Do technical and commercial biases contribute to the pharmaceutical industry's productivity problems? An analysis of how reordering priorities can improve productivity

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Of the many issues that contribute to the pharmaceutical industry's productivity problems, biases in the drug discovery and development (DDD) process should be included on the list. The dominant bias pervading the early DDD process is the requirement to identify and develop a commercializable molecule, long before the importance of the target in human disease is understood. That requirement filters out many potentially valuable projects. By changing the emphasis from identifying a commercializable molecule to using molecular tools to test the relevance of the mechanism in humans, the projected number of proofs of concept and subsequent launches could increase up to fivefold. Because this tool paradigm requires resources, one consideration is to form a consortium to share the burden, benefiting both the industry and patients in need.

Introduction

Although the productivity problems of the pharmaceutical industry are well recognized [1] (http://www.accenture.com/Global/Research_and_Insights/By_Industry/Life-Sciences/PharmaceuticalCostDrivers.htm), paradoxically they come at a time of unequaled scientific and technologic wealth. Our present knowledge base is the greatest ever assembled, including – but not limited to – the identification of many new molecular targets. In addition, there have been considerable advances in the modalities with which we can manipulate these targets [2], including improved design and production of new chemical entities (NCEs), antibodies, peptides, and RNAi. Despite all of the technologic wealth, productivity (as measured by new and innovative therapies) continues to be low [3,4]. Although there are several contributing factors proffered as the explanation [5–7], this problem seems to be centered in Phase II, where the majority of attrition is attributed to lack of efficacy [8–11].

Success rates, starting from discovery

Although lack of efficacy in Phase II is a major cause of project loss, the productivity problem has earlier roots in the drug discovery and development (DDD) process. Figure 1 summarizes published success rates for NCEs, spanning from Discovery through to launch. There are two important points. First, articles on attrition in DDD generally focus on attrition after identification of the development candidate. In those papers, a sponsor needs molecules from ~13 candidate programs to enter early development to achieve one launch [5,12]. Yet it is a lesser-known observation that 80% of NCE discovery programs fail to produce a candidate [8]. To identify 13 development-worthy candidates, therefore, sponsors need to pursue at least 65 programs in Discovery to achieve that launch (Figure 1). That is, the greatest loss of targets (and potential value) is in Discovery, and the probability of success from target selection is $P < 0.02$. On both a fractional and a numerical basis, more projects are lost in Discovery than elsewhere (including Phase II) in the DDD process.

Second, these statistics reflect an unknown blend of both precedented and unprecedented mechanisms of action. Unprecedented targets, the focus of this paper, have a much lower success rate than the precedented category [11,13,14]. For these novel targets, the NCE candidate identification success rates have been cited as low as 3–5% [14,15]. Sponsors would need to prosecute several hundred more unprecedented targets to achieve one launch, estimated at 260–400; most will be selected out in Discovery. Coupled with drop-out along the development path, these low success rates in Discovery partly explain the negative net present value associated with small molecule discovery and development [1].

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1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2010.06.010

