

Received: 2004.03.04
Accepted: 2004.04.30
Published: 2005.01.01

Drug industry in “depression”

Dov M. Almog

University of Rochester Eastman Dental Center, Rochester, NY, U.S.A.

Source of support: Self financing.

Summary

The productivity crisis in pharmaceuticals is an important problem that should be seriously addressed by academic scientists and NIH administrators. It is true that most academic scientists avidly practice the reductionist approach and tend to neglect the big picture. However, in light of the crisis, that should change. To stimulate such a change, scientists should see publications addressing big picture issues, and specifically publications which present analyses of the productivity crisis in pharmaceuticals.

Although the public media recently published a series of articles reporting the crisis, so far, the peer-reviewed professional journals tended to avoid the issue.

There seems to be a consensus that there is no successful drug discovery without reasonable biology. The Drug industry in “Depression” paper provides an opportunity to balance the picture and entice discussions on the relationships between academic research practices, NIH policies, and success in drug discovery. Academia and the drug industry must adopt a unified biomedical research approach rather than a multitude of what appears to be unrelated reduction methodologies, especially the basic science/biology end of it.

key words:

drug industry • crisis in the pharmaceutical industry • drug discovery • academic research practices • biological theory

Full-text PDF:

http://www.MedSciMonit.com/pub/vol_11/no_1/5267.pdf

Word count:

2184

Tables:

–

Figures:

1

References:

14

Author's address:

Dov M. Almog, Medical Director, Associate Professor, Prosthodontics, University of Rochester Eastman Dental Center, 625 Elmwood Ave, Box 683, Rochester, NY 14620 U.S.A., e-mail: dov_almog@urmc.rochester.edu

SR

BACKGROUND

Propelled by chemistry but increasingly directed by pharmacology and the clinical sciences, drug research has contributed more to the advancement of medicine during the past century than any other scientific factor [1].

It is a common view shared by the National Institutes of Health (NIH) and the pharmaceutical industry that the biologists discover the disruption (mutation, pathogen, toxin, etc.) that causes the disease and the chemists find the compounds that reverse the effect of the disruption. Therefore, without biology there is no chemistry.

According to this simplified description, every new drug application sent to the FDA starts with a scientist working in the lab at a certain academic institution, trying to understand the biology of a disease.

Historically, the pharmaceutical industry recognized the importance of biology and accepted academia as the one making the discoveries in basic science and biology, while it played the role of the chemist (Figure 1).

The following statements by Merck, Galxo-Wellcome, and Vertex, two of the largest pharmaceutical companies in the world and a successful biotechnology company, illustrate the significance of biology in drug discovery:

According to Merck, all research projects for new vaccines and drugs begin with basic research. Whether the objective is to isolate, synthesize, or rationally design drug candidates, "a thorough understanding of the targeted disease at a molecular level is essential [2]."

Galxo-Wellcome also insists that the gene product under investigation must be placed in "a general biological context," in order to increase the chances of finding a valid target [3].

Additionally, Vertex (the biotech company), insists that they do not undertake projects where the biology is "uncertain." "We look for the biology to be well understood. We look for the chemistry and the biophysics to be doable in a short period of time [4]."

Ironically, Joshua Boger, the CEO of Vertex, chose FKBP-12 as a target for drug development since he believed that its biology was well understood. Then, Professor Stuart Schreiber from Harvard University announced that FKBP-12 binds to calcineurin, implying that Vertex is developing a drug for the wrong target. Imagine the anxiety at Vertex when they realized they are possibly clinging to the wrong biology. "They were horrified, irate, that Vertex was claiming to do structure-based drug design while it still wasn't clear what they were designing molecules to do. ... If FKBP wasn't the right target, then all Vertex's work was suddenly voided – everything. What good were better inhibitors of a protein that was biologically irrelevant?" [5].

