**DRUG DEVELOPMENT**

**An End to the Myth: There Is No Drug Development Pipeline**

Kristin Baxter,1,2 Elizabeth Horn,1 Neely Gal-Edd,1 Kristi Zonno,1,3 James O’Leary,1 Patrick F. Terry,4 Sharon F. Terry1*

A new map is presented for creating an open, collaborative, and coordinated system for drug development.

**THE CURRENT MODEL IS DEFUNCT**

There is abundant evidence that the current drug development system is inadequate, unsustainable, and failing those who need it most: people affected by diseases (1). Current projections estimate that it takes more than 1 billion U.S. dollars and between 10 to 15 years to bring a new drug to market (2, 3). Attrition rates of new drugs entering phase I are as high as 92% (3). Further, many diseases in need of new therapies are underserved by the current drug development model. For example, the vast majority of the estimated rare 7000 genetic diseases lack any available medical therapy, in part because the small and geographically dispersed patient populations make it difficult to amass sufficient data for clinical and translational research, and a lack of clear reimbursement strategies dilute most financial incentives (4). At first glance, these challenges may appear to be specific to Mendelian disorders. However, as genomic tools stratify disease, “common” diseases segregate into hundreds of rarer ones.

Although external pressures—increased regulatory burden and the economic downturn—undoubtedly hamper the development and approval of new therapies, a fundamental problem with drug development arises from the design of the system itself, including challenges in translational research, regulatory science, and reimbursement. To begin to address these challenges, we used the extensive findings of the Institute of Medicine (IOM) (5) as a basis for engaging senior management from (i) 60 biotechnology and pharmaceutical companies, (ii) the U.S. and European government agencies, (iii) health-care payers, (iv) patient advocacy groups, and (v) academic scientists and administrators in surveys, salons, and structured interviews. As a result of this information gathering, we propose a new model for depicting the drug development process that reflects the primary concerns of these stakeholders: that the ecosystem is larger than any one stakeholder group and needs to be better networked.

The current drug development system is a reflection of a deeply ingrained culture that was useful in the age in which it was established: the industrial age, which was characterized by a scarcity of raw materials and robust competition in all industries. Now, information is the major commodity, and its abundance necessitates a shift from competition to open-source network models. These types of models have been successful in other information industries: music, publishing, semiconductors, and software development. Models are important because they convey fundamental truths about a system and give resources (both human and material) a structure around which to coalesce.

**A NEW MODEL**

Drug development is most often depicted as a closed linear path with divided segments from target identification to approved compound. However, this linear pipeline is a gross oversimplification of a complex process, and those who are intimately involved in drug development use network models and management tools with parallel, iterative, and self-learning components to orchestrate their projects. Successful drug development in the networked information age requires teams of basic and translational scientists; clinical services; policy, regulatory, and reimbursement specialists; and consumers, patients, and advocates. These teams require a model that is sufficiently complex but allows these normally disparate players to assemble.

To illustrate these observations, we created a networked systems model called Navigating the Ecosystem of Translational Sciences (NETS) (Fig. 1). This model is not the only possible model of drug development but is offered as a representation that reflects a culture of openness and transparency, seeks to alleviate misaligned incentives, acknowledges the nuances of the process, and provides a map for creating an open, collaborative, and coordinated system for drug development in the 21st century.

**NETWORK APPROACH**

The NETS model of drug development provides a systems and network perspective that transcends a focus on traditional components. Systems thinking requires that drug development be viewed as parts of a whole, and the network perspective is manifested in a collection of interconnected processes, with iterative feedback loops, rather than a series of discrete steps. By placing emphasis on connections rather than boundaries, the system becomes more integrated and efficient.

For example, in the NETS model an approved compound is a junction rather than an end point or discrete boundary line. The junction links the end of one research study with the beginning of another and promotes essential data collection in a postmarket phase for the first product and perhaps new development for a second one. The resources used to provide care to patients can be harnessed and repurposed to generate needed clinical data, for example, to fuel outcome studies or biomarker research to distinguish responders from nonresponders. In doing so, therapeutic development and health care become a single learning system capable of using the clinical data it generates to improve patient care (6). The system also incentivizes more efficient research strategies, such as clinical trials that require fewer participants and less time to establish efficacy before receiving provisional approval for continued surveillance in all participants (7). In short, this network approach emphasizes synergies that can be exploited for improved efficiency.

The NETS model highlights activities that benefit from inter- as well as intrastakeholder collaborations. Unlike the traditional model in which rigid boundaries discourage stakeholder interactions, each of the interfaces between the various “neighborhoods” [highlighted in different colors on the map (Fig. 1)] presents an opportunity for stakeholders to work together in a dynamic network. As an example, patient registries and
Fig. 1. Using NETS to catch new therapies. This model provides a map for creating an open, collaborative, and coordinated system for drug development in the 21st century. Collaborative activities include basic science and therapeutic target discovery (orange and green), therapeutic discovery and nonclinical research (blue), regulatory science (purple), and clinical research (pink)—all of which impinge on a single goal: Patient access to modern therapeutic strategies. Dotted lines are work-arounds or alternative pathways. A Map with links to resources is available online at www.geneti-caliance.org/nets_fullview.
Role for Disease Advocacy Organizations

Disease advocacy organizations (DAOs) are trusted agents and well connected to potential clinical research participants. These groups have a long-term, vested interest in a particular disease, making them ideal candidates to serve as the stewards of registries and repositories (9–11). DAOs are aware of, and part of the accelerant for, participatory research principles; they are leading research by providing funding, generating hypotheses, and developing tools and have several distinct advantages, including an enduring trust relationship with the disease community.

