GILDER
BIOTECH
REPORT

February 2003
Vol. 3, No. 2

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Published by Gilder Publishing, LLC

Looking Back

A two-year review of GBR's players

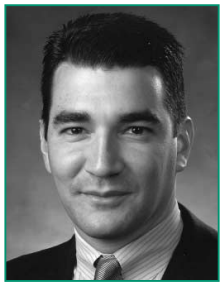
The *Gilder Biotech Report* was inaugurated almost two years ago on the fundamental premise that the marriage of medicine and microchips would open up fabulous new opportunities. That vision remains in force, as drug development and discovery continues to be moved onto in silico platforms, where researchers can harness the fabulous wealth of abundant processing power.

Over the last two years, even while the equity markets have been battered by economic meltdown on Wall Street, the early movers to this paradigm now find themselves with a technological edge over their competitors. In this issue we want to look back on that paradigm, identifying where it continues to be validated and finding a few places where it has gone astray.

New possibilities have indeed emerged, as drug discovery becomes an information-based science. New drugs currently in clinical trials are no longer scattershot, one-size-fits-all affairs, but carefully targeted to the molecular fingerprints of specific diseases. Some of these drugs are even targeted to a patient's unique DNA profile.

As we predicted two years ago, medicine continues to move from the species level—the ingrained assumption that drugs and diseases work the same in all human beings—to the individual level, unlocking new healing possibilities in minute differences between different diseases and their victims. If over the past two years, the markets haven't reliably rewarded this approach or provided validation to the sweeping impact of these new tools, the pharmaceutical industry has. This was made manifest by the number of big drug companies that made deals with in silico biotechnology companies specializing in computational modeling.

Consider **Tripos** (TRPS), which develops software for modeling, screening, and analyzing compounds and platforms for managing drug discovery data. Tripos struck deals with **Merck** (MRK), **Pfizer** (PFE), and **AstraZeneca** (AZN) since we first identified the company in one of our very first issues. These big drug companies, and others, were slow to develop their own in silico tools. (Merck lost many of their best researchers in this area to **Vertex Pharmaceuticals** (VRTX.)) Instead, big drug companies remained dependent on their old, wet-biology approach for far too long. Deals like those with Tripos are proof that Big Pharma now finds itself behind the technology curve, and it is scrambling to catch up by buying the expertise from others.



Dr. Scott Gottlieb

New drugs currently in clinical trials are no longer scattershot, one-size-fits-all affairs, but carefully targeted to the molecular fingerprints of specific diseases.

INSIDE:

The New Paradigm

Listening to the new technology two years ago, we identified three legs of an evolving paradigm, and we have chronicled these technology segments since. The first was chip-based diagnostics; the second, rational drug design; and the third, targeted treatments.

There was an internal logic to viewing the new paradigm this way. Each technology segment represents one important component of the new development and treatment continuum, from precision diagnosis, to the design of targeted drugs, to the ultimate prescription of those treatments. At each point in this therapeutic arc, the marriage of microchips with medicine has changed the way doctors and scientists do their business.

Medicine continues to move from the species level to the individual level, unlocking new healing possibilities

Rational Drug Design

First, consider how microchips are changing the way researchers develop drugs, through a process called rational drug design. As we've chronicled in these reports, traditionally pharmaceutical companies found new drug leads through a process akin mostly to blind luck. Most drugs work by binding to proteins and altering their function in some small way. So the first step en route to new miracle cures is finding a molecule that binds to a protein.

In the old wet-lab drug discovery model employed by the big pharmaceutical companies that means mixing millions of different chemicals and hoping one of them sticks. Pharmaceutical companies have sunk billions into technology upgrades that have made this antiquated model work a little faster—with automated systems that have helped scientists synthesize and survey thousands of chemical compounds a week, hoping to stumble upon a few hits. Still, many of these sticky compounds fail the minute they leave the test tube.

Companies such as Vertex Pharmaceuticals, **Gilead Sciences** (GILD), and the privately held **Quorex Pharmaceuticals** all specialize in rational or so-called "structure-based" drug design, deploying information technology intelligently to design druglike qualities right into the molecules from the very start. Instead of mixing compounds in test tubes at random, this process begins by teaching computers what the molecular structure of an effective drug ought to look like and what molecular structures it ought to avoid.