Likewise, the government expresses similar views [6]. In their 2001 "Bypass Budget," intended to define new research opportunities, the National Cancer Institute (NCI) stated the importance of research focusing on molecular targets for

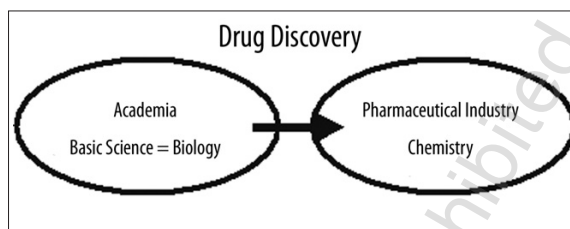


Figure 1. Academia is where discoveries in basic science and biology are made. The pharmaceutical companies play the role of the chemist.

the discovery and clinical testing of new anticancer agents "based on the molecular mechanisms that underlie neoplastic transformations, cancer growth and metastasis." This document understands that, in the past twenty years, we have seen an explosion in our understanding of how cancer cells work. Scientists have identified specific molecules that cause the initiation and progressive growth of tumors, something which has provoked a fundamental rethinking of how scientists must go about discovering and developing drugs for the treatment and prevention of cancer. As this report points out, there is now the opportunity to back off from screening agents by their effects on tumor cell growth, *in vivo* or *in vitro*, and targets that have been systematically exploited. While these methods might continue to be the basis for the development of clinically useful agents, these agents may not be the best lead compounds that affect a particular pathway of biologic importance specific for cancer formation or progression.

The NCI has suggested that drugs which have been discovered and developed by these earlier methods have often been shown to be clearly limited in their scope [6]. Their hope is that innovative drugs, which target newly recognized molecular aberration in cancer cells, will provide more effective therapy or prevention approaches, that is, reverse, stop, or delay cancer progression. As the report states, it is noteworthy that in this process the pharmaceutical industry has clearly seized a defining role in expeditiously advancing potentially useful compounds to a clinical test. However, in each of the instances cited, the pioneering studies on the targets to which these drugs are directed occurred largely in the academic sector.

Additionally, according to the NCI, traditional methods in drug discovery produce drugs with limited efficacy. Moreover, one cannot expect any new drugs to come from using the old approach. To find new drugs, not copycats, one needs a solid understanding of the basic biological mechanism that underlies the disease [6].

Consistent with the NIH Panel on AIDS Research Program Evaluation, the contribution of biological understanding to the discovery and development of treatment is undeniable. The NIH funds scientists who generate much of the basic science information about the biology of the pathogens responsible for AIDS associated opportunistic infections that provides the necessary foundation for successful drug development efforts. That is, advancement in understanding the fundamental biology and pathogenesis of these diseases is necessary if prevention and treatment of AIDS-associated opportunistic infections is to be achieved [7].

To sum up, there is a consensus that there is no successful drug discovery without reasonable biology. The pharmaceutical industry understands this relationship and therefore has assigned this job to the government. The government accepts the responsibility and allocates funds to academic institutions for researching the biology of disease, (better known as basic research). The Office of Budget (OB) is at the hub of program budget and resource allocation at the National Institutes of Health (NIH), reconciling a \$20.3 billion budget in FY 2001 with appropriations to 25 institutes and centers within the NIH. Given the importance of medical research in fighting disease and improving the nation's health, the enormous range of possible subjects of research, and the thousands of talented investigators who seek funding, the National Institutes of Health (NIH) must make choices about where and how it spends its money [8].

DISCUSSION

When the basic science/biology of disease is not available, no new drugs come to market and or the use of surrogates as targets in drug discovery becomes inevitable.

Although we can be justifiably proud of our research discoveries, if we do not bridge the profound disconnect between these often atomistic research functions, our progress against suffering and mortality from devastating chronic diseases will continue to be long-drawn-out, imbalanced, and incremental. Cancer, obesity, and atherosclerosis are not just scientific and medical issues, but represent moral and ethical challenges that must be met.

In a recent editorial, Marc Kaufman, Washington Post Staff Writer, wrote a pertinent article titled: "Decline in New Drugs Raises Concerns". It was an eye opener. Kaufman claims that the decline in the number of new drugs is most pronounced in the priority drugs category considered by the Food and Drug Administration to have the greatest promise for patients. Yet, the number of industry applications for ground-breaking new drugs is down significantly, and the average time needed by the FDA to review applications is ever-increasing. The net result of both trends is a steep decline in the number of new drugs coming to the market, and growing disappointment among many patients, their families and advocates. According to Kaufman, the possible reasons for the decline, whether it is a function of FDA caution after some high-profile drug withdrawals, industry shortcomings and strategies, or a combination of both, are the subject of an increasingly urgent debate [9].

