

DRUG DISCOVERY

AND GENOMIC TECHNOLOGIES

Impact of Genomics in Drug Discovery

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For the past decade, the promise of genomics has been eagerly anticipated. Among many aspirations, the genome was felt by many to be the key to revolutionizing innovation and productivity in drug discovery. Now that the sequence of the genome is known, will the promise be realized?

The Promise of Genomics in Drug Discovery

Drug discovery had its origins late in the 19th century with the manufacture of natural products and semi-synthetic products such as aspirin. By the turn of the 21st century, the pharmaceutical industry had grown to a \$385 billion business. Current drugs are known to modulate only approximately 480 gene products. Early in the 1990s, it was widely thought that the human genome would contain in the region of 150,000 genes—thus, the existing drugs modulated only a small fraction of gene function. Therefore, the pharmaceutical industry, spearheaded by a landmark \$145 million deal between SmithKline Beecham and Human Genome Sciences in

1993, invested heavily in genomics research to be at the front of the race to identify new genes as targets for important new therapies.

The Pharmaceutical Innovation and Productivity Gap

Over the past decade, the pharmaceutical industry has undertaken a number of big moves—investment in genomics research, outsourcing of critical clinical development, major mergers and acquisitions—all in an attempt to bridge a major deficit in innovation and productivity. To achieve even a 10% annual growth rate, Top Tier Pharma companies today need to bring to market 3–5 major new products each year—but none do (Figure 1). Average annual new drug approvals in the U.S. doubled from the 1970s to the 1990s, while R&D costs more than quintupled (2) (i.e., the industry is spending incrementally more than double for what it delivers). Currently, the cost to discover and develop a successful new therapeutic product reflects as much as a 75% expenditure on research and products that ultimately fail (5).

Genomics to the Rescue?

The primary goal of genomics research in the pharmaceutical industry in the 1990s was to identify not only new molecular targets but also more of them, and to be first to gain proprietary rights to use those targets. This goal has been successful—many, many more targets are known, intellectual property abounds, and some drugs emanating from these targets will indeed provide great benefits to pa-

2000 Pharma Sales (Example Companies Near Size)	Anticipated Sales From Current Products in 2010	Annual Real Growth Target (2000-2010)	Sales Gap for New Products to Fill in 2010	Estimated Number of NMEs Required to Fill Gap (Over 10 Years)	Year 2010 Required NME Output
\$15 Billion (e.g., GlaxoSmithKline, Aventis, Bristol-Myers Squibb)	\$10 B	8%	\$22 B	40-45	5.5-6.0
		6%	\$17 B	30-35	4.0-4.5
		4%	\$12 B	20-25	2.5-3.0
\$8 Billion (e.g., Eli Lilly, Bayer, Schering Plough)	\$5.5B	8%	\$12 B	20-25	3.0-3.5
		6%	\$9 B	15-20	2.0-2.5
		4%	\$6 B	10-15	1.0-1.5

■ Top-tier players must average 3 significant NME launches per year to continue rapid growth
 ■ Medium-sized companies must produce at least 1 NME per year to sustain average growth

Source: Executive Briefing, High Performance Drug Discovery: An Operating Model for a New Era, Accenture, 2000

Figure 1. Number of new NMEs required to meet 10-year growth objectives.

