Innovation Ecosystems in Pharma:

Collaboration at the Boundaries between Disciplines

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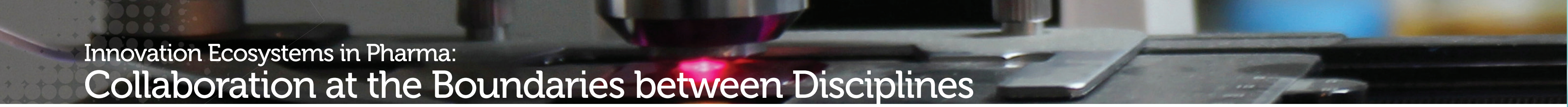

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Innovation is the introduction of new or improved products or services in the marketplace. The word speaks to the best of our creative spirit and suggests an optimism about the future when the shortcomings of the past are overcome.

In many ways, the pharmaceutical industry is awash in innovation. Each year brings new tools and techniques that offer new potential for advancement in science and technology.

It sometimes seems that if we just wait long enough, innovation will eventually solve our most intractable problems and bring important new medicines to the marketplace. A quick review of the current state of pharma research and development (R&D) certainly suggests we could use such a boost.

The cost of drug development continues to escalate, reflecting both the rising costs of R&D efforts and the lost investments of failed late-stage development programs. All of this has led to rising costs of new medicines, a loss of jobs in the R&D sector, and a questioning of the value of investing in the pharma and biotechnology industry.

But why is it that the steady advances in science and technology we have come to expect have not resulted in increased productivity of the pharma R&D effort? We can increase the speed and efficiency of high-throughput screening, for example, but this has not led to a greater number of successful new therapies.

We can use *in silico* techniques like modeling and simulation to estimate the probability of success in phase 3, but we have not seen a substantial improvement in the productivity of the pharma R&D effort. We just seem to arrive at failure more often and at greater expense.

INVENTION VERSUS INNOVATION

The geniuses of the early 20th century—such as Thomas Edison, Henry Ford, and the Wright Brothers—are often identified with their iconic inventions. The light bulb, the Model T, and the flight at Kitty Hawk are widely recognized as fruits of years of experimentation and tinkering.

But the genius of these inventors is not in their invention themselves. Their genius is in the recognition and development of the systems required to fully implement their ideas and enable society to realize the benefits of their inventions.[1]

Before the light bulb could shine over the family dinner table, Edison had to conceive of an infrastructure for generating, distributing, and utilizing electricity. Ford's Model T was a marvelous invention, and Ford's efforts at designing and optimizing the assembly line dropped the production time for a Model T from 12½ hours to 90 minutes. This allowed a reduction in price that resulted in a cultural revolution.

And while the Wright brothers are often remembered as bicycle repairmen who tinkered with an airplane, they were, in fact, serious scientists who systematically performed experiments to understand the aerodynamics of mechanized flight. The work of these innovative geniuses helped define the concept of excellence in R&D.

Moreover, scientists began to gain a better appreciation of what was required to bring innovations to the marketplace. Not surprisingly, the need for a complex innovation ecosystem emerged.

INNOVATION ECOSYSTEMS

With its origins in biology, the term "ecosystem" conveys the idea of the complex and intricate relationships between all the organisms found in a particular physical environment. This definition of ecosystem has since been extended to include any complex system that resembles the intricacy of biologic systems, such as pharma R&D.

Within the pharma R&D ecosystem, there are many constituent components, including the companies that supply the organizational structure and funding, the departments within the company that execute specific tasks and functions, and the scientists who, by virtue of their training and interest, gravitate toward different areas of specialty. All these components function within the cultural and economic milieu that their home country has established via governmental and regulatory policies.

The distinction between an invention (an idea) and innovation (the implementation of a useful product or process based on the idea) is especially relevant in the current R&D ecosystem. Successful innovation is a complex process that requires not just one brilliant scientist with an idea but also the expertise and interactions of many people with many different skills to turn that idea into a useful result.

Interdisciplinary collaboration is no longer nice to have. It is a necessity for us to overcome the diminishing productivity of pharma R&D.[2]

EXCELLENCE IN SCIENCE

Most of us have a sense, or definition, of excellence that we bring to our work. For example, a scientist may have personal expectations of what it means to do a good job, such as meeting certain standards for professional behavior.

