The Challenge of Drug Discovery in the 21st Century

Allen B. Reitz* and Kathleen M. Czupich

Pennsylvania Center for Drug Discovery, Pennsylvania Biotechnology Center, 3805 Old Easton Rd., Doylestown, PA 18902, USA

Abstract: The major challenge facing drug discovery research today is the lack of productivity as measured by the introduction of new molecular entities (NMEs) into therapy. Only 21 NMEs were approved by the U.S. Food and Drug Administration in 2008, the same level of productivity as the 1950's even though spending on drug discovery research is many times higher. The drug discovery process can take as long as 8-12 yrs between the initial synthesis of a drug candidate and commercialization, and it is costly requiring well over $1 billion on average for every marketed drug that enters clinical practice. We have founded the Pennsylvania Center for Drug Discovery (PCDD) at the Pennsylvania Biotechnology Center (PBC) in Doylestown, Pennsylvania USA. The PBC is a mixed use academic-industrial biotechnology facility with >220 total employees. We have developed programs to advance the mission of accelerating the translation of new basic discoveries into therapies suitable for human clinical evaluation. The PCDD drug discovery capability is built upon a network of non-profit research institutions and small biotechnology companies using industry-standard metrics for the identification of hits, leads and preclinical development compounds, risk analysis and development. The PCDD is also meant to serve as an international think tank to brainstorm ways of improving efficiencies and productivity in early drug discovery. Jobs are already being created in the companies associated with the PCDD, helping to reintegrate senior-level biomedical drug discovery researchers who have been displaced elsewhere due to industrial downsizing into the workforce.

Keywords: Drug discovery, biomedical research, innovation, public private partnerships, Pennsylvania Center for Drug Discovery.

INTRODUCTION

The discovery of new drugs to treat unmet medical need and relieve suffering is a worthy human endeavor. New advances in our understanding of the molecular basis of disease have resulted in innovative small-molecule therapeutics that have revolutionized patient care for many indications. However, worldwide drug discovery research has seen an unexpected stagnation in productivity and innovation as measured by the number of new molecular entities (NMEs) approved and entering therapy each year (Fig. **1**) [1]. In 2008, only 21 NMEs were approved by the U.S. Food and Drug Administration (FDA) although spending on drug discovery research is many times higher than in previous decades. From 1950 to the early 1990s the level of innovation was fairly constant at 10-25 per year, but in 1996 this increased dramatically to 51 which is due in part to greater staff review at the FDA because the Prescription Drug User Fee Act had recently increased funds for the agency. Since 1996, the level of productivity as measured by the introductions of NMEs into therapy has declined to previous levels even though important new enabling technologies have been developed and validated.

This pipeline productivity problem is now often called the "valley of death" and reflects a disconnect between the translation of exciting new discoveries concerning the molecular basis of disease into preclinical development compounds suitable for acceptance into the risky and costly preclinical and clinical development programs required prior to human clinical use. This challenge is particularly severe for the tropical, neglected diseases that afflict one-sixth of humanity and are less well-funded than other indications with larger potential commercial return [2]. There are several reasons that are widely accepted as to reasons for this lack of productivity. An important factor is an increased standard of care after the introduction of each additional therapeutic onto the market, and especially after older drugs in any given indication go off patent. It is a high bar to justify new premium-priced therapy when less expensive generic drugs are available in the same therapeutic category, and ~65% of prescriptions are currently generic. Safety and regulatory requirements have increased due to both a greater understanding of the molecular basis of toxicities and the high profile withdrawal of major drugs from the marketplace due to safety concerns including refecoxib (Vioxx™, Merck) and cisapride (Propulsid™, Janssen). Further, the development of new drugs is very expensive and is estimated to be $800 million to $3.9 billion per NME approved depending on the method of calculation [1,3]. These trends have resulted in a reliance on blockbuster drugs (>$1 billion per year sales) on the part of the major pharmaceutical companies. The financial pressures for short-term financial return have resulted in large mergers and acquisitions, most notably between Pfizer and Wyeth, Merck and Schering-Plough, and Roche and Genentech in the past year. Substantial workforce attrition has occurred in the pharmaceutical industry with >120,000 jobs lost since 2000. Many would say that visionary leadership is often lacking,

