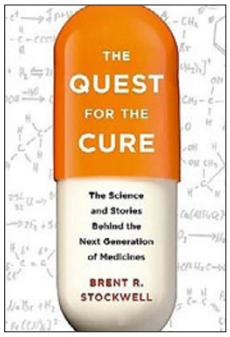
The obscure targets of desire



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

Brent R. Stockwell

Columbia University Press, 2011
284 pp., hardcover, $27.95
ISBN: 0231152124

Reviewed by Garret A FitzGerald

Brent R. Stockwell, an associate professor of biological sciences and chemistry at Columbia University in New York, advances the thesis that we have a drug discovery crisis driven by a paucity of new druggable proteins. In this challenge, he sees the prospect of breakthrough, which promises a dramatic expansion of drug targets. He begins his book with a quote from Pliny the Elder: "How many things, too, are looked upon as quite impossible until they have actually been effected?" This, and the advice from his father-in-law to focus on "first the goal, then the means," sets the stage for an entertaining review of what is now known as chemical biology against a backdrop of Stockwell's pessimistic anticipation of "the end of pharmaceutical medicine."

Stockwell argues that the ~20,000 US Food and Drug Administration (FDA)-approved drugs are directed at only 2% of the protein repertoire. He further cites that ~3,000 proteins—roughly 15% of all proteins— are druggable while estimating that only 10–15% of those, maybe 350–450, are disease modifying. This bumps up against the number of proteins—almost 400—that have already been targeted with small molecules. Hence the crisis; 'the cure' for this crisis then depends on developing strategies to drug the undruggable.

My initial enthusiasm, on casual perusal, for reading this book was quite low. First, the number of drugs approved by the FDA has remained relatively constant for the past 50 years. How real are the estimates used by Stockwell to suggest that the cupboard is bare? Surely whether something is druggable is a question of imagination, current technology and luck. Also, it should be noted that it is the estimated cost of bringing a drug to market that has exploded over time. In fact, one might argue that drug target discovery has been revolutionized and is doing rather well, whereas drug development is particularly inefficient and needs to be reformed. Thus, Stockwell's suggestion that all that is needed to deliver the cure is an expansion of the number of drug targets smacks of looking for the car keys where the light is. So although Stockwell specializes in the discovery of drug targets and we need more of what he does, we also need more efficiency in developing these preclinical targets into approved therapeutics, especially as many of the drugs approved each year are not 'first in class', but rather 'me too'.

Nonetheless, in spite of my initial reluctance to read the book in detail, the new approaches he outlines to unlocking the therapeutic potential of protein-protein interactions are ripe with a promise that lured me in, and I'm glad that I succumbed. Stockwell writes well—his prose is accessible to the educated reader, irrespective of his or her background. All of the personalities, errors and successes in contemporary drug discovery are presented. Stockwell enlivens their stories with anecdotes: a common interest in the cello as the basis for a fortuitous hire, a lab accident leading to the use and abuse of nitrogen mustard, the serendipity of Sternbach sending Librium for functional screening in a laboratory cleanup three years after its synthesis. He animates the connecting thread between discoveries—for example, the young Max Perutz consulting the 'Sage', Irishman Desmond Bernal, as to how he could solve the secret of life. "The secret of life lies in the structure of proteins, and there is only one way of solving it, and that is by X-ray crystallography," said Bernal, and off went Perutz, Hodgkin, Crick and Watson to prove him right.

In addition to the historical discourse, Stockwell also leads us through the more technical aspects of drug discovery and drug development, including rational drug design, fragment-based and virtual screening, and drug repurposing, before tackling how the often tiny and sometimes transient sites of protein-protein interactions might be disrupted to therapeutic benefit. Privileged scaffolds, combinatorial chemistry and phage display, catalytic antibodies, foldamers and stapled peptides are clearly and entertainingly described for the nonexpert reader. Who would have thought of using hard-boiled eggs to explain solid-state synthesis or chewing gum on the side of a crystal pitcher to explain nonspecific binding? Going further, Stockwell also recounts his co-founding of CombinatoRx, as well as its expansion and ultimate demise, in his rather wishful approach to drug combination. But this narrative, although reminding us why he, as a chemical biologist, is qualified to write this book, highlights the need for a pharmacological aspect to his reasoning. Its absence is a limitation to the central thesis of his book. Furthermore, there is no mention of stem cells, gene therapy or vaccines in this quest for the cure and no consideration of how poorly we understand either how the many complex steps in drug discovery interact or, more commonly, fail to do so. Also, his call for an international priority to make all proteins druggable, complete with a large billboard in Times Square, seems like a stretch. But in spite of all this, the book is a good read.

Drug discovery and development present a complex set of challenges that interlock, like proteins, in poorly understood ways. As we contemplate the advent of the National Center for Advancing Translational Science of the US National Institutes of Health, it is worth remembering another of Pliny the Elder's (borrowed from Terence) aphorisms: "fortune favors the brave," which he declaimed on his ship during an ill-fated mission to Vesuvius in AD 79. Given the challenges to this program, outlined in this book, perhaps discretion is indeed often the better part of valor.

Garret A. FitzGerald is Chair of Pharmacology and directs the Institute for Translational Medicine and Therapeutics at the University of Pennsylvania, Philadelphia, Pennsylvania, USA.
e-mail: garret@upenn.edu

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.