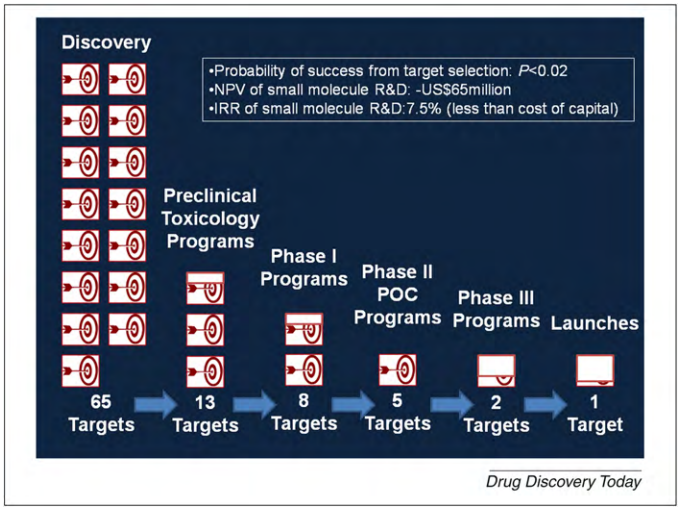

FIGURE 1

Projected decline in the number of targets or mechanisms of action through the drug discovery and development phases. Each target pictorially represents five targets. As shown, the largest loss for programs seeking an NCE is in Discovery. Numerically, as well as fractionally, the losses after candidate identification are far fewer. Overall, the probability of success from target selection to launch is $P < 0.02$. These numbers, however, represent a mix of precedented and unprecedented targets. For unprecedented targets, the Discovery success rates (and Development success rates) are lower than presented in the figure. Discovery success rates for unprecedented targets have been estimated at 3–5%, which would translate to approximately two targets with commercializable NCEs identified out of 65. Alternately stated, ~260 targets would need to be prosecuted to yield one launch. The inset summarizes findings of David and Zemmel [1] that the net present value (NPV) for small molecule R&D is negative, with a low internal rate of return (IRR). That is, small molecule drug discovery and development on a portfolio basis is projected to not be a successful proposition.

Identifying the selection biases in drug discovery and development

A central tenet of this paper is that an enormous number of unprecedented targets go untested in humans because of the filters inserted early in the process. Many of these targets are 'deselected' for good reasons; however, a common reason for terminating a project is that the team did not believe that they can achieve the major goal of the entire process: to create a commercializable molecule. To do so, there is a long list of criteria regarding selection of the target and the characteristics of the molecules to modulate it.

For target selection, the four major criteria are scientific rationale, technical doability, safety considerations, and commercial drivers. Figure 2 illustrates some of the issues underneath each of these headings. The target selection step is of great import because it sets into motion the progressive commitment of resources to identify a molecule that can manipulate the target. Because every organization has resource limitations, the act of selection also reflects opportunity costs for those targets that are of interest but not pursued.

The candidate identification step includes many of the criteria necessary for the new product to be competitive in the marketplace (e.g. sufficiently long half-life, no drug–drug interactions, and so on) (Table 1). In addition, the process of candidate identification often includes the use of animal models of disease to establish the rationale for efficacy and determine the predicted efficacious dose in humans. Finally, once the molecule has entered development, the testing paradigm is also focused on the same question: can this molecule become a product? For if it does not look like it could be commercialized, then why spend any more resources on it?

By using complex decision paradigms to select only those candidates that have the best chance for long-term success, we create fine filters that let only a few compounds through. These filters are *de facto* selection biases that could have several consequences. First, it is possible that several salutary and commercially valuable targets are left behind in the lab. Second, it is also possible that the 'technically doable and commercially desirable' targets (and respective molecules) that make it through these filters are not as valuable as some of those left behind. It is proposed that this selection process forces us to frequently miss the most important question in the entire process: does manipulation of this unprecedented mechanism affect the disease in humans?

Bias #1: only a commercializable molecule can advance through the process

This is the most impactful of the biases because it pervades every step through the discovery and development process. Beginning at target selection, if Discovery scientists do not believe that a commercializable molecule can be made, then the target will probably not be prosecuted. Or perhaps leads are identified, but all of them have extremely short half-lives; if the team is unsuccessful in correcting this or other problems, the project will probably be set aside. There will be multiple other reasons to select molecules out of the path (e.g. selectivity, potency or potential drug–drug interactions). Finally, perhaps a biologic would be a technically successful approach but commercially unjustifiable.

If these targets are discarded, however, then we never learn whether their therapeutic potential could be realized. Aside from safety problems, many projects are dropped for technical reasons, rather than because of a change in the target's perceived scientific import. That is, scientists originally chose to create a drug to agonize or antagonize a mechanism because the science behind it was credible enough to find out whether it works in humans. Despite this intent, they cannot fabricate a commercially viable molecule with a moderate amount of effort and, because of competing time and resource requirements, the project will often terminate.

Although useful for guidance, it is very difficult to predict the commercial landscape at least a decade ahead, especially when we have no knowledge of the importance of the mechanism in humans. The most important part of commercial predictions at an early stage is the decision to make an investment in the therapeutic area and the potential types of profiles that a project might have. To emphasize criteria any more at this stage imprints bias on the project that could lead to its ultimate failure. The impact of commercial considerations on R&D has also been emphasized by Cuatrecasas and Horrobin [16,17].