These expectations are likely guided by the community of practice and reinforced by fellow scientists' behavior patterns. These standards and norms are welcomed because they provide guidelines for improving a person's chances of successfully defending study design decisions, data collection strategies, analyses procedures, and the conclusions drawn from an experiment.

A desire for personal excellence can lead to a virtuous cycle of continued education and personal improvement. In the right circumstances, it also translates into functional area excellence, wherein the other scientists in a department share a desire for excellence that provides the motivation to design state-of-the-art experiments and perform them in an elegant way in the shortest period of time possible.

In short, the pursuit of excellence is one of the main drivers of innovation. As we explore new areas of knowledge, we recognize opportunities to refine processes and introduce new technologies that can translate into new approaches for dealing with old challenges.

Unfortunately, we often optimize the tools, techniques, and data collection strategies used within our specialty area of interest without consideration of the bigger system in which these processes function and the implications for downstream collaborators. These collaborators might include personnel from other disciplines or departments who need or want to use the data we generate for different but complementary purposes in the evolution of a useful product or process.

DISTANCE BETWEEN DISCIPLINES

Three changes occur as the knowledge base in a specialty area of science expands in complexity and sophistication. First, an entirely new language may arise to facilitate communications between knowledgeable practitioners. Consequently, the vocabulary used to describe phenomena becomes more arcane and idiomatic, even to scientists in a closely allied field, such as the difficulty in communication between a pharmacometrician and a statistician or clinician.

Second, as technology evolves so does the instrumentation that uses that technology. But in seeking to increase the speed of throughput and accuracy of results, the nature of that which is being measured may also change or the interpretation of the result may change in significant and important ways. For example, the value of in vitro potency generated by high-throughput screening may not be directly useful in predicting concentration-response relationships.[3, 4]

Third, innovations that arise in a specialty area that could significantly benefit an adjacent specialty may not be recognized as such. Consequently, these innovations may be implemented as a partial solution such that the larger enterprise does not realize the full benefit of the innovation. The limited utilization of microdosing studies enabled by the exploratory investigational new drug guidance[5] across companies because of internal hurdles in defining the value of this option is an example of the latter.[6]

Developing scientific and innovative excellence in pharma R&D requires attempts to bridge these distances between disciplines with a structure and data definitions that all team members can understand and use.

A TEAM SPORT

A comprehensive, interdisciplinary synthesis of available data and experience plays a central role in the innovation that leads to new medicines. This knowledge synthesis is essential for the proper design, analysis, and interpretation of studies; the development of effective research and development plans; and the assembly and presentation of evidence for successful regulatory submissions. In other words, knowledge synthesis is needed for all the activities required to successfully deliver innovative medicines to the marketplace.

But cross-functional, interdisciplinary knowledge synthesis is lacking in many R&D programs. Instead, various functional areas are assigned to write separate and distinct sections of investigator brochures, team presentations, and early R&D plans.

Each section reflects the group that prepared it. "Synthesis" is merely a collection of separate facts and study results from the various disciplines.

This lack of cross-functional synthesis has two important consequences: knowledge gaps between disciplines are not identified and rectified, and research plans are developed based on experimental intuition rather than an analytical synthesis of interdisciplinary knowledge. The result can be erroneous assessments of the value of drug assets, causing allocation of resources to unproductive development programs.

The task of knowledge synthesis becomes ever more difficult as our understanding of the pathophysiology of disease and the pharmacokinetics and pharmacodynamics of candidate compounds expand at an exponential rate. No longer can one scientist, however accomplished, understand the entire project, discern its weakest point, and imagine the proper strategy. A framework for synthesis of the enormous amount of interdisciplinary knowledge generated during the R&D process is required.

FRAMEWORK FOR EXCELLENCE

While *in silico* models used in clinical pharmacology and translational research have emerged as a critical component of model-based drug development (MBDD),[7] the mathematical equations used to represent the disease state and drug effects have received more emphasis than the conceptual understanding of disease mechanisms and disease-drug interactions that underlie the mathematical equations.

This emphasis on math rather than mechanism has been a barrier to effective communication between the extended members of the R&D team. To make the disease-drug processes a focal point for interdisciplinary collaboration, the responsibility for development of the conceptual schema for an R&D program must be assigned to multidisciplinary teams.

