POLYPHARMACOLOGY IN DRUG DISCOVERY

Edited by Jens-Uwe Peters

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Contents

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Preface

Polypharmacology, the activity of compounds at multiple targets, has been gaining increasing attention since the 1990s, and is currently a hot topic in industrial drug discovery, as well as in academia. The 1990s witnessed the withdrawal of several drugs due to severe adverse effects, which led to permanent injury or deaths, with multi-billion-dollar legal damages. Some of these adverse effects have been linked to unintended interactions with specific off-targets, namely, the serotonin 5HT2B receptor for fenfluramine; the cardiac hERG channel for astemizole, terfenadine, and grepafloxacin; and the M2 receptor for rapacuronium. During this time, large screening panels were established by drug discovery and contract research organizations, which made it possible to recognize a wide range of off-target activities during the discovery process. As a consequence, more recent research has focused on identifying exquisitely selective drugs, with an expectation to avoid adverse drug reactions (ADRs), to improve compliance, and to gain a competitive advantage over less selective drugs.

On the other hand, the “one drug–one target” paradigm has been increasingly challenged in recent years. Not only has it been associated with a productivity decline throughout the pharmaceutical industry; it has also been increasingly being recognized that the therapy for polygenic diseases benefits more from a polypharmacological approach, which modulates a network of disease-related targets, rather than “switching” a single target on or off. For instance, despite a long quest for selective drugs, all clinically established antipsychotics today are polypharmacological drugs, with the gold standard clozapine having nanomolar activities at more than 25 targets. Polypharmacological therapies are often superior in the prevention of drug resistance, which is a major issue in

the treatment of infections and cancer. In some disease areas, such as inflammatory diseases, the parallel inhibition of redundant disease-relevant pathways may be an attractive strategy for pharmacological intervention. In many instances, the inhibition of several targets may have synergistic therapeutic effects and may thus lead to more efficacious drugs. Additionally, polypharmacological drug discovery provides an opportunity to diversify research, to obtain drug candidates with unique pharmacological profiles, and to avoid a heavy focus on single targets that are often pursued across the whole industry at the same time.

Moreover, the idea that highly selective drugs are inherently safer and better tolerated than multitargeted drugs has been questioned. Rofecoxib may be a point in case; this drug, as well as other “coxibs,” was designed to more selective, and thus to be safer, than older antiinflammatory drugs such as ibuprofen. Rofecoxib was, however, found to increase the risk for cardiovascular events such as myocardial infarction and stroke. These cardiovascular risks are believed to be the result of rofecoxib's selectivity for one cyclooxygenase isoform, and have led to the withdrawal of this multi-billion-dollar drug in 2004. Another example are the selective serotonin reuptake inhibitiors (SSRIs) and serotonin / norepinephrine reuptake inhibitiors (SNRIs); although they are considered to be very safe antidepressants, they have a high incidence of unpleasant side effects, which contribute to a high discontinuation rate. These side effects, such as disrupted sleep, sexual dysfunction, and acute nausea and anxiety, are thought to be alleviated by intervention at additional targets. Consequently, several ongoing research programs aim to combine reuptake inhibition with, for example, antagonism at certain serotonin receptors for an improved tolerability. As a more general concept, it has been argued

that polypharmacological drugs can even have a safety advantage, because the modulation of target networks, without permanent, full blockade or activation of a single target, may reduce target-related adverse effects, or may lead to lower efficacious doses.

Thus, there are two sides of the polypharmacology coin: (1) unwanted off-target activities may lead to adverse drug reactions and need to be avoided, while (2) polypharmacological drugs with multiple activities across a disease-relevant target class, such as G-protein-coupled receptors (GPCRs), ion channels, or kinases represent opportunities for improved therapies, as illustrated by the approvals of asenapine (2009), dronedarone (2009), and sunitinib (2006), respectively. Both of these sides will be discussed in this book. For an easy orientation according to the reader's background and interests, the book is divided in four parts:

Part A. Unintended activities at “antitargets” are typically discovered late in the drug discovery process, and have been a reason for late-stage failures, or at least a major hurdle in late lead optimization. The first part of the book discusses concepts and tools that help to recognize, interpret, and address such “antitarget” liabilities early in the drug discovery process, and thus to reduce costly late-stage attrition. Part A opens with an introduction to the relevance of polypharmacology for the safety of drugs, illustrated with salient cases of drugs and drug candidates with off-target-related toxicity. This is followed by an insightful guide to why, when, and how to screen for off-target activities, and how to predict and mitigate potential ADRs. The avoidance of promiscuity-related molecular properties as a strategy to reduce the risk for promiscuity is discussed in the third chapter. Numerous important antitargets will be introduced in these first three chapters, with a focus on GPCR targets. Two other

classes of frequently encountered antitargets, kinases and cardiac ion channels, are discussed next in dedicated chapters. Part A concludes with a chapter on data mining and pharmacological “fingerprint” profiling, which allows for the prediction of otherwise nonobvious ADRs. All this is supported by useful reference information, such as lists of off-targets associated with potential ADRs, frequently hit off-targets, and practical examples of lead optimization.