Bias # 2: preclinical models of disease accurately predict clinical responses

Beyond identification of new insights into disease pathophysiology in an academic setting, preclinical models of disease are often

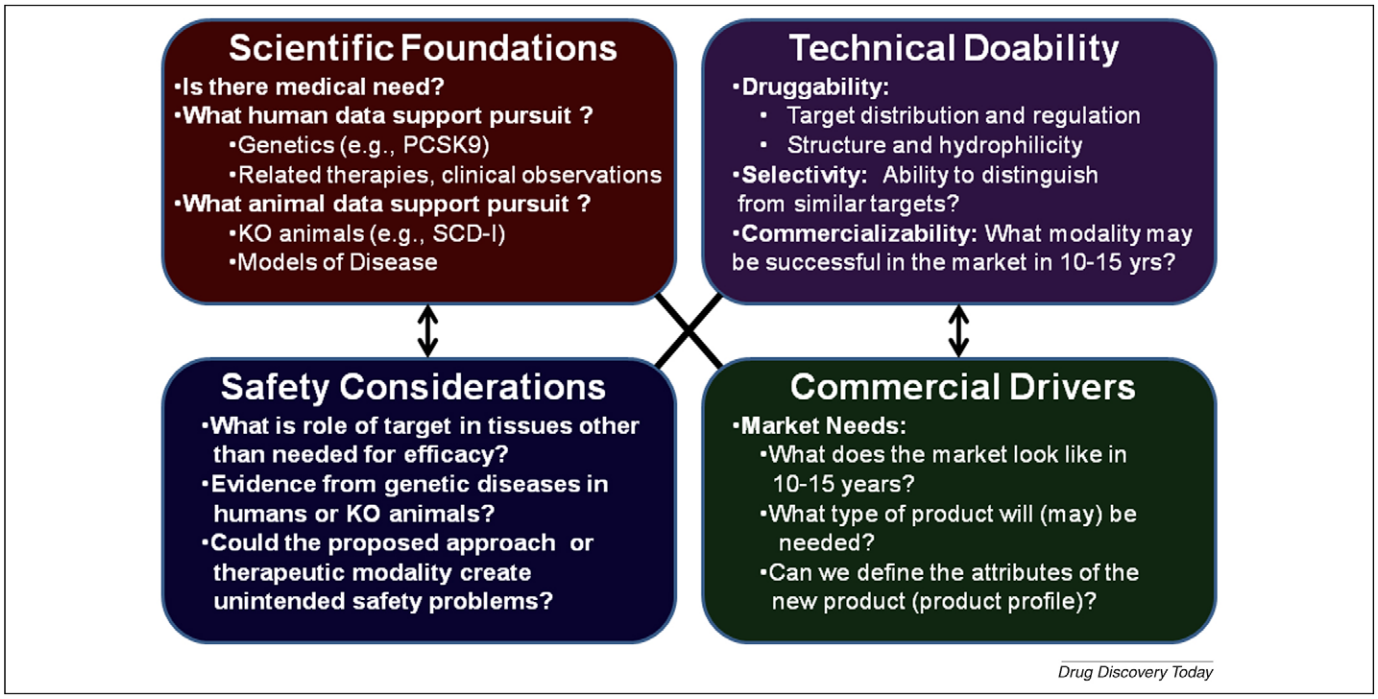

FIGURE 2

The four general criteria of target selection. Once placed on the 'for consideration' list, criteria used to decide on further investment include: scientific foundation for efficacy, safety concerns, technical doability, and predicted commercial success. The scientific criteria portending future efficacy include the strength of the biologic data, particularly human data. Potential safety issues of target manipulation must also enter into the selection process at this early stage. Where is the target expressed and what is its role in that tissue? What is known about the phenotype of genetic variation of the target or related targets in humans and animals? Technical doability reflects the broad question 'Can we probably make a commercializable entity against the target?' Can an *in vitro* screen be established? What tissue types does the drug need to access? How will we demonstrate that the molecule is exerting the desired pharmacology? What preclinical disease models (if any) will be used to support advancing the candidate into the clinic? What related targets will this new NCE need to be screened against to avoid unwanted spillover? Is there freedom to operate regarding intellectual property space? Finally, commercial considerations at this stage include the market needs for the indication and the chosen therapeutic modality, in addition to the mechanism of action. For example, if a sponsor is interested in developing a new therapy to treat inflammation and pain in rheumatoid arthritis, what will the future market look like, and is the new therapy likely to have a valuable enough market share? Although separated into discrete categories, the scientific rationale, safety, technical doability, and commercial considerations are all intertwined and change and influence one another.

