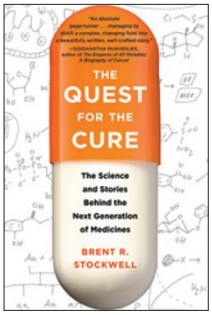
The valiant interrogator



The Quest for the Cure: The Science and Stories Behind the Next Generation of Medicines

by Brent R. Stockwell

COLUMBIA UNIVERSITY PRESS; 2011. 249 PP £19.95

As a boy growing up within view of the Hoffmann–LaRoche tower in Nutley, New Jersey, I wasn't terribly unusual in wishing to pursue a career in pharmaceutical research. But when I chose to go to the Philadelphia College of Pharmacy and Science for their undergraduate programme in toxicology, the then-girlfriend of my still-dear high-school mate asked why I'd want to stuff animals for a living! Even when I went on to study pharmacology in graduate school, friends and family didn't understand that I wasn't going to be dispensing drugs at a local pharmacy.

Google 'careers in drug discovery' and you'll find articles no more recent than 2004 or 2006. And, although nearly everyone in developed nations has taken a drug at one time or another, few people outside of academia and industrial sciences fully appreciate the tortuous, obstacle-laden path from chemical to drug.

In *The Quest for the Cure*, Columbia University associate professor of biological sciences and chemistry Brent Stockwell introduces himself to general audiences by providing a digestible overview of the history and future of drug discovery. His central goal is to dissect whether the decline in the annual rate of drug approvals is caused by constraints of biology — are we approaching the limit of disease-causing protein targets — or is it that our technical methods have led us to incorrectly characterize some proteins as 'undruggable'?

A former principal of a start-up drug company, trainee of Harvard chemist Stuart Schreiber, and an accomplished Howard Hughes Medical Institute Early Career Scientist at the interface of chemistry and biology, Stockwell is in the middle of a robust career in academic drug discovery. He holds ten US patents and has published over 60 papers in some of the world's top-tier journals. But his expressed intention is to have written a book for the general public, one that provides an approachable glimpse into pharmaceutical breakthroughs. The audience may not be a general as he desires but the majority of the book is certainly accessible to the typical *Scientific American* reader. Despite that, the book could easily serve in an undergraduate or graduate level course on drug discovery, by requiring reading of any number of the original articles cited in the highly-detailed notes.

Stockwell cites his own trigger for pursuing science: "learning organic chemistry and seeing how all of life's processes are simply the interactions and reactions of molecules". But he also has another gift to convey to the next generation of scientists: a reverence for the past and the value of thoughtful discussion during downtime. His personal anecdotes on brainstorming in Vernon Ingram's office at MIT and written correspondence with 'oncogene addiction' visionary Bernard Weinstein are sharp contrasts to contemporary academic scenarios of incessant attention to e-mail and buzzing smartphones. Stockwell doesn't sacrifice scientific rigour in showing his humanity; an admirable quality I'm delighted to see publicly presented by a scientist. The book opens not with hardcore science but rather two stories of the author's personal losses from cancer.

The book's discussion of the complex route from chemical to drug harkens back to the origins of pharmacology, truly the original field of chemical biology. Students may not appreciate that early pharmacologists had the comprehensive, integrated grasp of chemistry and biology that has suddenly become in vogue over the last 15 years. In fact, Stockwell's historical accounts of drug discovery are reminiscent of the small print sections of Goodman and Gilman's *The Pharmacological Basis of Therapeutics* but are told in a far more interesting manner and with an eye toward the future.

Physical and synthetic organic chemistry play central roles in the historical accounts, from Desmond Bernal's pioneering work on protein X-ray crystallography and Stephen Fesick's structure activity relationships by NMR spectroscopy to the highly relevant distinction between fulminic and isocyanic acids and the design of HIV protease inhibitors. These stories aren't provided solely for science-history buffs but rather as the basis for understanding why new approaches to drug discovery are needed. For the history enthusiast an excellent comprehensive companion to *The Quest for the Cure* is Walter Sneader's *Drug Discovery: A History*, a microfont tome that extends even further back to medicines of the early Greeks, Romans and prehistoric evidence of medicinal plant use.

More contemporarily, Stockwell's background as a co-founder of CombinatoRx provides a superb Chapter 4 that details the rollercoaster of scientific discovery, angel investors and venture capitalists, and 'phagocytosis' by a larger firm. One partial absence from his overall work is how large drug companies search for drugs — understandable given his background and perhaps owing further to an uninspiring research experience at a major company early in his career. He does touch on academic collaborations with industry in the example of Brian Druker and imatinib (Glivec, Gleevec) and Sir James Black and propranolol (Inderal). His expert treatment of discovery rather than development tends to underemphasize pharmacokinetic contributions to drug-approval failures. A more comprehensive view of industrial drug discovery would be gained with Robert Rydzewski's *Real World Drug Discovery: A Chemist's Guide to Biotech and Pharmaceutical Research*.

The latter chapters of *The Quest for the Cure* propose technical solutions to the crisis in new drug approvals. Both small-molecule and biological approaches are described to overcome the mindset of 'undruggable' targets such as protein–protein interactions, particularly in light of the early dismissal of anticancer kinase inhibitors. Several peptide- and protein-based approaches are suggested, one building on the protein-transduction property of the *Drosophila antennapaedia* protein. Stockwell also maintains guarded enthusiasm for natural products, particularly those with large-scale resupply possibilities.

The reader is not only left with a satisfying overview of the proud history and future challenges of finding new medicines but also encouragement that Stockwell and his contemporaries are creatively committed to academic drug discovery. Whether these efforts influence the shortage of newly approved drugs remains to be seen. ❐

REVIEWED BY DAVID KROLL

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