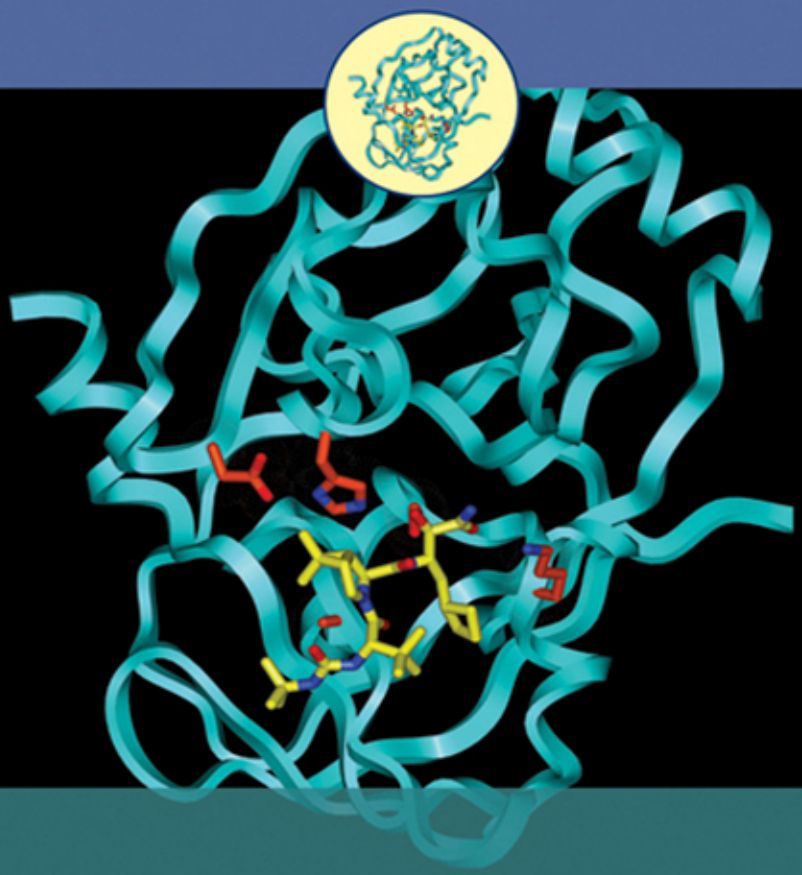
CASE STUDIES IN MODERN DRUG DISCOVERY AND DEVELOPMENT

EDITED BY
XIANHAI HUANG
ROBERT G. ASLANIAN



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Bob would like to dedicate the book to his wife Antoinette and his boys, Thomas, James and Andrew, who make it all worthwhile.

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PREFACE

The discovery of a new drug is a challenging, complicated, and expensive endeavor. Although exact figures are hard to come by, recent published data indicate that it takes about 10 years and close to $1 billion to develop and bring a new drug to market. Additionally, according to a recent analysis only 11 out of 100 drug candidates entering Phase I clinical trials, and one out of 10 entering Phase III, will become marketed drugs. Many of these drugs will never make back the money invested in their development. These are dismal statistics. Improving the success rate of the discovery and development process is a key factor that will weigh heavily on the success, and perhaps the survival, of the pharmaceutical industry in the future. There are numerous reasons for the current lack of new molecules reaching patients. To address the problem, many large pharmaceutical companies have tried to reinvent themselves over the last 10 to 15 years. The methods employed have included incorporation of what could be described as the latest fads in drug discovery into research operations, internal reorganizations or, as a last resort, mergers. None of these approaches has helped to solve the dearth of new drugs coming from the industry. Another approach to solving this conundrum is to look to the past to see what has previously worked in successful drug discovery programs and try to apply the knowledge gained in those programs to current efforts. Therefore, the critical question becomes how to more efficiently apply proven drug discovery principles and technologies to increase the probability of success for new projects. Knowledge gained from the successful discovery and launch of marketed drugs can provide a very useful template for future drug design and discovery. This rationale was a major factor for compiling *Case Studies in Modern Drug Discovery and Development*.

