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Drug discovery dilemma and Cura Quartet collaboration

Salim Shah[1], ss234@georgetown.edu and Howard J. Federoff[2], hjf8@georgetown.edu

Many parties contribute to discovery of new drugs – academic researchers, industry scientists, government agencies, and disease foundation helping to corral the resources necessary to sustain research efforts – but it has never been more apparent until now that these parties must work together to accomplish the shared goal of improving health. At a recent conference at the Georgetown University Medical Center, a group of prominent scientists from the academic, industry, government and disease advocacy communities came together to discuss new paths forward for stronger inter-institutional collaboration to establish a framework for translating new discoveries into drugs, improving proof of concept (PoC) studies, and reducing attrition at the clinical stage of drug development.

Introduction

It is widely appreciated that there is a dearth of new molecular entities (NMEs) and that the drug development pipelines of pharmaceutical companies are drying up (Figure 1). At the same time, there is increasing urgency to discover novel drugs to treat devastating diseases such as cancer and Alzheimer's disease. This profound reality is challenging the 'Cura Quartet' of academic institutions, government agencies, patient advocacy groups, and pharmaceutical companies to find ways to accelerate drug development and to reduce attrition rate in clinical phases.

In a typical drug development process (Figure 2), points of attrition are marked as decisional nodes, which are binary Go/No-Go decision steps. Examination of these nodes in different therapeutic area reveals that attrition was highest in oncology drugs (95%) and lowest for cardiovascular drugs (80%) [1] (Figure 3a), and in the clinical phases, phase 2 has highest attrition, even in oncology, where phase 1 studies are generally conducted in patients [2] (Figure 3b).

To examine the reasons of high attrition rate and to develop solutions to this problem, Georgetown University Medical Center (GUMC) recently hosted a one-day workshop that brought together more than 50 participants from the Cura Quartet to discuss the 'Drug Discovery Dilemma.' The participants included prominent scientists, industry leaders, advocacy groups and government representatives, and they were charged to identify decisional nodes in the drug development process and to find new paths for creating effective synergy and stronger collaboration between their respective sectors. Discussions were pursued on four topics—academic drug discovery, target validation and biomarker discovery, animal models, and proof of concept (PoC) and what emerged was a consensus that the time to forge meaningful inter-sector relationships is now.

Academic drug discovery

Should academic institutions be in the drug discovery space? Some argue that academic institutions have comparatively small medicinal chemistry programs and lack infrastructure required for high throughput processes; therefore, academia is a non-significant player in this space. However, these arguments confuse drug discovery with drug development.

Drug discovery involves selecting a target, screening of compound libraries against target modulation or for phenotypic effects, scoring hits, identifying leads, performing chemical modification, laboratory scale synthesis and testing leads in *in vitro* and *in vivo* systems for intended effects. By contrast, drug development involves measures of absorption, distribution, metabolism, and excretion (ADME) of a drug, toxicological studies, scaled synthesis, formulations, clinical trials and post clinical monitoring. Drug discovery is intrinsically more innovative and scientifically grounded, associated with

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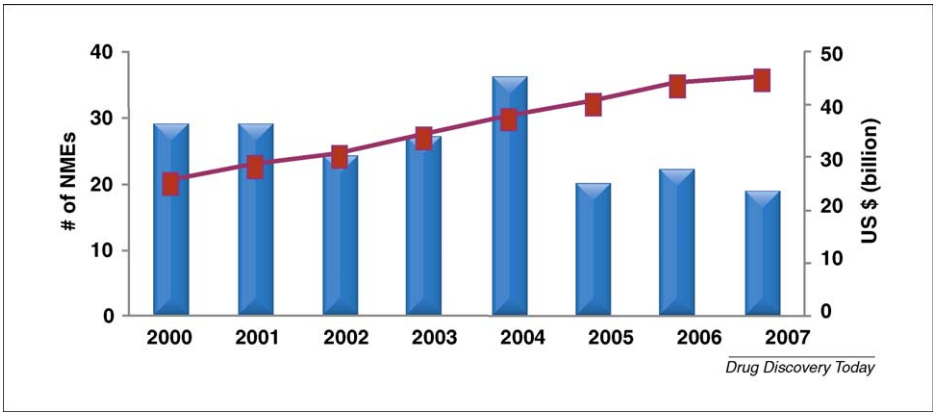

FIGURE 1

Approval of new molecular entities (chemical entities, blue bars and biologics, red squares) from 2000 to 2007 decreased even though R&D expenditures have increased significantly.