used to support advancing a drug discovery project into humans. This use of models demands a high degree of faith in their relevance to the human disease [18–20]. Although the model might have a phenotype that seems consistent with the disease (e.g. elevated glucose), how that glucose level was achieved can be markedly different from the human circumstance. For example, although the study of the *ob*/*ob* or leptin-deficient mouse has contributed enormously to our understanding of the physiology of leptin, it is a much larger assumption that this model broadly reflects human type 2 diabetes mellitus. If the team is seeking inhibitors of a new glucose-lowering agent (e.g. inhibitor of steroyl coA desaturase I, or SCD-I), how does genetically induced leptin deficiency affect the regulation of SCD-I and the predicted human response to an intervention? Hinging key program viability decisions on these models reflects another potential bias [21].

Superimposed on these assumptions are compound-specific issues, including the affinity and accessibility of the investigational compound to the target, relative to models' species. In the compound screening process, for example, the estimated efficacious dose might exceed the commercial tolerance level for cost of goods or perhaps predict a substandard response. This could cause a compound to be prematurely 'deselected.' Consider the example of metformin. In animals, it is efficacious only at very high doses (>300 mg/kg) and in micromolar plasma concentrations, depending on the animal model tested [22,23]. In today's paradigm, metformin would probably have been deselected in the quest for a more potent molecule. A very beneficial and successful therapy might never have been available.

Changing the paradigm, step 1: make tools first, not products

What if we changed our goal of developing a new commercial product to answering the Phase IIa (proof-of-concept, or POC) question? That is, the focus is whether manipulation of the mechanism has potential importance as a therapy, not whether the new molecule can be a product. To do this, the stringency characteristics of the test molecule or tool drop markedly. For example, it would not be a concern that the projected half-life of the tool is three hours; that could be managed in an exploratory trial. Or if the potency is low, subjects might take three tablets per dose. The goal is to bring forward to the clinic compounds (tools) that can test the mechanism in a fit-for-purpose manner (i.e. they can effectively elicit the desired pharmacology at a safe and well-tolerated dose). 'Fit for purpose' does not mean that there is any change in stringency regarding safety: all safety requirements would need to be met.

A similar approach was described by Kim from Merck and Co. at the December 2006 analysts meeting (Presentation by Peter S. Kim, slide 42). In that presentation, the use of 'POC molecules', such as

TABLE 1

Partial list of testing categories and examples undertaken in the quest to identify a development NCE candidate[a]

Categories	*Examples*
Pharmacokinetics	Half-life, metabolites
Drug–drug or drug–transporter interactions	3A4, P-gp inhibitors
Potency, bioavailability	Size of tablets, cost of goods
Non-target receptor effects	Binding to muscarinic, beta-adrenergic, other receptors
Preclinical pharmacology	Animal responses demonstrating mechanism of action
Preclinical models of disease; dose–response	*Ob/ob* mouse model of diabetes; rodent conditioned avoidance model of schizophrenia