The primary target audience for *Case Studies in Modern Drug Discovery and Development* is undergraduate and graduate students in chemistry, although all scientists with an interest in the drug discovery process should benefit from these case studies. Most chemists who work in the early stages of drug discovery in the pharmaceutical industry do not train to be medicinal chemists. They train in synthetic organic chemistry, either total synthesis, methodology, or a combination of the two. There is a good reason for this: chemists need to be able to make the compounds they design as quickly as possible so as to drive structure–activity relationships (SAR) to meet project criteria. But prior to starting their careers in the industry, many chemists wonder how they can quickly master the necessary skills and knowledge of the drug discovery process including SAR, pharmacology, drug metabolism, biology, drug development, and clinical studies. Besides providing a roadmap of successful drug development for application to current problems, *Case Studies in Modern Drug Discovery and Development* illustrates these concepts through the use of examples of successful, and not so successful, drug discovery programs. Written by acknowledged leaders in the field from both academia and industry, this book covers many aspects of the drug discovery process with detailed examples that showcase the science and technology that go into drug discovery. We hope that *Case Studies in Modern Drug Discovery and Development* will be suitable for all levels of scientists who have an interest in drug discovery. Additionally, with the comprehensive information included in each independent chapter, it is suitable for professional seminars or courses that relate to drug design. Finally, the drugs collected in this book include some of the most important

and life-saving medications currently prescribed, so the information included should be of interest to the public who want to learn more about the drugs that they are taking.

We have to admit that we totally underestimated the amount of work involved in the editing of this case study book. It took more than 3 years from the conception of the book, author recruiting and chapter editing to the publication of the book. During this long process, there are many friends and colleagues who helped to make it happen. We would like to thank Wiley editor Jonathan Rose for initiating the process, giving us the opportunity, and trusting us in editing the book. He always quickly replied to every question that we raised during the process. We would also like to thank all the authors who dedicated their time to contribute to the chapters and their respective companies for permission to publish their work. We believe that all the chapters will have an important impact on future drug discovery programs and benefit future scientists of this field for generations to come. We salute them for their time, effort, and dedication. We would like to thank the reviewers of our book proposal for their valuable suggestions and critiques. Based on their suggestions we have collected examples of drugs that failed to advance to the market to showcase the "dark" side of the drug discovery and development process where huge amounts of work and resources are expended with no obvious return. We would like to thank Drs. Sandy Mills, Ann Webber, William Greenlee, Guoxin Zhu, An-hu Li, David Gray, and Markus Follmann for their assistance in recruiting the chapter authors.

One of our colleagues has said "If you must begin then go all the way, because if you begin and quit, the unfinished business you have left behind begins to haunt you all the time." We as scientists have chosen to make a difference in the improvement of human health, and we need to consistently empower ourselves in knowledge and experience. We hope that this book will help our readers to achieve their goals.

