Getting to Rational Drug Design – at Last

The industry now has the research tools to pursue rational drug design successfully, but a new hurdle is being raised: finding a way to generate data and manage our knowledge of disease that maximizes the value of that knowledge.

In our last column (September/October 2002, PharmaGenomics, p. 26), we began to explore the paradigm shift that is unfolding in the pharmaceutical industry. This shift is being driven by the challenges posed by the many new structures developed through combinatorial chemistry, ever-increasing research and development costs, clinical trials that continue to grow in complexity and cost-reduction pressures from the marketplace. Two multifaceted issues are at the center of this shift. One has to do with the pharmacy of the future and the products it would provide to patients. The other is whether or not drug discovery can be made more efficient and effective.

Let’s look at the second issue. For years, scientists both in and out of the pharmaceutical industry have been talking about “rational” drug design. This discussion began when crystallographic structures of target proteins became more readily available. The argument was that it would be easier to find molecules that would interact more efficiently in an active protein site once the three-dimensional structure was known because chemists then would be able to see how to design more efficient drugs. Rational design became the calling card of a number of start-up companies and drug discovery groups within the industry.

However, this approach did not deliver on its promise for a couple of reasons. One is that a crystal structure does not always accurately depict how a molecule will behave in vivo. Also, medicinal chemists often found it difficult to develop new structures for the “rational” approach. This led to the development of combinatorial chemistry to provide large, diverse libraries for drug discovery. A decade later, however, few would argue that the current process for drug discovery and development truly is rational.

Genomics, proteomics, metabolomics and all the other “omics” offer new opportunities for achieving rationality. The scientific advances those disciplines represent already are streamlining drug discovery and development, although there’s still a long way to go. Researchers continue to expand their capabilities to look at disease from both the level of the whole individual down to the molecules, and from molecules to cellular organelles and back up to the whole individual. As the ability to refine the understanding of pathogenesis grows (Figure 1), the next hurdle looms just ahead.

A ‘Tyranny of Data’

As this process of integrating a complex systems biology approach to pharmaceutical research becomes the norm, the various contributors to the field will generate huge amounts of data and information. This presents a situation not much different from that faced by electrical engineers in the mid-20th century. They could design circuits to do certain tasks, but no one had figured out how to build the circuits because they involved hand soldering thousands of transistors onto a circuit board. This problem came to be known as the “tyranny of numbers,” and brought electronics to a virtual standstill in the 1950s. It took Jack Kilby of Texas Instruments and Robert Noyce of Fairchild Semiconductor to develop the solution of integrating all those transistors on a single
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silicon wafer. Thus, the integrated circuit solved the tyranny of numbers (1).

Today’s pharmaceutical industry faces its own tyrannical regime: the “tyranny of data” (2) in which researchers have made great advances in discovery but haven’t figured out all that’s necessary for development. We are in a period of unprecedented data generation, data that must be translated into knowledge that is useful from both drug discovery and business points of view. So, there needs to be a way to collect and process this information so that it can be reduced to useful clinical units. This suggests a type of knowledge management function, one that also addresses how to transfer the knowledge from the scientific to the business components of the pharmaceutical industry. The key will be figuring out which information is worth putting together with other information, as well as finding ways to communicate efficiently with the various data platforms.

Understanding Complexity
A number of specific steps is needed to overcome the tyranny of data. Much drug discovery and development data are about biological systems investigated under a given set of conditions at a given time. But patients age, so we need to know the time-dependence of biological responses. A single snapshot in time is just not sufficient.

This makes for a far more complex challenge. To collect data at a virtually infinite number of points, we need to employ time-series methods. Time-series data will lead to a clearer understanding of biological processes, and hence to a set of networks. And as we move more and more into network biology — that is, the quantitative description of all the cellular communication networks and how they integrate — we’ll need yet another tool: a way to validate networks.

At least two methods are required to validate a network biology analysis. One is to use statistical tools that allow for estimates of robustness of the parameters and network structures. The second is to identify and confirm genetic regulation mechanisms by applying fundamental genetics and biochemistry.

We’ll also need to gain a greater recognition of regulatory interactions between genes and proteins that are not necessarily linear. It will be critical to understand that while the inhibition of a given enzyme by a small amount can have a large effect on a biological response, increasing the level of inhibition doesn’t necessarily increase that response. In other words, taking a double dose of Lipitor® doesn’t mean you’ll double the reduction of your bad cholesterol.