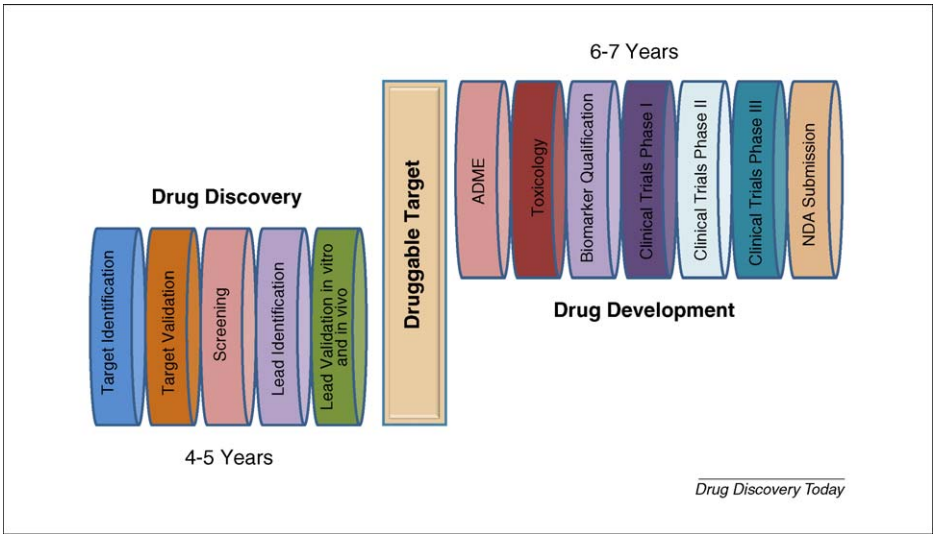

FIGURE 2

Points of attrition and decisional nodes in drug discovery and drug development process. Druggable target sits in the middle of drug discovery and drug development process, and the identification of a druggable target the first step in drug development. However, drug discovery does not require druggable target because making a target druggable is one of the core functions of drug discovery.

higher risk and requires a commitment to mechanism; whereas, drug development is more formulaic, being concerned with adverse event detection, clinical trial design, and execution and expediting a drug to regulatory approval. It is clear that industry is optimally positioned for drug development, but academia has an edge in drug discovery.

First, academics select targets because they are often characterized in the context of human pathobiology and are interested in understanding their complex mechanisms of action. They are willing to undertake risky and potentially time-consuming paths to discovery. Pharmaceutical drug discovery programs employ more conservative approaches. This distinction can cast the academic scientist as a 'champion of a target/compound' [3], who has passion for it and contributes throughout the process [4].

Second, academic health centers are the only venue supporting research on neglected diseases and clinical areas of unmet need. Despite the progress in drug discovery and development, tropical diseases such as malaria, leishmaniasis, and schistosomiasis continue to cause significant morbidity and mortality, mainly in developing countries [5]. Because drug discovery and in particular drug development are capital intensive and largely driven by market incentives, industry may not have a strong business motivation for development of therapeutics for these diseases. As the market forces do not drive the academic drug discovery, this again underscores a potential complementarity between the two efforts.

Third, less celebrated drug targets that are eschewed by the industrial pipeline can be well suited for academic drug discovery programs. Moreover, 'off the shelf' drugs or nutrient-like compounds that may not be patentable but still capable of yielding medical benefits are an academic prerogative. In the past 50 years, there are many examples of academic pursuit of seemingly obscure targets that have resulted in blockbuster drugs.

However, irrespective of which sector best prosecutes drug discovery, an important issue is to decrease attrition and increase efficiency in drug discovery. Several examples were put forward by workshop participants. First, industry, governmental agencies and academic institutions all maintain large chemical databases, but these resources are fragmented, reducing the utility of this information. There is a need to integrate these into a common resource so that both academic and industrial scientists can access and mine them. Second, drug molecules that have failed at various stages of clinical development currently lay dormant in pharmaceutical companies. These molecules and their associated data should be made available to the scientific community, allowing academic and non-profit organization researchers to use this knowledge to evaluate applicability in different clinical indications. Third, there should be broad collaboration between industry and academia, with the support of government institutions and disease specific and policy-related foundations. Productive recent examples that may be emulated more broadly include GlaxoSmithKline and the Immune Disease Institute, Boston; AstraZeneca and the Noami Berrie Diabetes Center at Columbia University; and Pfizer and University of California in San Francisco, all in past year [6]. But still more is needed to harness the latent power of academic–industry collaborations.

Animal models

Are animal models predictive of human responses to a drug with respect to efficacy and safety? If they are not, how to refine models and who should bear the cost of their refinement? These questions were raised and discussed in the workshop.

