Productivity Shortfalls in Drug Discovery: Contributions from the Preclinical Sciences?

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ABSTRACT
An inverse relationship between human and financial investment and productivity, in the form of new drug approvals, has been a consistent theme in drug discovery for more than a decade. There appear to be many causes and solutions for this, but few tangible outcomes. Although Food and Drug Administration regulators, the constraints resulting from short-term business decisions, and the harvesting of all “low-hanging fruit,” have been cited as the major causes for the decreased productivity, a change in the preclinical research culture is equally culpable. Current trends in biomedical research have led to a decreased emphasis on the null hypothesis/data-driven approach; a trend toward qualitative rather than quantitative science; an implicit assumption that all targets represent a viable starting point for drug discovery efforts; and the replacement of the creativity, objectivity, passion, and logic characteristic of the drug hunter with consensus-dependent, technology-driven research cultures. In addition, the euphoria following the mapping of the human genome and its implicit potential as a source for new drug targets has given way to disillusionment as the relevance, tractability, and complexity of novel disease-associated targets have become recognized as significant challenges. Biomedical research efforts directed toward drug discovery, both in academia and industry, must prioritize genuine innovation over technology and thus allow efforts in preclinical research to play a key role in the solution to the shortfall in new drug applications.

Introduction
In the second decade of the 21st century, rarely a week has passed without a review or an article in the popular press lamenting the inverse relationship between the investment in the drug research and development process and the continued shortfall in productivity, the latter being assessed in the lack of robustness of clinical pipelines and the reduced number of new drug approvals (Munos, 2009; Carmichael and Begley, 2010). Despite optimistic declarations that a “golden age” in drug discovery now exists (http://www.bloomberg.com/apps/news?pid=newsarchive&sid=avss9uE1DgWM#), there is little to objectively support such claims, especially when approximately 35,000 jobs have been eliminated in the pharmaceutical industry in the first half of 2010 (http://www.fiercepharma.com/node/22199). And as the research and development environment becomes increasingly unstable because of mergers and/or downsizing, the ability to develop medications for treating diseases that threaten to undermine the economic viability of healthcare systems worldwide, e.g., Alzheimer’s disease (AD), becomes ever more difficult to address.

This lack of productivity has been ascribed to increasing stringent regulations from regulatory authorities, including the FDA (Carpenter, 2010); the overt, “crippling” influence of business decisions on basic science because of short-term profitability goals (Weisbach and Moos, 1995; Cuatrecasas, 2006), which has resulted in pharma research and development being viewed as an expense rather than an opportunity—“a drain on the balance sheet” (Carr, 2010); and the postulate that drugs for all the “easy” targets, the “low-hanging fruit,” have been discovered, with those remaining being difficult to reduce to practice/products. Although these are undeniably important factors that affect success in drug discovery, there are also shortcomings in the preclinical space that result from a change in the culture of biomedical science that originated in...
Biomedical Research in the Commercial Setting

Effect of the Biotech Revolution on Drug Discovery

The biotech revolution began in the mid-1980s with the founding of Genentech and attracted venture capitalists to drug discovery as a value proposition on par with the then-successful Silicon Valley dot coms. More than 3000 biotech companies were founded, the great majority of which failed, both in terms of successfully using their core “technology platform” and compounds to find viable clinical drug candidates and/or in generating the necessary revenues to survive (Pisano, 2006). This, however, did not prevent many investors, founders, and company employees from becoming wealthy, regardless of the companies’ fates and/or the science, with money frequently being a driver for the basic science. This situation was the antithesis of the pharma industry view in the mid-20th century, when George W. Merck, the president of Merck and Co., noted that “We try never to forget that medicine is for the people. It is not for the industry view in the mid-20th century, when George W. Merck, the president of Merck and Co., noted that “We try never to forget that medicine is for the people. It is not for the profits. The profits follow, and if we have remembered that, they have never failed to appear. The better we have remembered it, the larger they have been” (Merck, 1950).

The biotech revolution also engendered a change in the culture of biomedical science that was far more entrepreneurial and risk-oriented than that practiced in big pharma. This resulted in a new type of research and development leader—energetic and visionary, committed to operating “outside the box” with “a bias for action and a winning attitude” (Douglas et al., 2010) and, perhaps most importantly, facile in translating the often-abstract complexity of science to the business world. Although such changes were critical to the new business model at the strategic and leadership levels, they inevitably led to an oversimplification or “dumbing down” of the basic science, its practice as well as its presentation, such that sound bites and PowerPoint slides, rather than peer-reviewed publications, increasingly came to reflect the intrinsic scientific content and intent of a drug discovery effort. At times, this unfortunately led to marked disconnects between the enthusiasm of the vision and the data, doing little to enhance credibility (Prud’homme, 2004).

