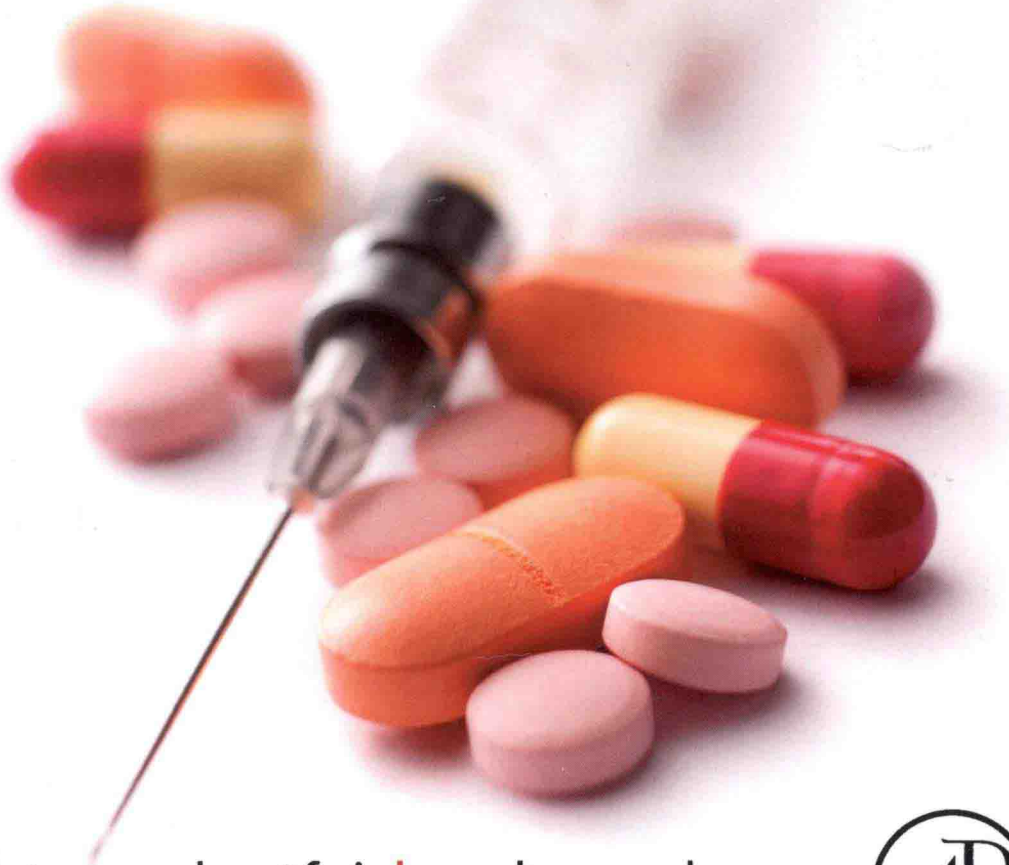
The Future of Drug Discovery

who decides which diseases to treat?



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Who Decides Which Diseases to Treat?

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Academic Press is an imprint of Elsevier

Academic Press is an imprint of Elsevier
32 Jamestown Road, London NW1 7BY, UK
225 Wyman Street, Waltham, MA 02451, USA
525 B Street, Suite 1800, San Diego, CA 92101-4495, USA

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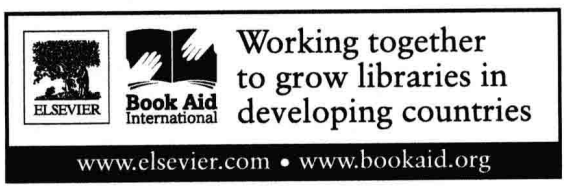
British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN: 978-0-12-407180-3

Typeset by TNQ Books and Journals Pvt Ltd.
www.tnq.co.in

Printed and bound by CPI Group (UK) Ltd, Croydon, CR0 4YY



Expert Reviews for The Future of Drug Discovery: Who Decides Which Diseases to Treat?

