THE FRONT ROW
at Scripps Research

Expanding the drug target universe

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ABOUT THE LECTURE

Despite revolutionary advances in understanding the mechanisms and causes of disease, patients are often left with limited therapeutic options due to challenges associated with novel drug development. In his Front Row lecture, Scripps Research Professor Benjamin Cravatt explained how his laboratory has pioneered a new approach to finding therapeutics. Leveraging large-scale protein profiling and innovative chemical technologies, Cravatt's team can now identify novel drugs for therapeutic targets previously deemed "undruggable." His translational work has led to the formation of multiple local biotechnology companies developing first-in-class candidate medicines, demonstrating how breakthrough discoveries can rapidly advance from laboratory to clinic.

TOP TAKEAWAY POINTS

- Traditional drug discovery has been constrained to targeting only proteins whose structure easily lends to binding with drugs. These structures, known as deep binding pockets, exist in only in a small fraction of all proteins in our bodies—leaving the vast majority of disease-relevant proteins "undruggable" because they only have cryptic (flat, shallow and dynamic) binding sites.

- Current approaches to developing therapeutics involve isolating proteins, placing them in test tubes, and screening for compounds that bind well to them. This method requires significant effort, resources and time—slowing drug discovery and limiting our understanding of protein function within the context of the cell.

- Cravatt and his lab have pioneered an approach called "activity-based proteomics," which aims to address these challenges and accelerate the treatments available to patients. Activity-based proteomics focuses on scaling protein profiling, studying proteins within the cell, and applying "permanent chemistry".

- Permanent chemistry, also called covalent chemistry, involves using drugs that create lasting bonds with target proteins to provide ongoing therapeutic benefit. This approach had historically been rejected by the pharmaceutical industry due to the potential for these compounds to bind to too many proteins, leading to life-threatening complications. However, Cravatt has demonstrated that in combination with activity-based proteomics, permanent chemistry is an innovative solution to developing novel therapeutics that target proteins with cryptic sites previously deemed undruggable.

- In the next phase of their research, the team aims to continue to break down the complex nature of proteins and illuminate new drug targets. This breakthrough method holds the promise of creating precision medicines for patients facing diseases that have long been considered untreatable such as cancer, neurological disorders and autoimmune diseases.

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