# Innovative Approaches in Drug Discovery

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## Ethnopharmacology, Systems Biology, and Holistic Targeting

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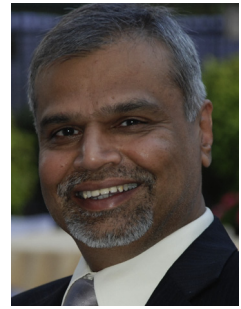

**Bhushan Patwardhan,** Professor and Director of the Interdisciplinary School of Health Sciences, Savitribai Phule Pune University in Pune, India, is an internationally recognized expert on ethnopharmacology and integrative health. He brings a unique blend of industry/academia executive culture in advancing evidence-based Ayurveda. He is also Chairman of the Academic Planning and Development Committee at the National Institute of Pharmaceutical Education and Research in Mohali, India. He served as advisor for several policy-making bodies, including the Task Forces of the National Knowledge Commission and the Planning Commission, and Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) of the World Health Organization. Prof Patwardhan is a Fellow of the National Academy of Medical Sciences in India, and the founder and Editor-in-Chief of the *Journal of Ayurveda and Integrative Medicine*, as well as member of the editorial boards of several other journals. He is the recipient of many awards and orations including Parkhe Award for industrial excellence, Dewang Mehta Award for educational excellence, and Sir Ram Nath Chopra Oration. He has guided 18 PhD students, holds eight Indian patents, two US patents, and has written more than 120 research publications. He received his PhD in Biochemistry from the Haffkine Institute in Mumbai, and University of Pune in Pune, India.

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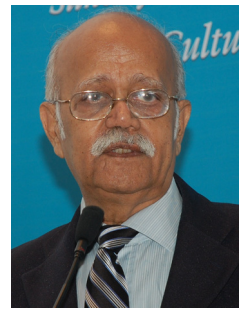

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**Anuradha Roy**, PhD, has been the director of the High Throughput Screening (HTS) Laboratory at the University of Kansas, Lawrence, KS, United States, since 2013. She has 23 years of academic and biotech experience, and has managed development, optimization and execution of early drug discovery projects from target identification, and assay development for high-throughput screening campaigns. As director of the HTS core, her professional responsibilities include helping academic investigators across state universities through the process of developing their target ideas into screenable assays for probe identification. She received her doctoral as well as her MD in Life Sciences from Jawaharlal Nehru University in New Delhi, India.

**Kalpana Joshi**, received her PhD in Microbiology from the Biochemical Science Division of National Chemical Laboratory (CSIR-NCL), and has worked at Lupin R&D as drug discovery manager. At present, she is Professor and Head of the Department of Biotechnology at Sinhgad College of Engineering, SP Pune University, in Pune, India. She has taught for more than 20 years and has lead several prestigious projects funded by DST, ICMR, the Office of the Principal Scientific Adviser (Government of India), and several private companies like Intel, and Glenmark. Her research specialization is molecular and cell biology, pharmacogenomics, biochemistry, immunology, and network pharmacology, whereas the main focus of her research are maternal health and nutrition, pharmacogenomics and ayurvedic biology are her research interests.

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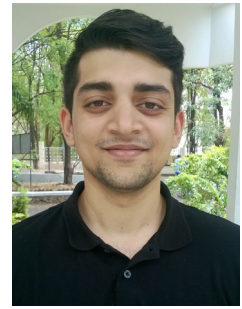
**Tejas Shah** holds an MD in Biomedical Sciences, with a specialization in Drug Discovery and Development, and is pursuing a PhD. He has worked on a number of prestigious projects funded by different government agencies such as DST, ICMR, and the Department of AYUSH, and is Senior Research Fellow at the Sinhagad College of Engineering. He has acquired expertise in developing animal models for diseases such as diabetes and GDM. His areas of interest are molecular and cell biology, molecular pharmacology, and pharmacogenomics.