Tamas Bartfai & Graham V Lees

"A remarkable compendium of hard data and wise prescriptions for the pharmaceutical industry."

—Michael S Brown, *1985 Nobel Laureate in Medicine or Physiology, UT Southwestern Medical Center*

"[This] is a remarkable and timely book ... remarkable, as it is an insightful and careful analysis of the many factors determining success in this challenging area of human endeavor ... [and] timely, as the crisis in drug discovery has already begun ... The authors really prove their credentials with a thorough and expert review of the factors influencing the future of drug discovery delivering a detailed analysis of the biological and technical challenges ... The authors strategize on alternative business models and propose viable choices ... there is light at the end of the tunnel."

—Graeme Bilbe, *Drugs for Neglected Disease initiative, former Senior VP Novartis*, from his *Foreword*

"The future of drug discovery is compromised by interests driven by concerns other than science or health ... This is not an indictment of the pharmaceutical industry, but rather an exposition of various ills that exist in the present iteration of Pharma that need to be remedied so that the future promise of Pharma can be realized. The book is both enlightening and disturbing. It should serve as a call to action to use these facts and suggestions to help Pharma do what we need it to do—to create drugs that are effective in treating human illnesses."

—James H Eberwine, *University of Pennsylvania Perelman School of Medicine*, from his *Foreword*

"This book [offers] thoughtful and at times provocative proposals. [The authors] give a strong wake-up call in favor of continuing efforts and desperately needed investments into research and development to create new innovative medicines. Anyone who is looking for a thorough appraisal of current drug development issues combined with optimistic insight into the challenges, opportunities and specific needs of developing new medicines will benefit from reading this book. For individuals who are currently in or are planning to become involved with pharmaceutical or biotech industries, regulatory bodies or NGOs, academia or any form of biotech-focused financial investment - or just for getting a better understanding of the future of drug development - this book will be an excellent 'starter dose'."

—Eduard E Holdener, *NovImmune, former Head of Clinical Development, Roche-Genentech*, from his *Foreword*

"This book is a must read for students, prescribing physicians, academic and industry researchers, analysts, patient groups, business and science journalists, and importantly, Policy Makers. More than ever before, drug development is a complex scientific, industrial, and societal endeavor that needs the combined attention of Governments, Academics, and Big Pharma; it cannot be left to Wall Street alone."

—Daniel Hoyer, *Dept Pharmacology, U Melbourne, former Distinguished Scientist, Novartis*

"Bartfai and Lees raise critical issues confronting the search for new medicines. Their analysis is cogent, and their proposals thoughtful and thought provoking. For anyone curious about where new medicines come from, and what it will take for the BioPharma industry to bring new treatments to patients with Alzheimer's disease, diabetes, depression, cancer, and more, this is a must read."

—Michael D Ehlers, Senior VP *Pfizer & CSO Neuroscience, former Howard Hughes Investigator, Duke University*

"The global recession has caused unprecedented anxiety in many commercial areas, and the pharmaceutical industry is no exception. Armed with hard facts and their own real life experiences, Bartfai and Lees dissect the clinical needs, the marketplace, and the risk/benefit ratios of various strategies needed to survive the Valley of Death. In contrast to the worldwide somber mood, they see a glass that is half full and an industry with unprecedented opportunity. Courage is required of the pharmaceutical leadership charged with navigating these waters. The concrete, specific, and clear-eyed analysis of Bartfai and Lees make this an essential reference for entrepreneurs looking for optimism leavened with specific advice on strategies and mindsets that are likely to lead to success."

—Samuel E Gandy, *Mount Sinai Alzheimer's Disease Research Center*

"This insightful (and bracing) analysis provides a detailed 'lay of the land' with respect to the opportunities for and barriers to the development of new medicines by the world's pharmaceutical and biotech industries. Bartfai and Lees outline a set of proposals to revitalize the analysis and development of orphan drugs, to reform US patent guidelines and intellectual property protection, and to shorten the timeline between drug development in biotech and drug implementation by large pharma. Most importantly, they make a compelling case that substantive progress will not be made without restored - indeed, increased and sustained - investment in both basic research and its translational development."

