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BOOK REVIEW

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Book Review of Accounts in Drug Discovery. Case Studies in Medicinal Chemistry

Accounts in Drug Discovery. Case Studies in Medicinal Chemistry. Edited by Joel C. Barrish, Percy H. Carter, Peter T. W. Cheng, and Robert Zahler. The Royal Society of Chemistry, Cambridge, U.K. 2011. xvi + 379 pp. 16.5 × 24 cm. ISBN 978-1-84973-126-3. £132.99.

The editors and authors of this volume are medicinal chemists with broad industrial experience in the synthetic and biotech sectors who are, or were, associated with Bristol Meyers Squibb, Merck, Hoffman-La Roche, OSI Pharmaceuticals, Pfizer (U.S. and U.K.), Gilead, Pharmasset, and Amgen. As explained in the preface, their intent was "to cover a wide range of therapeutic areas and medicinal chemistry strategies, including lead optimization starting from high-throughput screening 'hits' and rational structure-based design ... including the optimization of metabolism and pharmacokinetics, toxicology, pharmaceutics, pharmacology ... (and) proof-of-concept in the clinic."

The book comprises 15 chapters written by a total of 35 authors. Chapters 1, 5, and 9 describe, respectively, the discovery, successful clinical development, and registration of the antidiabetic saxagliptin (2009), the anticancer gemtuzumab ozogamicin (2000), and the HIV antiviral maraviroc (2007). Interestingly, the saxagliptin team decided against lead generation by high throughput screening as "too time consuming to rapidly afford a chemical starting point" and chose instead to "initially adopt a design optimization approach, improving upon the leads" reported by competitive groups.

I take issue with the view expressed in the summary to Chapter 1 that a novel concept of rational drug design based on "a target's relevance to a disease state, a mechanistic understanding of biological function of the target, and an ability to design small molecules to interact with critical elements of the target's active site" was developed with the invention of captopril (1977). The concept of an "active site" was developed independently by Fischer (1894) as an enzyme "active site" that bound substrates by "lock and key" fitting, as a "receptor" by Ehrlich (1900) and as a "receptive substance" by Langley (1905). Structurally specific covalent inhibition of the active site of acetylcholine esterase by anticholinesterases was proposed by Wilson, who developed praldoxime chloride (1955), still in use today as an antidote. The concept of drugs as structural antimetabolites was formalized in the Woods−Fildes theory of sulfonamide action (1940) and was a basis of the Nobel Prize (1988) shared by Elion and Hitchings for their work (initiated in the 1950s) on antineoplastic, antiviral, and immunosuppressive purine and pyrimidine derivatives and by Black for his achievements in receptor antagonists (initiated in the 1960s).

Discovery programs based on structure based drug design beginning with HTS leads or privileged scaffolds are discussed in Chapters 4, 8, 10, and 14; however, clinical evaluation of the resulting candidates is stated to be either in early stages or on hold. Chapter 2 discusses the discovery and ongoing phase III work related to the thrombin receptor antagonist vorapaxar at the time of publication. However, in early 2011 Merck stopped one of these phase III trials and removed 25% of the patients from another. This chapter is sobering evidence of the enormous financial risk inherent in even the most expert modern drug discovery research. Here, clinical trials involving 35 000 patients either were stopped altogether or were sharply reduced.

Other discovery programs that ended in clinical failure are described in Chapters 3, 6, 7, 13, and 15. Work in Chapter 15 was directed to the discovery of α7 nicotinic acetylcholine receptor agonists for cognition enhancement. Strenuous attempts were made to broaden high throughput screening to include the Lipinsky "drugability" factors, as well as lack of toxic functionality, receptor selectivity, optimized pharmacokinetic properties, metabolic stability, high oral bioavailability, minimal hERG activity, and optimal CNS penetration. Disappointingly, the resulting three clinical candidates produced a low incidence of asymptomatic nonsustained ventricular tachycardia (NSVT) in normal volunteers, and the candidates were discontinued. In Chapters 11 and 12, workers also attempted to avoid unexpected problems in the development phase by using broad in vitro and in vivo screens in the discovery phase that included such selection criteria as clogP, log $D_{7.4}$, CYP2D6, CYP inhibition and metabolism, hERG binding, potency, GI, blood, hepatic stability, cytotoxicity, mitochondrial and bone marrow toxicity, rat and dog iv and oral pharmacokinetics, and rat toxicity. Both chapters emphasize the importance of selection criteria controlling for CYP2D6 metabolism because of genetic variability resulting in "poor metabolizers" and "ultrarapid metabolizers". The studies in both chapters delivered clinical candidates.

This book is expensive but highly informative, with useful illustrations, some in color, and a 17-page index. It could serve as a text for a seminar course for graduate students and postdocs or for discussion groups for workers in the pharma industry. This book is also recommended for the libraries that serve these groups.

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