Use of animal models in drug discovery and development is quite prevalent, and it may be helpful to divide their use into two broad categories. The first includes genetically engineered mouse models for studying human diseases (disease modeling), validating targets, testing

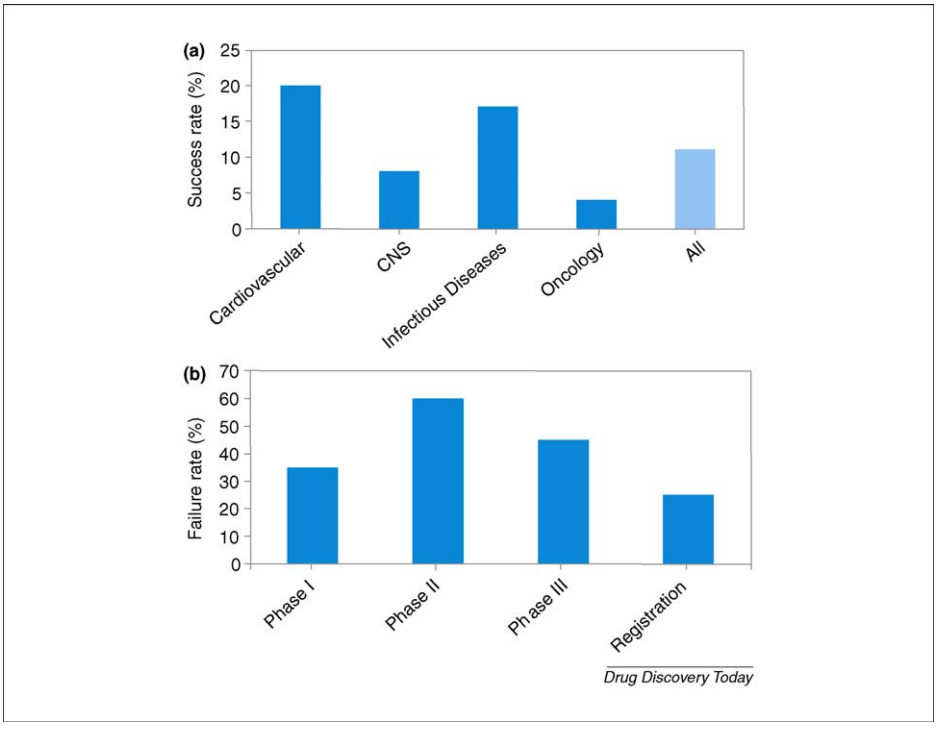

FIGURE 3

Rate of success in various therapeutic areas from first-in-human to registration stage (1991–2000). Oncology (95%) has highest attrition rate followed by CNS (93%). Rate of attrition in clinical studies: It shows that percentage rate of failure of compounds entering clinical phases 1–3 and reaches to the registration stage. The rate of failure remains highest in phase 2, that is, clinical PoC phase for efficacy.

candidate compounds for *in vivo* efficacy (preclinical proof of concept) and identifying and developing biomarkers. The second category includes use of animals to study dose escalation, off-target effects, and toxicity studies.

Genetically altered mouse models have contributed significantly to understanding molecular mechanisms of disease. However, the obvious differences in anatomy, histology, physiology and network responses at the systems level between animal models and humans have limited the former's ability to contribute to drug discovery. The differences in etiology and pathobiology are particularly stark for cancer and neurological disorders because they are complex disorders and their initiation and progression depends on the perturbation of many gene networks. Therefore, it is no coincidence that cancer and neurological drugs have the highest failure rate in clinical trials evaluating efficacy.

Nevertheless, in many other respects animal models replicate human disease conditions. Genome sequencing, quantitative trait loci (QTL) and knockout (KO) phenotypes all offer evidence of a match between animal models and human disease conditions can exist. It is important however that similarity in molecular mechanism, with respect to human pathobiology, should go beyond proximate mechanism to include characterization of molecular, cellular and perhaps organismal networks. Ideally, drug–target interaction should elicit a phylogenetically scalable response that yields integrated biological response predictors across species. With such knowledge researchers may refine existing models and possibly create newer models with more optimal predictive characteristics. The Collaborative Cross (CC) and Genetically Engineered Mouse Models (GEMM) are examples of this newer approach, although they too have their limitations (for detailed discussion see [7]).

The cost of producing refined animal models and to ensure that they are widely available to the scientific community is a challenging task. There was consensus however, that animal models are valuable, critical for drug discovery and worthy of investment even if not fully predictive of human disease. Furthermore the Cura Quartet proposed that developing and refining models are quintessentially a 'pre-competitive' activity, and it intrinsic value independent of a specific drug target. The workshop participants supported the idea of a consortium model akin to SNP Consortium for refining models, in which resources can be leveraged from industry, foundations and government to underwrite animal model research.

