Getting pharmaceutical R&D back on target

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The pharmaceutical industry is in a period of crisis due to the low number of new drug approvals relative to the high levels of R&D investment. It is argued here that improving the quality of target selection is the single most important factor to transform industry productivity and bring innovative new medicines to patients.

"Give me but one firm spot on which to stand, and I will move the earth."

—Archimedes

The productivity challenges facing the pharmaceutical industry are alarming. Large pharma productivity for the period 2005–2010 is illustrated in **Figure 1**, which shows the number of FDA-approved new molecular entities (NMEs) each year relative to R&D spending[1]. During this period, the nine large companies used in this analysis achieved an average overall output of ~7 approved NMEs per year between them (an average of <1 per company per year) against a backdrop of a combined annual R&D expenditure that has steadily increased toward a staggering $60 billion. The most recent data are particularly stark, with just two approved NMEs secured from across all these companies in 2010 (**Fig. 1**). It is clear that such a business model is unsustainable and that if the pharmaceutical industry is to survive over the longer term, it is essential to transform R&D productivity. In this article it will be argued that improving target selection is the key to tackling this challenge and that wider collaboration across traditional disciplines, and between industry and academia, will be crucial.

Drug discovery is a complex, time-consuming and very costly process. Recent data from the Pharmaceutical Benchmarking Forum (PBF; http://kmrgroup.com/ForumsPharma.html) indicate that the median cycle time for introduction of an NME now averages over 13 years from project inception to market—with approximately 4 years spent in preclinical research and around 9 years required for a drug candidate to progress through the clinical phases of development. The costs of development are also increasing, and it can take as much as $1 billion to develop a new drug, depending on the therapeutic area[2]. However, despite the clear time and cost challenges in developing each successful drug, the biggest issue facing the pharmaceutical industry overall is the 'curse of attrition'. Current industry performance data for survival through the development process are illustrated in **Figure 2**. Overall, it can be seen that about 24 development candidates enter development for every launched NME. The survival data by development phase are especially noteworthy, highlighting attrition in phase 2 as the key industry challenge: only 25% of the compounds that currently enter phase 2 proceed through into full phase 3 clinical studies. This low survival percentage is further exacerbated by the very high costs associated with attrition at such an advanced stage. Improving phase 2 survival thus represents the biggest single opportunity to tackle the industry's R&D productivity issues.

Phase 2 is the development stage at which pivotal clinical 'proof-of-concept' (POC) studies are conducted. Assuming that these studies are well designed, using tolerated clinical doses that drive a biomarker response consistent with target engagement, then the POC study in essence represents the experimental 'read-out' on the key project hypothesis—that is, that modulation of a given biological target will have efficacy in treating disease in patients. As many of the POC studies included within the analysis in **Figure 2** are likely to assess new agents against known targets (so-called 'me-too' or 'me-better' drugs), the 25% survival figure rate may be a significant overestimate of this target-disease hypothesis success rate.

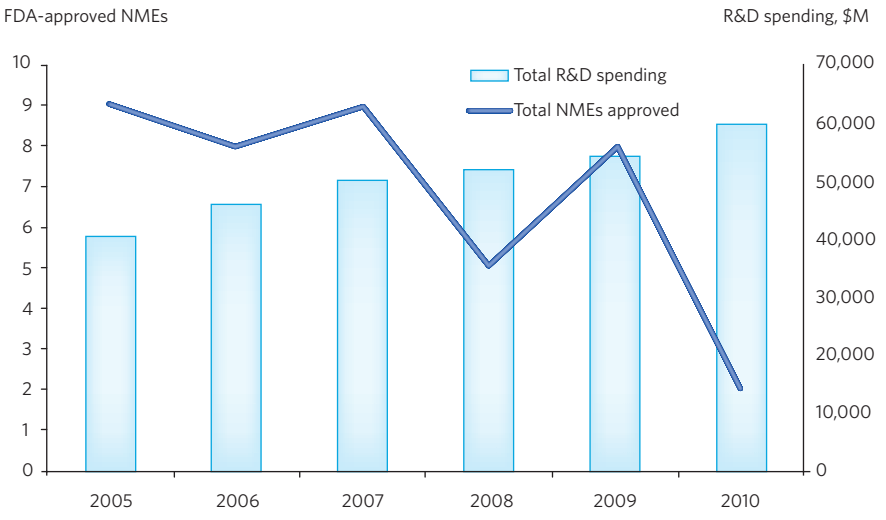

Figure 1 | Large pharma productivity from 2005–2010. Combined FDA-approved NMEs versus R&D spending for nine large pharmaceutical companies (AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Pfizer, Roche and Sanofi-Aventis). Figures shown are in millions of US dollars. Source: FDA CDER; Bernstein[1]. NME includes biologicals and vaccines.