*Address correspondence to this author at the Pennsylvania Center for Drug Discovery, Pennsylvania Biotechnology Center, 3805 Old Easton Rd., Doylestown, PA 18902, USA; Tel: 1-215-589-6435; Fax: 1-215-489-4920; E-mail: allen.reitz@ihvr.org

2210-2892/10

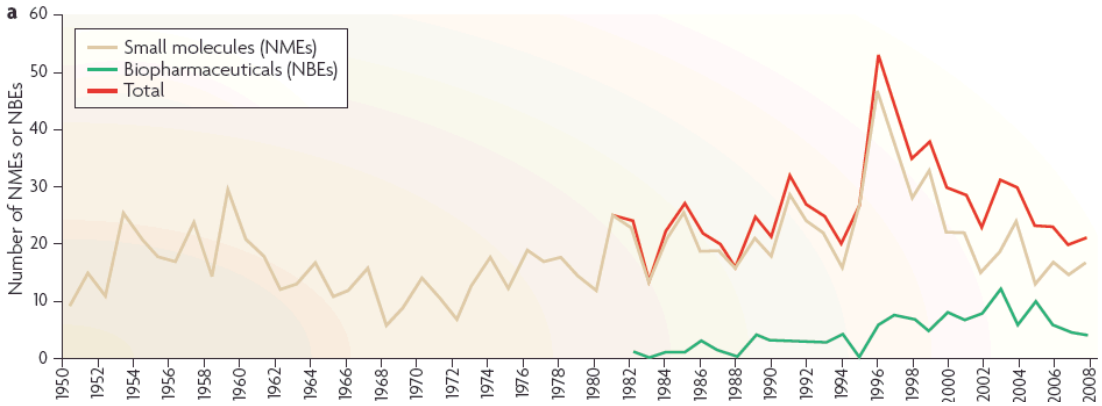

Fig. (1). Stagnant productivity of the introduction of new molecular entities (NMEs) into therapy by the U.S. Food and Drug Administration. From ref. 1, reprinted by permission from Macmillan Publishers Ltd: *Nat. Rev. Drug Disc.*, 2009.

and that a process, metrics-oriented approach is too prevalent in pharmaceutical company management [4].

Enabling tools such as high-content screening and fragment-based drug discovery have emerged in an attempt to improve efficiencies and de-risk early drug discovery research [5]. In addition, drug suitability profiling via *in vitro* absorption distribution metabolism excretion (ADME) testing is now commonly used to remove inappropriate chemotypes and individual compounds as early as possible.

An important trend is that research is now global to an extent never seen before. From the Far East such as in Singapore at The Biopolis and China at the Shanghai Zhangjiang Hi-Tech Park, to India, Europe and the U.S. in Florida and elsewhere, smaller biotechnology companies and non-profit research institutions are rapidly proliferating to capture new opportunities in biomedical research. Innovation is occurring more than ever before at these smaller biotechnology companies and the interface between private companies and academia or other public institutions (public private partnerships, PPPs). Small companies now contribute an equivalent number of NMEs into therapy as do large ones, and the trend suggests an even greater contribution from smaller organizations in the future (Fig. **2**).

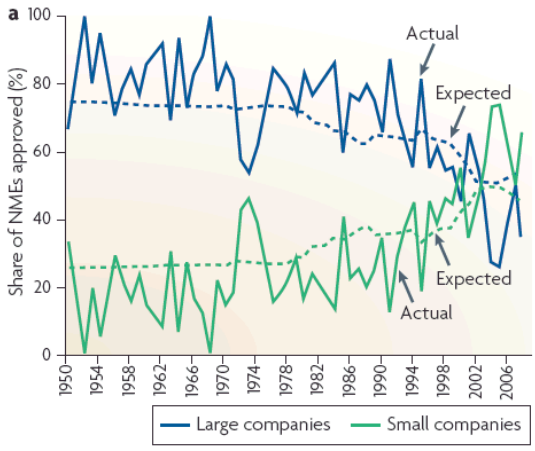

Fig. (2). Innovation as measured by the introduction of FDA-approved NMEs into therapy from large (top 15) and small (all others) pharmaceutical companies (from ref. 1, reprinted by permission from Macmillan Publishers Ltd: *Nat. Rev. Drug Disc.*, 2009).

