First-ever covalent irreversible inhibition of a protease central to hepatitis C infection

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Avila Therapeutics, Inc., a biotechnology company developing novel targeted covalent drugs, has published research in *Nature Chemical Biology* demonstrating the first-ever selective irreversible inhibition of a viral protease using a targeted covalent drug. In the paper titled "Selective Irreversible Inhibition of a Protease by Targeting a Non-Catalytic Cysteine", Avila used its proprietary Avilomics platform to design covalent irreversible protease inhibitors that are highly selective, potent and with superior duration of action as compared to conventional protease inhibitors.

Importantly, the published research demonstrates that covalent drugs can be designed and targeted to irreversibly and covalently bond to molecular domains specific to proteases. This is the first report of the irreversible covalent approach being successfully extended to proteases, a very broad class of proteins that includes many important potential drug targets.

"This research elevates covalent drug design to a fundamentally new level," said Simon Campbell, PhD, CBE, FMedSci, FRS, a renowned scientist and former Senior Vice President for Worldwide Drug Discovery and Medicinal R&D Europe of Pfizer. "By creating extremely selective protease inhibitors with their platform, Avila is showing the remarkable therapeutic potential of irreversible covalent drugs to address a broad spectrum of drug targets."

"This publication showcases the creation of a whole new class of small molecule drugs," said Juswinder Singh, PhD, Chief Scientific Officer of

Avila and a co-author of the paper. "This approach can make a difference to patients living with HCV infection, and we expect to make an impact in other important areas such as cancer and inflammatory disease."

In order to maximize selectivity and minimize off-target effects, the irreversible covalent inhibitors of HCV protease were designed to covalently target a unique structure in the HCV protease not found in human proteases. Key findings include:

- A representative irreversible covalent inhibitor designed, by Avila, was shown to inhibit the HCV protease (also known as "NS3") in cells at a concentration of 6 nM .
- Specific covalent bond formation between the drug and target protease was demonstrated through use of mass spectrometry and also x-ray crystallography.
- Very high selectivity of the Avila compounds was demonstrated by showing no notable inhibition of a panel of human proteases in biochemical assays with additional specificity demonstrated in cellular assays; this was contrasted experimentally with Telaprevir, an HCV protease inhibitor in late-stage clinical testing which demonstrated off-target biochemical activity against several human targets.

Avila has subsequently optimized additional drug candidates, yielding current development candidates, AVL-181 and AVL-192, which have excellent pharmacokinetics and bind potently to wild- type HCV protease as well as multiple genotypes and mutant forms of HCV protease.

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