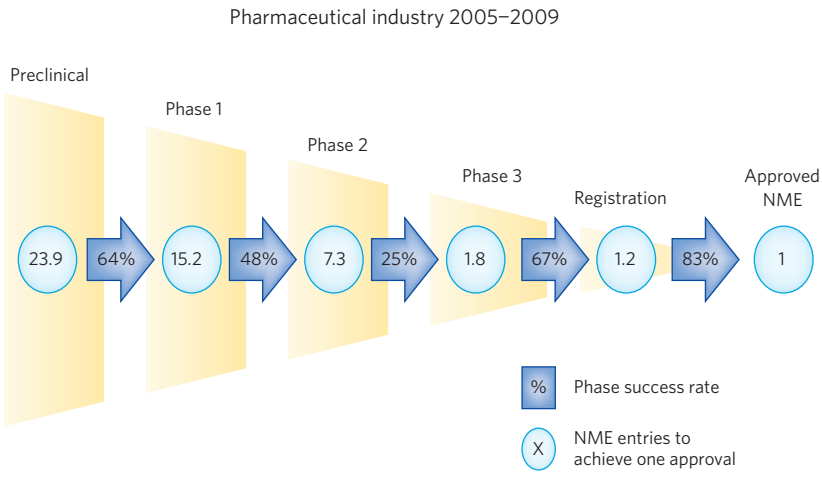

Figure 2 | NME success rate by phase. Combined R&D survival by development phase for 14 large pharmaceutical companies (Abbott, AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis and Schering-Plough). Data from the Pharmaceutical Benchmarking Forum (http://kmrgroup.com/ForumsPharma.html). Approval data is based on approval of NME by a regulatory authority in a major market (EU, US or Japan).

In summary, the poor survival in phase 2 suggests that the pharmaceutical industry has not been anywhere near good enough at selecting biological targets that influence disease.

A rich and expanding target universe

Of the ~30,000 genes in the human genome, it has been estimated that only around 10% express proteins that are likely to be suitable for modulation via classical rule-of-five–compliant small-molecule drugs (constituting 'the druggable genome'[3]). Combining this with an estimate of the likely number of genes that may be relevant to disease, early analyses suggested there might be as few as 600 viable drug targets in humans[3]—many of which have already served as the source of drugs currently on the market. Such analyses have led some to conclude that the opportunities for new drug discovery may be narrowing. In reality, a number of factors suggest that the opposite is true. First, even within the well-characterized protein families, biomedical research has focused on very few targets. For example, although the human kinome encodes over 500 protein kinases, a recent analysis[4] showed that only a small subset of the kinome has attracted significant research interest and that the biology of the majority of kinase targets is largely unexplored. In addition, a number of new target families are now emerging that are generating significant excitement in the biomedical community for their potential disease relevance. For example, the area of epigenetics is attracting much attention, and the 'epigenome'—the various enzymes ('writers' and 'erasers') and recognition ('reader') proteins that are involved in epigenetic regulation—already comprises at least 230 members and continues to grow (http://www.thesgc.org/resources/). The ubiquitin-proteasome system represents another target family of contemporary interest for drug discovery[5], and over 700 members of the 'ubiquitome' have already been identified[6]. In addition to such emerging families, significant untapped opportunity also remains in established gene families with well-precedented evidence of druggability, such as G protein–coupled receptors (GPCRs), enzymes, ion channels and nuclear hormone receptors, among others.

In addition to the daunting array of 'druggable' biological targets that could be of relevance to human disease, there has been considerable recent progress in the medicinal chemistry of hitherto 'undruggable' targets, such as protein-protein interactions (PPIs)[7]. Indeed, PPI medicinal chemistry has witnessed clear progress in recent years[8], either through small molecules that exploit more tractable protein-surface interactions (recent examples include BRD4 inhibitors[9,10] and LEDGF/p75 inhibitors[11]) or through new types of protein mimetic scaffolds that have potential drug-like properties (such as stapled peptides[12] and natural product–inspired macrocycles[13]). The human 'interactome'[14] is estimated to number between ~130,000 (ref. 15) and ~650,000 (ref. 16) protein-protein interactions, and even if only a small fraction of these interactions were disease relevant and amenable to disruption via drugs, it is clear that this would represent another vast area of untapped target opportunity.

