# Constraining Evolution ⇒ Avoiding Drug Resistance: Lessons from Viruses

Celia Schiffer[1]

[1]*University of Massachusetts Medical School*

*Celia.Schiffer@umassmed.edu*

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. This rationale was derived from our lab's experience with substrate recognition and drug resistance in HIV, HCV and most recently applying to emerging targets of HTLV-1 and SARS-CoV-2. This resulted in our development of the strategy of the substrate envelope as an explicit method to avoid drug resistance and develop robust inhibitors. We have acquired a rich and versatile experimental dataset of viral proteases, integrating alterations in both the protein sequence and the inhibitor with changes in potency and map this data to our crystallographic structures and parallel molecular dynamics in an internally consistent manner with machine learning to elucidate molecular mechanisms of drug resistance. These principals are generally applicable to other quickly evolving diseases where drug resistance is quickly evolving.