A conceptual schema (see Figure 1) is used to compile and structure (preferably in a process flow format) the current knowledge, hypotheses, and all available data regarding the disease process and drug effects, including any existing *in silico* models and results from prior investigations. It draws data and analytic results from all functional areas and provides strategic guidance, which will allow data to be integrated across functional areas to yield new results or insights.

The conceptual schema for an R&D program defines the known elements of the disease process, the hypothesized interrelationships between disease process and drug effects, and the assumptions required to generate research plans, analyses, and experiments that will validate or invalidate the hypotheses. The hepatitis C viral kinetic model explaining sustained viral response is an example of a comprehensive conceptual schema.[8]

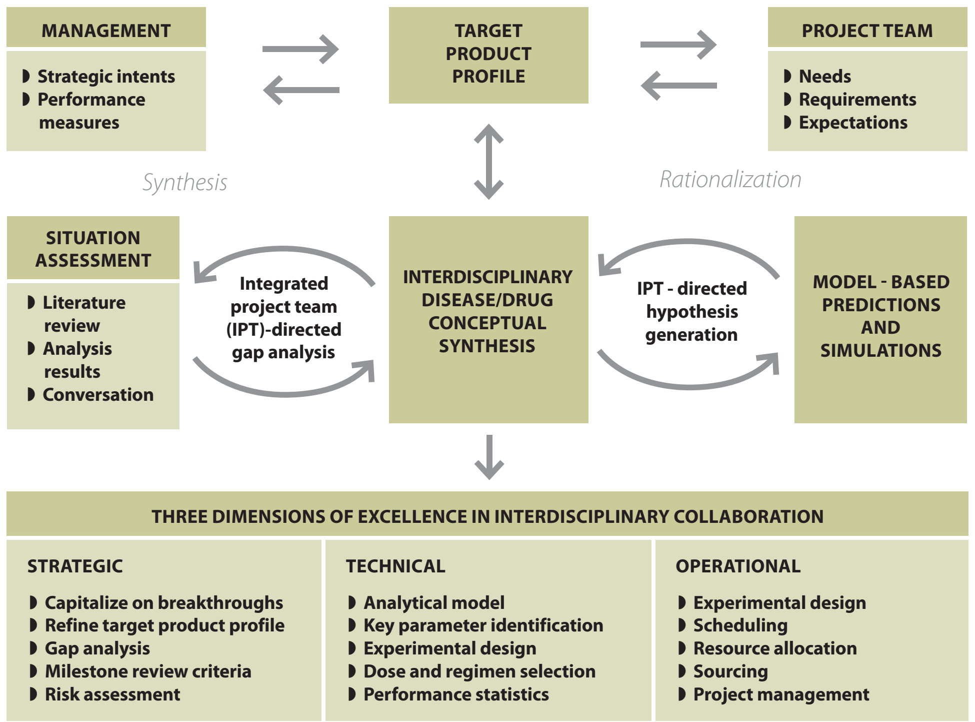


Figure 1: Framework for Interdisciplinary Collaboration
The development of a conceptual schema is initiated by a target product profile that defines the therapeutic indications for which the candidate compound(s) should be investigated, outcome indicators, and desired results compared to currently available treatments. The integrated project team (IPT) of cross-functional specialists then narrows the scope of the synthesis to a manageable set of investigations and experiments in a subset of the disease where recent advances have opened up opportunities for a breakthrough. The emphasis is on developing conceptual schema and mathematical models that the IPT can use for hypothesis generation, experimental design, and for predicting experiment outcome. The experiments then become a validation of the model or, alternatively, provide data for subsequent model improvement. The goal is to create a model and related data that predict disease behavior and mimic the impact of the proposed intervention. The complexity, utility, and validity of the model are a function of the quality of interdisciplinary collaboration and the state of understanding of the underlying disease process and drug effects.

Once developed, the first and most critical use of the conceptual schema is to clearly define the gaps in knowledge, including gaps between disciplines, that the R&D team must investigate. The therapeutic area managers and scientists then utilize this management guidance to develop their analytical and experimental investigation plans and models. Additionally, the *in silico* team members utilize the conceptual schema to identify key interfunctional parameters and develop data for the therapeutic areas to use to design their analyses and experiments in a manner that will be most useful to downstream collaborators and stakeholders.

