2013-2014 POCC Lecture Series

October 31, 2013, 8:00 PM

≈ Allan R. Day Awardee ≈

Prof. Stuart L. Schreiber

Harvard University

Towards a Chemistry-Enabled Patient-Based Drug Discovery

Carolyn Hoff Lynch Lecture Hall
Chemistry Building, University of Pennsylvania

The Philadelphia Organic Chemist's Club

POCClub.org

Stuart L. Schreiber, Ph.D. is the Director of the Center for the Science of Therapeutics at and a Founding Member of the Broad Institute of Harvard and MIT, where he is a Howard Hughes Medical Institute Investigator. He is also the Morris Loeb Professor of Chemistry and Chemical Biology at Harvard University, and a member of the National Academy of Sciences.

Dr. Schreiber is known for having developed systematic ways to explore biology, especially disease biology, using small molecules and for his role in the development of the field of chemical biology. He discovered principles that underlie information transfer and storage in cells, specifically discoveries relating to signaling by the phosphatase calcineurin and kinase mTOR (demonstrating for the first time that drugs can result from the targeting of protein kinases and protein phosphatases), gene regulation by chromatin-modifying histone deacetylases, small-molecule dimerizers that activate cellular processes by enforced proximity, and small-molecule probes of challenging targets and processes (e.g., transcription factors, oncogenes, protein/protein interactions, transdifferentiation) that relate to human disease. His work has contributed to diversity-oriented synthesis (DOS) and discovery-based small-molecule screening in an open data-sharing environment. His research has been reported in over 500 publications (H index = 124).

Four new anti-cancer drugs that target proteins discovered in the Schreiber laboratory have been approved by the U.S. FDA: temsirolimus (Wyeth) and everolimus (Novartis), which target mTOR (discovered using rapamycin in 1994), for renal cancer, and vorinostat (Merck) and romidepsin (Celgene), which target HDACs (discovered using trapoxin in 1996), for cutaneous T-cell lymphoma. A small-molecule dimerizer drug (AP1903) reversed the effects of graft-versus-host disease in acute leukemia patients receiving hematopoietic stem cells engineered to express caspase-9 fused to a drug-responsive, FKBP12-based dimerization domain (NEJM, 2011). Proteins first shown by Schreiber to be targeted by a small molecule have been validated therapeutically by the FDA-approval process: tacrolimus (calcineurin/immu¬nosuppres¬sion/1994; Schreiber's study of FK506) and bortezomib (proteasome/multiple myeloma/2003; Schreiber's study of lactacystin). Schreiber extended chemical biology principles to medicine by participating in the founding of four biotech companies, each of which has devised novel therapeutic agents that are being tested in human clinical trials or used as FDA-approved drugs: Vertex Pharmaceuticals (founded 1989: fosamprenavir/Lexiva; telaprevir/Incivek; ivacaftor/Kalydeco), ARIAD Pharmaceuticals (founded 1991: ponatinib/Iclusig; AP26113), ARIAD Gene Thera¬peutics (founded 1994: ridaforolimus; AP1903), and Infinity Pharmaceuticals (founded 2001: reta¬spimycin; IPI-145). More recently, he has co-founded two currently private companies that pursue a chemical biology-based approach to drug discovery: Forma Therapeutics and H3 Biomedicines.

Abstract: Small-molecule drugs were originally discovered using compound-based drug discovery: opportunistic discovery of a biologically active compound, often a natural product (e.g., penicillin) followed by a search for a disease that might be treated with the compound. This remains a common approach to modern drug discovery (e.g., rapamycin and analogs for use as antifungal agents; immune suppression agents; anti-cancer agents; possibly others in the future).

The advent of recombinant DNA accelerated a second approach – target-based drug discovery – where the therapeutic target is selected and subjected to methods that yield candidate drugs (mechanism-based design; structure-based design; screening). But this approach has well-documented shortcomings associated with unanticipated toxicity and lack of efficacy despite successful modulation of the target. Selecting therapeutic targets based on information derived from surrogates of patients has proved challenging.

Advances in human biology, including human genetics and physiology, and in small-molecule science, including chemistry and chemical biology, are now accelerating a third approach – patient-based drug discovery. This lecture will present examples that aim to use: 1) information from heritable or somatic human genetics in human disease; for example, in Crohn's Disease and cancer, 2) advances in diversity-oriented synthetic chemistry and chemical biology to accelerate the discovery of novel small-molecule modulators, and 3) an understanding of the relationship of human genetic variation to drug efficacy.