Target validation and biomarker discovery

A target is defined as a disease-linked protein or other macromolecule that can be used for therapeutic intervention. The target validation process seeks to link the target to a disease process (disease modeling) and through its modulation produces a therapeutic effect (i.e. druggability) [8]. Although target is not really validated until an explicit molecular mechanism is known and demonstrated critical for efficacy in clinical trials, it is commonly used to describe genetic and molecular information, which provides rational for drug development.

Target is typically validated via gain or loss-of-function studies in cell culture and in genetically tractable animals. However in some cases establishing a relationship between target and a disease may require a more nuanced approach, particularly when post-translational modifications are relevant to the etiopathogenesis of the disease or modulation of more than one target is necessary for effective therapy. Target validation also has a pragmatic extension: Is it druggable? Although understanding of any given target's role in the disease mechanism could in theory allow one to design a chemical moiety to successfully 'drug' the target. However, in practice some targets are more druggable than others. By some estimates, only 10% of genes in the human genome encode druggable products, and only 5% are both druggable and disease relevant [9]. Progress is being made to expand this universe. Until recently, kinases and phosphatases were not considered druggable targets but advances in structural biology have made it possible to design inhibitors for these targets.

In addition to target validation, identification of better biomarkers is paramount for drug discovery. A biomarker is objectively measured, characterized and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic response to a therapeutic intervention [10]. Biomarkers that can be substituted for clinical endpoints as surrogates are predictive of clinical benefits, adverse events, and pathophysiologic effects and thereby significantly reduce trial failures, cost of development and perhaps augment statistical power in trial design [11].

Biomarkers can be predictive, prognostic, diagnostic or therapeutic. Predictive biomarkers, such as blood pressure or blood cholesterol levels, can prospectively identify individuals at increased risk for developing cardiovascular disease. Prognostic biomarkers stratify risk of

disease progression in patients undergoing definitive therapy. The treatment of breast cancer illustrates the utility of a prognostic biomarker: patients who overexpress HER2 are more likely to benefit from Herceptin treatment whereas those who express ER are more likely to benefit from Tamoxifen. Diagnostic biomarkers identify the presence of disease at the earliest stage and therapeutic biomarkers provide a quantifiable measure of response to therapy in patients undergoing treatment.

Necessity of appropriate biomarkers for drug discovery is evident from the FDA's Critical Path Opportunities List notes—'the process and criteria for qualifying biomarkers should be mapped. Clarity on the conceptual framework and evidentiary standards for qualifying a biomarker for various purposes would establish the path for developing predictive biomarkers' [11]. In addition to biomarker identification, biomarker validation is important and it involves accuracy verification, performance, and biomarker assay reproducibility over a range. Yet another concept is biomarker qualification, a process of building evidence for linking a biomarker and its associated clinical endpoints. Since this definition implies that a biomarker can only be valid for one well-defined purpose and context of use, any new or expanded use for a biomarker would require a requalification of the evidentiary link.

As requalification and refining of a biomarker is an important consideration, several consortia have come together for the sake of biomarker research and development, most notably the Biomarker Consortium, a public–private partnership managed by the Foundation for the National Institutes of Health (FNIH). The goals FNIH are to facilitate discovery and development of new biomarkers; validate their ability to diagnose disease; predict therapeutic response; and stratify diseases for better treatment [12].

Overall the Cura Quartet argues that collaboration at earlier stages of drug discovery is valuable. Specifically, at the animal model stage—to take advantage of academic expertise in target and biomarker identification and validation at pre-competitive and earlier stage. In addition, an expanded role for disease foundations in encouraging drug developers to share information on biomarkers associated with failed drugs and ensure that truly pre-competitive information – such as biomarker data indicative of toxicity – shared across the consortium.

Proof of concept

Drug discovery proceeds from target identification and validation to screening of a chemical library, virtual or real, to identify molecules that modulate target activity. Such molecules are called hits, which subsequently develop into leads. The lead is a potential drug candidate that is used to modulate target activity in *in vitro* and *in vivo* studies to provide a proof of concept (PoC)—preclinical and clinical. Preclinical PoC is usually demonstrated in animal models or human tissues/cells whereas clinical PoC efficacy is achieved in human. In transitioning from preclinical to clinical studies, extensive preclinical data on ADME, toxicity, and chemistry, manufacturing and controls (CMC) of a drug is required. However, these extensive preclinical data requirements, and years of time investment could not improve predictive value success in clinical phases and many drugs still fail owing to differences in metabolic activity and drug bioavailability between humans and animals. Therefore, it is suggested that human studies be conducted as early as possible to contract development time and reduce cost.