—Greg Lemke, *Molecular Neurobiology Laboratory, The Salk Institute*

"This is an extraordinary, insightful and provocative book that should be read by all those concerned by the progress of biomedicine, from scientists to politicians. It deals with the future of drug discovery and its present-day dramatic contradiction: should we develop new drugs to the benefit of humanity's welfare or should we consider as a priority the financial goals & benefits of pharmaceutical companies? Central to the book, the paradox is very well documented and ably illustrated. The authors demonstrate the unanticipated inverse relationship existing between our greatest medical needs and the number of projects pursued by the pharmaceutical industry. This is particularly true for brain diseases (Alzheimer's disease, schizophrenia, neuropathic pain, etc.) that represent the greatest health burden on the population. A conservative estimate is that, in a typical year in Europe, about 165 million people—38% of the total population of these countries—will have a fully-developed mental illness (H. U. Wittchen *et al. Eur. Neuropsychopharmacol.* **21,** 655-679; 2011). The response of major pharmaceutical companies to this exceptional situation has been, unexpectedly, to cut their programs in brain therapeutics, for the simple reason that they are financially too risky. Yet, and this is an interesting aspect of the book, the authors remain optimistic about the future. Among the arguments they develop in the last part of the book, the basic research on drug design is progressing faster than ever, and new economic models of pharmaceutical industry development may be suggested that would be financially stable. The debate is open in unambiguous terms about the future of drug discovery and development, which is, in my opinion, one of the major ethical responsibilities of today's societies."

—Jean-Pierre Changeux, *Collège de France & l'Institut Pasteur*

The Future of Drug Discovery

Who Decides Which Diseases to Treat?

to Sabine
Riitta
Pinja & Silja

Preface

Why this new book?

Our first book[1] is still very pertinent to the process of modern, target-based drug discovery in Big Pharma and biotech.

Since we wrote the last book, something dramatic has happened that fundamentally changes the path of drug discovery. Previously, a scientific advance into the mechanism of almost any disease led to a dedicated effort throughout the pharma industry to discover molecules that would provide a new, better treatment. Drug discovery followed the path of human endeavor and discovery. Pharma companies were set and willing to tackle almost any disease, providing scientific research had uncovered sufficient detail on the disease process. They were eager to be first to learn of the basic science discoveries made in the government-sponsored academic laboratories.

This is no longer true.

The largest pharma companies have narrowed their sights and have dramatically culled research programs to focus on "reliable" diseases where they are most likely to make a profit. They have discarded many of society's vitally important therapeutic areas. With a clear eye on stock price, shareholder value, and "Wall Street" perceptions, pharma has focused on finances not therapies.

What this means is that the gurus of Wall Street and the financially mindful chiefs of the industry are deciding which diseases to treat without apparent care or concern for society's needs. As an example, we can cite the *Financial Times* report of August 28, 2012, the day this preface was originally drafted. AstraZeneca, the Swedish-British pharma concern, cut its research and development (R&D) workforce by 23% and used $4 billion of its $33 billion sales revenues to buy back stock in order to prop up its

1 Bartfai T and Lees GV (2006) *Drug Discovery: from Bedside to Wall Street*. Elsevier/ Academic Press: Amsterdam.

stock price, which is very low; the market capitalization was only six times the earnings. This may have been prompted by the projection that by 2016 it would lose 50% of its revenue because of its patents expiring on its largest selling drugs.