At the overarching level, we need a strategy to gain more knowledge — not just information — about complexity because there are few one-gene-to-one-disease situations. Plus, we need a knowledge management system that can translate information obtained from drug discovery to the marketplace, and vice versa. This means new algorithm and transfer functions. And, we need a new quantitative business model that links research to drug commercialization strategies.

Investigating complex systems increases the amount of information generated, as any researcher can tell you. The knowledge management function would be concerned with increasing the “return” on that knowledge. In other words, ensuring that its maximum value is realized (Figure 2). All of this suggests that the pharmacy of the future might not be the only thing that looks different. It might well be that the pharmaceutical industry takes on a radically new shape.

From ‘FIPCO’ to Disease Management

Today, most companies employ as their business model the goal of becoming a fully integrated pharmaceutical company, or FIPCO. The FIPCO does its own research and development, takes its drugs through clinical trials and FDA approval, manufactures the drug and markets it to the healthcare community. Certainly, the pharmaceutical industry isn’t so monolithic today as to preclude other types of companies, but the FIPCO seems to be what most aspire to — and promise their potential shareholders.

We envision a drastically different future, one that will build on the exceptions to the FIPCO that we see today. The pharmaceutical industry, broadly defined, includes a growing biotechnology/biopharmaceutical component, so-called research “boutiques,” a wide variety of alliances and other collaborative enterprises, contract research organizations (CROs) that conduct clinical trials and myriad licensing agreements. We think this decentralization, if it can be termed as such, will become the norm.

Figure 1. Refining the understanding of pathogenesis.
The biggest players in the pharmaceutical industry of the future might be disease management companies that offer a range of pharmaceutical treatments, as well as all the services that go with providing those treatments.

The kinds of changes we envision already can be seen in the examples of companies with excess manufacturing capacity considering leasing out that capacity to other firms to make their drugs, especially small-molecule and chemically synthesized drugs. Generic companies have gotten awfully good at manufacturing and have shown themselves to be fully prepared to take over the production burden once a drug goes off patent. In the changing business model, it’s reasonable to expect these generic firms will become the recipients of outsourcing contracts to manufacture drugs for the “bigger” companies.

But that’s only a small piece of the future. We think the big changes come back to the issue of information. We wonder whether or not the biggest players in the pharmaceutical industry of the future won’t, in fact, be knowledge management companies, or perhaps disease management companies.

Consider one possibility: the company that provides “asthma management services” — with a range of pharmaceutical treatments for asthma — as well as all the services that go with providing those treatments. These might include the tests to detect asthma, which is the promise of pharmacogenomics approaches, bundled with a choice of appropriate therapies. Meanwhile, some other companies might be doing the research and development, the production and the clinical trials.

The drugs this imaginary company might provide are likely to be the sort we wrote about in our previous column. The “druglets” of the future are something quite different from the blockbuster drugs to which we’re all accustomed. These druglets will address, with better effectiveness, the unmet medical needs of smaller and smaller segments of the population. In fact, they might be geared to the individual patient, with the expected benefits derived from an understanding of the individual’s genetics, the drug and the disorder or condition for which the drug was prescribed.

Before we get to that future, though, a lot of changes have to take place. We’ve seen the first drugs to hit the marketplace that could be called druglets. A good example, to come back to asthma, is the leukotriene modifiers to which only certain people respond. At present, there is no way to know in advance whether a patient will respond because not all of the relevant biomarkers are known. There are other examples in diabetes, multiple sclerosis and arthritis, in which researchers have uncovered various markers for various kinds of conditions but no drugs have been developed yet.

New in silico technologies should aid in analyzing complexity in biological systems, as long as the technologies are made relevant biologically. Some have argued that these technologies “will enable drug manufacturers to accelerate the selection process, reduce the cost of preclinical and clinical studies and increase their overall chance of success…[and] collectively save at least $200m and two to three years per drug (3).”

Nevertheless, two big questions remain. How many billions of dollars will it take to get these in silico drug development technologies in place? Will the medical practices of personalized medicine — druglets — offset that cost?

The pharmaceutical industry needs to figure out the answers and make the case for societal support for this paradigm shift. Whether or not savings can offset the cost, we think it’s well worth considering. After all, the paradigm shift is all about getting to better specificity of treatments, which would, in turn, lead to better health. If that promise can be realized, the extra money society will have to contribute should provide a great return on investment.

References
2. T.G. Dewey. From microarrays to networks: mining expression time series. Drug Discovery Today suppl. 7(20), S170-S175.