Methods and Principles in Medicinal Chemistry

Edited by Roy J. Vaz and Thomas Klabunde

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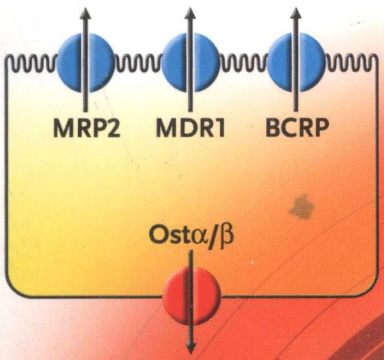
Antitargets

Prediction and Prevention of Drug Side Effects



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Series Editors:
R. Mannhold,
H. Kubinyi,
G. Folkers

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Cover Illustration
The cover shows a model of the hERG ion channel in the lower left (chapter 4), a CYP structure, lower right (chapter 10), a pharmacophore model for the alpha1a adrenergic receptor, upper right (chapter 6) and a schematic of the intestinal epithelium with some transporters, upper left (chapter 15).

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Preface

When the hammer hits your thumb in addition to, or instead of the nail - this clearly is an antitarget problem. In drug action and especially in drug-drug interactions, the situation is much more serious. There are numerous targets which should not be activated, induced, or inhibited by a drug. Adverse drug reactions (ADRs) are estimated to be one of the leading causes of morbidity and mortality in healthcare. Especially older patients receive up to 15 different medications, and even more, at the same time – no wonder that unfavorable drug-drug interactions happen, considering also the poor physical condition of such patients. In January 2000, the Institute of Medicine reported that in the US about 7000 deaths per year occur due to ADRs; the number may be even much larger, not to count the manyfold non-fatal side effects.

In defining the term "antitarget" one runs into some problems. Let us start with terfenadine, a non-sedating H1-antihistaminic. In its clinical studies it was obviously safe, with only minor side effects. However, after its broad therapeutic use it turned out to produce fatal arrhythmias. In addition to being an H1 antagonist, terfenadine is a potent hERG channel inhibitor. Under normal conditions, terfenadine is already metabolized in the intestinal wall; no measurable plasma levels and no cardiac side effects are observed. If CYP inhibitors prevent terfenadine metabolism, cardiac toxicity results. Thus, in addition to its H1 receptor antagonism, the compound inhibits the hERG channel, a most prominent antitarget. The terfenadine problem could be circumvented by replacing the compound by its active metabolite fexofenadine, which is not any longer a hERG channel inhibitor.

Already around 1990, David Bailey discovered that grapefruit (but not orange) juice significantly increases the bioavailability of some drugs, for example the calcium channel blockers felodipine and nifedipine. After some problems to publish this highly surprising observation, his manuscript was accepted by Lancet and many reports followed for other drugs. The whole story shall not be elaborated here in detail but it remains the question: is CYP3A4, which is inhibited by some flavonoid and furocoumarin constituents of grapefruit juice, an antitarget? It is: despite the fact that increase in bioavailability is a desirable effect, individual variation is too large to be of therapeutic value. Only in the case of clinically monitored drugs, for example cyclosporin, the co-medication of a CYP3A4 inhibitor, for example ketoconazole, is used to reduce the dose of this expensive drug.

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Recently it was discovered that grapefruit juice also induces the expression of intestinal drug transporters. With fexofenadine, the safe replacement of terfenadine, the paradox situation results that bioavailability of this drug decreases (!) after intake of grapefruit juice, due to induction of an efflux pump, the organic anion-transporting polypeptide 1A2 (OATP1A2). Kirby and Unadkat commented this paradox by asking the question "Grapefruit juice, a glass full of drug interactions?"

Not only food constituents but also OTC drugs may cause significant drug-drug interactions. One of the well-known examples is St. John's Wort (*Hypericum perforatum* L.) extract, supposed to be beneficial against mild depression. However, in addition to the phototoxic agent hypericin, the plant contains hyperforin, the strongest inducer of CYPs (especially CYP3A4) and drug transporters. In this manner, self-medication with St. John's Wort reduces the bioavailability and thus the activity of several drugs, whereas doses of some drugs have to be reduced after discontinuation of this extract because CYP and transporter levels return to normal.

There are many more antitargets, prominent ones being several G protein-coupled receptors. Thus, it is high time that a book on antitargets becomes available and we, as Editors of the series Methods and Principles in Medicinal Chemistry, are very much indebted to Roy Vaz and Thomas Klabunde, leading scientists in antitarget research, for editing such a monograph. The book starts with an introduction on the reasons why drugs fail in the clinics or after market introduction and a chapter on ADME and side effects prediction. The main two sections contain several chapters on antitargets and side effects (hERG channel and GPCR antitargets) and on antitargets in ADME (CYPs and drug transporters). The book concludes with some case studies of drug optimization against antitargets.