As a result, the rigor and transparency integral to the null hypothesis approach (Caldwell, 2009)2 were gradually replaced with an overtly reductionistic approach to data generation and interpretation that has increasingly relied on qualitative rather than quantitative science. Gone were the replicate PA2 and IC50 value determinations that had historically underpinned hypothesis generation. Instead, key decisions became focused on the “statistics-free” effects of a single, often arbitrarily selected dose/concentration of a compound, evaluated at a single time point using a transfected target or transgenic animal, with the experimental readout often being based on the “+/−, +, +/+” readout of the density of a gel band. This negated the basic premise of pharmacology, that of the Law of Mass Action, with “all-or-none” responses frequently being described as concentration/dose-response curves and with little consideration for either the structure-activity relationship of a compound as an integral component of the concentration/dose-response effect or its ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties.

Technology Imperatives

Rather than creating synergies by using multiple complementary technologies to find answers to discrete questions in a focused and coherent manner (Williams, 2005), technology-driven drug discovery has become a discipline that justifies its existence by searching for questions. An example of this is the proteomics approach to target validation, where the intrinsic complexity of the protein component of a cell or tissue necessitates a reductionistic approach where experimental samples must be separated into bins to facilitate analysis with timelines for data generation that can stretch into months or years.

To those with a technology bent, new iterations on a technology, regardless of its utility, inevitably become “must haves,” with acquisition and implementation becoming ends unto themselves. Each new software update, as well as each

1 Innovation is typically defined as the "introduction of new things or methods,” by which metric pharma can certainly be considered to have been very innovative. Beyond the noun, however, is a complex discipline that more accurately describes innovation as “a change in the thought process for doing something, or the useful application of new inventions or discoveries” (Burras, 1984). The introduction of "new things" without considering how they may fit into and improve existing “things” is where there has been a shortfall in what pharma has subscribed to as innovation. Instead, the latter has been largely treated as an obligatory sound bite, with the key follow-ons of ownership, integration, and value generation being largely overlooked. In general, failures in innovation have been ascribed at the organizational level to poor leadership, organization, communication, empowerment, and knowledge management, and at the individual level to poor goal definition, alignment of actions to goals, team participation, results monitoring, communication, and information access (O’Sullivan, 2002), all of which may resonate with those familiar with the endless reorganizations in pharma. From a technical perspective, the real innovation resulting from combinatorial chemistry, parallel chemical synthesis, or library synthesis occurred long after the practical utility of the former was questioned by bench scientists. Similarly, the innovation in Apple’s iPod was not in the basic idea of an mp3 player but in the strategy for its successful creation and application (Williams, 2005; Goodwin, 2010)—the technology also fulfilled a need, rather than looking to create one.

2 The null hypothesis, originally proposed by the statistician Ronald Fisher, is often considered by biomedical scientists as an arcane concept applicable only to statisticians. The basic premise of the null hypothesis is simply stated in that “There is no relationship between two quantities.” Thus in evaluating a hypothesis, the experimenter must design experiments with a “null” approach that assumes that any difference observed between two data sets (control versus test compound effects) is due purely to chance. When a data set that is designed to show no difference actually demonstrates a statistically significant difference, the null hypothesis can be refuted. As a practical example, an experiment that is limited to showing that Compound A is an antagonist of Target A can lead to possible spurious data when the effects of Compound A have not been evaluated at Target B. The null hypothesis in this instance would be that Compound A does not block Target B, which should be tested. Many studies defining the role of a kinase-signaling pathway in a target response are often limited to the use of a single kinase inhibitor of dubious selectivity at a single, micromolar concentration that provides, more often than not, far from convincing evidence, especially when the "n" value is 1 and statistics are absent.
iteration in high-throughput screening (HTS) and combinatorial/parallel chemistry while enhancing the number of compounds that could be made/screened, has led to a focus on productivity metrics that counts identified hits rather than drug-like lead molecules (Ullman and Bouttellier, 2008). Screening a compound library containing half a million compounds or new chemical entities (NCEs) at “x” targets in 1 to 2 weeks provided more data in a week than some scientists had seen in an entire career and frequently represented a self-contained task. If no drug-like hits resulted, there was always another target to take the place of the one that failed, thus justifying the strategy. However, as noted by Shaywitz and Taleb (2008), “spreadsheets are easy; science is hard.” Technologies did not always generate endpoints that added real value to the drug discovery process. An example of this was the solving of the x-ray structure of a target-optimized lead interaction concomitantly with the entry of the lead into clinical trials. This was elegant science temporarily disconnected from real-time need.