Califf RM and Kramer JM [10] reported that in some research situations (e.g., the evaluation of calcium channel blockers in the treatment of hypertension and angina), clinical investigation has stopped with the measurement of pathophysiological surrogates like blood pressure or clinical measurements that reflect a short-term outcome. If one does not understand the disease on a molecular or cellular level, one has to compromise, and use surrogates, however, the resulting new drugs are ineffective or even harmful.

Why isn't the basic science/biology of disease available? Individual discoveries in the biology of human disease are cornerstone in new treatments. However, in drug discovery, these basic science/biology discoveries are seeming-

ly unrelated dots. To connect the dots you need a theory. The Blind Men and the Elephant is a famous story about six blind men encountering an elephant for the first time. Each man, seizing on the single feature of the animal, which he appeared to have touched first, and being incapable of seeing it whole, loudly maintained his limited opinion on the nature of the beast. The elephant was considered a wall, a spear, a snake, a tree, a fan or a rope, depending on whether the blind men had first grasped the creature's side, tusk, trunk, knee, ear or tail. The story epitomizes the problem of the reductionist approach in biology. A recent book *Microcompetition with Foreign DNA and the Origin of Chronic Disease*, by Hanan Polansky [11], presents an alternative. The book identifies the disruption that causes atherosclerosis, cancer, obesity, osteoarthritis, type II diabetes, alopecia, type I diabetes, multiple sclerosis, asthma, lupus, thyroiditis, inflammatory bowel disease, rheumatoid arthritis, psoriasis, atopic dermatitis, graft versus host disease, and other chronic diseases, and describes the sequence of events that leads from the disruption to the molecular, cellular, and clinical effects.

Based on today's research environment, it is impossible for a scientist to see the whole picture. He may review a new idea/discovery with the greatest curiosity and scholarly care, studying its structure, analyzing, measuring, and trying to weigh its ultimate clinical significance, but he will never understand everything that potentially makes it a great biomedical discovery. He simply cannot help but perceive it from his own limited point of view, to which he has been conditioned and motivated by his previous academic/research experiences. It is therefore important to shift some of the focus to theoreticians who can start connect these seemingly unrelated observations.

How often do applicants conduct a compelling cost-benefit analysis? In many cases, the significance is noted, and if all the i's are dotted and the t's crossed, the proposal has a good chance to be funded. While there are numerous other criteria by which the proposal is reviewed, funding for research is more likely to occur if the investigation subject is popular or even innovative, regardless how far-off the surrogates' outcomes are or how focused it may be, let alone if the reviewers share the same paradigm. According to Califf RM [12], when finances are notably constrained, we must assess the value derived from spending money on health care projects, that is, exercise a cost-effectiveness analysis. Califf RM is using the case of the platelet glycoprotein IIb/IIIa inhibitor - abciximab, to illustrate many of the issues surrounding the collection, interpretation, and misapplication of cost-effectiveness data.

Similarly, conclusions about the efficacy of medical interventions are based on data presented in the scientific literature. The validity of these conclusions is threatened if publication bias results from investigators or editors making decisions about publishing study results on the basis of the direction or strength of the study findings [13].

Furthermore, Professor Thomas S. Kuhn made an interesting case in his book [14] that individuals who revolutionize and or discover a new paradigm are almost always very new to the field whose paradigm they change. These scientists have minor or no commitment to the traditional

rules of the science they practice. Granted that no theory can ever be exposed to all possible applicable tests, they ask not whether a theory has been verified but rather about its probability in the light of the evidence that actually exists. Professor Kuhn implied that the typical scientist is not an objective, free thinker and skeptic. Rather, he is a somewhat conservative individual who accepts what he was taught and applies his knowledge to solving the problems that come before him, i.e., he tends to solve problems in ways that keep the existing paradigm of scientific knowledge intact, rather than framing a way of thinking that asks new questions and makes new answers possible, even as it exposes the limits of the existing paradigm. This pattern is particularly true for those whose productive careers have committed them to an older, established tradition of what has become "normal" science.