There are many challenges to achieving effective team collaboration. Not the least of which is the difficulty in realizing a shared vision of the challenges to be overcome and a commitment to finding common ground for developing solutions.

Some people have extraordinary talents in accomplishing these tasks. Most often, though, the complexity of the problems in biology and drug development require the talents and experience of a broad range of individuals.

The shared responsibility for developing a clear conceptual schema of what is known and unknown will allow teams to better coordinate their efforts to improve productivity. However, the critical importance of interdisciplinary and interdepartmental collaboration and coordination requires a new definition of excellence.

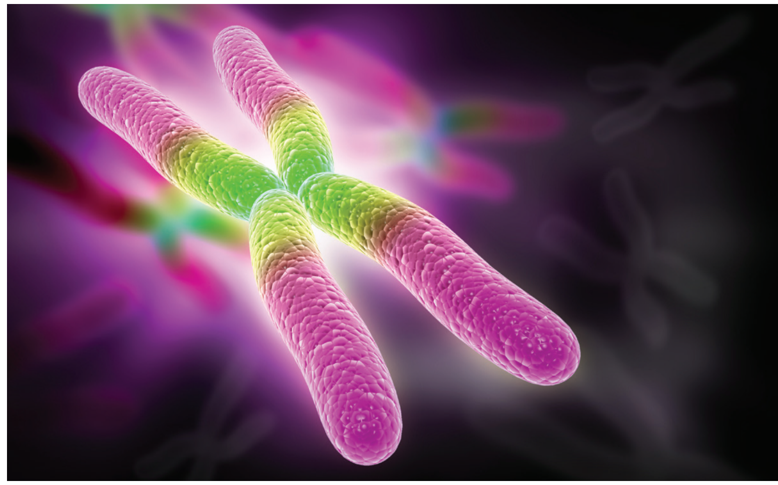
THREE DIMENSIONS OF EXCELLENCE

Scientific excellence—asking the right question, then designing and conducting a valid study that answers that question and influences future research—is widely accepted as a benchmark for success in research. However, excellence of a more complicated sort is required to enable innovation.

In this setting, there are at least three dimensions to excellence: strategic, operational, and technical excellence. Strategic excellence is demonstrated when existing knowledge about the disease and the drug is used to formulate goals and objectives, specify decision criteria for near-term reviews, and provide a rationale for proceeding with a development program.

Operational excellence is a result of careful study design, precise data selection and definition, and attention to detail in preparation of high-quality, error-free experimental results. And technical excellence results when scientists use their training and experience to identify cross-disciplinary relationships in the data, formulate and test hypotheses, and accurately represent the data in management reviews.

An obstacle in the pursuit of these three dimensions of excellence is the difficulty of creating a team with the requisite strategic, technical, and operational skills. The best teams include scientists with diverse skills and perspectives who have a shared sense of inquisitiveness and who trust and appreciate the skill set that each brings to the project.



METRICS OF INNOVATION

What metrics can be used to measure the productivity of the pharma R&D ecosystem? At present, we can readily track the financial inputs to the system.

We can also measure output by the extent to which compounds under development are progressing through the phases of clinical testing and the extent to which they have gotten through the regulatory process. In the future, new measures related to the impact of those products on health will likely become important if we are to move beyond blockbusters and justify the effort toward discovering personalized therapies.[9]

Measuring our progress toward the cultural changes needed to encourage interdisciplinary collaboration will also require metrics of a different sort. Perhaps one day we will measure the extent to which teams are meeting the conceptual schema-based decision criteria and by the extent to which they have generated the data necessary for effective decision-making.

The pharma R&D ecosystem is remarkably complex, and it can be intimidating to think that individuals can have an impact on the many different components and interrelations between stakeholders. The pursuit of excellence is a strong tradition in science, and harnessing this desire for excellence in the service of interdisciplinary collaboration to achieve real transformative innovation could be the key to achieving measurable gains in R&D productivity, which would ensure the future of the industry.

DISCUSSION POINT

We want to know your opinion! Please discuss the following question with your colleagues via AAPS' Facebook and Linked In pages. Go to the *AAPS Newsmagazine* digital edition to link to the AAPS Facebook and LinkedIn pages directly.

What does successful innovation in the pharmaceutical sciences look like to you?

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