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New Technology May Silence Unwanted Genes

Will RNAi Live Up to Its Potential?

In biotechnology "silence is golden," or so proclaimed a recent headline in the *Financial Time*s. The newspaper's pitch was for a "hot new technology" used to silence unwanted genes, called RNA interference, or *RNAi* for short. We brought the broader concept to you last year (*GBR*, July 2002) in our profile of **ISIS Pharmaceuticals** (ISIS), but RNAi is the new, new thing.

Since we first profiled ISIS, the general concept of interfering with RNA has gained traction in both scientific and investment circles. RNAi is now a popular concept in investment groups. Cash follows new science. New biotech companies are scrambling to develop drugs based on the technique, and some older companies, such as **Ribozyme Pharmaceuticals** (RZYM), are reorienting their R&D programs to capitalize on the newest technology. Venture capitalists are pouring in cash with the hope that they've discovered the "ics" in biotechnology. In fact, RNAi is nearly the only field for which the financially stressed biotechnology industry finds no difficulty in raising new funds.

Scientists think they've found their best hope yet of developing a magic bullet for treating diseases as diverse as hepatitis C and cancer.

RNAi has become the technology everyone, including our readers, has been asking about, so we'll spend some time reviewing it here. But from an investment standpoint, right now we'd sit and wait on the sidelines of the RNAi revolution. While the research is promising—for all the reasons we'll note in this issue of the *Gilder Biotech Report*—the fact remains that the technology is very new. And as we've discussed in these pages before, new concepts often take as long as a decade before all the kinks are worked out and an emerging scientific theory is ready to yield tangible therapeutic benefits.

Dr. Scott Gottlieb

The best way to play the concept of RNA-based drugs is through antisense inhibitors and companies such as ISIS Pharmaceuticals.

Making Sense of Antisense

Such was the case with monoclonal antibodies, with antisense inhibitors, and with angiogenesis and EGFR inhibitors. If RNAi pans out, and we think it very well may, we believe the same, long scientific cycles will remain in force. By that time, a

INSIDE:

few of today's RNAi-focused companies might be successful, while many more could be swallowed up. In fact, we think the best way to play the concept of RNA-based drugs is through antisense inhibitors and

New evidence suggests an intriguing possibility that some RNA is not merely the intermediary between DNA and protein, but the end-product

companies such as ISIS Pharmaceuticals, where the technology has evolved for more than a decade, and scientists have had time to refine rough theories and even rougher first-generation drugs. Antisense inhibition might one day prove to be a poor cousin of RNAi, but these drugs are already proving, nonetheless, their value in clinical trials.

RNAi, Breakthrough of 2002

All of these caveats notwithstanding, the renewed interest in RNA inhibition prompted the scientific journal *Science* to name discoveries in RNAi the "Breakthrough of the Year" for 2002 among all of the sciences. RNAi is clearly the popular new tool, and since the biotech market often moves up in bursts of new technology, we figured that RNAi is worth our considering.

GILDER BIOTECH REPORT

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It is only four years since scientists first used RNAi to switch off specific genes in the nematode worm C elegans—and less than two years since the technology was shown to work in mammalian cells. Yet already there are half a dozen biotech start-ups devoted solely to RNAi, dozens more using it as an important research tool, and probably hundreds of companies investigating the technology in their laboratories.

So what's the basic concept behind RNAi? As we've discussed on these pages, proteins run the show in our bodies. After water, our bodies are made mostly of proteins. Remove the moisture and protein from a typical adult and what's left won't quite fill a shoebox. Proteins occupy a similarly large place in medicine, because in addition to building bodies, they also regulate body functions.

It all begins with the "central dogma"—the scientific rule that prescribes how a gene is turned into a protein. Protein production is a complex, two-step process. Normally to produce a protein like insulin, our body first scans for the gene that contains the code for manufacturing insulin and then copies it out from the DNA into an intermediate set of instructions called messenger RNA (*mRNA*). The process of copying the gene into mRNA is called transcription. Afterward, another set of molecules called ribosomes are brought in to use the mRNA as templates upon which they manufacture proteins. The proteins themselves are built from amino acids floating in the viscous sea of cytoplasm found inside the cell. These amino acid links in the protein chain are coupled to each other in the precise order specified by the mRNA. So you can think of it this way: RNA is the messenger molecule that transfers genetic information from a cell's nucleus (where genes are found) to its cytoplasm (where the everyday business of staying alive is carried on). The finished product is a new protein.