**Ms. Kalyani Kumbhare** has a BA in Microbiology (Industrial Microbiology) and an MD in Health Sciences from the Interdisciplinary School of Health Sciences, Savitribai Phule Pune University in Pune, India. She has experience in animal handling and has worked in transdisciplinary projects involving herb-drug interactions of antidiabetic drugs, pharmacoepidemiology, and macrofungal diversity. She was awarded a scholarship in the Naturalist Scholarship Program, 2011, organized by the Research and Action in Natural Wealth Administration (RANWA) and has also presented a poster at the National Conference on Biodiversity Assessment, Conservation and Utilization in Pune, India.



**Neelay Mehendale** is a graduate of the Savitribai Phule Pune University in Pune, India. He has completed his Integrated MSc in Biotechnology from the Institute of Bioinformatics and Biotechnology, and has carried out his dissertation under the guidance of Prof Patwardhan. His research interest lay in the areas of biochemistry, biophysics, and computational biology. He is also an accomplished Indian classical vocalist.

**Saniya Patil** is currently in her fourth year of studies at the Institute of Bioinformatics and Biotechnology, Savitribai Phule Pune University in Pune, India, where she is pursuing her Integrated M.Sc. in Biotechnology. She has worked on projects involving network pharmacology to study the antimicrobial effect of Ayurvedic formulations, and the cytotoxic effect of gold nanoparticles on cancer cells.

**Jatinder K. Lamba** has around 20 years of expertise in the field of pharmacogenomics and is currently Associate Professor and Graduate Program Coordinator in the College of Pharmacy at the University of Florida in Gainesville, FL, United States; she has served as a grant reviewer for numerous NIH study sections and is currently a regular member of XNDA study section. Her research is focused on identification, characterization, and clinical validation of genomic/epigenomic markers predictive of therapeutic outcome in cancer patients, and it spans from preclinical basic research utilizing cell line model systems to translational/clinical phase in patient populations from multiinstitute clinical trials. Research in her laboratory on pharmacogenomics/epigenomics in pediatric AML is focused on identification, characterization, and clinical validation of predictive genetic markers of response to multiple anticancer agents used in AML treatment, and has been funded by NCI since 2008. Dr. Lamba's group is working on developing algorithms to incorporate pharmacogenomics/epigenomic markers with other prognostic factors to advance precision medicine in oncology; identification of such patients upfront will provide opportunity to tailor the initial chemotherapy to achieve maximum benefit.

# Foreword

## NATURAL PRODUCTS ARE DEAD—LONG LIVE NATURAL PRODUCTS!

We are pleased to write this Foreword for *Innovative Approaches in Drug Discovery: Ethnopharmacology, Systems Biology and Holistic Targeting*, by Bhushan Patwardhan and Rathnam Chaguturu. Both editors are experts in their fields, but more importantly they are original thinkers. Given that innovation may be the only way to survive "creative destruction," as described by McKinsey's Foster and Kaplan, it is important for readers to know that Drs. Patwardhan and Chaguturu understand this need fully. As the editors propose, the present book shows the ongoing revolution in biomedical research and development (R&D), reaching from yesterday's disease- and target-centric mindsets to the more person- and phenotype-centric therapeutic solutions of tomorrow. The book thus paints a "precision medicine" approach that builds on today's growing foundation of scientific insights, but realizes that "good enough never is." At its zenith, what is covered herein elucidates the perspective required to leverage the latest multitarget systems-based mindsets to achieve a better, more holistic, health care outcome. The final installment of the revolution we foresee in medicine will be counted in lives saved, every one of them a miracle made possible by the vision and creativity of people like the editors and authors of this book.