The majority of contemporary drug discovery efforts have followed a reductionist paradigm in which a highly selective drug is sought for a single biological target. It is notable, however, that many historical drugs are nonselective (that is, show 'polypharmacology') and may achieve efficacy by interacting with a number of targets in concert[17]. The increasingly sophisticated mapping of pharmacological space[18] through chemogenomic analyses provides for a future in which the rational design and optimization of small molecules to interact with multiple targets ('polypharmacology by design') may become possible. This also dramatically expands the potential 'opportunity space' for new drug discovery projects (notwithstanding the increased risk of safety liabilities for such approaches). Finally, even for a single-target approach, the approach to target modulation (for example, allosteric versus orthosteric inhibition, partial versus full agonism) and the chosen drug modalities (for example, small molecule versus biologic) may all drive differences in efficacy and safety profiles that could influence success, or lack thereof, in the clinic.

In summary, the issue faced by the pharmaceutical industry is not so much a diminishing arena of target opportunity for drug discovery but rather the challenge of selecting which targets are most likely to influence human disease.

One firm spot on which to stand

In view of the high levels of development attrition (**Fig. 2**), many pharmaceutical companies have sought a rich early pipeline of projects to maximize the chance of securing sufficient positive POC studies to fuel their phase 3 pipeline and NME launch ambitions. By and large, each drug discovery project represents a distinct biological target. It is clear that a vicious cycle can quickly emerge whereby filling the pipeline with projects for which the target rationales are weak can serve merely to increase downstream POC attrition and thus increase project demand further. Breaking this vicious cycle (which is also financially unsustainable) requires increased time and focus on the quality of target selection ahead of project initiation. Once a high-confidence target has been identified, the full power of the drug discovery engine—arguably the pharmaceutical industry's core strength—can be unleashed to try and identify and progress a quality drug for the chosen target. Indeed, it is argued here that the single most important factor for improving pharma R&D productivity overall is the establishment of strong foundations for all projects from the outset through selection of the highest-quality targets possible.

In addition to target selection, the pharmaceutical industry certainly has room to improve in many other areas, for example by designing drugs with lower risks of the safety, toxicology and toleration issues that are the main causes of early stage attrition (**Fig. 2**). Drug toleration is also a factor in phase 2 survival—because a poorly tolerated drug may not be amenable to dosing high enough to support full target engagement and proper testing of the clinical hypothesis. There is also a case for greater use of clinical biomarkers to confirm pharmacology and enable more accurate dose-setting ahead of pivotal POC studies, as well as for more careful selection of patient populations for these studies to maximize prospects for a positive outcome. In summary, pharma R&D has scope to improve in many areas, but it is the selection of a high-quality target at the beginning of a project that is the underpinning requirement essential for ultimate POC success—the 'one firm spot on which to stand'.

Choosing a perfect target

Human biology is enormously complex, and improving target selection decisions represents an undeniable challenge. Although there is no single defining attribute of target quality, an accumulation of evidence may suggest that a given target has much higher probability of disease relevance than other target options. A number of potential factors that one might consider as hallmarks of target quality are captured in **Box 1**. Of these, the availability of human data—for example, from human genetic association studies and/or preclinical experiments using isolated human tissue from affected patients—is particularly powerful. For example, the impact of human genetic data in target validation is illustrated by the discovery of maraviroc[19], a CCR5 antagonist used against HIV, which was inspired by the observation that deletion of the human CCR5 receptor conferred resistance to HIV infection. Another target of contemporary interest with strong human genetic data is the voltage-gated sodium channel known as Nav1.7. Loss-of-function genetic mutations affecting Nav1.7 are associated with a rare autosomal recessive disorder that leads to extreme insensitivity to pain in otherwise healthy individuals, whereas gain-of-function mutations in Nav1.7 have been shown to cause increased pain sensitivity[20]. In view of this compelling genetic evidence, there is considerable industry interest in Nav1.7 blockers as pain therapeutics.

One of the common lines of evidence often used for building confidence in a target is the animal model data. Although it is clear that animal models have an essential role to play in establishing pharmacology, pharmacokinetic-pharmacodynamic relationships and toxicology for a potential new drug, genuinely validated animal models of disease are rare, and predicting disease relevance on the basis of animal model data can be very risky indeed (especially in the absence of other supporting evidence of the types delineated in **Box 1**). The use of animal models is complicated by the fact that the mechanistic basis underpinning many such models is poorly understood and the efficacy endpoints used are often very different from those measured in the clinic (key exceptions here include diseases such as diabetes).