Xianhai Huang
Robert G. Aslanian

New Jersey
July, 2011

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CHAPTER 1

INTRODUCTION: DRUG DISCOVERY IN DIFFICULT TIMES

Malcolm MacCoss

At the time of writing (mid-2011), the pharmaceutical industry is facing probably its most difficult time in recent history. As little as a decade ago, the fact that the aging population in the Western world was increasing (i.e., the post-War baby boomer population was reaching retirement age and thus moving into a demographic that requires the use of more medications), coupled with the likelihood of worldwide expansion of modern medicine into large populations of developing countries, led to an assumption that this would move the industry into a golden era of drug discovery and commercial growth [1]. This was expected to be supplemented with the promise of the utilization of the fruits of modern molecular biology and genomics-based sciences following the completion of the Human Genome Project [2,3]. However, despite large increased investments by pharmaceutical companies in research and development (R&D), the number of new molecular entities (NME) approved by the U.S. FDA has not increased at the same rate as the increase in R&D investment [4]. This lack of productivity in the pharma R&D sector has been much analyzed and continues to be a topic of great concern and discussion both within and outside the industry [1,4–13], and ex-heads of research and development at major pharmaceutical companies have joined in the discourse [5,6,8,14,15]. In addition to this lack of productivity, we now find the industry under attack from a number of directions, and this has led to a dramatic reduction in the pharma workforce, at least in the Western world. In fact, since 2000, according to Challenger, Gray, and Christmas, as reported in Forbes [16], the pharmaceutical industry has been under such stress that it has cut 297,650 jobs, that is, about the size of the current Pfizer, Merck, and GlaxoSmithKline combined; thus, the manpower equivalent of three of the largest pharmaceutical houses in the world has been eliminated in a decade. Various mergers and acquisitions, driven by commercial and economic pressures, have led to eradication of a number of well-established pharmaceutical houses that for decades had provided the world with numerous life-saving and quality-of-life-enhancing medicines. The industry that was, for most of the past two decades of the twentieth century, the darling of Wall Street, with Merck, for example, being "America's Most Admired Company" for 7 years in a row, is now under major duress.

So what has gone so badly wrong with this once booming industry? This has been the subject of many editorials, publications, and blogs that are too numerous to mention here, but it all really stems from the coming together of a "perfect storm" of events and an industry that, apparently, was unprepared for the evolving situation.

Patent expirations, in particular, have become an issue for an industry that has been driven by a business model based on blockbuster drugs (generally considered to be a drug molecule that brings in more than $1 billion per year in sales). However, one result of this

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model is that the revenue created by a blockbuster drops dramatically overnight when the patent exclusivity expires and generics are allowed to enter the marketplace. This phenomenon, of course, is not new, but what is different now is that in the business model driven by one or two blockbusters per company rather than by a larger number of mid-sized products, the loss of a blockbuster has a much greater impact on any particular company. The research and development divisions of pharmaceutical companies have not been able to produce new replacement products for compounds going off patent in the time frames that the blockbuster products they are replacing have exclusivity in the marketplace. This issue is exacerbated by the increasing cost of research and development [4,5] and, in addition, the time frame that the first-in-class molecules are on the market before the "fast followers" or later entrant "best-in-class" molecules are approved for marketing is rapidly shrinking [5]. This problem has been noted for years. I well remember, in the mid-1980s when I had recently joined the industry, being told by high-level research managers that it was necessary to have a follow-up blockbuster already in place in the late-stage pipeline before the original one was approved, as this seemed to be the best approach to dealing with this conundrum. But the limitations of this approach are readily apparent. First, it is not clear that it is possible to predict with any degree of exactitude which project will lead to a blockbuster and which one will not. The time frame from initiating a project to the launch of an NME from that project is so long that much can change in the biomedical science environment and in the regulatory and commercial space during that period. Thus, companies have had to rely on bigger blockbusters at the expense of working on medicines for some diseases that were likely to bring in less revenues to the company – the inevitable spiral is then started, with more and more effort being put into products based on their commercial viability rather than on the unmet medical need that has driven the industry, and which has served it so well. In a speech made to the Medical College of Virginia in 1950 [17], George W. Merck made this famous comment, ". . . We never try to forget that medicine is for the people. It is not for the profits. The profits follow, and if we have remembered that, they have never failed to appear. The better we have remembered it, the larger they have been . . . How can we bring the best of medicine to each and every person? We cannot rest till the way has been found, with our help, to bring our finest achievement to everyone. . ." Recent trends in the industry (with some notable exceptions) suggest a drift from this mantra.