We are very grateful to all chapter authors and we thank the publisher Wiley-VCH, especially Dr. Frank Weinreich, for the ongoing support of our series, and Dr. Nicola Oberbeckmann-Winter for her contributions in the preparation of this volume.

October 2007

Raimund Mannhold, Düsseldorf
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A Personal Foreword

A single report of a drug reaction in a 39-year-old woman ultimately contributed to the removal of the allergy drug Seldane (terfenadine) from the market in 1998 [1]. Doctors at the National Naval Medical Center in Bethesda, Md., admitted the woman to the hospital because of fainting episodes. She had been prescribed Seldane (terfenadine) 10 days before. She also started using the prescription drug Nizoral (ketoconazole) for a vaginal yeast infection. That combination caused potentially fatal changes in her heart rhythm. The Food and Drug Administration (FDA) issued warnings indicating that ketoconazole interfered with terfenadine's metabolism, which resulted in increased levels of terfenadine in the blood and slowed its elimination from the body. The FDA also warned that a similar effect could occur if Seldane was taken with the antibiotic erythromycin.

Thus the first awareness of antitargets was brought to the forefront with the withdrawal of terfenadine. Ketoconazole is a strong inhibitor of CYP3A4, which is also the primary enzyme responsible for the clearance of terfenadine. The inhibition of CYP3A4 leads to the increase in concentration of terfenadine in the blood. Terfenadine itself is a blocker of the ion channel hERG (human ether-a-go-go related gene) and caused a prolonged QT, leading to Torsades de Pointes and possibly death. Also ketoconazole inhibits the efflux transporter P-glycoprotein (P-gp) or MDR1 (multidrug resistance protein), for which terfenadine is a substrate. Hence when co-administered with ketoconazole, the concentration of terfenadine in blood would be much higher than if taken without other drugs such as ketoconazole. Therefore inhibition of both P-gp and CYP3A4 could lead to drug-drug interactions and inhibition of hERG either by the compound itself or its metabolite.

The example of terfenadine shows that toxic effects can be either induced directly by the action of a drug or a drug metabolite on an antitarget like the hERG channel. In addition, certain transporters and metabolizing enzymes, like P-gp and CYP3A4, need also be considered as antitargets as blocking their activity can change the concentration of a co-administered drug or its metabolite in blood, thus causing drug-drug interactions and potential toxicity.

Adverse drug reactions (ADRs) cost approximately one hundred and thirty nine billion dollars annually [2–4] in the United States. This number is larger than the

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cost of cardiovascular or diabetic care. ADRs cause 1 out of 5 injuries or deaths per year to hospitalized patients and the mean length of stay, the cost and the mortality for patients admitted due to an ADR are double that for control patients. Many ADRs are due to off-target and antitarget interactions. Some of these have lead to withdrawal of the drug(s) from the marketplace.

Since terfenadine, there have been other market withdrawals of drugs. As shown in the first chapter of the book the main cause for the 16 drug withdrawals from 1992 to 2002 was toxicity, mainly cardiovascular toxicity or hepatotoxicity. Only recently Vioxx (rofecoxib) had to be withdrawn from the market. In contrast to terfenadine, where the molecular mechanism of its side effects has been fully understood, the underlying mechanism by which rofecoxib, a selective cyclooxygenase 2 inhibitor that exhibits cardiovascular effects is still unclear [5]. Pondimin (fenfluramine), a serotonergic anorectic, was withdrawn in 1997 due to the risk of development of primary pulmonary hypertension or valvular heart disease. The first case of fenfluramine associated valvular heart disease discovered 7 years after discontinuation of treatment and requiring double valve replacement 2 years later has just been reported [6]. For fenfluramine the mechanism by which it causes valvular heart disease has recently been uncovered showing a causal association between agonism on the G-protein coupled receptor (GPCR) 5-HT_{2B} and valvular heart disease (Chapter 7 in the book).

According to FDA experts, discovering terfenadine's interactions with other drugs marked a significant advance. These and other discoveries improved the ability of the FDA and drug manufacturers to test for drug interactions and to investigate risks of heart rhythm abnormalities and other toxicities before drugs could be marketed. In addition, unraveling the mechanism of drug toxicities and identifying specific channels, receptors including nuclear receptors, transporters or enzymes as antitargets enabled establishment of *in vitro* test systems to monitor potential antitarget mediated side effects and toxicity in the drug discovery phase. The list of antitargets is still being compiled but the events that have lead to the discovery of the known antitargets has impacted the way research is conducted during drug discovery today.