At a core level, the present book is about "pharmacognosy," and the possibility that its reintroduction into the fundamentals and modern practice of biomedical R&D may provide the necessary insights that catapult the next generation of drugs to success. What is pharmacognosy? If you look in a dictionary, you will first see that pharmacognosy is pronounced [färməˈkägnəsē]. You will next see that it is a noun meaning a "branch of knowledge dealing with medicinal drugs that are obtained from plants or other natural sources." Indeed, the word's origin is said to trace back to the mid-1800s, from "pharmaco," which means "of drugs," and "gnosis," which means "knowledge." From this definition, readers will rightly conclude that, in many cases, pharmacognosy involves the study of natural products. As long-time students and practitioners of biotechnology and pharmaceutical R&D, we know about pharmacognosy, but many of today's educators and researchers have forgotten about its importance. The present book is thus

even more important in correcting such a significant lapse in institutional memory.

Why are natural products so important? Natural products have always been an integral part of an almost infinite molecular diversity that accesses interesting biology, and during our careers we have been front and center in characterizing and filling this chemical space. Recent estimates suggest that natural products account for a large proportion of drugs on the market today. For example, Newman and Cragg in their analysis on sources of new drugs for the period of the 1940s through 2014 concluded that roughly 50% of the anticancer drugs approved in that timeframe were either natural products or drugs derived directly from natural products. Numerous examples of natural products and drugs derived therefrom can be found throughout major treatises on medicinal chemistry. In sum, this certainly sounds like an important area!

Noteworthy leadership in natural products discovery and development was evident at many longstanding pharmaceutical leaders a few decades ago. Roche, e.g., was particularly invested in marine natural products. Their Australian Research Institute of Marine Pharmacology discovered a number of interesting and unusual but still drug-like molecules, including nucleosides such 1-methylisoguanosine, also known as doridosine. Doridosine bound to adenosine receptors, an important pharmaceutical target at the time, and a class of targets that are still the subject of ongoing R&D today. Many of us were fascinated by the creativity of nature in devising these novel chemical structures.

As cell and molecular biology, genomics, high-throughput screening, and structure-based design technologies advanced through the 1980s, 1990s, and 2000s, progressively only those drugs with a selective activity against an isolated molecular target were in favor in the pharmaceutical industry. While new approaches to discovering natural products continued to be developed during this same period of time using technologies such as proteomics, natural products, as the basis for drug discovery in large pharmaceutical companies ("Big Pharma"), fell out of favor. Among other factors, high-throughput screening of natural product extracts proved difficult, which contributed to Big Pharma's move away from natural products. In fact, we personally witnessed the closure of natural products efforts during our careers at a large pharmaceutical company in the 1990s.

Another reason for the exit of Big Pharma from natural products R&D was the difficulty of synthesizing large quantities of complicated organic molecules cost effectively. Discodermolide, an anticancer polyketide lactone with 13 stereogenic centers isolated from a Caribbean sponge, proved to be a rare example of at least a chemical if not a human safety and efficacy success on the latter front. Novartis required a more than 30-step synthesis to produce just a few tens of grams of material for clinical trials, and also required the use of fragments prepared by fermentation. The other example

that comes readily to mind is the anticancer agent, paclitaxel (Taxol). It took nearly 25 years to realize commercial success from the original discovery to total synthesis and scaleup, even with a number of the best academic minds hard at work on the problem.

Other questions have been raised about natural products in recent years, such as invalid bioactives possibly undermining drug discovery. This concern stems from the recent elucidation of pan-assay interference compounds, so-called PAINs, which can give rise to false positives in drug screening campaigns. But the same issues with promiscuous compounds have been known for a long time to present themselves for nonnatural product leads, and if one isn't careful, good leads can be discarded by being too worried about PAINs. Recent natural products-based efforts have even run into problems of possible misidentification of chemical structures. If the chemical structure is correct, then perhaps the biology or purity of the active pharmaceutical ingredient are in question. Consider, e.g., the controversy with antroquinonol A, a fungal-derived anticancer compound being developed by Golden Biotechnology. However, this type of issue isn't only a problem for natural products, as another finding outside the natural products arena uncovered a chemical structure error in an Oncoceutics drug. Thus, there are complexities to worry about with natural products, but they are often no different than with any source of chemical diversity being explored in drug discovery and development.

