inhibitor of HIV-1 protease. The inhibitory action of ATBI on HIV infection in cell cultures to understand the precise mechanism of action is in progress. Based on the sequence of inhibitor, synthetic peptide had been made and is being evaluated for its potency.

ATBI showed effective inhibition against the phytopathogenic and saprophytic fungi. The inhibitor was found very effective against the human pathogenic yeast such as Candida. kefyr and C. krusei. The efficacy of inhibitor was evaluated in animal model infected with C. albicans and a significant reduction in the C. albicans cell count per gram of kidney tissue was observed. ATBI is also a potent inhibitor of xylanase an enzyme that deconstructs plant structural material by breaking down hemicellulose, a major component of the plant cell wall. Plant cell walls are necessary to maintain physical integrity and are a barrier against invasion of pathogens. Antixylanolytic activity of ATBI led NCL scientists to envisage a paradigm shift in the concept of fungal growth inhibition. The research team also established the bifunctional nature of an aspartic protease inhibitor pepstatin using a glycosidase. Currently investigations are on to exploit the antifungal property of the inhibitor against plant diseases.

NCL scientists have also isolated and purified several other protease inhibitors from different natural sources. Currently, ATBI and the other purified inhibitors are being studied as a lead molecule for designing potent inhibitors.


US patent No. 6,514,748 (2003): J.V.Vernekar, M.S.Ghatge, Mala Rao, V.V.Deshpande, Strain of Streptomyces for the preparation of an alkaline protease inhibitor.


For further information on this work, contact Dr. Mala Rao

To see the list of all R&D features, click here