New evidence suggests an intriguing possibility that some RNA is not merely the intermediary between DNA and protein, but the end-product. Some huge stretches of DNA that do not contain protein-coding genes, and considered "'junk," actually hold the code for some of this RNA. A study published in May by scientists at **Affymetrix** (AFFX), of Santa Clara, California, a maker of gene chips, reported that in addition to the DNA's containing the recipes for proteins, a lot more DNA was being copied into RNA. The recently deciphered mouse genome was found to have about twice as much in common with the human genome as could be accounted for by

protein-coding genes. Areas of the genome that are similar are thought to have important functions, explaining why they have not mutated as species evolved. At least part of this overlap appears to be genes that produce RNA as their end-product. What all of this RNA is doing is not clear, and much of it may have no function. But mounting evidence suggests that at least some RNA is involved in regulating the way genes are turned on or off. That's where RNAi comes in.

RNAi is comprised of double-stranded molecules of RNA (ribonucleic acid). In living cells, RNA occurs only in the single-stranded form known as messenger RNA. But some harmful viruses are composed entirely of double-stranded RNA, including AIDS and hepatitis C. RNAi seems to work by reawakening some ancient defense mechanism. When short, synthetic stretches of double-stranded RNA are introduced into a cell, special enzymes destroy all messenger RNA that has the same genetic sequence. This effectively switches off the corresponding gene, and, in turn, switches off production of the corresponding protein. So if you can engineer a strip of RNA that codes for the production of a harmful protein in a disease like cancer or diabetes, you can effectively turn off production of that harmful end-product.

Individual RNA molecules are edited copies of the nuclear genes, and RNAi stops them from delivering their messages. Like antisense inhibitors, RNAi doesn't simply mop up or destroy the harmful proteins that cells produce—RNAi drugs can actually prevent these proteins from ever being created. Or if you can duplicate the RNA found in a virus like hepatitis C, voilà, a new way to knock down viral replication.

RNA interference burst into the consciousness of the scientific world at the annual meeting of the RNA Society in Banff, Alberta, in May 2001. There, Sayda Elbashir, a postdoctoral student in the lab of biochemist Thomas Tuschl at the Max Planck Institute for Biophysical Chemistry in Gottingen, Germany, stunned his listeners with the news that tiny double-stranded RNA fragments quickly, easily, and specifically turned off genes in human cells, a role researchers had never before seen RNA play. "Most of the audience was just sitting there saying to themselves: Science has just changed," said University of Michigan biochemist David Engelke in a recent issue of the magazine *Technology Review*.

The effect from RNAi is said to be far more powerful than existing silencing technologies, such as transgenic "knock-outs" in experimental mice and "antisense" drugs for human therapy. And that's what has people excited. The concept received another boost just this past month in a series of studies by Greg Hannon at Cold Spring Harbor Laboratory in New York that have shown that RNAi can be used to regulate the level of gene activity in cancer. And in yet another recent study published in *Nature*, researchers at Harvard and Massachusetts General Hospital used RNA interference to turn off almost all of a worm's genes, one at a time, to discover those linked to obesity.

Doctors hope that RNA interference will one day be used for medicine, inactivating genes, say, in tumors or viruses. Scientists have recently reported that Prader-Willi and Fragile X syndromes, each leading to mental retardation and chronic lymphocytic leukemia, may be linked to RNA defects. Biologists studying other species are also looking to RNA for answers to unsolved mysteries. It seems that one function of this RNA defense is to attack suspicious gene sequences that might have come from viruses or other genetic parasites, rather like the way the body's main immune system attacks suspicious proteins—or the way policemen pull over cars going suspiciously fast.

As the publication *New Scientist* recently detailed, scientists stumbled upon RNA interference entirely by accident, like many other remarkable discoveries. A decade ago, Richard Jorgensen, now at the University of Arizona, and Joseph Mol, working independently at the Free University in Amsterdam, were experimenting with genes for flower color in petunias. Both of them gave the flowers an extra copy of a gene coding for a purple pigment, expecting to produce a more intense color. But often the flowers were simply white, suggesting that the extra gene not only "played dead" but somehow stopped the plants' original pigment genes from working.

Doctors hope that RNA interference will one day be used for medicine, inactivating genes in tumors or viruses

This discovery left the teams scratching their heads. Adding more genes should only boost the levels of protein encoded by those genes, making the flowers deeper purple, not white. Meanwhile, flowers weren't

the only organisms flaunting their disregard for genetic theory. Other researchers working on mold and tiny soil worms were also finding that adding extra genetic DNA, or even just incomplete RNA copies, could actually result in less gene activity.