Can a small biotechnology company succeed where Big Pharma has chosen not to go? Kosan is one example of a biotech venture that worked successfully on complex natural products and derivatives, especially polyketides. It was founded in 1995 and ultimately acquired by Bristol-Myers Squibb in 2008, which, interestingly, had substantially reduced its natural products programs in the late 1990s. Thus, in this case, Big Pharma chose to buy rather than (re)build its own natural products pipeline. Nereus is another example of a meaningfully successful natural products venture, founded in 1998 to exploit new therapeutics derived from marine microbial sources. Nereus had founder ties to the Scripps Institution of Oceanography, part of the University of California San Diego, which may have helped to extend its lifetime as an independent company. However, while Nereus discoveries reached clinical trials, it was ultimately acquired too, in 2012, by Triphase. With these and a few other rare historical exceptions, natural products-based biotech and pharma efforts have been hard to find lately.

It is important to note that challenges remain to find therapies for malaria and drug-resistant tuberculosis, among many other chronic ailments. Nonetheless, the future awaits exactly what is discussed in this book. Powerful new technologies should over time help to reignite natural products R&D in biotech and pharma concerns. For example, Amyris was founded in 2003 to exploit biotechnology and chemical engineering in a number of industries, ranging from petroleum products to pharmaceuticals. Early work

on the chemical biology-assisted semi-synthetic approaches to the antimalarial drug, artemisinin, led by University of California Berkeley's Keasling, garnered much attention. These techniques will increasingly buttress work on drugs with structures even more complicated than the artemisinin, discodermolide, and Taxol examples noted above. Novel application of natural molecules may offer an avenue to revisit old ailments with old cures!

No doubt there are many lessons left for us to ponder as we revisit natural molecules. New approaches to integrate high-content screening with the latest omics technologies are appearing in the literature regularly. For sure, new ways to connect chemotypes with phenotypes in natural products are more and more evident, providing yet one more tool to accelerate the essential work of drug hunters. Can a powerful reemergence of natural products in all their glory be far away?

Hopefully you, the reader, will get a sense of the excitement of these times through this book.

Enjoy!

**K. Kodukula[1] and W.H. Moos[2]**

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# Preface

*Imagine a world free of diseases!*

What a wonderful thought and sight. A pinnacle of unimaginable human achievement, a defining hallmark of excellence in human endeavor, and a lofty goal from times immemorial, but *not* yet achieved. The utopian thought is nowhere near our sightline. On the other hand, *is* it ever achievable?

According to the US Center for Disease Control and Prevention, people tend to die of 113 causes, categorized in to 20 categories. Cancer is the most prevalent for the age group in its 60s, and for children it is infectious diseases. Keeping the disparity among rural and urban populations aside, almost 90% of deaths in the developed nations were caused by noncommunicable, lifestyle, chronic diseases; in low-income countries (Asia, Africa, and the Americas), people predominantly die of communicable (infectious and parasitic) diseases. A majority of the anticancer and antibacterial drugs have originated with natural products; yet natural product-based drug discovery efforts were deemphasized about two decades ago because of the issues of gaining intellectual property (IP) rights with regard to composition of matter, material sourcing, complex chemistry, total synthesis and scaleup, and the advent of combinatorial chemistry.

New drugs entering the market are, for the most part, new and improved old wine in new bottles! New derivatives, new targets, new analogues, new scaffolds, but no real breakthroughs. The heat of innovation deficit intensified during the global financial crisis that we witnessed during the last decade. The pharmaceutical industry's response mainly was around business strategy, consolidation, cost cutting, layoffs, and such measures. The era has also witnessed an increased incidence of drug recalls and withdrawals due to untoward effects and drug toxicity. The industry experienced several closures and acquisitions. During the last two decades we also witnessed rapid growth in biologicals.