Recently, we have noted progress being made at Vertex and Gilead. Quorex also continues to move forward, identifying new drug targets and consummating the purchase of the privately held bioinformatics company **Protein Vision, Inc**. The acquisition gives Quorex added capability for three-dimensional modeling of new compounds as well as functional analysis of protein drug targets. These are the fundamental tasks of structure-based drug design. Quorex also raised an additional $10 million this year. It remains a private company worth keeping on your radar screen. With any upward turn in the equity market, Quorex could quickly IPO.

The benefits of rationally designing new drugs were made manifest this month when one of our favorite rational designers, Gilead, released impressive results with its newest drug Viread for the treatment of HIV infection. Viread was developed as a follow-on to Gilead's first-generation protease inhibitor using the aid of computational tools. The idea was to design into Viread those properties that would make it a more potent, more tolerable drug. Recent data shows Gilead has succeeded. A new study demonstrates that Viread is a potent antiviral, but it's also less likely to trigger the side effects plaguing other protease inhibitors, such as a propensity to dramatically increase a patient's cholesterol level.

While rational drug design is gaining fans inside Big Pharma, the major drug companies have been slow to develop these technologies on their own. As a result, they

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Gilder Biotech Report is published monthly by Gilder Publishing, LLC. Editorial and Business address: 291A Main Street, Great Barrington, MA 01230.

now find themselves behind the curve. As we mentioned, they've recently been playing catch up by acquiring tools from companies such as Tripos, **ArQule** (ARQL), **ChemBridge**, **Entelos**, **Discovery Partners** (DPII), **Syrrx**, and **Structural Bioinformatics**, all of which offer in silico drug modeling. In some cases, Big Pharma companies have been buying exclusive rights to these technologies through technology transfer deals. In other cases, drug companies have been striking alliances with smaller biotech companies in order to capture their cutting-edge know-how.

Big Pharma Partners with Small Innovators

Consider Pfizer's expanding partnerships with Tripos and ArQule, which the pharmaceutical giant refers to as "key sources" of innovation. ArQule offers a technology platform based on computational models that simulate human drug toxicity characteristics. While their technology models all of these parameters, their researchers have focused on drug metabolism. The only input needed for them is the compound's structure. Tripos recently introduced its VolSurf system, which predicts drug properties using pre-calculated models. The system uses QSAR (quantitative structure-activity relationships) by reading or computing 3-D molecular interactions of new drug compounds. Tripos and ArQule are back on Wall Street's radar as a result of the deals each has been striking with pharma partners.

Pfizer recently expanded its relationship with Tripos and ArQule, having gained confidence in their capabilities from the initial transaction, thus entrusting them with more and more richly reimbursed responsibilities in the second. Such sequential alliances are a hallmark of high-value deals in which values of niche biotech companies can increase not merely in dollar terms, but in less quantifiable ways. Consider this: in its first deal with Pfizer, ArQule created compounds to match Pfizer's designs. Through the collaboration, ArQule got more than cash—it got some Big Pharma know-how, learning Pfizer's requirements for druggable molecules. That was knowledge ArQule put to good use, striking the second and more lucrative deal with Pfizer. Now ArQule is designing compounds for Pfizer, without guidance, having learned—from watching Pfizer—what good compounds should look like.

Standouts in Targeted-Treatment Design

Moving on from rational drug design, another leg in the in silico discovery paradigm is the ability to use information about disease pathways, gleaned through genomics and protein discovery, to develop targeted treatments. We've considered **Millennium Pharmaceuticals** (MLNM), **OSI Pharmaceuticals** (OSIP), and **CuraGen Corporation** (CRGN). These companies are still standouts, using genomic and proteomic tools to design targeted treatments.

The other company we considered in this space was **Human Genome Sciences** (HGSI). Human Genome has given us pause over the past year, as it seems to be moving away from some of its core expertise in gene-based target discovery. In lieu of this technology, Human Genome has grown more dependent on an old technology that it owns: albumin fusion technology. Albumin fusion allows Human Genome to create an altered version of a therapeutic protein by fusing the gene for human albumin to the gene that encodes the active protein drug. Binding albumin to a drug makes a drug hang around longer in the blood. The albumin makes the drug hard to clear. Using this technology, protein drugs that were once administered every day can be given every week; drugs given every week can now be given every month.