A compound library acquisition/synthesis and HTS approach is integral to the Molecular Libraries Initiative component of the National Institutes of Health’s Roadmap (Austin et al., 2004), which has as its mission “to facilitate the use of HTS to identify small molecules...by rapidly and efficiently screening a large number of compounds that encompasses a broad range of novel targets and activities...” Although well intentioned, this approach has been viewed as having questionable success by experts in pharma (Kaiser, 2008) and has been further limited by a lack of funding to assess the drug-like properties of a compound that “turn a discovery into a drug” (Carmichael and Begley, 2010).

**Target Tractability**

Implicit in the HTS/combinatorial chemistry paradigm was/is that each target was equally facile as a starting point for a drug discovery project. The mapping of the human genome (International Human Genome Sequencing Consortium, 2004) provided an apparently infinite potential for identifying a host of new targets against which to screen compound libraries. The more targets, the more compounds, the more data sets, the greater the opportunity for success (Fryburg, 2010; Miller, 2010). However, the initial euphoria for the human gene map and its myriad solutions to the treatment of human disease (Collins et al., 2003) has gradually given way to disillusionment and frustration as it became apparent that the disease association of many of the newly identified targets became less robust as additional data became available. Craig Venter, who led the private sector initiative to map the human genome, has recently been quoted as saying that “the medical benefits derived from the human genome [are] close to zero” (Boyer, 2010).

As an example, the Val(158)Met polymorphism in catechol-O-methyl transferase (EC 2.1.1.6) that represented a new human genome [are] close to zero” (Boyer, 2010). With the cloning of the M1-M5 receptor family (Corbett et al., 2006), which has as its mission “to facilitate the use of HTS to identify small molecules...by rapidly and efficiently screening a large number of compounds that encompasses a broad range of novel targets and activities...” Although well intentioned, this approach has been viewed as having questionable success by experts in pharma (Kaiser, 2008) and has been further limited by a lack of funding to assess the drug-like properties of a compound that “turn a discovery into a drug” (Carmichael and Begley, 2010).

**Something Old**

**Opioid Receptor Agonists.** Drugs active at opioid receptors remain the gold standard of analgesic care and include morphine, codeine, and oxycodone. With the discovery of the µ, δ, and κ receptor subtypes in the 1970s, it was anticipated that development of selective agonists for these receptors would result in drugs that had a reduced liability for the respiratory depression, tolerance, constipation, and addiction associated with classical opioids. Some 40 years later, despite considerable efforts in medicinal chemistry and molecular biology to refine/define the structural characteristics of receptor-selective NCEs, the “holy grail” of side effect-free opioids appears as elusive as ever, with a multitude of compounds showing compelling preclinical data but failing to demonstrate these properties in the clinic (Corbett et al., 2006).

**Muscarinic Receptor Agonists, Antagonists, and Modulators.** With the cloning of the M₁-M₅ receptor family in 1989, it was also anticipated that new drugs with greater therapeutic efficacy and/or reduced side effect liabilities would be found to replace drugs like scopolamine, atropine, oxybutynin, and others that have major side effect liabilities. This would occur by tweaking the selectivity and efficacy of NCEs for the various muscarinic receptor subtypes, an un-
dertaking facilitated by the many hundreds of NCEs synthesized for this receptor family as it was used to generically understand G-protein coupled receptor function at the molecular level (Wess et al., 2007). As with the newer opioid NCEs, drug-like muscarinic NCEs with robust selectivity attributes at the molecular level have failed to live up to expectations in terms of the anticipated clinical outcomes. Xanomeline, an M₁/M₄ agonist targeted for AD (Mirza et al., 2003), had side effects sufficient to result in high dropout rates in pivotal clinical trials, in addition to also precluding dosing to efficacious levels. Similarly, the M₄ allosteric modulator, desmethylclozapine, which was targeted for schizophrenia (Mendoza and Lindenmayer, 2009), failed to show robust human efficacy.

Thus, for both of these G protein-coupled receptor families, a major question is whether their function is so critical, nuanced, and complex as to preclude advances based on the molecular approaches currently being used that may lack the necessary heuristic relationship to the complexity/redundancies of the systems present in a more physiological or disease-related milieu. Based on progress over the past 40 years, it may well be concluded that the opioid and muscarinic receptor families represent intractable targets in the search for improved small-molecule therapeutics. But maybe the next NCE...???