We have recently founded the Pennsylvania Center for Drug Discovery (PCDD) at the Pennsylvania Biotechnology Center (PBC). We have developed programs to advance the mission of accelerating the translation of new basic discoveries into therapies suitable for human clinical evaluation. The PCDD drug discovery capability is built upon a network of non-profit research institutions and small biotechnology companies using industry-standard metrics for the identification of hits, leads and preclinical development compounds, risk analysis and development. The PCDD is also meant to serve as a think tank to brainstorm ways to improve efficiencies and productivity in early drug discovery research, attracting top scientists from around the world. Jobs are already being created in the companies associated with the PCDD, helping to reintegrate biomedical scientists into the workforce who have been laid-off elsewhere.

When the PCDD was created, we conducted a review of similar Drug Discovery Centers or Institutes present in the U.S. There are ~75 of these which are either directed toward product development and commercialization or are research focused. The product development drug discovery centers are staffed largely by experienced researchers with an industrial background and have a technology transfer, applied emphasis. Examples of such organizations in Pennsylvania are found at Temple and Drexel Universities. The research focused drug discovery centers have as a primary goal the raising of funds to support the basic research of academic scientists related to drug discovery and associated with the host institution. The PCDD is relatively unique in that it seeks to focus heavily on the applied and technology transfer components of the biomedical research process. We also serve as a partner in the U.S. for international researchers and institutions to collaborate with relative to accessing U.S. expertise and potential funding opportunities such as from the National Institutes of Health (NIH). The PCDD plays a central and pivotal role in helping new biotechnology businesses start, and managing and advancing intellectual property from universities and other sources (Fig. **3**).

The PCDD currently has five programs that it has initiated, as listed below.

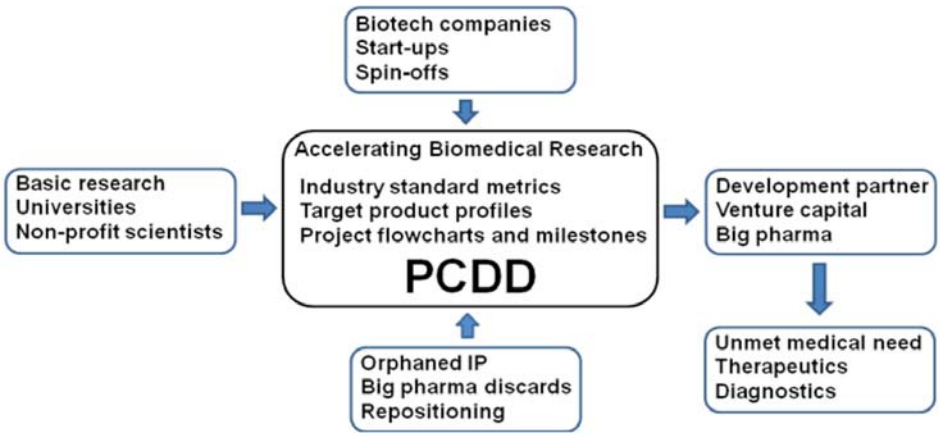

Fig. (3). Central role of the PCDD to facilitate the commercialization of basic research technologies from universities and other sources by conducting value-added applied research and forming partnerships to move into further commercialization and development.

1. Up and Out Program™

This program seeks to promote workforce rentry assistance to qualified biomedical researchers in Pennsylvania who have recently lost their jobs due to no fault of their own because of mergers, acquisitions and downsizing. Large numbers of highly-trained Pennsylvanians have been impacted by pharmaceutical and biotechnology company layoffs during the past two months. Nearly all of these are highly trained scientists, and many have advanced academic degrees (Ph.D. or M.S.). In addition, many researchers who live in Pennsylvania but work in New Jersey have also been similarly impacted; for example, the former Wyeth (now Pfizer) facility in Princeton, New Jersey has now closed. These job losses in the pharmaceutical and biotechnology industry disproportionately cluster in southeastern Pennsylvania. Through the Up and Out Program, qualified senior-level research scientists locate at the PCDD and are mentored in developing research plans and teams. Researchers are given an affiliation with the PCDD and career development advice and assistance, especially regarding forming collaborations and accessing federal and other funding. Program members are encouraged to participate in the seminars, journal clubs, research rounds and ad hoc interactions that are hallmark features of the collaborative spirit fostered by the PBC.

