Efficient Lead Optimization Guided by Free-Energy Calculations

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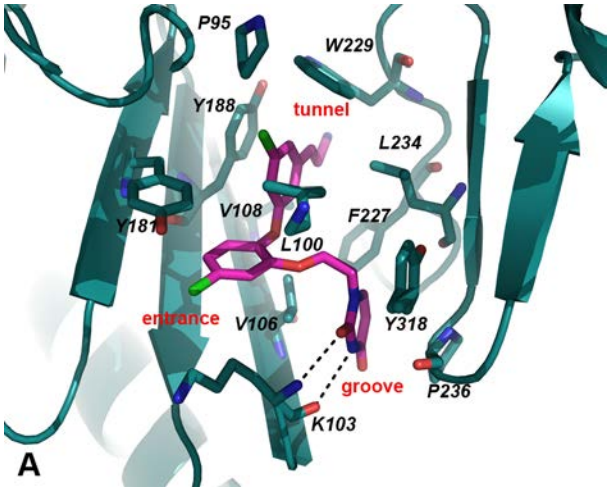

Crystal structure of a 55-pM inhibitor bound to
HIV-1 reverse transcriptase.

Drug discovery is being pursued through computer-aided design, synthesis, biological assaying, and crystallography. Lead identification features *de novo* design with the ligand growing program *BOMB* or docking of commercial compound libraries. The cheminformatics program *QikProp* is applied to filter candidate molecules to ensure that they have drug-like properties. The focus of this lecture will be optimization of the resultant leads to yield potent inhibitors. Specifically, Monte Carlo/free-energy perturbation simulations are executed to identify the most promising choices for substituents on rings, heterocycles, and linking groups. The designed compounds are then synthesized and assayed. Successful application has been achieved in multiple cases, e.g., for HIV reverse transcriptase, and human and *Plasmodium falciparum* macrophage migration inhibitory factor (MIF); micromolar leads have been rapidly advanced to low nanomolar or picomolar inhibitors. Numerous crystal structures for the protein-inhibitor complexes have been obtained for HIV-RT and MIF.

Recent References:

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