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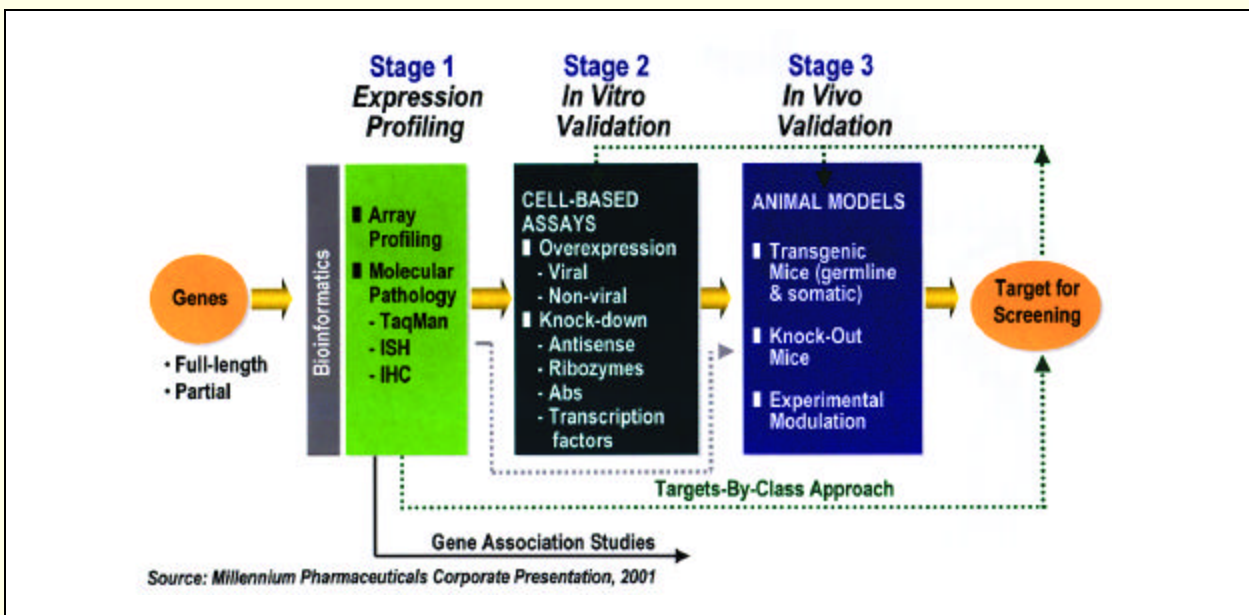


Figure 2. Efficient processes for finding more targets.

