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HIV Protease Drug Resistance and its Impact on Inhibitor Design

Paul J. Ala[1], and Chong-Hwan Chang[2,*]

[1]Scriptgen Pharmaceuticals, 610 Lincoln Street, Waltham, MA 02154, USA

[2]Experimental Station, DuPont Pharmaceuticals, Wilmington, DE 19880, USA

In the early 80's, the human immunodeficiency virus (HIV) was identified as the causal agent of the acquired immunodeficiency syndrome (AIDS). By 1987, the FDA had approved the first anti-HIV agent, AZT, a nucleoside analogue that inhibits reverse transcriptase (RT). During the next fifteen years, the FDA approved nine additional nucleoside and non-nucleoside RT inhibitors. From the early 90's, scientists started develope a new class of inhibitors that target the viral protease. This enzyme plays a pivotal role in the maturation of virus particles, as it processes the polyprotein gene products of *gag* and *gag-pol* into structural and replicative proteins. In addition, it is structurally distinct from mammalian aspartyl proteases and it has a well-defined active site. The latter feature is particularly important because it has allowed researchers to design many potent inhibitors. In just four years, the FDA approved the used of five protease inhibitors: saquinavir (Invirase/Fortovase®, Hoffmann-LaRoche), ritonavir (Norvir®, Abbott Laboratories), indinavir (Crixivan®, Merck & Co), nelfinavir (Viracept®, Agouron Pharmaceuticals), and amprenavir (Agenerase®, Vertex/GlaxoWellcome); and many more compounds are in the earlier stages of development. The rapid development of these therapeutic agents has been remarkable and is certainly one of the most successful structure based drug design stories of our time.

However, the recent emergence of drug-resistant variants has cast doubt on the long-term therapeutic benefit of these antiretroviral drugs. The primary cause of resistance to the currently available HIV protease inhibitors is the accumulation of mutations in the viral protease, that reduce the protease's affinity for inhibitors or enhance its catalytic efficiency. So far more than 20 substitutions have been observed in its active site, dimer interface, surface loops and flaps. This high degree of genetic flexibility has made the protease an elusive drug target. In this talk, the design of the next generation of HIV protease inhibitors will be discussed in light of the resistance problem.

*Correspondence should be addressed to C.-H. C. at DuPont Pharmaceuticals, Experimental Station, P.O. Box 80353, Wilmington, DE 19880-00353; Tel.: (302) 695-1787; Fax: (302) 695-8667; Email: chong-hwan.chang@dupontpharma.com.