But the demise of the blockbuster business model is certainly not the only driver of the present situation. Some companies have attempted to overcome the problem of stagnant pipelines by acquiring, or merging with, other pharmaceutical companies that had, apparently, a more robust array of later stage products. The trouble with this approach is that the respite is at best temporary, and the merging of different corporate cultures has usually taken much longer to sort out than even the pessimists had predicted. In addition, there are an inevitable number of lay-offs (as already pointed out) that occur due to redundancies and overlaps in the merging of two large organizations, and such cost cutting is at least partially a result of the need to show a stronger balance sheet after the merger. Each of these acquisitions has left the preponderance of leadership and middle management in the new organization coming from the original company that had the deficient pipeline. It is not always clear whether the reasons for that deficiency had been fully understood – thus, eventually leading down the line to another pipeline crisis and leaving the true problem(s) unsolved. At best, these mergers have bought some time for the company making the acquisition, but several studies have questioned whether in the middle-to-long term they have provided a solution or even whether they have given rise to a stronger and more robust company than what would have been the case if the merger had not occurred and the two companies had progressed independently [4,18]. Altogether, this has resulted in a longer

downtime for productivity in the research operations of the new organization than expected and, in particular, the effects on morale have been devastating. How this has impacted the innovation effort is difficult to quantify, but it has to be considerable. It is generally considered that innovation, particularly innovation that often takes years to mature in the extended time lines of drug discovery, needs a stable and secure nonjob-threatening environment to allow appropriate risk taking for the great discoveries to occur. The insidious low morale seen in many pharmaceutical research organizations now makes it very hard for even the most motivated drug researcher to put in the extra hours that were once commonplace and which are often necessary to produce hand-crafted molecules with the right properties to be drug candidates for human use. The loss in productivity of this lost extra time investment is impossible to calculate, but it must be huge.

In the midst of all of this turmoil, companies have been desperately trying to reinvent themselves and to understand why the productivity of their research endeavors has been so poor. All the major pharmaceutical companies have undergone much introspection leading to reorganization and revamping of the way they do things. Mostly, this has been driven by two goals: first, to pinpoint excesses and overspending in their operations and to eliminate them, and second, to highlight better ways of carrying out their operations to become more efficient and streamlined so that they can get to the finish line faster and with a better potential product [19]. Both of these are perfectly laudable and appropriate goals. Unfortunately, it is difficult to quantify precisely the elements that go into making an innovative and creative research environment. These two goals are driven by hard numbers, and Six Sigma-type methods have been extensively used to quantify and then to drive all the excess spending out of the system to give a lean, flexible work environment. Such an environment requires much attention to the process involved and thus a close monitoring of the discovery process. While this undoubtedly has had the desired effect of reducing costs, it is very unclear whether it has at the same time improved the productivity of the research groups. Much innovation and true problem solving goes on "under the radar" and emerges when sufficient information has been gleaned to qualify it for consideration. Unfortunately, this is difficult to justify in the process-driven environment described above. True innovation does require pressure to deliver on time lines, but it also often requires individual freedom to operate and for everyone to live with the consequences. Often, innovation is also enabled by some amount of extra resources over the strict minimum calculated by methods mentioned above to allow researchers to follow-up on unexpected findings.

Any evaluation of a complex research environment requires that the entire operation be broken down into numerous smaller categories, with each of these being closely interrogated. It is often the way these operations are flexibly integrated at the macro level that determines the overall productivity of a complex organization – not necessarily the optimization of the specific parts. Nevertheless, the current paradigm is to break down the drug discovery process, up to the delivery of a candidate for toxicity testing, into target identification and validation, hit identification, hit-to-lead, lead optimization, and candidate selection. It is fair to say that this is a relatively new consideration. A decade ago, it was considered one continuous process with much overlap of the above-mentioned categories. This continuous operation gave a certain amount of autonomy to the scientists involved and certainly gave ownership of projects to the project team members. The more recent breakdown of the drug discovery process into its constituent parts has led to smaller companies being able to specialize in various elements of the overall endeavor, and nowadays the use of specialist contract research organizations (CROs) for various parts of the process is commonplace. A decade ago, such companies would have been based in the United States or Europe and were used primarily to prepare chemical libraries in new areas of research or to supplement in-house research to help with load leveling within the internal