FUTURE DIRECTIONS

Academia and the drug industry must adopt a unified biomedical research approach rather than a multitude of what appears to be unrelated reduction methodologies, especially the basic science/biology end of it. What we need today in biology is good theories, more system thinking, and more collaborative cross-laboratory research.

Additionally, we must provide incentives to those theoreticians, that have the ability to imagine, reflect and conduct research in a unified manner, that is, encourage those that see patterns that others can not perceive, namely, see the human body (the "elephant") as a whole.

And last but not least, select research problems that are of higher priority. Rationalize research projects that are narrow-minded and/or have no significant consequences, that is, are in fact unrelated and limited.

REFERENCES:

1. Drews J: Drug discovery: a historical perspective. *Science* 2000; 287:1960-64
2. <http://www.merck.com/!!EIB2jbtEIB2jbo/careers/mrl/basic.html>
3. <http://www.glaxowellcom.co.uk/science/targint.html>
4. Werth B: *The Billion Dollar Molecule, One Company's Quest for the Perfect Drug*. New York: Simon and Schuster, 1995; p.360-61
5. Werth B: *The Billion Dollar Molecule, One Company's Quest for the Perfect Drug*. New York: Simon and Schuster, 1995; p.234
6. Molecular Target Drug Discovery for Cancer: Exploratory Grants. NCI 2000 Feb 16. Available from: URL:<http://grants2.nih.gov/grants/guide/pa-files/PAR-00-060.html>
7. http://kali.ucsf.edu/social/oar_reports/2098.2299.html
8. <http://public-council.nih.gov/SettingResearchPriorities.htm>
9. Kaufman M. Decline in New Drugs Raises Concerns, FDA Approvals Are Lowest in a Decade. *Wash Post* 2002 Nov 18; Page A01. Available from: <http://www.washingtonpost.com/wp-dyn/articles/A3265-2002Nov17.html>.
10. Robert M, Califf, Judith M, Kramer: What Have We Learned From the Calcium Channel Blocker Controversy? *Circulation*, 1998; 97:1529-31
11. Polansky H: *Microcompetition with Foreign DNA and the Origin of Chronic Disease*. 1st ed. Rochester (NY): CBCD Publishing, 2003
12. Califf RM: Evaluating the costs and effectiveness of cardiovascular therapies: who cares about economic analyses? *Stat Med*; 21: 2889-97
13. Dickersin K, Min YI: Publication bias: the problem that won't go away. *Ann NY Acad Sci*, 1993; 703: 135-48
14. Kuhn TS: *The Structure of Scientific Revolutions*. 3rd ed. The University of Chicago Press, 1966 p.144-51

Index Copernicus

Global Scientific Information Systems for Scientists by Scientists

www.IndexCopernicus.com



TM
INDEX
COPERNICUS
INTERNATIONAL

EVALUATION & BENCHMARKING

PROFILED INFORMATION

NETWORKING & COOPERATION

VIRTUAL RESEARCH GROUPS

GRANTS

PATENTS

CLINICAL TRIALS

JOBS

STRATEGIC & FINANCIAL DECISIONS

Index Copernicus integrates

IC Journal Master List

Scientific literature database, including abstracts, full text, and journal ranking. Instructions for authors available from selected journals.

IC Conferences

Effective search tool for worldwide medical conferences and local meetings.

IC Scientists

Effective search tool for collaborators worldwide. Provides easy global networking for scientists. C.V.'s and dossiers on selected scientists available. Increase your professional visibility.

IC Patents

Provides information on patent registration process, patent offices and other legal issues. Provides links to companies that may want to license or purchase a patent.

IC Grant Awareness

Need grant assistance? Step-by-step information on how to apply for a grant. Provides a list of grant institutions and their requirements.

IC Virtual Research Groups [VRG]

Web-based complete research environment which enables researchers to work on one project from distant locations. VRG provides:

- ④ customizable and individually self-tailored electronic research protocols and data capture tools,
- ④ statistical analysis and report creation tools,
- ④ profiled information on literature, publications, grants and patents related to the research project,
- ④ administration tools.

IC Lab & Clinical Trial Register

Provides list of on-going laboratory or clinical trials, including research summaries and calls for co-investigators.