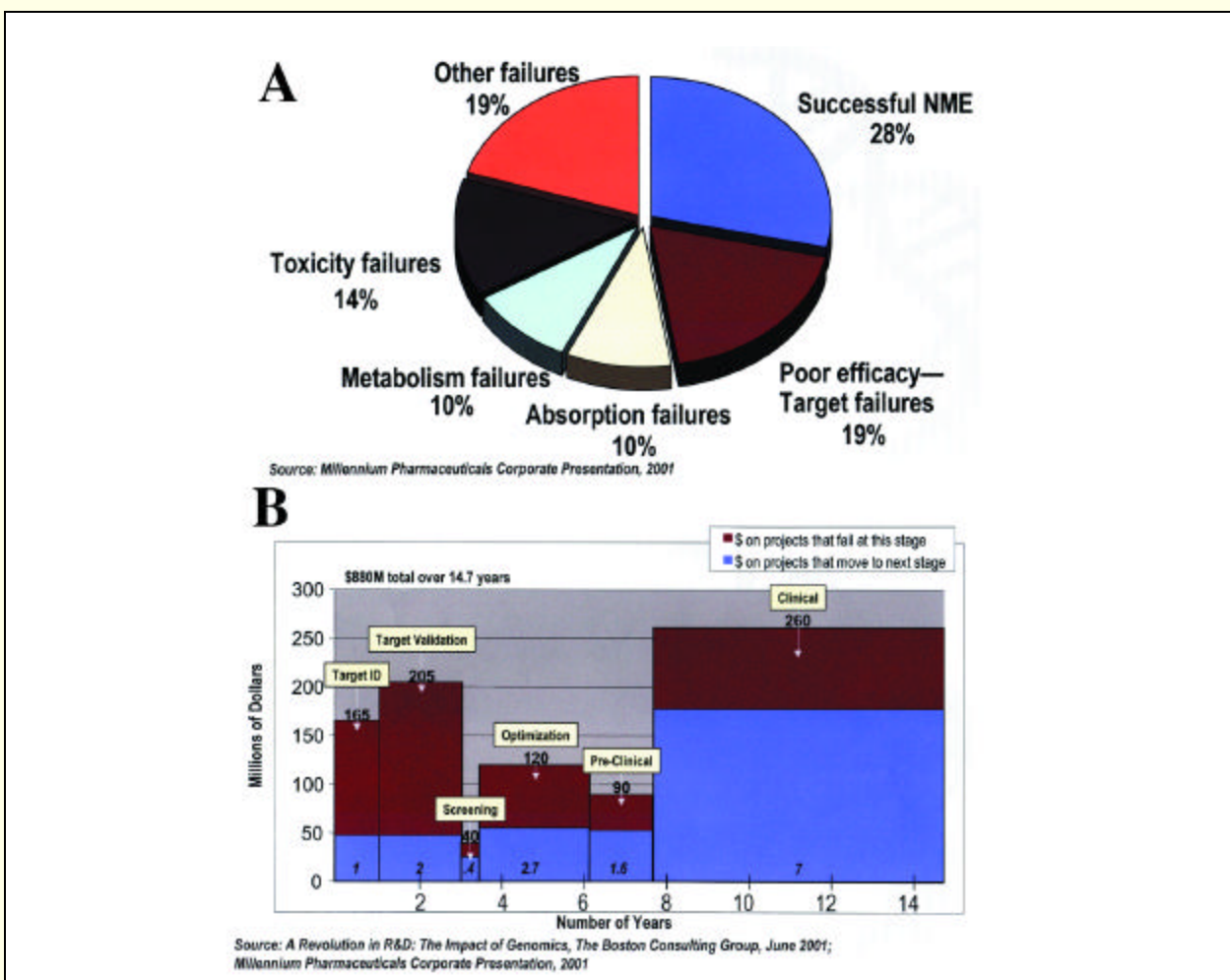


Figure 3. Causes of failure—where do the wasted dollars go in the industry-standard process? (A) Causes of project termination. (B) Investment by stage and outcome.

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tients (1). Moreover, the efficiency of identifying targets from the genome has increased markedly. The process of identifying genes, profiling them, and establishing a moderate level of validation of their potential utility in addressing disease was once a lifetime's work—now, many elements of this process have been industrialized. Millennium Pharmaceuticals, for example, is noted for its industrialization of the gene-to-target process (Figure 2) and striking yearly advances in making the process more efficient—in 2000, Millennium more than doubled its output from this process with no change in costs over 1999 expenditure, purely from process mapping and process enhancement.

To date, however, relatively few targets from genomics research have produced clinical candidates—the forerunners being Human Genome Sciences and GlaxoSmithKline. Despite great advances in the efficiency of identifying new targets, it is even less clear that the fundamental issue of productivity has been addressed. To understand why finding more new targets from genomics does not in and of itself solve the productivity and innovation gap in the industry, we need to look at the sources of lost productivity in the R&D process.

Cost of Failure in the Pharmaceutical R&D Process

For every dollar spent in the R&D process, an average of 25 cents is spent on the product that is eventually brought successfully to the patient (Figure 3). Historically, drugs have failed about equally for the following reasons: poor efficacy (the wrong target in the first place), poor

drug disposition, unacceptable toxicities or side effects, and “other” (including erroneous commercial projections, changes in management, fiscal constraints, etc.). Of course, the later in development that a product fails, the more will have been spent to reach the no-go point. Thus, some of the biggest gains in productivity will be made by eliminating future failures sooner and avoiding as much as feasible of the 75% of total R&D that is spent on ultimate failures. Clearly, drug discovery that has a higher-quality output—a clinical candidate that is less likely to fail—can make a big dent in the productivity gap. A change of only 5% in the attrition rate creates as much as a \$100 million increase in net present value (NPV) of the pipeline in a company previously delivering one new molecular entity (NME) a year at industry-average productivity.

Potential Value of Genomics on Productivity in Drug Discovery

Increasingly throughout the 1990s, genomics has been used broadly to identify additional gene family members and to create screens that chemists can use to identify drug candidates that are much more selective for their target protein than is typical historically. Identification of orthologs in species used for in vivo efficacy models or toxicological and drug disposition studies has also proven valuable to understanding drug behavior, especially in cases when compounds have differential affinity or activity at the target protein across species. Though there are many anecdotes to suggest their value, data on the extent