operations. However, the past decade has seen a dramatic shift of the preparation of chemical libraries (to supplement and diversify internal repositories that tend to be a footprint of previous in-house programs) to CROs in the emerging nations of China and India where a highly skilled workforce, supplemented by a scientific diaspora of Chinese and Indian scientists trained in the West and returning home, was able to take on these tasks at a reduced full time equivalent (FTE) rate lower than in the United States or Europe. The explosion of science now being witnessed in this area has become transformative, with all companies now associated in some way with out-sourcing of some elements of their research operations. Many consider that the big winners of the future will be those who are the most successful at this venture, and some major pharmaceutical companies have relocated entire research groups and/or therapeutic areas to China or India. This "outsourcing" has greatly increased the complexity of research operations and the operational landscape has changed overnight. The planning, oversight, and monitoring of drug discovery programs with parts of the work going on in different regions of the world, in distant time zones, and sometimes with language issues, has become a huge factor in any pharmaceutical company. Thus, the deep discussions on the last day's results over coffee after work in a close working laboratory environment with friends and colleagues has been replaced with late-night (or early morning) teleconferences with specialist scientists one might never get to meet in person. It remains to be seen if this sea change in the way we do research will be appropriately productive in the long run, but certainly in the short term, because of the financial savings involved, it is a process now taken very seriously by management in pharma operations. My own view is that it will all depend on whether this can deliver the quality drug candidates necessary to sustain the growth of the multibillion dollar pharmaceutical companies, and the ones that will be the most successful are those that will blend the appropriate skill sets of their CRO colleagues with the in-house skills to get the job done quicker and cheaper than it was done previously. But costs in China and India are already starting to rise, and there is always, even in today's electronic world, an issue of turnaround time in the iterative "design – synthesis – assay – redesign – synthesis" drug discovery cycle that is so much an important driver of the productivity and speed of delivery of drug candidates. This point is being addressed now by "full-service" CROs in India and China that are taking on more and more of the early biochemical and biological assays as well as the chemical synthesis, thus, shortening the iterative cycle by having the full cycle performed on the same site.

Of course, there are several other elements to the "perfect storm" that has hit the industry. Certainly, since the voluntary removal of Vioxx from the market because of cardiac issues, there has been an intense scrutiny of other drugs that have been introduced, particularly with regard to cardiovascular issues. Although these have been seen as the Food and Drug Administration (FDA) being more vigilant, it is certainly appropriate that all new medicines are carefully scrutinized for their safety before being approved. New advances and initiatives are ongoing in all companies to consider earlier evaluations of potential toxicity in drug candidates, so that compounds that are likely to fail will do so early on in the process and so save downstream investment from going to waste. While much of this is driven by advances in *in vitro* studies, there remains a need for measures of acute *in vivo* toxicity earlier in the process and this, in turn, brings a need for earlier scale-ups of the active pharmaceutical ingredient (API), which itself can add more time, resources, and costs to the discovery process. The main issue here is that we must be sure that when we kill compounds early, we are indeed killing the appropriate molecules, that is, the introduction of earlier *in vitro* toxicity studies must produce robust "kills," we must not have increased numbers of false positives that throw out the baby with the bath water. We *must* make safer drugs (between 1991 and 2000, ~30% of drug candidates failed for toxicity and clinical

safety reasons [6,7]) and when we err, we *must* err on the side of safety, but it has long been known that all xenobiotics have some risk associated with them [20] and the design and discovery of safe drugs is all about the therapeutic ratio and how one assesses the risk involved with any new medicine. There will be any number of iterations of the steps involved at various companies to find the best way forward in this regard, but advances in this area can only lead to a safer armamentarium of medicines for patients.

