ULTRA-LARGE LIBRARY DOCKING FOR NEW CHEMOTYPES WITH NEW BIOLOGY

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报告摘要:

Docking screens compound libraries for molecules that complement the structures of protein targets, seeking novel chemotypes. Often, these new chemotypes can confer new biology. Recently, our libraries have expanded from 3 million "off-the-shelf" to over 1 billion "make-on-demand" molecules. We first explored the pragmatism of such ultra-large, virtual libraries in prospective campaigns against β-lactamase and the dopamine D4 receptor, where new docking hits were tested functionally and, where possible, by crystallography (1). By testing over 500 new-to-the-planet molecules, we could correlate docking score and likelihood of binding, for the first time. Subsequently, we expanded these studies to discovering biologically active lead molecules for the melatonin receptor (2), the 5HT2a receptor, and the sigma2 receptor, where again we have been able to test hundreds of molecules and test the relationship between docking score and hit rate. Opportunities and challenges from this 100-fold increase in community-accessible chemical space will be considered.

References:

(1) Lyu J et al. Ultra-large library docking for discovering new chemotypes. *Nature* 2019 566, 224-229.
(2) Stein RM et al. Virtual discovery of melatonin receptor ligands to modulate circadian rhythms. *Nature*. 2020, 579, 609-614

报告人简介: Brian Shoichet received B.Sc. degrees in Chemistry and in History from MIT (1985). He did his doctoral work with Tack Kuntz at UCSF in molecular docking (1991) before moving to the Institute of Molecular Biology to work with Brian Matthews on protein structure and stability-function trade-offs (to 1996). He started his lab in the Dept. of Molecular Pharmacology at Northwestern University Med. School (1996) before being recruited back to UCSF, where he is now a professor of Pharmaceutical Chemistry. Taking a target-based approach, his lab uses molecular docking to discover novel ligands. Taking a chemoinformatics approach, they seek to find targets based on shared ligand patterns. A focus for both has been GPCRs. Methods development in the lab goes back and forth between computation and experimental testing in model systems in the lab, which has led to the discovery of important confounds in drug discovery, such as colloidal aggregation and recently phospholipidosis. The work is funded by the NIH and by DARPA. Recent papers include:

* Tummino T et al., Phospholipidosis is a shared mechanism underlying the in vitro antiviral activity of many repurposed drugs against SARS-CoV-2. *BioRxiv*, 2021.

* Pottel J et al. The activities of drug inactive ingredients on biological targets. *Science,* 2020 369, 403-413.
* Gordon Det al., Human Protein-Protein Interaction Map Reveals Drug Targets and Potential Drug-Repurposing. *Nature* 2020 583 459–468
* Stein RM et al. Virtual discovery of melatonin receptor ligands to modulate circadian rhythms. *Nature*. 2020, 579, 609-614
* Lyu J et al. Ultra-large library docking for discovering new chemotypes. *Nature* 2019 566, 224-229.