It's a fine strategy for generating some near-term revenue while Human Genome continues to work on developing novel drugs from its genomics tools. But recently, we've become worried that Human Genome may be losing some of its swagger—and that it views albumin fusion as a path away from its genomics-driven discovery platform and its various genomic-derived drugs that have been coming up short in clinical trials.

Millennium, OSI, and CuraGen—by contrast—have each remained true to their original vision, and to ours. Each has had significant preclinical and clinical developments over the past year. Millennium and OSI we've written about recently. CuraGen, which we haven't profiled in a while, also continues to make progress and to validate the value of its genomics-based discovery technology. The company's progress is worth reviewing.

CuraGen's Progress

CuraGen currently has more than two hundred projects based upon newly discovered drug targets in obesity and diabetes, cancer, inflammation, and central nervous system disorders, including 57 protein projects, 5 of which have been advanced into validated therapeutic candidates; 96 antibody projects, from which 28 fully human monoclonal antibodies are being evaluated in conjunction with their partner **Abgenix** (ABGX) as potential therapeutics; and 55 small molecule projects, of which 17 screens are in progress or have been completed through their partnership with **Bayer** (BAY).

Of these, three products are in advanced preclinical

development. Two are protein therapeutics. The third is an antibody. In the second half of this year, CuraGen expects to file its first investigation, new drug application on one of these drugs in order to conduct human trials. It's for CG53135, a fibroblast growth factor for the treatment of mucositis (a common side effect of cancer treatments, where mucous membranes, like the gut lining, become irritated), and eventually Crohn's disease and ulcerative colitis. In addition to advancing its preclinical pipeline, CuraGen continues to generate near-term revenue through strategic collaborations and service agreements that monetize its technological prowess.

For example, CuraGen recently finished development of a toxicogenomics chip that enables reliable high-throughput prediction of liver toxicity. Since the chip's launch in September, CuraGen has signed up three partners (in addition to Bayer) which are using the chip to prioritize their own drug pipelines.

Of course CuraGen is trading below cash value of $5.39 net cash per share. That's largely because Wall Street is ignoring early-stage genomics-powered discovery engines like CuraGen, in favor of companies with products already on the market or in late-stage clinical trials. We continue to see significant value in CuraGen's approach, particularly from its commanding IP in genomics and its drug-discovery technology platform. And we continue to believe CuraGen will emerge a long-term winner. It's trading now at venture capital prices—a significant bargain if you share our vision.

Using Antibodies as Drugs

CuraGen, Millennium, and OSI all make small-molecule drugs, the kind that come in pills. But Millennium and CuraGen are also developing monoclonal antibodies. As we've noted before, antibodies in many ways are the low-hanging fruit borne by this new paradigm. The concept of using an antibody as a drug is simple enough, which is why these drugs are some of the first targeted treatments to make it into patients. The first step is to identify a marker known as an antigen that can be found on the surface of a disease-causing cell. In the case of cancer, researchers identify a protein expressed on the surface of every cancer cell and then engineer an antibody that is programmed to recognize and attach itself to that protein. Once attached to its target cell, monoclonal antibodies can be engineered to disable a protein, flag a diseased cell for destruction by a person's own immune system, or kill a cell outright by interfering with its growth or by punching holes into it.

Gene Chips as Diagnostics

Finally, we consider how the new technology is changing the way doctors diagnose disease. In conventional medicine, diagnosis remains mostly the art of neglecting remote dangers in favor of likelier ones. Doctors can save more patients that way. Diagnostic tools are too expensive or too inaccurate to be widely deployed. In the near future that will change, as diagnostic gene chips are used not for spying crude symptom formation, but for detecting the underlying molecular processes that trigger disease weeks, months, or even years before the patient feels a twinge.

As we've detailed on these pages, DNA chips are elegantly simple in concept: thin wafers of glass or plastic embedded with strips of DNA rather than tiny transistors, like silicon chips. They exploit the natural tendency of double-stranded DNA molecules to bind with their complementary partner, in a process called hybridization. Once researchers have identified a particular strip of DNA within a virus or bacteria or genetic disease, that strip can be used to track down a matching strand from a sample of a patient's blood or a biopsy specimen.