In addressing early human studies, the FDA's Critical Path Initiative as well as the European Medicines Agency (EMEA) road map to 2010 call for an initiative known as the Exploratory Investigational New Drug (expIND) and Clinical Trial Application (CTAs) respectively. Since expIND provides a mechanism to conduct first-in-human studies early on, the FDA has explained in guidelines to industry that the purpose of expIND is to support phase 1 clinical trials, and it involves a very limited human exposure and no therapeutic or diagnostic intent (See [12] for details). The expIND can help in determining whether a mechanism of action defined in experimental systems can also be observed in humans. The expIND may also facilitate selection of the most promising lead compound from a group of candidates on the basis of pharmacokinetics (PK) and pharmacodynamics (PD) properties. Because expIND studies present fewer potential risks than the traditional phase 1 studies, expIND investigations in humans can be initiated with less, or different, preclinical support than is required for traditional IND application. Furthermore, because expIND studies involve administering either subpharmacologic doses of a product (micro dose), or doses to produce a detectable pharmacologic effect, the potential risk to human subjects is less minimal as compared to a traditional dose escalation phase 1 study where maximum tolerated dose (MTD) may be an endpoint. In fact, FDA has emphasized that the expIND study should be designed to investigate a PD endpoint, not to determine the limits of dose tolerability.

Clinical studies under expIND (phase 0) are front-loaded and require a well-integrated infrastructure, multi-disciplinary team of professionals, and biomarker assay development and qualification before initiation of studies. In addition, these studies require validated assays for target modulation, pharmacokinetic analysis, and real-time analysis of patient samples during the study. That means, there should be a close collaboration between clinical and laboratory personnel. Furthermore, there should be an optimal acquisition and tissue-handling procedures, and standard operating procedures (SOPs) for assay development and validation to ensure reproducibility.

There are several ethical issues with phase 0 trials as well. For example, informed consent must clearly document that the dose of the investigative agent administered will be lower than would be required for therapeutic benefit and may cause appreciable toxicity. The non-therapeutic nature of the phase 0 trial and need for serial biosample collections, should be clearly communicated. As there is no intended therapeutic benefit for participants in phase 0 trials, the purpose of the biosampling procedure must be clear to the patients. Moreover, it should be communicated that participation in a trial might result in delay or even possible future exclusion from participation in certain other clinical trials.

In the workshop, Cura Quartet participants agreed that increasing the number of 'shots on goal' through phase 0 trials coupled with radioimaging techniques would increase success rate and decrease off target drug effects. The Cura Quartet representatives acquiesced that to increase the overall value of clinical trials there should be a mechanism for sharing information across communities especially on drugs that failed in phase 2b or phase 3 of clinical trials. At the moment, much of the data on the failed compounds is unpublished, but making it available via an academic–industry consortium could be helpful in finding ways to 'repurpose' these drugs.

Industry–academia partnership

It is important to take these ideas on enhancing collaborations and put them to work in increasing the number of drugs being delivered to patients, industry and academia should adopt a common approach to tackle issues of intellectual property early on by engaging high-level university administrators [13]. At the moment, negotiating a contract between industry and academic partners require lengthy discussions. The workshop attendees showed a strong interest in finding or developing general

mechanisms to structure academic–industry collaboration. Indeed, several of the academic representatives at the workshop pledged to join forces over the next several months to construct a consortium for future interactions with industry.

Conclusion

What is now needed is momentum toward establishing a true and sustainable solution to reducing costs and increasing efficacy within the drug discovery pipeline. This can only come from alliances between industry, government, academia and non-profit organizations (the Cura Quartet) designed to identify areas of pre-competitive research and provide an environment for crafting innovative solutions. Stakeholder participating in the workshop can help by encouraging dialogue needed to work together to improve discovery translation. Even with different perspectives, the Cura Quartet has a common goal: To accelerate bringing new medicines to patients, to increase the delivery of clinical proof of concept (PoC) and reduce attrition in drug development.

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Salim Shah

Office of Planning and Enterprise Development, Georgetown University Medical Center, 4000 Reservoir Road, NW, Washington DC 20057, United States
Howard J. Federoff
Georgetown University Medical Center, 4000 Reservoir Road, NW, Washington DC 20057, United States

E-mail Addresses:
hjf8@georgetown.edu
ss234@georgetown.edu