Any pragmatic discussion on pharmaceutical innovation almost always brings up the topic of rare and neglected diseases. Rare diseases are those that affect a smaller population, while neglected diseases are, in general, infectious diseases that are endemic or prevalent in developing countries. Because of the affected population size (rare) or the affordability (neglected) constraints, pharmaceutical companies have traditionally shied away in

developing drugs against these health concerns. But in recent years the mind-set has changed, if nothing else, because of improved public relations. Given the promiscuity of leading drugs and the very limited capital expenditure expected/involved, finding new uses for old (and new) drugs (drug repurposing/repositioning) has taken on a new dimension in recent years for their curative potential against risky, rare, and neglected disease targets, but the path for commercialization seems not quite thought through or bumpy.

Medicines are the greatest gift to humanity, by way of pharmacognosy and ethnopharmacology, the bedrock foundation for modern medicine. Yet, we have forgotten this monumental truth that has saved millions of lives over the last several decades. For the last quarter century, we succeeded in sequencing the human genome. We have developed high-throughput infrastructures that encompass robust assay formats, robotics, and signal-detection technologies. We conquered the ensuing Big Data (volume, velocity, variety, and veracity) with the aid of crowdsourcing and chemo/bio informatics. Combinatorial chemistry has come of age to fill the chemistry space more than ever. Open innovation, collaborative or otherwise, has become the mantra to reenergize pharmaceutical innovation. Personalized/precision medicine, making the treatment as individualized and customized as the disease, and immune-therapeutics have become the emerging paradigms for combating hard-to-treat diseases. Yet, the past two decades have become an era of "high throughput and low output." Could it be that the consequence of a one protein-one drug-one disease paradigm, an otherwise blind-sided, singular focus on developing highly selective drug leads to acting on individual therapeutic protein targets, aka, target-site—based, bench-to-bedside endeavors? Simply put, we are paying the price for pursuing the modern reductionist approach, in place of the yesteryear, proven, holistic reverse pharmacology endeavors.

We now have come to realize that any disease we encounter is almost certainly the tip of an iceberg, with a "disease syndrome" lurking underneath. Instead of a holistic approach, the current health care system focuses on a "reactive response" to a specific disease with a specific drug, while the disease syndrome culprits go unchecked. We face unique challenges in the diagnosis and treatment of each and every disease indication, which goes on to manifest from a simple disease to a more complex, multifactorial risk factors (syndrome), warranting a unified approach from several fronts. This calls for a new paradigm in how we deliver health care to the patient. Think about diabetes, for example. It is no longer a case of simple elevation of blood glucose levels. Prediabetic conditions eventually lead, according to Yensen and Naylor, to type 1, type 2 or gestational diabetes, with several associated risk factors: abdominal obesity, elevated blood triglyceride levels, low HDL cholesterol, high blood pressure, and high-fasting blood sugar. Diabetic complications, if unchecked, lead to retinopathy, coronary heart disease, nephropathy, peripheral vascular disease of the lower limbs,

cerebrovascular disease, pregnancy complications, peripheral vascular neuropathy (CNS, diabetic foot), etc. Hence, diseases may initially manifest symptoms that outwardly look simplistic, but masquerade underneath with octopus-like tentacles affecting and invading many physiological processes. The holistic approach of treating the underlying causes of the symptoms, the principle way of ethnopharmacology, begs for serious reconsideration.