The first step is to fix a single strand of a known DNA sequence (or hundreds of such known disease-causing sequences) to a chip so that it can be used to search and bind a complementary strand found in a patient's blood sample. In hours, a remarkable feat of pattern matching occurs. Genes from the blood sample are allowed to bind to their complementary probes on the silicon surface of the gene chip. Then the entire chip is placed in an analyzer that can read the patterns of gene binding and transfer the information directly into computers capable of interpreting the results.

Today, 60 percent of gene chips are sold for research purposes, where they are speeding up drug design and helping researchers mine genomic databases. But that's changing, thanks to recent improvements in biochip platforms along with a tsunami of new genomic knowledge that forms the probes that dot the surface of these chips. Gene chips are bursting out of the confines of the research lab and into the hands of doctors and hospitals, transformed from research aides into amazing diagnostic tools. In the not-too-distant future, a single gene chip will be able to screen for hundreds of diseases from heart disease to diabetes, sometimes years before patients develop symptoms.

Gene chips were born at the intersection of microelectronics and molecular biology, brainchild of recent advances in microfabrication, microfluidics, and microelectromechanical systems (aka MEMS) married with

genomics. Like most great ideas, biochips are simple in concept: thin wafers of glass or plastic etched not with tiny transistors, like ordinary microchips, but with strips of DNA. All biochip platforms, whether designed for clinical or research use, exploit the natural tendency of double-stranded DNA molecules (once separated) to rejoin their complementary partner, a process called hybridization. Separate the twisting pairs of a single DNA fragment, and you create an amazingly elegant system for new diagnostics.

Here's the basic idea: one-half of a DNA pair is isolated from a patient's sample. It's then washed over a chip embedded with potential mates—DNA strands associated with particular diseases (known to the trade as DNA probes). After minutes, or more usually hours, some of the DNA strands re-entwine. These DNA hits allow researchers to identify promising new drugs. They help mine genomic databases for new disease markers, and they are also the key to fast, accurate chip-based diagnostics.

The first step is to saturate the gene chip with the sample of a patient's DNA or messenger RNA (*mRNA*, to be exact). Gene chips have built-in "laboratories" that exploit microfluidics—a fancy way of saying they use minute quantities of chemicals mixed and channeled in microscopic wells to multiply a few copies of DNA into millions (a process called DNA amplification). The point is to make sure the DNA sample fully saturates all the DNA probes embedded on the chip. Next, the amplified double strands of DNA are split up, then washed over the chip. In hours, the remarkable feat of pattern matching occurs. Strips of DNA from the blood sample will bind naturally to their complementary probes on the silicon surface of the gene chip.

But how to read the submicroscopic DNA that hits quickly and accurately? As we've detailed in the *Gilder Biotech Report*, different biochip platforms have come up with different answers. The very first idea, which is still in wide use today, was brilliantly simple: use fluorescent dye to tag the patient's DNA samples a different color than the DNA probes embedded on the chips. DNA hits take on a unique coloration caused by the merger of the two dyes. Imagine the patient sample is dyed yellow and the DNA probes are dyed blue. DNA hits would glow vibrant green, easily detected and catalogued by a computer.

Affymetrix's Success

Today's undisputed market leader is **Affymetrix** (AFFX), with its 60 percent share of the current biochip market. Affymetrix's GeneChip is heavily used in genomic research labs, selling more than 150,000 units annually, at anywhere from $45 to $2,000 each. But they're making serious strides to becoming a dominant platform in the clinical market as well, where their current products include an HIV chip that detects drug-resistant HIV strains, a p53 chip for detecting mutations that predispose people to cancer, and a cytochrome P450 chip for identifying which people's livers will have difficulty metabolizing common drugs.

But we've previously said that the diagnostic side of Affymetrix's biochip technology platform leaves something to be desired. That's still true. For one thing, Affymetrix's chip platform is comparatively slow. Affymetrix GeneChips use a passive technique called hybridization to allow separated DNA strands to bind spontaneously with complementary strands embedded in chips. That takes time. Researchers using GeneChips often leave them overnight, just to make sure all the DNA probes have time to bind. For researchers that is a small price to pay in exchange for the ability to test thousands more possibilities. But if you are a doctor trying to figure out how to treat a patient suffering from a rapidly spreading infection, speed and accuracy are a premium.