Is cutting one's R&D the right strategy for preserving one's long-term viability? AstraZeneca is currently clinging onto a top 11 spot in the world's biggest pharma. The 10 companies above it have also been indulging in R&D cuts and stock buybacks. It is not streamlining based upon any technological development; it is backing away from a whole cadre of diseases that need treatment—some of them urgently. Some diseases, for which we have no effective treatments, will become epidemics. Alzheimer's disease (AD) is a condition looming on many of our horizons. Yet we have no immediate prospect of treating the condition, and pharma has almost universally dropped it from its R&D. There are too few attempts to produce antibiotics, yet the latest estimates are that 50% of new cases of tuberculosis (TB) are drug resistant to present antibiotics. The best antipsychotic drugs are causing metabolic syndrome and diabetes, and few attempts are being made to find safer ones for this prevalent and lifelong disease. Obesity is a growing epidemic, but all recent pharmacological attempts to address the problem safely have failed.

The latest news is that the trials to combat AD by Lilly, which has invested a huge amount in AD drug development, have basically failed to reach both clinical end points. This is regrettably not an isolated incident. Trials by others have brought or are likely to bring similar disappointments. We can almost say this for certain because all of the drugs in development targeting AD are targeting the same molecular mechanism. The protein folding error in AD is common in several diseases, yet we do not honestly know if fixing it is key to AD treatment that will affect, slow, or stop memory loss. The failures, partly stemming from a narrow research focus, reinforce pharma's decisions that AD is too complicated a disease and drug development is long and risky, and even the potentially large payoff is not

attractive to remain in this race in the present risk-averse environment that promotes cost-cutting executives, who proudly announce no more new research centers: "We are cutting research and development COST!" Such pronouncements are erroneously applauded by Wall Street and short-term shareholders.

Why would pharma back away from therapeutic areas that should yield multibillion dollar revenues? The reason is relatively simple: the companies cannot see a way to develop drugs for "difficult" diseases in an economically viable way. The trials take too long, the risks are too great, and there are easier ways to make money. They are less motivated to be pioneers. If another company does it, they can copy them with similar drugs. Maybe. But with huge irreversible cuts in R&D worldwide, nothing is certain.

It is, frankly, easy to write a book "revealing" the well-documented excesses of the pharma industry: overzealous sales reps, unsafe drugs, exorbitant prices, advertising to patients, and lobbying of physicians and Congress. Those are separate, important ethical issues. This book is not devoted to them; there are other scandal-oriented authors doing a better job on those plentiful excesses.

Our thesis in this book is that the pharmaceutical industry is still the only source of new drugs. Some, maybe 1-2%, are discovered in academia, but the crucial clinical trials and marketing require the almost century-long experience, as well as the financial muscle, of the industry. There is as yet no other viable candidate in the foreseeable future. Biotechs can be pioneers, but they often do not have the resources to fund a phase 3 clinical trial, which often results in failure. Many successful phase 2 drugs, for which some efficacy and safety have been demonstrated, are just dropped in pharma and not picked up from biotech either, because of marketing decisions, not clinical viability.

The result of these trends is a major gap between the medical need and the focus of pharma companies; this new book is all about this and more. We identify the problems and the reasons behind them. We also offer solutions.

The scientific effort needs to be upgraded. It has, over the past 50 years, cost hundreds of billions of dollars to begin to tackle some cancers. It has been a superb government-led effort, rapidly joined by industry, to understand and begin to tackle HIV/AIDS and in 30 years turn a death sentence to a treatable, severe chronic disease. The abandoned and neglected diseases need major governmental investment if one is to identify new drug targets for pharma to exploit. The government budgets for research have been redirected toward so-called translational research, but the amounts being dedicated cannot fund important trials and government remains a very junior partner to industry in translational research, while it does cutting-edge basic research when it is the only major actor and produces breakthrough results.

Pharma needs to be incentivized. It is impossible to expect pharma to develop drugs that take much more than 10 years to develop, only for its patent to expire shortly thereafter. The tax incentives available for "orphan" or "rare" diseases should be extended to diseases identified as important for society, yet now abandoned. Governments, which have a track record for conducting clinical trials, need to support some phase 3 trials, not just safety and "evidence-based medicine" (EBM) trials.