[a] For an NCE, these criteria include, among many others, solubility, bioavailability, potency, selectivity, clearance (half-life), routes of metabolism, metabolites, and cost of goods. The intent of the team is to select a clinical drug candidate that would potentially enable it to proceed all the way through to approval. This is an extremely important point because failure to meet all of these criteria and identify a clinical candidate is very common (failure rate >=80% [8]). Many teams add an additional requirement: demonstration of preclinical efficacy. The preclinical efficacy results can be used for two purposes. First, they might be the basis of a dichotomous 'go–no-go' decision regarding continued progression of a program. Positive results would signal to continue preparations to study humans. Negative results could convince a team to stop working on a mechanism or look for an alternative animal model to demonstrate efficacy. The second and more demanding use is the prediction of the efficacious dose in humans. That is, estimation of the efficacious human dose from the degree of glucose lowering in a rodent model of diabetes or conditional avoidance behavior in rats for a new therapy in schizophrenia further challenges the predictive utility of the disease model. For unprecedented mechanisms, however, animal models of disease are not validated to reflect the human response [18–20,36–40]. Although a widely recognized problem, there is not a large literature on this subject, probably because of negative publication bias [19,41].

those with poor pharmacokinetics or bioavailability (IV administration), were cited as methods to apply in early development. Further details about this effort are not available.

Changing the paradigm, step 2: use animal models of disease differently

For this paradigm change, project teams make the *a priori* decision that a target is potentially valuable. At this stage, instead of seeking additional validation through animal models of disease, the aim is to identify a tool to test the hypothesis in humans. Animal studies are done to define the dose response for the pharmacology of the target and to provide linkage of pharmacokinetics and pharmacology to the toxicology studies. No animal models of disease studies are required at this point. Teams can design Phases I and II to meet their individual program goals. It is important, however, to be able to make a decision about the target as quickly as possible to minimize resource consumption. This means that there needs to be a clinical endpoint or biomarker with which the team can make a high-quality decision, preferably within four weeks of dosing. Once a positive POC is achieved, however, animal disease models could be tested to identify those that best mirrored the human response and which future agents against that target might be tested (i.e. 'reverse translational pharmacology and pharmacodynamics').

Justifying the tool paradigm

At first glance, one might reject this paradigm because it will take several years and consume resources to get to a POC decision for the test molecule. For any individual target, the project team might rather see their efforts invested in a molecule that can be a product, even knowing that they will most likely never find one. Management might concur because there is intense pressure to identify and develop products, not probes, as rapidly as possible.

Companies, however, also make decisions on a portfolio basis (i.e. what is the aggregate impact of this approach at steady state?). Table 2 illustrates some potential outcomes of the tool paradigm on POC study number, depending on assumptions regarding the starting number of targets and the percentage of the failing NCE projects that could make tools. In addition, a team could decide to use a biologic tool to test POC, even if commercialization of a biologic would be considered undesirable by marketing. The major reason for considering biologics as test molecules is that the likelihood of identifying a fit-for-purpose biologic tool for short-term studies is higher than NCEs (although more resource intensive to manufacture). When carried forward through Phase II and assuming the standard success rates in toxicology and Phase I, the number of POCs would be predicted to increase twofold to fivefold (Table 2). Similarly, the number of positive POCs should rise proportionately; instead of 1–2 positive POCs, the sponsor could anticipate 6–10. Finally, there are reasons to believe that the projected output could be even higher.

What is more important than the number of POCs, however, is the number of launches. It is only through the creation of new products that this paradigm shift adds value and underwrites the investment of resources. On the simplest level, and using the standard industry attrition rates, the number of launches should increase proportionately to the number of POC studies. That is, a threefold increase in positive POCs should increase the number of launches threefold. The success rates for programs seeking to identify commercializable candidates for these now partially precedented or validated targets will have increased markedly.

This simple scenario does not take full advantage of the many possibilities that the positive POC will bring. Some of these include: identifying and nominating a diverse array of commercializable candidates, increasing the chances of success; including a biologic (or other) approach; possibility of the tool becoming a product—although that is not the initial intention, in a minority of cases, the tool might be suitable as a product; and identifying targets related to the seminal (or first) target. In this last case, in addition to the receptor (the seminal target), an additional target might be the ligand for the receptor or another target that regulates that receptor. Taken together, there are multiple reasons to believe that identification of the positive POC can open many opportunities and that success is driven by the willingness to invest in a mechanism.