We expect Affymetrix to increase its hold on the market for chips in clinical diagnostics

So when we originally looked at gene chips, we identified San Diego-based **Nanogen Inc.** (NGNE) as a standout. Nanogen's NanoChip technology makes use of bioelectricity and customized chips to speed the binding process between the DNA and the probes, about a thousand times faster than Affymetrix's GeneChip, generating results in just a few minutes compared with hours or days for the latter's passive hybridization process. Nanogen has ingeniously designed a way to use DNA's natural electrical properties to bring the DNA probe and test site together, quickly and efficiently. (See *GBR*, October 2001.)

Nanogen's technology still allows it to set itself apart from its competition, and, in particular, Affymetrix. But what's becoming apparent in our meetings with doctors and clinical lab technicians over the past year is that in the clinical diagnostics space, sometimes "good enough" is all that's being demanded. What matters more, especially to the technicians who are conducting these tests

and the labs that are buying these testing platforms, is familiarity and integration. Labs want systems that their technicians are familiar with, and most of all, they don't want to have to train their people on a new box. That means they're often willing to accept the second best chip if it's cheap and easy.

To those ends, a recent deal that Affymetrix struck with the leader in clinical diagnostics, **Roche Diagnostics** (ROCZ), gives us pause to reconsider Affymetrix and its potential to become a long-term player in the clinical diagnostics space. First consider Roche's slow, clumsy entry into the gene chip space to understand why its deal with Affymetrix is different. When Roche acquired Boehringer Mannheim in 1997, the idea was to combine therapeutics and diagnostics to deliver point-of-care genotyping, diagnostics, and, ultimately, personalized medicine. As with many intellectually compelling ideas, practical progress was been slow. Boehringer wasn't a household name in this space and didn't have a lot of genotyping equipment in clinical use. Affymetrix does, penetrating key labs and becoming an industry standard. That makes this deal different.

Under the terms of the deal, Roche is paying $70 million upfront to Affymetrix for up to eighteen years of nonexclusive access to Affymetrix's GeneChip technologies to develop and market diagnostics for cancer, osteoporosis, and other diseases. According to Roche, the company will be the first to target the clinical diagnostics market with high-content chips, although the initial analysis will be in centralized and reference labs, not point-of-care.

Roche already has several therapeutic and diagnostic combinations on the market, so it knows how to successfully hawk these wares. These include a test to identify candidates to receive Herceptin to treat breast cancer; a paraffin embedded tissue PCR test to identify cancer patients for treatment with Xeloda capecitabine; HIV-PCR diagnostics to determine HIV therapy; and a hepatitis C virus detection test given before patients start treatment with Pegasys peginterferon.

For the most part, Roche expects the first generation of tests from the deal to be for high-throughput systems with medium content chips (100 to 5,000 spots). The goal is to place them in clinical and reference labs, where they will be married with Roche's PCR and sample preparation systems. The chips will be focused on specific therapeutic markers and marker profiles. The chips initially will run on Affymetrix scanners, but Roche plans to develop its own devices integrated with its clinical high-throughput PCR systems in three to five years. This will give technicians time to climb up the technology curve on the boxes they often have in their laboratories already.

One way to think of Roche's contribution to the technology mix: the company sells the chemicals that bathe these chips and make the reactions on their surfaces run. As we've written before, Roche may eventually be displaced by better chemistries, and we noted one such platform in the December 2002 issue of the *Gilder Biotech Report*—one developed by **Third Wave Technologies** (TWTI) and its Invader product. But for now, Roche is what a lot of the marketplace is using, largely, we believe, because of familiarity. So the deal Affymetrix struck with Roche makes Affy an easy choice for doctors looking to take that step and bring gene chips significantly into the clinical setting for the first time. It moves Affy closer to being the industry standard itself.

The first diagnostic, which the partners hope to launch next quarter, will be an upgraded p450 chip to analyze complex metabolic and drug dynamic predispositions, such as those used for dosing warfarin in cardiovascular applications and for dosing antidepressants. Both classes of drugs need to be finely tuned to the metabolism of the patient. Roche expects sales of $100 million in four to five years. The company is also developing an array for leukemia that will combine on one chip the eight to ten tests currently required to determine the nature of the leukemia and which therapies might work best. Roche expects that chip to be launched in 2006.

