

Bhushan Patwardhan | Rathnam Chaguturu

INNOVATIVE APPROACHES IN DRUG DISCOVERY

Ethnopharmacology, Systems Biology
and Holistic Targeting



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Holistic Targeting

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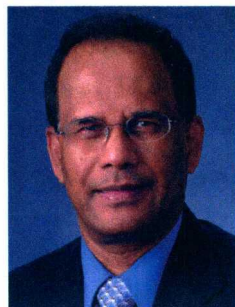
Innovative Approaches in Drug Discovery

About the Editors

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 (CIPRH) 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.



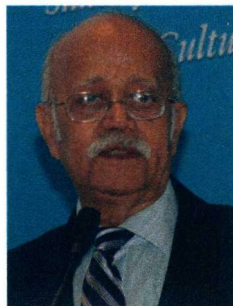
Rathnam Chaguturu is the Founder and CEO of iDDPartners, a nonprofit think-tank focused on pharmaceutical innovation. He has more than 35 years of experience in academia and industry, managing new lead discovery projects and forging collaborative partnerships with academia, disease foundations, nonprofits, and government agencies. He is the Founding President of the International Chemical Biology Society, one of the founding members of the Society for Biomolecular Sciences,



and Editor-in-Chief of the journal *Combinatorial Chemistry and High Throughput Screening*, and he serves on several editorial and scientific advisory boards. Dr Chaguturu has edited the widely received, first-of-its-kind book, *Collaborative Innovation in Drug Discovery: Strategies for Public and Private Partnerships*. And he is also a sought-after speaker at major national and international conferences, where he passionately discusses the need for the reemergence of pharmacognosy, the threat of scientific misconduct in biomedical sciences, and advocates for the virtues of collaborative partnerships in addressing the pharmaceutical innovation crisis. He received his PhD with an award-winning thesis from Sri Venkateswara University, Tirupati, India.

About the Authors

Ashok D.B. Vaidya, MD (Medicine), PhD (Clinical Pharmacology), is currently Research Director and the Advanced Centre of Reverse Pharmacology, Kasturba Health Society in Mumbai, India. He has a long family lineage of medicine and Ayurveda. Formerly at the helm of affairs at CIBA-GEIGY with an expertise in clinical phases of several new drug molecules, Prof Vaidya has remained engaged in pioneering the development of clinical pharmacology at KEM Hospital, a modern medical institute devoted to drug discovery and development from natural products at RAPMC, an Ayurvedic institution. Prof Vaidya has been an expert consultant to government agencies, industries, and research institutes receiving several honors and awards, and has traveled extensively, being a much-sought speaker at scientific conferences and meetings.



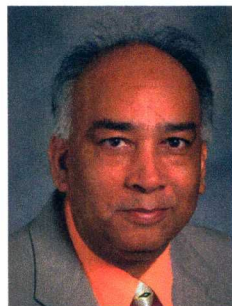
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Bharat B. Aggarwal is founding Director of the Anti-inflammation Research Institute in San Diego, CA, United States, and former Professor of Experimental Therapeutics, Cancer Medicine and Immunology, at the University of Texas MD Anderson Cancer Center in Houston, TX, United States. He has been investigating the role of inflammatory pathways mediated through TNFs, NF-kappaB and STAT3, for the prevention and therapy of chronic diseases. While searching for safe antiinflammatory agents, his group has identified more than 50 novel compounds from natural sources that interrupt these cell-signaling pathways. He has published more than 600 papers, edited more than a dozen books, and has been cited by ISI since 2001 as one of the most well-regarded scientists in the world.

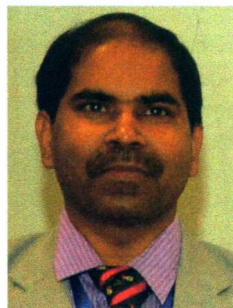


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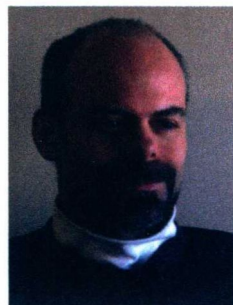
TX, United States, (2005–08) and his second postdoctoral work at the National Cancer Institute of National Institutes of Health (NCI/NIH), Bethesda, MD, where he was subsequently employed as a NIH scientist. His research interests include the role of inflammatory pathways in cancer development, anti-inflammatory agents in cancer prevention and treatment, chemosensitization of cancer by natural products, and identification of novel biomarkers for cancer diagnosis and prognosis. He is credited with the publication of more than 80 research articles, and he has more than 11,000 citations with an h-index of >37 ; his work is cited more than 1700 times in the literature annually. Dr. Kunnumakkara has also edited two monographs entitled *Molecular Targets and Therapeutic Uses of Spices: Modern Uses for Ancient Medicine* and *Anticancer Properties of Fruits and Vegetables: A Scientific Review*.

Subash Chandra Gupta, is an Assistant Professor at the Department of Biochemistry, Institute of Science in Banaras Hindu University, India. Dr. Gupta did his postdoctoral training at the Ohio State University and the University of Texas MD Anderson Cancer Center in Houston, TX, and was instructor at the University of Mississippi Medical Center, Jackson, MS, United States. His current research is focused on uncovering the mechanism by which an acidic microenvironment promotes cancer growth. Dr Gupta is



also working on cancer chemoprevention and on projects to elucidate the role of inflammatory pathways, cancer stem cells, exosomal microRNAs, and long noncoding RNAs in regulating tumor development. He has published more than 50 peer-reviewed articles in highly prestigious journals and has written several books as well as coedited special issues of scientific journals. He has been honored with prestigious national and international awards, and is member of the editorial board in two reputed scientific journals.