On the other hand, drugs that are failing in the later phases of development, are not just failing because of toxicities that are being seen in preclinical and clinical studies. Drug candidates are also failing in clinical trials because of lack of efficacy. Despite the recent increase in our biomedical knowledge and our increased understanding of the molecular mechanisms of disease, ~30% of attrition in potential drug candidates is due to lack of efficacy in clinical trials [6,7] although this is somewhat therapeutic area dependent [6]. For instance, some of this might well be due to notoriously unpredictive animal models of efficacy such as in CNS diseases and for oncology [21], both of which have higher failure rates in phase II and III trials. It is disconcerting that positive results in the smaller highly controlled phase II trials don't always replicate in the larger population bases used in phase III trials. But the take-home message is that compounds failing this late in the development process are causing an enormous drain on resources and the "kill early" concept for drug candidates is now the mantra in the pharmaceutical world. In addition, the rate of attrition of compounds working by novel mechanisms is higher than for those working with previously precedented mechanisms [6]. If one makes the assumption that toxicities due to nonmechanism-based side effects (i.e., molecule-specific off-target activities) are likely to be the same across both types of mechanisms, then this implies that the higher attrition rate for novel mechanisms might be due to mechanism-based toxicities that occur because of an incomplete biological understanding of the novel target or due to a lack of efficacy because the target protein is not playing the attributed role in the disease state in humans. One likely outcome of this is that risk-averse organizations might choose to work primarily on precedented mechanisms.

Perhaps more difficult to assess is the commercial need by payers to address the worth of any new treatment that is being proposed. Thus, any new medicine must demonstrate that it provides a measurable increase in value both to the patient and to the payers (governments or insurance companies, or both), not just that it provides a new pill for an old disease, for which older, cheaper medicines might already serve adequately. The question of value will always be somewhat subjective (e.g. cost versus quality of life versus increased life span) and the clinical trials that are sometimes necessary to demonstrate such improvement in a chronic disease, requiring prolonged dosing and being run head-to-head with a current standard of care, in addition to placebo where possible, are often extremely large, long, and expensive. Sometimes, knowing this ahead of time has dissuaded organizations from working in that area. It should be noted that the aging population, and by definition a smaller tax base to support that demographic group, which as mentioned earlier has been a driver for more revenues for the industry, is layered on to the fact that health care systems in the Western world are having a difficult time meeting the financial demands of the increased need for health care in that population – including the costs of new medicines. However, we should not forget that the cost of drugs is still a small percentage of the total healthcare budget and for the large part good medicines allow patients to spend less time in hospitals and other health care institutions.

All these issues have come together in the past decade to increase greatly the cost of drug discovery, despite the industry's efforts to cut costs (see above). The cost to discover a new drug is estimated to be well over $1 billion and there seems to be no end to the increased costs in sight.

Of course, there are other, more scientific issues that over the past decade have changed the playing field upon which we practice our art of medicinal chemistry. Combinatorial chemistry has come and gone, and has now been replaced to a large degree by parallel and high-throughput synthesis of individual molecules. These rapid synthesis methods, along with high-throughput screening (HTS) methods have been major enablers of getting lots of data on lots of molecules. However, I believe a more subtle change is also occurring and that has to do with the nature of the targets that we now address. Before the Human Genome Project, we basically addressed targets such as enzymes, G-protein-coupled receptors (GPCRs), ion channels, and nuclear receptors, targets that had been well studied biochemically prior to the medicinal chemist getting involved on a project. After the Human Genome Project, we were able to associate various proteins with different disease states. Many of these proteins were without any known enzymatic or receptor-driven activity and we have started to attack the problem of making protein–protein interaction inhibitors (PPIs). This new trend has been addressed in a number of ways, but one of the preferred methods has come from using fragment-based hit identification methods coupled with rapid throughput structural biology and chemistry, and computational chemistry methods. Taken together, this has required the preparation of new, hitherto unprecedented, libraries as starting points, as well as improvements in X-ray crystallography and NMR methods to determine how the fragments bind. These developments are taking time to come to full fruition, but there are now numerous examples of these applications in various pipelines. Not too long ago, a medicinal chemistry program could be initiated without a lot of structural information if the correct biochemical assays were in place. Nowadays, the contributions of structural biology to hit identification and hit-to-lead activities can be seen in almost all programs. As we emerge from the postkinase era and more into the PPI era, the companies that are best equipped with these modern methods will benefit the most. There will be a short time lag as these methods get honed, but I believe it will drive us into much newer chemical space and very novel approaches to drug design.