**Something New**

The human kinome consists of approximately 518 mammalian protein kinases (Manning et al., 2002) and collectively represents a major set of potential disease targets. From a drug discovery perspective, however, the kinome was considered by many to be an intractable target, as competitive inhibitors, which act by blocking access of the substrate ATP, would by definition lack selectivity, leading to promiscuous interactions with all kinases, resulting in an unacceptable side effect profile. In addition, in many instances, the discrete protein substrate(s) of a given kinase, its endogenous activity (often dependent on the ATP level in the microenvironment), and the redundancies in kinases for substrates and substrates for kinases were unknown. The seminal kinase inhibitor, the naturally occurring bisindole alkaloid, staurosporine, was notably nonselective in its kinase specificity (Karaman et al., 2008) (not that medicinal chemists were not able to improve on its promiscuity) but proved to be benign in vivo, which may be attributed to its inherently poor solubility. However, molecular profiling of 20 other kinase inhibitors, 16 of which were either approved drugs or in clinical development, showed that they had markedly different kinase inhibitory specificities that could not be correlated with either their structure or their activity at the intended target (Fabian et al., 2005). This suggests that in disease states in which aberrant kinase activity plays a key role, specificity may be dictated by the target enzyme being induced, abnormally expressed, or hyperactive. Alternatively, it has been repeatedly suggested, albeit with less-than convincing data, that excess ATP may be causal in tumor growth, and in this context, inhibition of ATP synthase has been shown to modulate breast carcinoma growth (Huang et al., 2008).

Compounds active at the supposedly intractable kinome target, including imatinib, sorafenib, and erlotinib, have revolutionized cancer treatment (Zhang et al., 2009) even though their kinase selectivity is far from absolute. The B-Raf kinase inhibitor, sorafenib, has only modest activity at its stated target, compared with other kinases (Fabian et al., 2005), a reflection of an inability at the time of its discovery to access assays that could facilely interrogate other members of the kinome. Second-generation kinase inhibitors, including the B-Raf(V600E) kinase inhibitor, PLX4032, thought to be related to PLX4720 (Tsai et al., 2008) for the treatment of metastatic melanoma, and AC220, a Flt3 kinase inhibitor (Zarrinkar et al., 2009) for the treatment of acute myeloid leukemia, have been developed and are considerably more selective for their targets than the earlier kinase inhibitors. Additional approaches to address kinase inhibition include allosteric/noncompetitive inhibition (Karginov et al., 2010; Weisberg et al., 2010) and the modulation of kinase-signaling pathways via traditional cell surface receptor modulation. Thus the kinome, considered by many as too promiscuous to yield useful drugs, has, at least in the area of oncology, provided NCEs that represent a major advance in cancer therapy.

**And the Future...?**

The intent of the present perspective is obviously to highlight the need for data and individual contributions from the innovative “true believers” (Douglas et al., 2010) rather than technology, prejudice, bureaucracy, and defeatism (“all the easy data-independent targets have been done”) to drive the preclinical drug discovery process. The current trend in ignoring the null hypothesis approach (and statistics), combined with the move toward qualitative rather than quantitative data sets, can contribute equally to the reduced number of new drug approvals, as the infamously short-term business decisions, FDA regulations, and the newer targets become more “difficult” to reduce to practice. The interrogation of targets almost exclusively in transfected systems, where the physiology of the target and its ancillary proteins are usually lacking, has led to some embarrassing surprises in both animal models and the clinic, where antagonists were found to behave as full or partial agonists because of their incomplete evaluation in the preclinical setting. Thus the imperative in addressing pipeline deficits should be to focus on an iterative, data-driven approach involving both chemists and pharmacologists, coupled with the creativity, objectivity, passion, and logic characteristic of the drug hunter persona (Uitdehaag, 2007). Accordingly, a few areas that could potentially “revitalize the industry” at the preclinical level are outlined in Table 1.