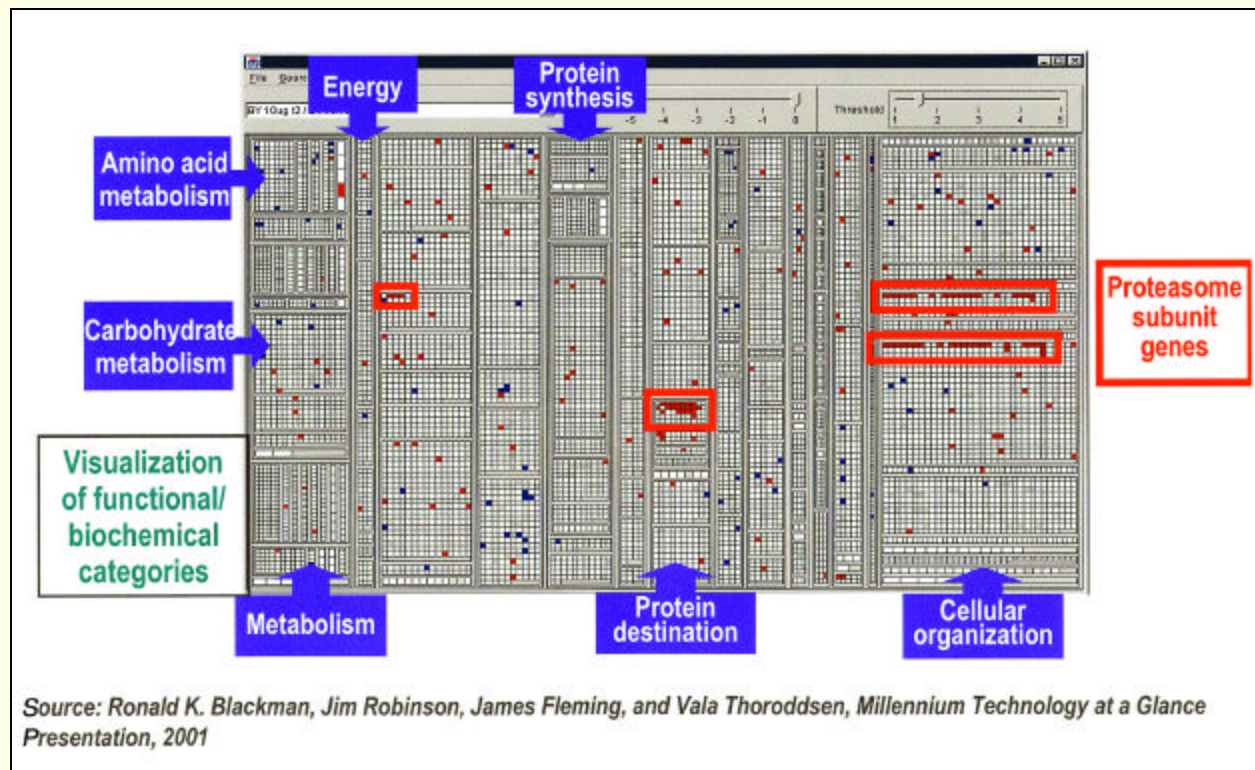


Figure 4. A better way to visualize the data: linking biology with transcriptional profiling.

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to which these advances have translated into improved success rates in the clinic are not yet available.

The genome has provided us with many new “targets” for pharmaceutical drug research and development. The value of having more targets is that it should provide the basis for making *better choices* of targets to work on. The key to *making* these better choices is using the knowledge and tools of genomics to better understand the molecular pathways underlying disease. It stands to reason that the more one understands the complete linkage of genes, transcription factors, enzymes, receptors, modulators, etc., and their aberrations in disease, the more one can make rational choices of the best point in a pathway to intervene—choices driven by the sensitivity of the desired output from a pathway to different points of intervention, accessibility, and tractability to modulation by drugs, etc. A variety of genomically driven tools and technical capabilities will be important to make the “better choices” revolution real.

Transcriptional Profiling

Transcriptional profiling is a key technology used to profile genes and identify their association with disease. Over- or under-expression of genes in a given situation

provides a valuable window into the underlying molecular state. Comparisons that reflect perturbation of a system in multiple ways—for example, between diseased and normal cells, between drug-treated and placebo-treated cells, or between diseased cells responsive to therapy and those resistant to it—are particularly valuable. While regulated genes themselves may or may not be targets for drug intervention, they represent excellent clues that, with the help of software algorithms linking genes with proteins and known functions, can point researchers toward known pathways, new elements, or new pathways in disease.