I also feel that the time has come to reassess the very way in which we practice medicinal chemistry. Over the past decade, collectively we have become very good at both solving the problems of acute toxicities (hERG binding, acute liver toxicity, etc.) and solving some of the drug metabolism, absorption, distribution, metabolism, and excretion (ADME) issues while addressing the pharmaceutical properties of the molecules (absorption using Caco-2 cells, metabolic liability using microsomes or hepatocytes, Cyp450 inhibition, brain penetration, log *P*, polar surface area, solubility, Lipinsky guidelines [22], etc.) and the roles that these all play in *in vivo* readouts and in the big picture of drug discovery and molecule optimization. This is borne out by the much lower attrition rates for drug candidates in the phase I stage than were apparent a decade earlier [6,23]. These improvements occurred because research organizations identified the problem (it was demonstrated that in the 1980s drugs failed primarily because of PK and ADME issues in phase I [6,23]) and drug companies put in place assays and procedures to address the issues. Also, with the advent of high-throughput assays it was possible to get large amounts of data, with a quick turnaround time so that they could meaningfully impact on the next round of synthesis activity, on all these potential issues so the structure–activity relationships (SARs) that drove them were quickly understood. At that time, this represented a sea change from primarily addressing the SAR on just the target protein [23].

However, there is another side to this story. Since the advent of these technologies that allow for rapid evaluation of molecules, there has been a significant trend in the past decade toward making lots of compounds using routine and relatively straightforward chemistries to improve the likelihood of better understanding the numerous (sometimes orthogonal) SARs. This approach has led to many two-dimensional, high molecular weight molecules

that often don't explore enough three-dimensional space, and I often wonder if enough time is spent making targeted, three-dimensional molecules to answer specific structural or SAR-related questions. It is this overreliance on "more is better," but with relatively straightforward chemistries involved and where easier metrics can be applied irrespective of the outcome, that has been one of the contributors to the outsourcing phenomenon mentioned earlier. This topic has been discussed by Roughley and Jordan in a paper [24] describing the most frequently used reactions in medicinal chemistry (e.g., amide bond formations, 22%; Suzuki/Sonogoshira reactions, ~10%; and protecting group manipulations, ~20%) and the average number of steps per synthesis (3–4 steps); the publication has stimulated a healthy discussion [25].

Advances in synthesis methods to influence stereo control have made syntheses of chiral molecules from achiral precursors more readily available and the growth of chiral chromatography and SFC methods make access to more complicated (and thus more information-rich) molecules much more feasible. In fact, this issue has recently been discussed in some detail by several authors [26–28] who have clearly demonstrated that molecular complexity and the presence of chiral centers in a candidate drug molecule correlates directly with success as molecules transition from discovery, through clinical testing and to drugs. However, the ability to regularly make meaningful complex molecules, on the shortened timescale we have become used to in medicinal chemistry lead optimization programs, is still some way into the future. Throughout a project we must constantly try to understand all the contacts that a molecule needs to make with its target protein to drive specificity into as small a molecule as possible – this often requires small, complex three-dimensional molecules. Structural biology (X-ray and NMR) and computational chemistry (rational design) can help with the selection of which molecules to make. This understanding of the structural interactions between a target protein and a drug candidate can work well in the early stages of a project with >100 nM potency compounds, before hydration–dehydration effects on binding make the predictions more difficult. This last point is important because one of the drivers of the "more is best" thought process is that, correctly so, most chemists don't want to engage in a long synthesis with only a poor chance of success at the end – better to make a larger number of molecules even if the information obtained from them is less because one sometimes gets surprises that can take the SAR into a completely novel direction. To be sure, I am a believer in making large numbers of molecules by relatively simple chemistries – and weekly, more complex chemistry is being applied to the rapid analogue synthetic armamentarium – but it is important to choose when that particular tool is applied in the drug discovery process. Certainly, in the early hit identification and hit-to-lead space, such methods play an important role, but there comes a clear point in a program where taking time to make the "right" compound(s) is much preferred to making lots more molecules that don't meaningfully advance the understanding of the SAR. Also, it is clear that not all drugs have to be complex molecules, and some good drugs are indeed simple achiral structures. However, because the binding sites on proteins are three-dimensional, it is likely that the more selective small molecules will have more points of contact with the protein surface, and hence have chirality associated with them.