A number of non-mutually exclusive suggestions are given especially in the final chapter. If an "expert reader" just wants the suggested answers, without full consideration of the questions, then please turn to the second part of Chapter 12 (under Drug development is moving, but not completely, *et seq.*). We hope you will then turn back to the important middle and fully appreciate the essential information in the debate. The majority of Chapter 11 is reasonably essential background in terms of organizing the future of drug discovery (under Filling the strategic vacuum, *et seq.*) An expert reader might be, perhaps, someone who can read Chapter 04 without learning anything.

Society needs to be more aware of what is going on and why they should be concerned. Its elected officials should be cognizant of how to ensure that the economic cost of the looming epidemics does not cripple

the economy. The world cannot sustain untreatable infections, worldwide microbial epidemics, and a growing population over 80 with AD who will drain most of our resources, because they need 24/7 care. We need to change course as soon as possible.

We hope this book provokes scientists to lobby for more funds for basic research, for pharma to be reminded that the risks are worth taking, and that government spends more on research in order to reduce and break the trend of increasing healthcare costs. The examples of good new drugs saving lives and reducing suffering, while saving funds as well, are plentiful. We need to use the accumulating scientific data to make new drugs in areas where society needs them most, and not only in areas where pharma presently flocks to make copies of one another's medicines.

Tamas Bartfai PhD
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Foreword by Graeme Bilbe PhD

The *Future of Drug Discovery* is a remarkable and timely book; remarkable, as it is an insightful and careful analysis of the many factors determining success in this challenging area of human endeavor. Bartfai is the insider with a successful track record in both academia and industry, speaking with authority on key issues. The communicator, Lees, demonstrated in the first book (*Drug Discovery: from Bedside to Wall Street*) that a complex theme like drug discovery can be made accessible to an audience less well versed in some of the intricacies of the "art." This book is also timely, as the crisis in drug discovery has already begun.

Societies in the modern world view easy (and sometimes almost free) access to health care as a human right. Accordingly, governments should be invested in making sure that their citizens are healthy, as healthy citizens make vibrant and successful economies. However, the current model of drug discovery, where large, asset-rich pharma companies freely pursue drug discovery and developments in those diseases with a large return on investment, is less and less aligned with the medical needs of an aging demographic and a society facing lifestyle challenges that hugely impact disease.

The drug industry is distinct from other industries. Drug development life cycles are 10-12 years long. The in-position life expectancy of CEOs in Big Pharma is 5-7 years. And no longer are scientific or clinical experts leading these companies. The markets demand quarter on quarter growth in company performance and double-digit returns. As a result, pharma companies are hemorrhaging knowledge workers trying to maintain their profit lines at market expectations. That is a central theme in this book. Key knowledge and expertise for drug discovery and development is disappearing, just when looming epidemics of diabetes and Alzheimer's disease are already measurable and beginning to influence society's ability to bear the cost of care and treatment.

If this book merely described the maladies of the pharma industry and its imminent end, as many treatises in the popular press as well as from analysts and consultants would have us believe, then there really is a dismal future. The authors of this book really prove their credentials with a thorough and expert review of the factors influencing the future of drug discovery by delivering a detailed analysis of the biological and technical challenges. With enough money, time, and insight these factors are all surmountable. Nevertheless, a little more challenging will be aligning the forces to do so and likely building a new model for drug discovery and development.

For several decades, the pharma industry has translated academic research into novel therapeutics for unmet needs. This has been very successfully applied to the diseases attacked so far. Now the challenge for drug discovery and development is to find novel therapies for more complex diseases where validated starting points for drug discovery are harder to identify. Further, well-characterized populations for clinical trials combined with diagnostics and surrogates to enable rapid development or rejection of each therapeutic approach are less readily available. Taken together with a financing model poorly suited to support the development of therapies outside the remit of the pharma industry and a product life cycle of 10-12 years, action must be taken now. It will require the commitment of many sectors and interests, from academic research groups to financial institutions and most likely strategic government funding. Plus the heat needs turning up on the political debate.