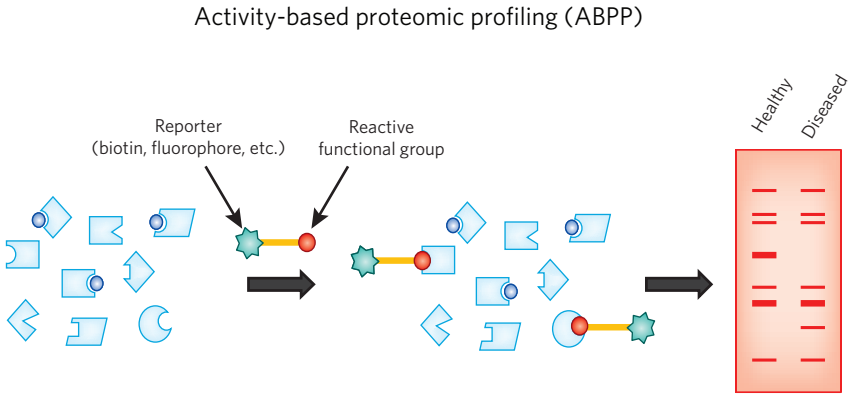

Figure 3 | Chemical biology in target validation. Activity-based proteomic profiling (ABPP) to establish the active proteome of a target family in physiologically-relevant systems such as whole cells. ABPP of 'healthy' and 'disease' cells can help determine the active proteins relevant to the healthy/disease phenotype. ABPP can also be used to explore target selectivity of small-molecule inhibitors (shown in blue circles) in the whole-cell setting.

Overall, it could be said that an over-reliance on animal models of disease has in part led to the current poor levels of phase 2 survival.

Although it is essential to consider target quality in terms of disease rationale, it is also important to address target tractability; some hallmarks of quality in this context are included in **Box 2**. Overall, it is argued here that a significant improvement in target selection decisions—and thus industry productivity—can be achieved if most, if not all, of the quality hallmarks in **Box 1** and **Box 2** are demonstrated as part of any new drug discovery effort.

Box 1 | Sample hallmarks of target quality: disease rationale

Genetics. Human genetic data available that supports functional relevance of target in disease (for example, genetic mutation linked to disease phenotype).

Expression. Evidence of up- or downregulation of target in disease-relevant human cells/tissues (ideally via both transcriptional and proteomic profiling).

Preclinical tool validation. Selective chemical probes and/or biological tools (such as small interfering RNA) modulate disease phenotype in disease-relevant preclinical assay (using human cells or tissues); validation includes studies aligned with chosen therapeutic modality (for example, chemical probe for a small-molecule approach).

Differentiation. Clear rationale for how modulation of chosen target in given disease has potential to drive differentiation over current standard of care.

Pathway knowledge. Disease relevance of biological pathway, or associated protein interactome, already validated (ideally in clinic).

Target safety. Evidence that modulation of target (or pathway) does not carry an intrinsic safety or toxicity liability.

Animal models. Animal model data that provides additional support for role of target in disease (for example, genetic knockouts and/or clinically validated disease model).

Box 2 | Sample hallmarks of target quality: tractability

Screening cascade. Viable screening cascade, including disease-relevant (cell-based) functional assay and ideally native tissue functional assay (if possible with both healthy and diseased tissue to assess for differing pharmacology).

Chemical doability. Evidence that target is 'druggable' via chosen therapeutic modality (that is, small molecule or biologic).

Dose prediction. Good understanding of efficacy concentration (C_{eff}) and receptor occupancy in preclinical pharmacology models to support high-confidence dose prediction to human (ideally using a pharmacokinetic-pharmacodynamic model that incorporates pharmacokinetics, safety, pharmacology, efficacy and differentiation to improve quantitative translation to and from the clinic).

Clinical development. Robust efficacy endpoints that can be monitored in (early) patient studies; translatable biomarker to support dose setting; early biomarker to demonstrate target engagement and pharmacology at site of action; well-defined patient population for POC studies.

An evolving R&D ecosystem

The low R&D productivity discussed herein is leading to considerable change across pharmaceutical companies as part of a quest to improve R&D output and/or reduce costs. One of the key strategic drivers now being pursued by many large companies is the approach of localizing therapeutic-area research in biomedical research centers close to major academic institutions and teaching hospitals. This change in model reflects the reality that the vast majority of the initial breakthroughs in target biology research occur in the academic research environment[21]. It is thus considered essential for pharmaceutical companies and their scientists to become better connected with the external research environment and develop a more extended network of partnerships and genuine collaborations with academia. Through close partnerships of this kind, a much broader span of research across the available target universe can be explored than any company could encompass by operating in isolation. Furthermore, active external partnerships can be key enablers for building the deep target knowledge required to improve overall target quality.