The Up and Out Program of active mentoring and support has already been successful in the initiation of several biotechnology start-up businesses, as listed below:

ALS Biopharma, LLC

Founded May, 2009, venture capital funded ($1.8M, www.alsbiopharma.com). ALS Biopharma targets the orphan and debilitating indication of Lou Gehrig's disease. This company required ~1.5 years of focused activity prior to achieving initial funding. It currently has 3 fulltime and 4 part-time employees.

Fox Chase Chemical Diversity Center, Inc.

Founded Nov., 2008 ($2.4M in funded grants and contracts). Fox Chase Chemical Diversity Center, Inc. is an early-stage translational drug discovery research company, with strong medicinal chemistry capability and five current collaborations and partners. This company required 6 months of focused activity to achieve initial funding, and presently has 4 employees and 4 associated part-time support staff.

Advanced Neural Dynamics, Inc.

Founded Nov., 2008 ($0.6M in a funded NIH grant). The focus of Advanced Neural Dynamics is on neurodegeneration and neuroprotection, as as for the treatment of epilepsy. This company required 6 months of focused activity to achieve initial funding.

The Up and Out Program provides guidance and consulting, tours of the PBC and PCDD, and role-models for how to start up new or join existing biotech ventures. We help craft both the research plan and the team required to be successful when starting a new company, as shown below (Fig. **4**).

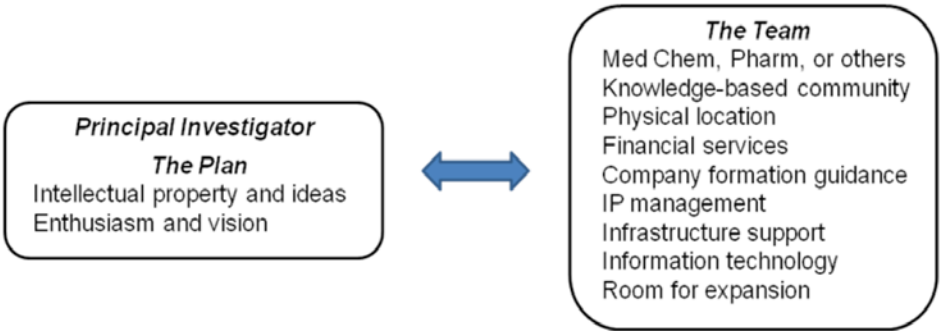

Fig. (4). The coordination and creation of the Plan and the Team required for successful startup of a small biotechnology company.

2. Industry-Standard Due Diligence Review

We also take advantage of the immense talent pool in southeastern Pennsylvania by creating an expert's list of highly-qualified reviewers and mentors by disciplines to evaluate basic discoveries at academic and non-profit institutions by an industry-standard due diligence review process. Many professors and principal investigators are conducting important basic research, but do not have the expertise required for the applied value-added experiments and studies needed prior to generating commercial interest. We provide advice on project flowchart design and the interpretation of data. We can also help to coordinate projects *via* project teams located here at the PBC. The due diligence review starts by initial evaluation of the technology by PCDD Directors. This is followed by the creation of six to eight person due diligence teams, comprised of members who have self-identified as being interested in such activities. The teams encompass all of the required disciplines represented in modern industrial research including medicinal chemistry (if relevant), pharmacology, toxicology, regulatory affairs, preclinical development, intellectual property and commercial review.

The recommendations from such review are invaluable, and help to promote the discovery and commercialization of new technologies in the healthcare area. The reviewers may suggest additional studies to be performed or new collaborators that add value to the program under study. They may also suggest specific steps to create and protect intellectual property by virtue of patent protection, or avenues to pursue for additional funding or evaluation. Finally, such a panel may recommend the creation of one or more associated spin-off companies which could add value to the technology and create new jobs and expertise.