From a strategic perspective, the deal represents a major shift similar to Roche's acquisition of PCR technology in the early 1990s. The pharma company brought PCR from research applications into the clinical lab, and PCR now provides $1.5 billion in annual revenues. Roche now intends to do the same with genotyping applications of the GeneChip. The aim is to tightly integrate PCR technology for sample preparation and automation with the GeneChip technology, ultimately streamlining the path from sample to readout. According to Roche, the integration of PCR and the Affymetrix technology will enable Roche Diagnostics to offer smaller companies with proprietary biomarkers a way to monetize their intellectual property. It will also offer labs an easy way to run those tests.

Affymetrix's Staying Power

Indeed, the marriage between a widely used chemistry and a widely used gene chip should give investors pause to reconsider the penetration of the Affymetrix GeneChip and the company's staying power. This is especially true as Affymetrix aims to penetrate clinical diagnostics, where

absolute sensitivity and specificity for new tests are often sacrificed in the name of convenience. Even if Roche is eventually displaced—and we hope it will be—technicians will still have learned to love the Affymetrix chip. These guys and gals stick with what they know. It's the case with more than a dozen tests where clinicians and clinical labs are willing to adopt tests that aren't the most accurate available, but the most convenient. For now, putting PCR on the Affymetrix chip gives clinical labs something they are especially familiar with and an easy way for them to quickly get into clinical diagnostics. We suspect many labs will leap at this opportunity. And as a result, we expect Affymetrix to increase its hold on the market for chips in clinical diagnostics.

To be sure, there will still be room in this vast market for companies with good technology, companies like Nanogen—especially for specialized applications where accuracy and speed count. But the marriage between PCR and the Affymetrix GeneChip will help the Affy chip become ubiquitous in a market where familiarity counts more than precision. While you may think you have missed the boat with the recent run-up in shares of Affymetrix, this is probably just the beginning, and Affy—which is on pace to do $400 million in sales in 2004—has plenty of room to run.

How much? Affy is set to generate about $200 million in true GeneChip sales in 2003, up more than 20 percent from its 2002 levels. It plans to ship about 550,000 chips to hit this sales number, up from 405,000 in 2002. Affymetrix is also moving aggressively to license proprietary intellectual property—represented in this case by collections of DNA markers able to predict disease and drug response—onto its platform. Since Affymetrix is the leader in the discovery space, and is fast becoming a standard in the diagnostics side of the chip business, it has a leg up in striking the best deals with IP providers. At the very least, the Roche deal validates the Affy platform and sets it up to remain a long-term player in the clinical diagnostics space and a "go" to test for genotyping.

Adapting to Change

As we noted in out very first issue, the merger of medicine and microchips is in one sense only natural. DNA can be thought of as a three-billion-year-old Fortran code easily transduced into bits of data, captured on databases, and analyzed with sophisticated software. But until recently the body's digital code was just too complex to crack. The true potential of emerging genetic knowledge remained locked in a box of complexity, awaiting the development of a sufficiently advanced information technology. The key is abundant processing power to generate and manage huge data sets linking gene sequences to body functions and dysfunctions.

Some analysts point to the declining number of completely novel drugs submitted for approval by the Food and Drug Administration over the past two years as evidence that this new technology is not yielding the types of breakthroughs once envisioned, despite increasing investments in research and development.

According to the pharmaceutical industry's calculation, its R&D investment doubled to an estimated $30.5 billion in 2001. Despite the increased effort, output as measured by the number of new drugs and biologics approved or submitted for approval has been steady or has declined

The merger of medicine and microchips is only natural

across almost every major therapeutic area. Meanwhile, if you look at the trend over the next five years, it is not likely to change dramatically. If the technology being brought to the task of drug development is so fabulous, the question is: Why haven't these innovations resulted in more new drugs being developed and approved?

We see another truth. The drug industry has been reorienting itself around new technology and has been adapting itself to the realization that its business model is to create medicine, not to identify targets or pathways. This fact is leading to a redeployment of the new science, putting the industry at a technical inflection point.

While the crunching of gene expression data and the elucidation of new pathways will surely bear fruit, it's a safe bet that some of the targets and some of the genes, proteins, and pathways will prove dead ends once they are tested in the whole organism. This is not because the science is wrong, but because humans are more than the sum of their parts, with redundant pathways that not only can override interventions, but also can cause unintended consequences.