In every family of biological targets there are antitargets. In this book, we have avoided discussion of kinases, which are still controversial as non-oncology targets and could probably command several chapters or volumes. Transporters and metabolizing enzymes like CYP450s that can mediate undesired drug-drug interactions have been mentioned before. In the area of potassium voltage-gated ion channels, there are therapeutic targets such as Kv1.3 and Kv1.5 but at the same time there are antitargets such as hERG. GPCRs form a large protein family that plays an important role in many physiological and patho-physiological processes. Especially the subfamily of biogenic amine binding GPCRs has provided excellent drug targets for the treatment of numerous diseases [7]. Although representing excellent therapeutic targets, the central role that many of the biogenic amine binding GPCRs play in cell signaling also poses a risk on new drug candidates which reveal side-affinities towards these receptor sites: These candidates bear the risk to interfere with the physiological signaling process and to cause undesired effects in preclinical or

clinical studies. Besides the 5-HT_{2B} receptor mentioned before, the α_{1A} adrenergic receptor, being a drug target for the treatment of benign prostatic hypertrophy (BPH), has been suggested as an antitarget at the same time that mediates cardiovascular side-effects of many drug candidates causing orthostatic hypotension, dizziness and fainting spells [8]. Other examples of GPCR antitargets are the muscarinic M1 receptor correlated with attention and memory deficits or the serotonin 5-HT_{2C} receptor associated with weight gain. As shown in one of the introductory chapters of this book, correlation between *in vitro* affinity and *in vivo* adverse effects can currently be recognized by profiling, hundreds of drugs with known ADRs using large panels of pharmacological *in vitro* assays.

There are several references made to both off-targets as well as antitargets in the literature. In this book we will primarily be attempting to cover the topic of antitargets. Off-target activity the way we interpret it, is activity for a particular compound towards a target that was not anticipated, when it was synthesized or isolated. For example, compounds that are designed or synthesized for activity towards serine proteases (not for thrombosis) are not expected to have any activity towards serine protease targets such as thrombin or others in the coagulation pathway, which could be anti-thrombotic targets themselves. The term off-targets includes antitargets and the off-target activities could be beneficial or detrimental. Antitargets on the other hand are targets that are detrimental towards progression of the compound towards becoming a drug.

Within recent years the understanding of the molecular interactions between antitargets and drugs or drug candidates has tremendously increased allowing *in silico* antitarget models to be established. 3-dimensional structures of several antitargets (often in complex with inhibitors) are now available either derived by homology modeling (e.g. the hERG channel or GPCRs) or by protein crystallography (e.g. cytochrome P450s). Structural chemical motifs often associated with antitarget interactions (e.g. for cytochrome P450 binding or inhibition) have been captured in knowledge databases. Computational models like 3D-pharmacophore or 3D-QSAR models (e.g. for GPCRs, hERG, CYPs, P-gp) have been established to not only recognize antitarget affinities in chemical lead series but also to guide the chemical optimization of these leads towards development candidates lacking undesired antitarget side affinities and thus potential side effects or toxicities. These models are captured – together with introductory chapters on the biological aspects – in the second (focusing on ion channels and GPCRs) and the third section of this book (describing antitargets mediating drug-drug interactions).

Examples of optimization of selectivity towards the antitargets have been well described in the recent literature such as illustrated in Gao et al. [9] and Kuduk *et al.* [10]. In the last section we have tried to include very specific case studies of successful drugs for which optimization of selectivity towards specific or general antitargets were successfully negotiated, e.g. for Januvia (chapter 17), a recently released DPP4 inhibitor or for PRX-00023, a selective 5-HT_{1A} agonist currently in phase IIb clinical trials (chapter 19).

We would first thank the editors of the series for enabling this volume in the Methods and Principles in Medicinal Chemistry series. We would like to sincerely

thank all chapter authors for making this book a reality. We would like to acknowledge their great enthusiasm in preparing their manuscripts and the high quality of their contributions. It has been a pleasure working with each and every one of them. The editors are also grateful to Frank Weinreich, Nicola Oberbeckmann-Winter and the staff of Wiley-VCH for their excellent support in the production of this book. We also thank the Sanofi-Aventis Discovery Management for enabling this book. We thank our families for putting up with us during the last few months.

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