3. PCDD Knowledge-Based Community

One of the strengths of the PBC is a knowledge-based community consisting of an active seminar program, frequent journal clubs, and sharing of information and equipment. The PCDD extends this spirit of collaboration into the applied arena of drug discovery research.

4. Network of Regional Drug Discovery Capabilities

Together with related organizations at Temple University, University of Pennsylvania, Drexel University and biotechnology companies in the area, we seek to compile networked lists of the providers of industry-standard tests required in modern drug discovery at steeply-discounted rates.

5. To Promote Public-Private Partnerships

We foster the interface between academia and non-profit research institutions and the private sector. We work together with academic researchers at the PBC and elsewhere in the region to facilitate the transfer of basic technology discoveries into commercial opportunities and promote the protection of intellectual property, such as by use of the legal counsel located at the PBC.

CONCLUSIONS

There is no better time than now to be in biomedical research. The research tools and reagents that are readily available are far superior to those in the past, and the entire scientific literature is only an internet click away. However, due to the increasing costs and difficulties associated with drug discovery and development, innovation as measured by the introduction of NMEs into therapy has remained stagnant at the same level now as it was in the 1950s, after a brief increase in the mid- to late-1990s. It is clear that the process of technology transfer and translational research itself has not worked as well as it could, and that improvements and advances in both of these areas must take place to improve biomedical research productivity. Innovation is now coming more commonly from smaller companies than before, and currently an roughly number of NMEs are being approved from small and large companies by the U.S. Food and Drug Administration. The Pennsylvania Center for Drug Discovery is an international think-tank for improving efficiencies in drug discovery, such as to help new entrepreneurs create the plan and team required to achieve initial funding. The PCDD also seeks to help in workforce reentry for qualified scientists who have been displaced elsewhere due to downsizing in the pharmaceutical industry and through no fault of their own. We live in a golden age of scientific discovery, and the future will belong to those with imagination working with more flexible models of operation and interaction.

ABBREVIATIONS

ADME = Absorption Distribution Metabolism Excretion

CV = Curriculum Vitae

FDA = Food and Drug Administration

LLC = Limited Liability Company

NBE = New Biopharmaceutical Entity

NIH = National Institutes of Health

NME = New Molecular Entity

PBC = Pennsylvania Biotechnology Center

PCDD = Pennsylvania Center for Drug Discovery

PPP = Public Private Partnership

ACKNOWLEDGEMENTS

The authors gratefully acknowledge grants from the Delaware Valley Innovation Network and the Pennsylvania Department of Economic Development, and a generous donation by Drs. Chuck and Kate Reynolds. Also, we are indebted to Dr. Tim Block, President of the Pennsylvania Biotechnology Center, for support and guidance. Finally, we thank management and staff who comprise the tenant companies associated with the PCDD. We also thank Dr. Eileen Jaffe of the Fox Chase Cancer Center for her collaboration and support.

REFERENCES

[1] Munos, B. Lessons from 60 Years of pharmaceutical innovation. *Nat. Rev. Drug Discov.*, **2009**, *8*, 959-68.

[2] Kozikowski, A. P.; Reitz, A. B. Fighting the pipeline for neglected diseases: creation of a medicinal chemistry-centric international drug discovery institute [iDDi]. *Drug Discov. Today*, **2008**, *13*, 97-8.

[3] DiMasi, J. A.; Hansen, R. W.; Grabowski, H. G. The price of innovation: new estimates of drug development costs. *J. Health Econ.*, **2003**, *22*, 151-85.

[4] Garnier, J.-P. Rebuilding the R&D engine in big pharma. *Harvard Bus. Rev.*, **2008**, *86*, 68-76.

[5] Farmer, B. T.; Reitz, A. B. *Fragment Based Drug Discovery, in The Practice of Medicinal Chemistry*, 3rd ed. Wermuth, C. G., Ed.; Elsevier: London, **2008**; pp. 228-43.

Received: January 18, 2010 Revised: May 20, 2010 Accepted: May 21, 2010