Part B. The productivity of the drug discovery industry as a whole has declined since the 1990s, with only ~20 new chemical entities per year reaching the market, despite ever-increasing research budgets. New discovery paradigms are therefore necessary to deviate from established research strategies, and to address those unmet medical needs that do not succumb to the ubiquitous “small molecule–single target protein” approach. Multitargeted, or polypharmacological, drug discovery may present opportunities where conventional approaches have been failing, especially for the treatment of diseases with multiple pathogenic factors, and diseases where resistance poses an important problem. Part B highlights four such disease areas: psychiatric diseases, cancer, bacterial infections, and epilepsy. Although the introductory chapter is dedicated to psychiatric drugs, the concepts discussed are instructive and generally applicable. In contrast to the antischizophrenia drugs, which were originally discovered serendipitously without knowledge of their polypharmacological nature, more recently approved kinase inhibitors for the treatment of cancer were developed with the knowledge of their polypharmacology, or were even deliberately designed to be polypharmacological, as outlined in the second chapter. The third chapter shows that most clinically established

antibiotics rely on the inhibition of several targets, or targets encoded by multiple genes. In contrast, targets encoded by single genes, such as those obtained from bacterial genomes, have not led to novel antibacterials, or are associated with rapid resistance mutations. The fourth chapter shows how antiepilepsy drugs often enhance or inhibit multiple ligand- or voltage-gated ion channels, and proposes a strategy for the discovery of novel, multitargeted antiepilesy therapies. The final chapter of the “opportunity” part of the book is not related to a disease area, but rather highlights an approach to lead finding that exploits the polypharmacology of existing drugs: the selective optimization of side activities (SOSA). This approach has been historically very successful, but has been neglected in more recent years in favor of high-throughput screening. The chapter shows how this concept can be revived and complemented with modern *in silico* methods. As Sir James Black states: “The most fruitful basis for the discovery of a new drug is to start with an old drug.”

Part C. Most of today's “multitargeted” drug discovery programs seem to have originated from the serendipitous discovery of dual, and sometimes multiple, ligands of often related disease-relevant targets. Apart from such obvious opportunities, multitargeted drug discovery is often perceived as not very feasible by industrial researchers, because of the more difficult lead finding, and the increased complexity of lead optimization. To illustrate how multitargeted drug discovery can be put into practice, a number of selected approaches are presented in Part C. The first chapter discusses how starting points for multitargeted drug discovery programs may be obtained either by screening or rational framework combination, and how such compounds can be

optimized. This is illustrated with many examples. The *in silico* approaches for multitarget screening can be employed to find multitargeted drugs or repurposing opportunities for existing drugs. This is discussed in the second chapter, with a focus on the 2010 NIH Director's Pioneer Award–winning CANDO method. This chapter provides also a detailed introduction to *in silico* screening in general, and will certainly attract the interest of *in silico* experts and nonspecialists alike. The third chapter introduces an intriguing method of high-throughput *in vivo* screening, in which a large number of behavioral readouts are automatically recognized, processed, and compared with a database of behavioral signatures of central nervous system (CNS)-active drugs. Such methods may constitute a modern version of the physiologically based screening paradigm that was the mainstay of the golden era of drug discovery. Many other possibilities are perhaps more obvious and do not warrant a detailed discussion. For instance, the mining of proprietary high-throughput screening (HTS) or safety panel data, or commercial or public pharmacological databases may be a rich source of multitargeted leads as starting points for discovery projects. Also, the “anticonvulsants” chapter of Part B proposes a generally applicable screening strategy, where novel multitargeted leads are sought to mimic the profile of successful drugs. Finally, Part C is rounded off with an introduction to multicomponent therapeutics, and shows how combinations of drugs can be selectively synergistic for therapeutic versus adverse effects, because the drug targets of the components are expressed together only in the tissue that is responsible for the therapeutic effect.

Part D. The last part is a collection of various instructive case studies. Most of the chapters in this part are dedicated to the discovery of polypharmacological or

specifically multitargeted drugs, ranging from the highly promiscuous anticancer drug sunitinib and antipsychotics over broad-spectrum antidepressants to the dual-acting drug candidate licofelone for inflammatory diseases. The achievement of (reasonable) selectivity in the kinase field, and activity across mutant targets, is discussed in the imatinib case study. An untypical type of dual activity is displayed by the experimental drug PA1103, which is able to inhibit the polymerization of heme, as well as to alkylate heme, both validated concepts for the treatment of malaria. The penultimate chapter discusses multitargeted approaches to the treatment of Alzheimer's disease, and specific clinical and preclinical compounds. A final chapter is dedicated to the (off-target) activities of established drugs at carbonic anhydrases; this chapter illustrates the potential of target discovery, drug repurposing and the discovery of new drugs based on the polypharmacology of existing pharmaceuticals. Throughout Part D, many authors express their personal views on the future of polypharmacological drug discovery. These views, ranging from slight skepticism to enthusiasm, may provide the reader with a balanced and realistic impression of the promises and challenges of polypharmacological drug discovery.

This book is intended as a practical guide for drug hunters to successfully navigate around the dangers of promiscuous ligands and targets, as well as a source of inspiration for new polypharmacological drug discovery projects. However, this collection of reviews, opinions, and case studies is by no means an exhaustive treatment of all possible facets of polypharmacology. For instance, drug–drug interactions are not treated; although formally a polypharmacology issue, this is usually regarded as DMPK-related, and several excellent books cover this important topic. Similarly, pleiotropic effects through interaction with single targets,

the achievement of selectivity across related targets or within target classes, or the contribution of active metabolites to the pharmacological spectra of drugs may be regarded as “polypharmacology topics,” but were considered to be beyond scope of this text.

I am very grateful to the contributing authors, who invested their time and expertise in this book. Also, I would like to thank Jonathan Rose at Wiley for proposing this book, and for his continuous advice and support throughout this project.

Note: Color versions of select figures are available at ftp://ftp.wiley.com/public/sci_tech_med/polypharmacology.

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