Novel HIV-1 Protease Inhibitors

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US and foreign patent pending

Background

HIV protease has proven to be a powerful drug target in the treatment of HIV/AIDS. While the first generation of HIV-1 protease inhibitors (PIs) have been effective in slowing the spread of the virus, multiple drug resistant (MDR) forms of HIV have evolved that are not responsive to these inhibitors. While current PIs were designed to inhibit wild-type HIV-1 protease, our new structure-based drug design focuses on developing PIs that bind and inhibit multiple MDR protease variants by understanding how the enzyme recognizes substrates.

Technology

UMass Medical school investigator Dr. Celia Schiffer and colleagues have designed a new class of PIs that are more potent and less likely to induce drug resistance than inhibitors that are currently available. Dr. Schiffer and colleagues have designed competitive inhibitors based on a detailed understanding of the structures of the protease when complexed with its viral substrates (*Ali et al (2006) J Med Chem 49:7342*, *Reddy et al (2007) J Med Chem 50:4316, Chellappan et al (2007) Chem Biol Drug Des 69:298,* and *Altman et al (2008) J Am Chem Soc 130:6099*). These novel inhibitors bind within the consensus substrate binding region or "substrate envelope". Thus, with these PIs, resistance is less likely to occur while protease maintains substrate recognition. These next generation PIs are robust against resistance, demonstrating higher potency than Darunavir against patient derived MDR viruses with known protease resistance.

Patents Filed

WO 2007/002172 A2
WO 2008/118849 A2

Competitive Advantages

- ***Novel HIV-1 protease inhibitors:*** Designed based on a novel approach using the constraints of the substrate envelope combined with structure based drug design.
- ***Potent activity:*** Novel inhibitors are potent against drug resistant HIV-1 variants with subnanomolar IC_{50}s
- ***Resilience to mutations:*** Containment of these PI's within the substrate envelope allows these PIs to retain activity as new mutations appear, increasing the time for therapeutic efficacy
- ***High affinity binding:*** These novel PIs, although small, bind with high affinity picomolar affinity to a variety of HIV-1 protease variants that are resistant to most of the FDA approved drugs
- ***Ideal drug-like property:*** Calculated ClogP values compare favorably with FDA-approved HIV-1 PIs.

Business Opportunity

UMass OTM is seeking statements of interest from parties interested in licensing and/ or sponsoring collaborative research to commercialize this technology.

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