

Department of Medicinal Chemistry Seminar Series

Hosted by the
Department of Medicinal Chemistry

Predicting and Combating Antiviral Resistance with AI-driven Drug Discovery

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College of Pharmacy Building – Classroom 1300

Resistance evolution poses a major threat to sustained therapeutic efficacy. Evolution of just a single mutation can undermine the long-term effectiveness of drugs that require years of extensive research and development. In this seminar, I will present our multiscale approach to developing resistance-resilient antivirals including predicting which variants will emerge, determining how mutations alter protein structure and dynamics, and identifying compounds that inhibit resistant variants. First, I will introduce Mavenets, which combines machine learning (ML) and probabilistic sampling to predict variants of concern from multiplexed assays of variant effect, including deep mutational scanning. I will then describe how we use molecular dynamics (MD) simulations to uncover dynamic resistance mechanisms in the avian influenza PA endonuclease. Next, I will show how we integrate MD simulations with solution NMR to unravel the kinetic complexities of drug binding pathways in the SARS-CoV-2 main protease, supporting lead optimization through structure-kinetic relationships (SKRs). Finally, I will discuss our efforts to accelerate chemical space exploration by combining ML and physics-based methods with DNA-encoded library screening. Together, these efforts establish an integrated, AI-enabled platform for anticipating evolution, elucidating resistance mechanisms, and developing inhibitors resilient to emerging variants, shifting drug discovery from reacting to resistance toward designing for long-term therapeutic durability.