Beyond the direct productivity and alignment benefits, there are several other potential benefits. First, there is value in the negative (result) tool POC. For a Discovery team, the investment of thousands of person-hours to find a commercializable candidate is an opportunity cost because they are most likely going to be unsuccessful in that pursuit; even if they identify a commercializable NCE, the odds are against the candidate being efficacious. An

TABLE 2

Impact of tool paradigm on number of POCs[a]

Model	Discovery target number	Assumptions	Candidates or tools identified, progress to toxicology	Progress to Phase I	Progress to Phase II POCs	Estimated number of positive POCs
Traditional Yield	65	Published rates, precedented and unprecedented targets	13 (20%)	9 (70%)	5 (55%)	2
Tools (NCEs Only) + Traditional Yield	65	Identify NCE tools from 25% of failures (52)	26 (40%)	18 (70%)	10 (55%)	4
Tools (NCEs + Biologics) + Traditional Yield	65	Identify NCE tools from 25% of failures (52) and biologic tools in 10%	31 (47%)	23 (70% NCE; 90% biologic)	14 (55% NCE; 90% biologic)	6
Traditional Yield, Unprecedented Only	260	Published rates	13 (5%)	9 (70%)	5 (55%)	1–2
Tools (NCEs) + Traditional Yield, Unprecedented Only	260	Identify NCE tools from 25% of failures (247)	75 (29%)	53 (70%)	29 (55%)	6
Tools (NCEs and Biologics) + Traditional Yield, Unprecedented Only	260	Identify NCE tools from 25% of failures (247) and biologic tools in 10%	100 (38%)	75 (70% NCE; 90% biologic)	49 (55%; 90% biologic)	10

[a] Table summarizes some possible outcomes of the number of POCs yielded from variations of the tool paradigm. 'Traditional Yield' is the productivity of the current NCE DDD paradigm. POC estimates are presented for both a mix of precedented and unprecedented targets ($n = 65$) that are needed presently to yield one launched product as well as for unprecedented targets only. The $n = 260$ was generated from a more conservative estimate of 5% success from target selection to candidate identification [14]. Percentages in parentheses indicate success rates from the prior step. Standard success rates are used post candidate identification [12,42]. For the unprecedented only targets, the Phase II POC success rate was 20%; for the mix of unprecedented and precedented targets, the POC success rate employed in the table is 40%. As shown, application of this paradigm with either NCEs alone or in combination with biologic tools in 10% of failures should yield substantial increases in the number of POC studies. A conservative approach is to assume that 25% of the early "failures" could yield tools. Under the traditional approach, if a sponsor was starting with 65 targets in a portfolio, then it is expected that approximately 52 of the projects would fail and never identify a candidate to take into the clinic. From those 52, if 25% of those failures could be used as tools to safely test a mechanism, then the number of projects entering early development would double (added to traditional yield). For the unprecedented cohort, the number of POC studies would increase almost six-fold. With the addition of biological tools, the estimated number of POCs (using biologic success rates for these stages of development) would increase further, as shown in the table.

alternative strategy is to have Discovery teams cycle through more projects per unit of time—generating tools rather than more polished candidates. Learning early that the target is not worthy of investment would eliminate specific targets more quickly. Second, if the sponsor approached this problem strategically, tools could be made against key targets in pathways. Deciphering the importance of a pathway could help identify clusters of targets and might open more druggable space relative to the seminal target [24].

It is emphasized, however, that this paradigm requires a commitment to invest on a portfolio basis, not an individual target basis. Because most POCs will still be negative, sponsors must invest enough resources so that the positive POCs can be identified and, from those, reap the benefits. If approached as a single or small number of targets, it will be very difficult to develop and maintain the tool paradigm compared to the traditional path. Moreover, like many other innovative initiatives, this tool paradigm would probably only flourish under a protected structure (http://www.accenture.com/Global/Services/By_Industry/Life-Sciences/R-and-I/InnovationInnovation.htm).

After the tool POC: the impact of motivational psychology

After a positive POC, the galvanized organization can align resources with much more confidence in the target. This POC is important to the motivational psychology of both the individual scientist and the organization. For the scientist, knowledge that manipulation of the target will probably be fruitful is crucial at a personal level. Scientists, in general, are high achievers who are motivated by both the ability to contribute to society's well-being and the ability to gain personal recognition for their contributions [25–27]. Armed with the knowledge that the target is valuable, the scientist will probably invest more time and effort to overcome obstacles. Conversely, with more conjecture and less conviction, the scientist is recurrently nagged by the uncertainty of outcome of his or her investment. Is this project worth my time? This uncertainty can cause an effort to stall or cease, perhaps when it encounters a difficult problem that would require large investments of time, expertise, or money.