After mentioning above the difficulties that the medicinal chemistry community has had to face in the past decade, it is heartening indeed to see the chapters included in this volume. It is terrific to see the creativity, patience, and innovation needed to design the molecules included in the chapters that follow. It shows again the resilience of the practitioners of our craft who have managed to continue their deep intellectual commitment to drug design and synthesis despite all the difficulties in their work environment. Designing drugs and building them from scratch is one of the most complex tasks that scientists face;

I have heard it said that ". . . designing a successful drug from the initial, qualitative clinical assessment of the disease, through a complete understanding of the molecular pathways involved, to the delivery of a small molecule which interferes safely with a new biochemical mechanism to change the fate of patients suffering from that disease, is as complex as designing the space shuttle when one considers the number of issues that need to be taken into consideration and the hurdles one has to overcome . . ." This process is not something that can be commoditized; although clearly parts of the process can be repetitive, it requires the utmost in intellectual commitment and innovative endeavor.

Thus, it is on this difficult background that the noble endeavor of drug discovery must continue to move forward, even if the path is steep and the costs continue to rise. We must persevere because otherwise our children and their children will be restricted to using only the drugs of their parents to fight their battles with the same devastating diseases, despite all the wonderful discoveries in medicine and the biological sciences that fill academic journals with new understanding of the basic science underlying diseases. This information is derived and published so that those of us who practice medicinal chemistry can use it to design newer and better drugs. This is particularly relevant as we look at a world that is still ravaged by cancer and Alzheimer's disease in a rapidly aging population; in a world where obesity and diabetes are now epidemic; and in a world where humans are still devastated by malaria, tuberculosis, and HIV; and we must do it in a way that patients worldwide can afford and benefit from our endeavors.

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CHAPTER 2

DISCOVERY AND DEVELOPMENT OF THE DPP-4 INHIBITOR JANUVIA™ (SITAGLIPTIN)

Emma R. Parmee, Ranabir SinhaRoy, Feng Xu, Jeffrey C. Givand, and Lawrence A. Rosen

2.1 INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a global epidemic characterized by high blood sugar (hyperglycemia) due to insulin deficiency and tissue resistance to insulin-stimulated glucose uptake and utilization. The incidence of T2DM has been exacerbated by increased rates of obesity attributed to a ready availability of high calorie diets and increasingly sedentary lifestyles. It is estimated that at least 170 million people worldwide have diabetes, and this number is expected to double by 2030 [1]. The progressive nature of the disease manifests as a relentless decline in pancreatic islet function, specifically in the β-cells that secrete insulin, exacerbated by increased metabolic stress and secretory demand. Serious complications ensue as consequences of the metabolic derangement, including dyslipidemia, retinopathy, neuropathy, renal failure, and vascular disease. Although several medications are available for the treatment of T2DM, the initial correction of hyperglycemia is usually not sustained beyond a few years. These therapies may also be associated with side effects such as hypoglycemia, GI intolerance, and weight gain. None of these therapeutics is able to reverse or even delay the progressive decline in islet β-cell function. Hence, initial oral monotherapy is inevitably followed by a combination treatment to control blood sugar, and the average patient with type 2 diabetes has to resort to daily insulin injections for glucose control within 6 years of diagnosis [2]. Medications with increased safety and durability in controlling blood glucose levels are key unmet medical needs for this patient population.

2.2 DPP-4 INHIBITION AS A THERAPY FOR TYPE 2 DIABETES: IDENTIFICATION OF KEY DETERMINANTS FOR EFFICACY AND SAFETY

2.2.1 Incretin-Based Therapy for T2DM

Over the past 15 years, considerable research into new therapeutics for T2DM has focused on the physiology and pharmacology of two peptide hormones, glucagon-like peptide 1

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