What the Future Holds

If you look at genomics and proteomics as a way of finding novel ways of attacking a disease, the next step is to build an understanding of whatever biochemical pathway a new compound will attack and what role it will have in the entire organism. That's the technical challenge that the industry is grappling with and why it is

placed at a watershed moment in the evolution of its development skills.

As the respected industry publication *BioCentury* recently noted, the problem is one of figuring out how to integrate medicine into the equation when the work being done at the front end is very quantitative, particulate, and data-intensive, while the work being done at the medicine end deals with interactions of physiological systems that may be only partially understood, and is sometimes more of an art than a science. The answer is to transform some of the new tools so that they more closely mimic biological systems, which an increasing number of in silico companies are doing.

Traditional human efforts are being empowered with digital tools that annotate life and displace enormous material efforts with an exercise in artificial intelligence. As we wrote in our very first issue, computational tools have created a wealth of new opportunities. Moving from wet lab to computer, from random to rational drug design, from species biology to the individual, unique DNA profile, companies adopting this paradigm are unlocking the long-hyped promise of genomic medicine, making targeted drugs and diagnosis a reality, and drug development faster, cheaper, better.

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February 18, 2003

BIOTECH COMPANIES

COMPANY	TECHNOLOGY LEADERSHIP	REFERENCE DATE	REFERENCE PRICE	2/18/03 PRICE	52-WEEK RANGE	MARKET CAP
ABGENIX (ABGX)	ANTIBODY THERAPEUTICS	9/30/02	6.61	5.00	4.52 - 24.62	437.9M
CELL GENESYS (CEGE)	CANCER THERAPEUTICS	6/10/02	13.24	8.87	8.50 - 18.02	319.5M
COGENT NEUROSCIENCES (NONE*)	NEUROGENOMICS	5/2/02				
CURAGEN (CRGN)	CELLULAR SIGNALLING	3/13/02	17.67	3.75	3.40 - 18.55	184.9M
GILEAD SCIENCES (GILD)	RATIONAL DRUG DESIGN	12/05/01	33.88**	32.30	26.08 - 40.00	6.4B
HUMAN GENOME SCIENCES (HGSI)	CELLULAR SIGNALING	10/26/01	43.97	6.74	6.31 - 25.77	867.8M
IMPATH (IMPH)	GENOMIC DIAGNOSTICS	12/20/02	19.48	15.90	9.98 - 44.40	259.6M
ISIS PHARMACEUTICALS INC. (ISIS)	ANTISENSE THERAPEUTICS	7/9/02	7.30	4.81	4.65 - 18.40	265.2M
MDS PROTEOMICS (NONE*)	PROTEOMICS	2/05/02				
MILLENNIUM PHARMACEUTICALS (MLNM)	TARGETED DRUGS	11/29/02	10.01	6.97	6.24 - 25.55	2.0B
NANOGEN (NGEN)	BIOCHIPS	10/2/01	4.95	1.22	1.22 - 5.20	26.8M
OSI PHARMACEUTICALS (OSIP)	CANCER THERAPEUTICS	8/27/02	16.16	14.20	11.50 - 43.58	517.1M
QUOREX (NONE*)	RATIONAL DRUG DESIGN	12/05/01				
SEQUENOM (SQNM)	PHARMACOGENOMICS	1/09/02	9.00	1.76	1.25 - 7.66	69.3M
TRIAD THERAPEUTICS (NONE*)	RATIONAL DRUG DESIGN	4/9/02				
VERSICOR (VERS)	ANTI-INFECTIVES	10/29/02	10.00	10.50	7.65 - 20.54	277.0M
VERTEX (VRTX)	RATIONAL DRUG DESIGN	9/17/01	28.60	12.78	12.40 - 32.45	976.0M

* Pre-IPO startup companies.

** Split-adjusted price.

NOTE: This list of Gilder Biotech Report companies is not a model portfolio. It is a list of technologies in the biotech paradigm and of companies that lead in their applications. Companies appear on this list only for their technology leadership, without consideration of their current share price or the appropriate timing of an investment decision. The presence of a company on the list is not a recommendation to buy shares at the current price. Reference Price is the company's closing share price on the Reference Date, the day the company was added to the table, typically the last trading day of the month prior to publication. The author and other Gilder Publishing, LLC staff may hold positions in some or all of the companies listed or discussed in the issue.

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