

PERSPECTIVES & OPINIONS

Stuart L. Schreiber

SMALL  
MOLECULES  
FOR BIG  
MEDICINES

Leah Fasten

Drug discovery is an expensive process that can take dozens of years and result in only a few compounds making it to market. Stuart L. Schreiber, an HHMI investigator at the Broad Institute of Harvard and MIT, hopes to improve those odds using small molecule “bioprobes” to study the causes of diseases and to find better therapeutic targets for drug companies to explore.

The search for new drugs took an exciting turn in the past year when scientists linked variations in more than 50 genes in humans to their predisposition to develop more than a dozen diseases. While the ability to identify such links opened the door for potentially discovering the role of thousands of genes in diseases, it also posed new challenges to pharmaceutical companies. That’s because insights from research in human genetics aren’t made in a way that is compatible with how pharmaceutical companies traditionally practice drug discovery.

The pharmaceutical industry typically looks for treatments by first forming a hypothesis that a certain “target” molecule might be responsible for a disease, and then launching drug discovery efforts based on that assumption. Human genetics research, however, tends not to point to therapeutic targets, but rather to processes in the body that may have gone awry or imbalances that need to be corrected, such as insufficient insulin secretion.

Our lab has developed a set of tools and techniques we believe can help bridge this gap using small-molecule bioprobes. Small molecules have critical roles in all levels of biology—including cell growth, proliferation, sensing, and signaling—so researchers in academia and at pharmaceutical companies alike have a great interest in them. But instead of using small molecules as therapeutics, we are using them as bioprobes to examine the underlying causes of diseases. Our approach is discovery-based rather than hypothesis-driven. We want to define the properties of a cell in a particular state so we can study how they change as the cell becomes diseased. To understand a bodily process, it helps to perturb it with the bioprobes and determine the consequences. We believe this approach could lead us to choose more effective compounds as candidate probes, and as a result uncover more relevant therapeutic targets for drug discovery.

There already is evidence to indicate our method is working. Using small-molecule bioprobes, we identified two proteins that pharmaceutical companies subsequently developed as therapeutic targets with new mechanisms of action. Both won FDA approval in 2007. One drug, Torisel (temsirolimus) from Wyeth, treats renal cell carcinoma by inhibiting

mammalian target of rapamycin (mTOR) proteins. The other drug, Zolinza (vorinostat) from Merck, treats cutaneous T-cell lymphoma by modulating histone deacetylase (HDAC) proteins. We discovered that the mTOR and HDAC proteins might be good targets by using the small-molecule probes rapamycin and trapoxin, respectively, which cause behavioral changes in cells.

The field of biological research that focuses on the science of small molecules, called chemical biology, is relatively new. Its coemergence with modern human genetics is leading to enormous opportunities for synergies between these fields. In addition to information on genotype, or the inherited instructions carried by a human or other organism, modern human genetics is shining a bright light on the phenotype of diseases—that is, the change in morphology, development, or behavior of an organism as a result of disease. With chemical biology, we can provide powerful methods for studying phenotypes of disease and making sense of what we find. That’s where we can provide valuable information on likely targets to pharmaceutical companies.

Under a new chemical biology program called the Novel Therapeutics Initiative, the Broad Institute is further refining our thinking on effective drug discovery processes. Rather than trying to convince the pharmaceutical industry that an experimental lab technique is useful, we prefer to demonstrate the capabilities of our overall process in the context of especially challenging diseases, such as schizophrenia, diabetes, and cancers. If we can find highly unusual, highly effective therapeutic agents for these diseases that could not have been discovered otherwise, the pharmaceutical industry likely will pay attention. We’re encouraged by the outcomes with mTOR and HDAC inhibitors.

We don’t expect the pharmaceutical industry, which has spent millions of dollars and decades on its current drug discovery approaches, to slow down their process and switch to a new one. My hope is that applying chemical biology research and methods to drug discovery may serve as a way for the academic community to broaden its ties with the pharmaceutical industry, and demonstrate a path forward for developing better and safer drugs.

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INTERVIEW BY LORI VALIGRA. *The head of the chemical biology program at the Broad Institute, Stuart Schreiber received his B.A. in chemistry from the University of Virginia and his Ph.D. in organic chemistry from Harvard University.*