For the present time, as long as the FDA, business interests, and the targets are judged as being causal rather than the current scientific mindset, the considerable effort necessary to put better targets with improved compounds into the translational medicine interface (Enna and Williams, 2009b; Wehling, 2009) will not occur in a timely and productive manner but will, instead, sustain the disconnect between the

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3 Those who have spent a major part of their career making and testing opioid and muscarinic ligands in hopes of replacing morphine or finding an effective drug for AD, may take issue with why, given the numerous other receptor families that have yet to deliver a new therapeutic, e.g., neurokinin, galanin, CCK, β-secretase, and so on, opioids and muscarinics have been singled out. The answer is in the numbers. Searching Google Scholar back to its 1991 initial archive date gave 81,200 hits for opioids and 101,000 for muscarinics. The hits for neurokinin, galanin, CCK, or γ-secretase did not individually exceed 30,000.
TABLE 1
Revitalizing preclinical contributions to drug discovery—a data-independent assessment
This table was generated at the request of one of the reviewers. It could no doubt be enhanced and refined with additional input from the collective wisdom of those active in preclinical research.

Innovation

Individual

The published literature is not the only source of new ideas for first-in-class drugs—some of the most successful ideas came from within the industry (e.g., fluoxetine and cimetidine).

Get the data to support a new concept that you believe in before you try to sell it—ideas are a dime a dozen, and many people are unable to reduce a concept to a peer-reviewable data set.

Data are golden.

When working on a best-in-class generation project, make sure you understand what “improved” looks like, how it stacks up to the initial drugs in the class (always benchmark to the competition), and whether the postulated improvements can be realistically tested and proven in the clinic.

Management

Allow a scientist who is really passionate about a concept the time to gather the necessary data to convince his/her peers and you. A minimal investment allows the separation of the true drug hunters from the dilettantes, the misguided, and the politically motivated.

Mentor such people and recruit more of them.

Tolerate dissent and avoid group-think. Always look for the “devil’s advocate” viewpoint, and try not to shoot the messenger.

The grass is infrequently greener. An expert consultant is not necessarily objective, and may not know the correct solution to, or even understand, your problem. Your experts should be in house.

To paraphrase Orson Welles’s famous ad for Paul Masson wine, “Serve no drug before its time.” If the compound is first in class, make sure it is the very best it can be to avoid whiny post mortems along the lines of “right target, wrong compound,” which again will convince no one.

Data generation/experimentation

Individual

Use the null-hypothesis approach.

Apply appropriate statistical analysis to the data. An sample size of 1 convinces no one.

Avoid qualitative science. Apply the law of mass action, the concentration/dose response effect (Maddox, 1992), in using compounds to define target pharmacology and pathway involvement. An antagonist used at a single concentration of 1 μM to invoke a response mediated at a target where it is active at 2 μM may result in an erroneous conclusion.

Run appropriate controls. Do not rely on historical data or literature data obtained 15 to 20 years ago in a laboratory that no longer exists.

Do not ignore data because it does not conform to what was anticipated and/or wanted. The unexpected often represents a paradigm shift (e.g., if you expect a decrease and get an increase). Mother Nature may also be telling you something about whether you should be running experiments.

The null-hypothesis culture

Make decisions based on data.

Apply the concept of the null hypothesis to the project portfolio—assume that none of them are on target to deliver and be pleasantly surprised when you find they are.

Use a SWOT (strengths, weaknesses, opportunities, and threats) analysis approach to encourage transparency and disseminating viewpoints and to avoid complacency and the status quo.

Develop and maintain a balanced risk, diverse target portfolio with a 3- to 5-year timeframe (not 18–24 months).

Review projects regularly but not in a timeframe that precludes the time and effort necessary to gather the necessary data.

Integrate absorption, distribution, metabolism, excretion and pharmacodynamics (ADME/T) in the lead optimization paradigm. Although Scientific Advisory Board (SAB) meetings are usually events where everyone has a win-win agenda, remember that 90% of what is done in drug discovery, the events that occur between project initiation and selection of a compound as a potential investigational new drug do not build on either the experience or interest of an SAB.

Use retired pharmaceutical researchers as part of your SAB. Their prior experience can be very helpful, and at the very least, they will commiserate with you.

Avoid:

- dumbing down the scientific focus of a meeting to accommodate nonscientist participants.
- sunk-cost scenarios.
- not making decisions.

Prohibit the use of wireless Internet devices at any and all meetings where you expect informed decision making.

Building a robust pipeline

Make the translational medicine paradigm a reality in your organization, but first make sure everyone agrees to precisely what it is (Enna and Williams, 2009b; Wehling, 2009).

Attempt to develop a seamless preclinical/clinical interface through phase IIa involving preclinical champions.

Inolve clinical in the drug-discovery process, but diminish the impact of risk-averse clinicians who prefer working on “derisked” phase IIb in-licensing candidates.

Bench and the clinic (Horrobin, 2003) and further the “toxicology crisis” (Carr, 2010).

Authorship Contributions

Wrote the manuscript: Williams.

References


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