We have a translational gap. The public sector has stepped in a big way to understand disease biology and to find new and improved drugs, exemplified by the billions of dollars poured in by the governmental agencies in to the public sector. Venture-backed biopharmaceutical companies are sprouting across the globe to fill niche needs. Philanthropic disease foundations are making their mark against rare diseases—diseases with a personal family connection, and affecting few. Contract research organizations are here to augment preclinical proof of concept endeavors. Collaborative public−private partnerships are all around us, with some success at least in Europe. This dynamic landscape, call it a sort of a business model, while much desired and cherished, has very little in return to show for because of the uncoordinated translational gap. Pharmaceutical precompetitive collaborations should make note of the superb advances made by the automotive and computer (semiconductor and IT) industries in this respect and come up with effective models that accelerate the discovery and development of therapeutics. The pharmaceutical industry's vast experience in developing drugs has not effectively transcended to the academic corridors. The academic drug hunter is pursuing risky targets, largely defined and mandated by the funding agencies' directive. Because of the inherently limited perspective of the academic scientist, the therapeutic relevance of the target, in the context of the complex disease biology/physiology, is not always closely interconnected. The hits identified in academic high-throughput screening centers are riddled with Pan-Assay Interference Compounds, those that show activity across a range of assay platforms and against a range of proteins. The biology-centric academic drug hunters have no way of knowing this promiscuity due to their siloed approach and from not being the beneficiaries of comprehensive knowledge that comes from running screens against multiple targets. The drug hunters also are largely unaware of the compensating cellular mechanisms available when a protein therapeutic target is singularly cornered. This is where a comprehensive, multifactorial knowledge of systems biology/pharmacology or physiopathology (pathophysiology) comes to rescue an otherwise stellar therapeutic, target-driven drug discovery effort. It is therefore all too important to consider designing multitarget compounds or drug cocktails that would not only interact with the key therapeutic target but also with the allied, compensatory pathways, akin to the polypharmacology of plant extracts that are enriched toward achieving the desired biological effect. In the absence of an industry-trained medicinal chemist connected with the project, the drug leads identified through academic high-throughput screening endeavors find no real value,

and with no knowledge of translating the discoveries beyond target site efficacy. This is the new "valley of death" for academic discoveries. Clinical efficiency, and what is needed to navigate this valley of death, is a strength endemic to pharma, but is largely unknown to the academic scientist. Things would be different if he/she were to understand the principles of reverse pharmacology, the bedside-to-bench principle.

Monetization of IP, unlike the case with the highly profitable IT industry, drives the pharmaceutical sector. This promotes monopoly and kills innovation, and in turn deprives the discovery and development of life-saving medicines and making patients' lives better. The security of IP is essential, but the incentive model is simply outdated and needs to change; better yet, it should cease to exist. The pharmaceutical innovation model for the third millennium calls for outside-the-box thinking. Think of Uber, the world's largest taxi company that owns no cars; Facebook, the world's most popular social media site, creates no content; Alibaba, the world's most valuable retailer, owns no inventory, Airbnb, the world's largest hotelier, owns no real estate, etc. (Tom Goodwin, WetPaint). These are disruptive innovation models unlike any others.

There are about 7000 diseases that afflict mankind, but we only have treatments available for fewer than 2−3% of these diseases. The most curious thing is that we know the genetic basis for most of these diseases. There are about 25,500 protein-coding genes in the human genome, and a gazillion number of possible small molecules with 30 or fewer heavy atoms. Within the human genome, there are about 4500 genes that are disease relevant, and ~3000 are druggable by small molecules. About 12,000 of these are prime targets for protein therapeutics. However, FDA-approved drugs target less than 0.5% of the entire human genome. This means that there is plenty of opportunity to mine the human genome and identify new and novel therapeutic targets. Pharma and academia routinely screen large compound libraries, virtual compound collections, vendor's databases, etc., but with a very limited knowledge of what to look for, not exactly knowing the size or shape of the so called needle (in a haystack) or even if it is there. If we do find a hit, optimization of it to become a bona fide drug lead is a herculean task. There are about 143 well-defined substituents reported in the literature. If we use all of them in just three positions, we would have $143^3$ or 2,924,207 possible compounds. This just hints at the fact that we can never be certain. An experienced medicinal chemist might consider making a drastic structural change, based on (1) historical perspective, (2) prior hands-on knowledge, and (3) chemoinformatic input.