Gerald H. Lushington, brings a wealth of experience in simulations, data mining, and visualization to a diverse range of pharmaceutical and biotechnology research challenges. In addition to skilled application of numerous existing molecular modeling and chemical informatics software tools (including an avid interest in open source initiatives), he is an experienced programmer who has developed and published computational methods. With more than 150 peer-reviewed scientific



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Suresh Jadhav, PhD, M.Pharm., is the Executive Director of Serum Institute of India Pvt. Ltd in Pune, India. His 45 years of technical expertise includes QC/QA/cGMP/GLP/GCP techniques, inspections of laboratories and validation of various production and quality control processes, pharma/toxicological screening of various drugs, toxins and venoms, and drugs pricing. He successfully led the project of development and introduction of Meningococcal A conjugate vaccine in the sub-Saharan African belt, the development of seasonal and pandemic influenza vaccines, and has also played a major role in the acquisition of Bilthoven Biologicals in The Netherlands. Being associated with DCVMN since its inception, Dr. Jadhav was its President for 5 years. He has been on the board at the GAVI Programme and Policy Committee, and is also member of the European Vaccine Initiative, FastVac, and the Health Innovation in Practice Board, etc. He is closely associated with various advisory committees, like the Task Force of Sabin Vaccine Institute, WHO IVR-IVAC, and Decades of Vaccines (DoV), and is also affiliated with several Indian universities, AICTE, UGC, and the State Directorate of Technical Education. He is the Chairman of Expert Committee on Vaccines and other Biologicals and a member on the Scientific Body of Indian Pharmacopoeia Commission.



Sunil Gairola is a microbiologist, who graduated from the Department of Microbiology, Himachal Pradesh University in Shimla, India. He worked at the National Control Laboratory, Central Research Institute in Kasauli, and the Serum Institute of India Ltd., where he has been the Director of Quality Control since 2005. He has 30 years of technical experience in quality control of vaccines, adjuvant development, and managing quality control-related activities, and has significantly contributed towards the development and calibration of National Reference Standards for Vaccines and Antisera. Gairola has been a collaborator on many international initiatives of WHO, NVI, NIBSC, EDQM, and PATH, aimed at the harmonization of regulatory requirements, the establishment of international standards, and the development of quality control release assays



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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.



Kalpna 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.



Yogita A. Ghodke-Puranik received her PhD in Health Sciences (Human Genetics and Pharmacogenomics) in 2010 from the Interdisciplinary School of Health Sciences, University of Pune in Pune, India, before going to the University of Minnesota in Twin Cities, MN, United States, for her Postdoctoral training. During her PhD program, she has received several fellowships from the Government of India. She has more than 7 years of experience in the field of human genetics and has



worked in broad areas of drug metabolism pharmacogenetics of anticancer, anti-retroviral, antiepileptic, and antirheumatic agents, epigenetic regulation of drug response in cancer patients, as well as and explored the role of mRNAs and miRNAs in transcriptional regulation in human liver. As a research associate at the Mayo Clinic, Rochester, MN, her current research is focused on the genetics of type I interferon pathway in systemic lupus erythematosus patients. She serves as an expert reviewer for journals such as *Clinical and Developmental Immunology*, *Cytokine*, *Journal of Proteomics*, *International Journal of Rheumatic Diseases*, and the *Journal of Ayurveda and Integrative Medicine*. She has authored 19 peer-reviewed research articles and has received several highly cited reviews.

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Manish Gautam has a PhD in Pharmaceutical Sciences from the University of Pune in Pune, India, and currently works as team leader for analytics at Serum Institute of India Pvt Ltd. He is part of the vaccine development group and responsible for assay development, quality control activities, process characterization, and CMC activities for translation of multivalent vaccines from early phase to licensure. His expertise and research interests include immunopharmacology, adjuvant development, ethnopharmacology, glycobiology, and analytics of polysaccharide protein conjugate vaccines.



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has received a Hinduja Merit Scholarship, a Vaidya-Scientist Fellowship, and an Arogya Deep Award for his work in the field.

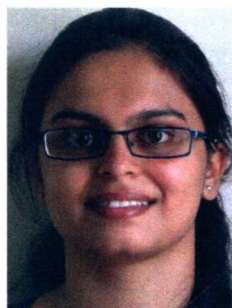
Uma Chandran, PhD, is a Dr. D.S. Kothari post-doctoral fellow at Savitribai Phule Pune University in Pune, India, under the mentorship of Prof Patwardhan. She graduated in Biotechnology from the Rajiv Gandhi Centre for Biotechnology (RGCB) in Kerala, a national research centre of the Government of India. Her research focuses on exploring the Ayurvedic system of medicine using a network pharmacology approach.



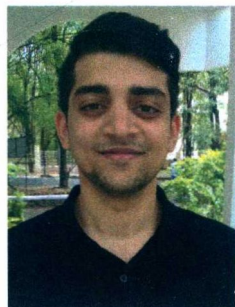
Tejas Shah holds an MD in Biomedical Sciences, with a specialization in Drug Discovery and Development, and is pursuing a PhD. He has worked on a number of prestigious projects funded by different government agencies such as DST, ICMR, and the Department of AYUSH, and is Senior Research Fellow at the Sinhgad 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 [färmə'kägnəsē]. 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