Engaging the DAO during the early stages of drug discovery and preclinical development can shorten timelines and capitalize on the synergies inherent in engaging all stakeholders in parallel tracks simultaneously. Likewise, the latent condition-specific knowledge and insight present within the advocacy community and advocacy-run registries can be used to both answer research questions and generate new hypotheses (10, 12). The potential impact is profound because decreasing costs overall and shortening the lengths of phases II or III—in which delays often occur because of an inability to meet targeted enrollment numbers—could potentially reduce the cost of new molecular entities by $200 million or more (13).

Redefining Disease

Breaking down the silos between diseases, which in many cases obscure the common underlying molecular pathology, would allow pathway and phenotypic therapies to be developed (14). The same type of systems thinking in the NETS model is also needed to improve our understanding of the underlying biology of disease. Cells and organisms are not composed of neat linear pathways, but rather, are complex systems, made up of highly interconnected circuitry with multiple feedback loops capable of buffering a surprising amount of perturbation (15). The distinctions we make between diseases are largely based on their phenotypic characteristics and obscure the fact that different diseases can share biological pathways (14). Because underlying biology is shared across diseases, it is important to also approach drug development from the vantage point of understanding biological networks, in addition to the traditional disease-by-disease approach or by continuing to characterize the pathways that have already been extensively characterized.

Sharing Data and Resources

Common mechanisms among diseases pave the way for a new approach to drug development that relies heavily on common infrastructure, shared tools, and a willingness to reprioritize research so that the aim is to pave the way for better therapies and thus improved patient care. The NETS model makes it readily apparent that addressing challenges in a more networked manner will necessitate shared, open-source infrastructure and tools to address these common obstacles. Shared data sets will be much larger and more powerful than any single data set that individual laboratories or organizations can hope to assemble (15, 16). Common tools made available to all, such as high-quality antibodies, can dramatically improve the breadth and depth of research that can be accomplished (17).

The precompetitive area of clinical trials needs to be expanded to phase Ib so that pharmaceutical companies compete to produce the best drug, rather than competing to identify the best drug targets (18). An extended precompetitive space requires access to information that previously has been considered proprietary, such as data from preclinical studies and failed clinical trials. Examples from other industries, such as the SEMATECH collaborative effort among semiconductor manufacturers, illustrate the strides that can be made through precompetitive collaborations. The SEMATECH experience has highlighted that stable funding through public-private partnerships, access to universities in order to draw on the creativity of academia, and providing incentives to attract the most qualified people are critical for collaborative efforts to succeed (19). Drug development needs a sustainable system that requires and rewards precompetitive collaborations with well-aligned incentives that benefit all participants. Enacting these dramatic changes, however, will not be simple and will require that we make equally dramatic changes to the incentives and reward structure that drives drug development. Citizen scientists are increasingly interested in sharing data and in transparency (20). This can be a positive catalyst for change in the drug development ecosystem.

Encouraging Risky Exploration

Publicly funded research reported in the scientific literature provides the foundation for private-sector drug development. Yet, the majority of publicly funded research continues to focus on the proteins that have already been extensively characterized, leaving a large pool of potential drug targets unexplored. For example, of the 500 kinases encoded by the human genome, more than 65% of the kinase papers published in 2009 focus on the 50 proteins that were extensively studied in the early 1990s (17). Thus, the vast majority of this research continues to concentrate on a very small subset of the genes and proteins implicated in human disease. The lack of research on the uncharted territory within the human proteome is not from lack of interest. Instead, it originates largely as a by-product of the current public sector funding mechanisms, which require applicants to submit an extensive background and rationale for grant proposals. With little known about this “dark matter” of the proteome, research proposals in these uncharted waters are virtually guaranteed to remain unfunded. Thus, these unknown proteins remain uncharacterized, limiting the potential pool of drug targets.

The Heavy Lift: Culture

It is simplistic to say that a conceptualization will have any meaningful impact on an entire system, particularly one that is so dysfunctional. The NETS model is simply offered as a means to a more important end: the culture shift required to accelerate therapy development. This reimagining requires risk in order to move from traditional interactions, competitive lines, intellectual property claims, and ego to transparent collaboration that remains focused on the end goal of accelerating therapy development. What if the current research and development systems are released to organically realign with society’s need for therapies?

The goal of drug development is clear and uncontroversial: safe and effective therapies delivered to consumers in a way that is time-
ly, cost effective, and sustainable. The NETS model provides a framework for thinking about necessary connectivity. To enable success, each contributor to the process must acknowledge his or her responsibility to the success of the whole. Every part must work together in order to form a cohesive and robust drug development system capable of shepherding therapies from discovery to cure. The public needs to become empowered to transition from subjects into active participants. Financial incentives will follow successes. The start of this brave new world requires leadership from the public and private sector—individuals and organizations willing to take enormous risks to move beyond the status quo. Risks are something individuals, families, and communities suffering from disease understand very well. It is time to pool the risks and accelerate the benefits.

REFERENCES AND NOTES

5. IOM Forum on Drug Discovery, Development, and Translation (www.iom.edu/Activities/Research/DrugForum.aspx); Cancer Policy Forum (www.iom.edu/Activities/Disease/NCPF.aspx); Roundtable on Translating Genomic-Based Research for Health (www.iom.edu/Activities/Research/GenomicBasedResearch.aspx); Rare Disease Study (www.iom.edu/Activities/Research/OrphanProductResearch.aspx).

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