It is all too common to see that most targets/assets fail in phase II. Poor understanding of human disease, inadequate biomarkers, and poorly predictive preclinical assays are some of the key contributing factors. It may come as a big surprise that nearly all novel targets, resulting from the mining of the genomic data, fail at clinical proof of concept. This failure is repeated

many times within each company and across the industry, a result of the non-sharing, secretive business model of the pharmaceutical industry. We tend to work under the lamp post (e.g., Kinome), and the animal models do not necessarily help prioritize therapeutic targets. How much does it cost to develop a drug? How long does it take? What is the attrition rate between phase I, II, III, and IV? Too many questions without any answers, exacerbated by the modus operandi of lack of public disclosure of key facts, thus enabling a "reinvent the wheel" syndrome over and over by each company, thus wasting precious resources and time and money countless times.

Even though there has been an uptick in the number of drugs approved by the FDA over the last 2 years, the pharmaceutical productivity defined by the number of diseases for which we have effective therapies remains almost unchanged despite huge investments in biomedical research infrastructure. The business model is a game of attrition, takes too long, costs too much, and with no guarantee of ensuring success. The origin of most modern medicines could be traced to an enlightened awareness and pursuit of anecdotal evidence from reverse pharmacology and bedside-to-bench observations. The rich potential of holistic ethnopharmacology and pharmacognosy has largely been forgotten, partly due to the difficulty in gaining rights to the associated IP, ambiguous claims, the advent of combinatorial chemistry, total reliance on bench-to-bedside strategies, and unproven clinical relevance of the therapeutic targets pursued. Pharma's innovation crisis is perhaps tied to its neglect of natural product-based drug discovery. This reminds us of the now famous quote by the late George Allen, Sr., "Forget the past, the future will give you plenty to worry about."

Both academia and pharma are now engaged in screening large compound libraries to identify lead drug candidates. Since the chemical diversity of these libraries is not always relevant to biological function, this approach has not been as successful as was hoped. With increased emphasis on high-throughput screening and combinatorial chemistry, and the clarity that target-based research provides with regard to the site of action as well as IP, there has been a deemphasis on natural product-based drug discovery programs over the last 20 years. The wealth of chemical diversity that has evolved with biological diversity is underrepresented in the commercial chemical library offerings, but needs to be expanded to strategically cover available chemical space and include drug-like compounds with improved pharmacologic, pharmacodynamic, and pharmacokinetic properties as compared to their current nitrogen-rich counterparts.

More than 80% of the world's population relies mainly on traditional medicines for its primary health care. The origins of many drugs that are currently in use could be traced to pharmacognosy and the fruits of reverse pharmacology. Natural products are "designed" to interact with enzymes and/or receptors. Natural products occupy an important part of small molecule space because they are recognized by at least two proteins: (1) the one

at the end of their biosynthetic pathway and (2) their evolutionary biological target. Natural products are the products of an organism's evolutionary path, successfully navigating the selective forces toward survival. Of the 325,000 plant species (compared to existing 1.6 million life forms) known to man, we have some knowledge of only about 1500 plants, and the therapeutic relevance of the rest of the plant species yet to be explored. The 1992 Rio convention on biodiversity laid the groundwork toward sustainable use of biodiversity, conservation and benefit sharing, and the legal framework in place to allow for bioprospection.

The authors vigorously argue that any drug, whether New Chemical Entity (NCE) or New Molecular Entity (NME), botanical or biologic, will have an inherent limitation due to a single-target approach in a multitarget and complex biological system. This book critically reviews the drug discovery strategies during the last five decades and analyzes reasons as to why drugs fail. Starting from thalidomide to rofecoxib, the contributing authors collectively analyze physiological reasons from systems biology perspective with chemistry, metabolic pathways, interactions, and cascading effects of one-target modulation on other metabolic processes. This argues for a reconsideration of the present one-target-one drug approach for a given disease. The genomic approach to personalized/precision medicine will be a long, expensive, and risky haul, whereas traditional, knowledge-inspired integrative personalized approaches will be the future of therapeutics. A clear distinction between drug discovery, medicine discovery, and treatment discovery is all too necessary at this critical juncture.