Precompetitive consortia are likely to play an ever-increasing role in this evolving R&D ecosystem, bringing multiple academic and industrial partners together to share the risk and cost of early exploratory research. A current example of such a model is the Structural Genomics Consortium collaboration in the field of epigenetics (http://www.thesgc.org/chemical_probes/epigenetics/), in which academic groups and pharmaceutical companies are working together to develop high-quality chemical probes for epigenetic targets that will be made available to the biomedical research community without restriction on use. It is anticipated that making these probes openly available will greatly accelerate research in this emerging field of science and help identify the proteins in the epigenome that have most potential as therapeutic targets. One of the very first probes to emerge from this effort, a bromodomain recognition inhibitor known as JQ-1 (ref. 9), has already supported the validation of bromodomain-containing protein 4 (BRD4) as a potential target for treatment of NUT midline carcinoma[9], an early indicator of the potential power of such open innovation models. It is likely that many more precompetitive consortia of this kind will now emerge in other areas of target space.

How can chemistry help?

In early pharmaceutical R&D, the interaction between biologists and chemists represents an essential partnership in exploratory research in which an active dialog on target rationale and druggability drives the selection of which targets to progress. Once a decision is made to work on a target, the drug discovery engine is often fully engaged, involving broad hit-seeking activities, lead optimization and ultimately candidate selection. In some cases, where the accumulated evidence supporting a given target may already be compelling (for example, human genetic validation of CCR5 or Nav1.7), backing the target to win in this way may well be justified. In other situations, in which the availability of a small molecule may actually be required to support further development of target rationale (**Box 1**), it may be judicious to apply a more limited chemistry effort to secure a quality chemical probe[22] for target validation studies. Because chemistry strategies to develop a chemical probe may be very different, and less resource intensive, than a traditional drug discovery paradigm, such an approach also avoids creating too much momentum in a drug discovery project before target quality has been assured. Indeed, medicinal chemists can perhaps help in target selection by resisting the 'druggability trap'—whereby the attraction of working on a tractable target (**Box 2**) draws teams into pushing forward projects with poor target quality (**Box 1**).

In addition to a greater focus on the use of chemical probes, there is also an opportunity for much broader use of other chemical biology approaches to support target validation in drug discovery. It is beyond the scope of this commentary to illustrate the various opportunities here, but chemical proteomic methods such as activity-based proteomic profiling (ABPP) can serve as an illustrative example. The ABPP paradigm, which has recently been reviewed[23], uses a chemical probe that can covalently capture the active proteome of a given target family within the whole-cell environment (**Fig. 3**). In a simple manifestation of this approach, the probe contains an appropriate reporter to enable in-gel analysis and/or pulldown of the active proteome in a given cell population. Such probes can also be used to compare 'normal' versus 'disease' cell populations, for example, to identify the changes in active proteome in a given disease state. Recent developments in ABPP have led to modular probe designs that allow a broad array of gene families to be profiled (for example, via photoactivatable linkers to capture nonreactive proteins). Techniques such as ABPP represent just one of a myriad of emerging chemical biology approaches that can provide additional evidence to help build target rationale, alongside other target quality attributes shown in **Box 1**. Such techniques can also be harnessed to enable drug discovery in other ways, including the development of occupancy biomarkers and delineation of mechanism of action from phenotypic screening paradigms. It is thus essential for medicinal chemists in industry to increase their awareness of chemical biology approaches and build these into their armamentarium to enable drug discovery[24].

Outlook

The need for new medicines is significant, with many areas of disease currently poorly treated, an aging population and an increasingly global healthcare market. Some of the major public health challenges of our time, including Alzheimer's disease, diabetes, chronic obstructive pulmonary disease and rheumatoid arthritis, as well as many infectious diseases and cancers, are in desperate need of innovative medicines[25], and the World Health Organization has

listed many hundreds of other diseases also in need of attention[26]. In the postgenomic era, human biology continues to reveal itself as highly complex, and there is no shortage of human targets that may be relevant to disease. The challenge facing the pharmaceutical industry is selecting the winners from the vast array of target options—indeed, it is argued here that a sharp focus on improving the quality of target selection is the single biggest factor that can transform overall R&D productivity. Despite the challenge and change in the industry, there is much cause for optimism. An evolving R&D ecosystem is driving a much closer partnership between industry and academia, and precompetitive consortia are emerging that see companies working closely together to discover the key targets that are most likely to influence disease. A deeper understanding of human biology is enabled by an array of new tools and techniques, including many arising from research in chemical biology. Although this is a time of crisis for the pharmaceutical industry, it is thus also a time of opportunity. It is now essential to grasp this opportunity to improve R&D productivity and bring important new medicines to patients in need.

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Competing financial interests

The author declares competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturechemicalbiology/.