In spite of all that, there is light at the end of the tunnel. The authors strategize on alternative business models and propose viable choices. It will require the combined efforts of government, industry, and the markets plus new ways to incentivize and reward innovators. That this is possible is clear. Solutions to two great scourges, the HIV epidemic and some cancers, have been found as a result of recognizing the issues, summoning the political will, providing sustained funding, and aligning

all constituencies to a common purpose. Whether this will happen in the near future for other diseases, the authors leave open for us to judge.

Graeme Bilbe PhD
Research and Development Director
Drugs for Neglected Disease initiative

Foreword by James H Eberwine PhD

Facts are facts ... The future of drug discovery is compromised by interests driven by concerns other than science or health. This is one of the basic tenets of Bartfai and Lees' new book *The Future of Drug Discovery*. This is not an indictment of the pharmaceutical industry, but rather an exposition of various ills that exist in the present iteration of pharma that need to be remedied so that the future promise of pharma can be realized.

As a scientist performing fundamental (basic) research, I cannot help but marvel at the process of translating discoveries made in the lab to therapeutics that are used to ease human suffering. The nature of scientific discovery is agnostic to human need; however, when aligned, the results of fundamental science can have dramatic individual and societal impact. There are growing individual and national efforts to reinvent and reinvigorate the field of translational medicine so that results from fundamental studies can be more readily transitioned to the clinic. There are three fundamental decisions to be made in developing therapeutic drugs: What disease area will be targeted? How much of a resource investment should the company provide? When to stop development because of adverse effects or inefficacy of drug action? These three decisions are intricately intertwined, with the first and second among the most important issues discussed in this book.

There was a time not so long ago when drug companies were run by scientists or MDs. This is no longer the case, and now only one of the major drug companies, Novartis, is headed by an MD. The CEOs of the other companies and the trend in CEO recruitment is to hire business professionals. This illustrates one of the themes of the book, which is that medical/research decisions are being made by people without extensive training in the field. While most Big Pharma are publicly traded companies with a fiscal responsibility to their shareholders, the makers of our medicines—the deciders of which diseases will be investigated so that treatments may be

forthcoming—must be held to a different standard of success than the simply quantifiable potential profitability of a research program.

In highlighting the impediments to the future of drug discovery, the authors go to great lengths to suggest remedies, thereby providing one of the most thought-provoking chapters of the book, Chapter 12. The suggestions run the gamut of pharma being more open to the rescue of phase 2 drugs that have failed either for their primary indication or because of the testing conditions, to encouraging governments to rewrite patent guidelines (particularly in the United States), thereby allowing pharma to make up for the long development time and high costs associated with the long process from initial patenting to receipt of Food and Drug Administration approval. Several of these ideas are intriguing but will come at a cost to the consumer, and hence warrant serious discussion.

Of course, academic efforts in translational science are also discussed in the book, highlighting academia's overall lack of success in bringing new drugs to the market. This is explained in several ways, including the existence of unfounded biases of academicians concerning the difficulty and scientific worthiness of work done in pharma (making it difficult to work with pharma) and the lack of sufficient government funds for performing the necessary clinical development. While pointing out these inadequacies, the authors are also hopeful that governmental funding agencies and pharma are seeing the need to work together, as evidenced by the Alzheimer's disease clinical trial to be carried out in an extended Colombian family that was initiated by Genentech and jointly funded by the National Institutes of Health, non-governmental organizations, and pharma. Drs. Bartfai and Lees see such collaborations (as discussed in their first book *Drug Discovery: from Bedside to Wall Street*) as necessary and integral to the future development of drugs. Sharing the monetary and failure risks through involvement of multiple groups working closely together seems like a reasonable approach to take on the risks of drug development for complex multigenic diseases, as well as orphan diseases.