Several thematic concepts are articulated in this book. First, as editors, we emphasize the need for innovative, integrated, interdisciplinary approaches and include knowledge gained from natural product-based, traditional and alternative medicines to drive future drug discovery efforts. Natural products offer an almost infinite structural diversity that accesses interesting, therapeutically relevant biology. As such, systematic, genome-wide, bioinformatics-based, disease-centered, chemotype-to-phenotype systems biology approaches are required to take advantage of the recent advances in omics technologies and to identify novel therapeutic targets. A process is presented for the seamless use of bioinformatics, chemical biology, proteomics, structural biology, and medicinal chemistry−based approaches along with high-throughput, cell-free and cell-based assays to identify novel, druggable protein targets and novel "drug-like" chemical probes. New techniques and resources, grounded in sound scientific reasoning and rational, well-validated approaches that exploit a growing volume of publically available data, stand to become cornerstones of the new pharmaceutics arena (see Chapter 6: Genomics-Driven Drug Discovery Process). A compelling case is then presented by Anu Roy for holistic drug targeting. While preferential drug specificity toward a target is effective against diseases that are monogenic, a majority of the diseases are complex and

multifactorial, and are modulated by genetics, environment, age, and sometimes, gender. Successful outcomes may rely on polypharmacology of a given drug or drug cocktails, a new emerging paradigm for targeting multifactorial complex diseases. Patil et al. boils down the causative factors involved in the failure of drugs leading to their eventual recall. Drug toxicity, the primary cause for a drug recall, is primarily due to a cumulative effect of target modulation and intrinsic property of drugs, widely known as "toxicity triangle effect" or "butterfly effect."

Ethnopharmacology, natural products, and traditional medicine systems are considered by Chandran et al. (see Chapter 5: Network Pharmacology) as attractive options to overcome the drug discovery impasse. Network ethnopharmacology of botanical bioactives can serve as a valuable tool for evidence-based Ayurveda and Traditional Chinese Medicine to understand the medicines' putative actions, indications, and mechanisms. We also caution that consumers find it very frustrating to sort through a lot of ambiguous information put out by natural product manufacturers who cannot legally label their goods with condition-specificity. Warude (see Chapter 5: Network Pharmacology) lays out a path for assuring the quality and safety of the herbal products. A cost-effective and time-effective approach to drug discovery could effectively come from reverse pharmacology, a trans-discipline that strikes a balance between relevant pharmacology/toxicity sciences and clinic-centric approaches (see Chapter 9: Proteomics). Proteomics, pharmacogenomics, epigenetics, and transcriptomics are integral to a comprehensive understanding of systems biology of disease pathophysiology, thus leading a desired shift from target-centric approach to disease-centric approach. Collaborative public−private partnerships are integral to the paradigm shift espoused in the new pharma business models, but to be successful, the public must be allowed to share in profits that result from federally financed research. The concluding chapter brings forth the point that there is no use in attempting revolutionary new paradigms unless we also devote our attention to how irreproducibility has pervaded our discipline, and what resources and strategies exist to counteract the problems.

Finally, a greater acceptance of natural product extracts as a key (if complex) source of novel chemistries as well as increased appreciation for holistic approaches in therapeutic optimization, offers critical avenues for growing the pipeline of new candidate prospects, and achieving more systematic guidance regarding the most important optimization criteria for safe, effective medicines (see Chapter 6: Genomics-Driven Drug Discovery Process). Finally, the drug discovery efforts need not be limited to a pharmacology approach with "drug" as a chemical or biological entity. The new discovery paradigm should also include physiological interventions where meditation, diet, exercise, and behavioral changes play an important role, especially in the management of chronic conditions and lifestyle diseases. The authors critically explore these seemingly divergent, albeit fundamental