Model Systems

Most research is conducted on model systems of disease, which have historically had varying degrees of success in accurately predicting drugs that will have efficacy in Phase 2 clinical trials. Clearly, the power of model systems to more efficiently identify good drug targets and drug candidates is predicated almost entirely on the extent to which the model system truly reflects the human disease state. The capabilities of genomics, particularly transcriptional profiling and proteomic analysis, provide a powerful assessment at the molecular level of how well

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a model system reflects disease and, thus, the likelihood that it will adequately predict the relevance of therapeutic targets and drug action.

Genomics tools can have comparable value in assessing, or even creating, new systems that model drug disposition or toxicity. The recent introduction of an isozyme of human cytochrome P450 into mice in which the murine version had been knocked out is likely just the beginning of a new paradigm of model systems to assess drug disposition. Finally, as genomics technologies accelerate the rate at which model systems become amenable to formatting on a micro-scale, the medicinal chemistry cycle of design-make-test will continue to become much more efficient, taking additional costs out of the drug discovery process.

Chemical Genomics

The convergence of combinatorial chemistry, transcriptional profiling, proteomics, informatics, and miniaturization technologies has fostered the emergence of “chemical genomics” as an approach to target and drug discovery. In this paradigm, a desired phenotype or phenotypic change in a model system is sought by screening large libraries of diverse compounds. “Hits” are not only starting points for medicinal chemistry but also represent tools to dissect the molecular events and pathways underlying the observed phenotypic change. Pioneers of this approach include Stuart L. Schreiber (4) (Howard Hughes Medical Institute, Harvard University), Peter G. Schultz (3) (Scripps Research Institute), and Vertex Pharmaceuticals Incorporated.

In one sense, this paradigm is a return to the empirical drug discovery paradigm of 20–50 years ago, when screening of potential drugs/drug starting points was often conducted in functional systems to identify a desired phenotypic change (e.g., drop in blood pressure, inhibition of seizures, change in electrical responsiveness of guinea-pig ileum, growth of cells in culture, etc.), without knowledge of the molecular entity for which compounds tested may have had affinity. Though largely a process “blind” to the molecular events in disease, this paradigm was in fact quite successful and brought many important drugs to patients. Conducted with today’s powerful tools, this concept can be conducted at a massively higher scale (orders of magnitude), at a greatly reduced cost, and by using model systems and phenotypic read-outs that can be validated on a molecular level. Coupled with the potential of chemical leads to also illuminate important pathways and the molecular targets at which they interact, this approach has the potential to meld the best benefits and attributes of the two fundamentally different drug discovery paradigms of the last century.

Knowledge Management

The explosion of genomics information over the past decade is likely to dwarf the upcoming explosion of genomics, proteomics, and chemical genomics information of the post-genomic era. Ironically, the sheer volume of

information can reduce, rather than enhance, understanding and productivity, unless the information is ordered logically. A simple example of this principle is illustrated in Figure 4, which shows the transcriptional response of yeast cells to PS-341, an agent under investigation by Millennium Pharmaceuticals for the treatment of cancer. Viewing the array of 5500 expressed genes is uninformative; viewing the same information through a filter that organizes genes by their function shows very clearly that the compound affects the proteasome.

The key drivers of turning the existing and upcoming masses of data and information into knowledge will be software algorithms and computer systems that can sensibly filter information into usable knowledge. Technologies that turn information into computable form, broad ontological frameworks adopted by the community at large, and simulation technologies will all be critical.

The Promise and the Reality

In this author’s opinion, the promise of genomics is intact. This article has explored the value of genomics in drug discovery, illustrating a few benefits already realized and the potential for many more. The value of genomics will likely extend far beyond drug discovery, helping to identify patients whose disease, based on its molecular fingerprint, is better suited to one particular therapy over another—for example, as already happens in the prescribing of Herceptin and Tamoxifen preferentially in patients with HER-2-expressing or estrogen-dependent cancers. As a community, we are still on the early part of the learning curve, and it will take time for the full promise of genomics to be realized. But it is already evident that genomics can be a key driver of meeting the innovation and productivity gap in the pharmaceutical industry.

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Suggestions for contributions to the “Drug Discovery and Genomic Technologies” section are welcomed by its editor, Dr. Tomi K. Sawyer (tomi.sawyer@ariad.com)

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