Microsymposium

MS05.O01

Combatting Drug Resistance: Lessons from the viral proteases of HIV and HCV

C. Schiffer[1]

[1]*UMass Medical School, Department of Biochemistry and Molecular Pharmacology, Worcester, MA, USA*

Drug resistance negatively impacts the lives of millions of patients and costs our society billions of dollars by limiting the longevity of many of our most potent drugs. Drug resistance can be caused by a change in the balance of molecular recognition events that selectively weakens inhibitor binding but maintains the biological function of the target. To reduce the likelihood of drug resistance, a detailed understanding of the target's function is necessary. Both structure at atomic resolution and evolutionarily constraints on its variation is required. "Resilient" targets are less susceptible to drug resistance due to their key location in a particular pathway. This rationale was derived through crystallographic studies elucidating substrate recognition and drug resistance in HIV-1 protease and Hepatitis C (HCV) NS3/4A protease. Both are key therapeutic targets and are potentially "resilient" targets where resistant mutations occur outside of the substrate binding site. To reduce the probability of drug resistance inhibitors should be designed to fit within what we define as the "substrate envelope". These principals are likely more generally applicable to other quickly evolving diseases where drug resistance is quickly evolving. http://www.umassmed.edu/schifferlab/index.aspx

[1] *Chem Biol. 2013 Sep 19;20(9):1116-24. doi: 10.1016/j.chembiol.2013.07.014.,* ***[2]*** *ACS Chem Biol. 2012 Sep 21;7(9):1536-46. Epub 2012 Jul 2.,* ***[3]*** *J Virol. 2013 Apr;87(8):4176-84. doi: 10.1128/JVI.03486-12. Epub 2013 Jan 30.*

Keywords: Drug Resistance, Substrate Envelope