Within a large pharmaceutical company, many projects compete for resources that need to be coordinated across multiple lines and functions. Because the state of validity of most of these unprecedented targets is relatively low, many of them are cautiously pursued with limited investments. If the sponsor can commit to a better validated project and entrain resources to accelerate that project's development, however, then the effectiveness and efficiency of the sponsor's investment should improve.

Balancing risks and benefits to enable more and better drugs: collaborative discovery through a consortium

Ultimately, each sponsor can use his own success, attrition, and cost data to estimate the return on investment of this paradigm. For any individual organization, however, instituting the test molecule paradigm will be more expensive than the traditional path, when most targets drop out in Discovery, putting money and internal resource at risk. This paradigm, therefore, might be too great a burden for any single sponsor. Moreover, unless sheltered with separate resources, it is easy to envision deprioritization of efforts devoted to test molecule production in favor of commercializable projects when resource limitations arise.

An alternative is to consider organizing a consortium of companies and, potentially, academic, research, and governmental organizations, as well as private foundations. Public–private

partnerships such as the Foundation for the NIH or Innovation in Medicine Initiative are now active within the pharmaceutical industry, including in the discovery and development of new treatments, biomarkers, genotyping, and so on [28–30] (http://www.imi-europe.org/Pages/default.aspx). This collaborative model has been described for drug discovery, too [31–34]. For a target validation consortium, collaborative teams can be created for separate indications. Targets would be selected and prosecuted by these teams, supported by the consortium members. Pending results, each organization could decide on their proprietary strategy to prosecute the target should the outcome be positive. Results would be released simultaneously to the entire consortium and expect to be published. Ultimately, the conduct of collaborative research in this manner would probably improve drug discovery, enhance overall industry productivity, and increase scientific transparency, enabling new breakthroughs to be shared at a much more rapid pace. The sponsors of the effort will share the burden, tremendously reducing their cost in prosecution of a target.

Why should this be of interest to the industry? For some pharmaceutical scientists and commercial experts, this idea might be anathema. Part of the traditional thrill of this work is the race for first-in-class and/or best product. That race is not gone, however. Once results are known, each company can decide upon the strategy to create proprietary products. Moreover, because there is considerable overlap across most pharmaceutical companies' portfolios, individual companies are spending redundant resources prosecuting targets [35] that will most likely not yield success for anyone. As part of a consortium, if the tool results are negative, then companies have not invested much in that target. Their teams would be focused on higher value targets in a better-staffed, better-focused race to make the best product in the shortest period of time. Although there are several key issues that would need to be resolved, including ownership of intellectual property, the reporting of results, and so on, with open mindedness to this open-innovation approach, these problems are probably conquerable.

It is already recognized by a large number of pharmaceutical executives that drug discovery and early development will occur largely outside their companies (http://www.deloitte.com/view/en_GX/global/article/41ed0b98fc001210VgnVCM100000ba42f00aRCRD.htm). Many executives have realized that with a negative internal rate of return and a return less than the cost of capital (a negative net present value), small molecule drug discovery and development as it is currently conducted is not sustainable [1]. Something has to be done that changes the situation. If we do nothing, this problem threatens not only the industry but also global health in fewer and less innovative products.

Benjamin Franklin wrote: 'An investment in knowledge always pays the best interest' (http://thinkexist.com/quotation/an_investment_in_knowledge_always_pays_the_best/161325.html). As proposed in this paper, there is a great need for a directed investment to determine the value of targets in human disease as rapidly as possible before committing to making a product. By undertaking this paradigm, especially in a collaboration, we can probably improve productivity in the industry and simultaneously benefit all parties, particularly patients.

Acknowledgements

The author gratefully acknowledges the helpful comments of J. Fryburg, B. Littman, A. Poirier, L. Ratcliffe, and R. Stevenson.

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