Scientists are talking about RNAi as the most important biotech discovery of the past decade

The researchers were stumped. Their findings completely contradicted every tenet of textbook biology. It's supposed to work like this. But Jorgensen's peculiar petunias gave the first clues that there could be more to RNA than its presumably simple role. Researchers realized that when they added a gene to a cell, any of the cell's own genes that had a similar sequence got shut down. It turned out that the messenger RNA from these genes was being destroyed before it could be used to make a protein. The flow of information from DNA to protein was being blocked, but no one knew how or why.

A big breakthrough came four years ago from Andrew Fire at the Carnegie Institute of Washington in Baltimore and a team at the University of Massachusetts. They discovered that a potent trigger for this gene shutdown was double-stranded RNA—two strings joined together just as they are in the DNA double helix. Most cells have only single-stranded RNA, but some viruses have the double-stranded variety. Suddenly the cell's motivation was perfectly clear: it thought it was under attack and was trying to close down the supposed invader's genes. In the ultimate application, small interfering RNAs might themselves be drugs: rather than blocking a particular protein, as standard drugs do, RNAi would prevent the protein from ever being made.

Antisense vs. RNAi Technology

As we've already mentioned, if RNAi sounds familiar to our readers, it very well should. It is the basic concept behind antisense technology and one of our favorite companies, ISIS. Let's say you know the gene that codes for the production of a protein involved in diabetes. You design an antisense compound to attach to the specific messenger RNA coded for by that gene, thereby preventing the production of proteins involved in the disease. In that way, antisense technology also uses synthetic DNA or RNA—called *oligonucleotides*—to block the production of faulty proteins. These custom-designed compounds are called antisense drugs because their molecular structure is the opposite of the "sense" or pattern of the original mRNA. The goal of the resulting antisense is to treat disease by blocking the activity of specific genes associated with a given condition.

Whether RNAi will trump antisense, or, more likely, if it will suit different or perhaps complementary therapeutic purposes still remains an open question. The antisense people insist that there really aren't any advantages to the RNAi approach. The difference between RNAi and antisense is that antisense tries to thwart RNA by saturating the body with dummy RNA. In contrast, RNAi works by tricking the body into destroying it. Toxicity is the main reason some people find RNAi more attractive than antisense. Naysayers argue that the toxicity to small-molecule antisense drugs arises from lack of specificity to protein and gene targets, respectively, as well as from poorly understood mechanism-related effects.

Scientists are talking about RNAi as the most important biotech discovery of the past decade because it gives them, for the first time, a quick and clean way of silencing specific genes—and stopping them cold from producing their disease-causing proteins. It's clear to everyone that RNAi promises to be a vital tool for research and development. What's less clear is whether it will be a source of a new class of drugs, particularly to treat cancer and viral disease. In principle, viral disease could be cured without side effects by silencing a gene that is essential for viral replication inside human cells. And many tumors are caused by viral genes incorporated in the human genome; if RNAi can silence the genes, it should stop the cancer.

Clinical trials to discover how well RNAi works in practice could start as early as next year. **Ribopharma**, a German company, is talking about testing RNAi drugs on patients with hepatitis C, glioblastoma (a brain tumor), or pancreatic cancer. Last year Nobel Prize winner Philip Sharp co-founded **Alnylam Pharmaceuticals**, based in Cambridge, Massachusetts, raising a whopping $17 million in start-up venture capital, to pursue RNAi-based therapies for cancer, viruses, and autoimmune diseases.

Ribozyme is yet another company taking up the challenge and is one of the few publicly traded companies to dedicate itself to this space. Recently,

Ribozyme staved-off insolvency after a consortium of venture capital investors agreed to invest $48 million in its RNA-interference technology. Howard Robin, Ribozyme's chief executive, said the PIPE (Public into Private Equity) deal gave the company enough cash to take its first RNAi drugs into clinical trials, probably in 2005. The company's first targets look to be the hepatitis B virus and macular degeneration, an ophthalmic disorder.

In all, more than a dozen companies are dedicated, like Ribozyme, to finding therapeutics based primarily on RNAi. Another way to play this technology is through delivery systems. By far the most significant scientific and medical challenge for RNAi-based drugs is getting the stretches of dummy RNA into cells. It's a problem of delivery—how to get the active ingredients to the cells that need them.

Teams of scientists are working on the delivery problem, and experiments on mice indicate that RNAi treatment will be easier on organs that have a rich blood supply, such as the liver and the kidneys. Several companies are involved, many borrowing technology from antisense. About ten companies offer reagents for delivering RNAi. Unfortunately, if you like the concept of RNAi, you'll probably have to wait at least a year to make a significant investment in any of them, since most of the pure plays dedicated to this technology are still private. But with enthusiasm building for this new science, some of these same companies could go public soon. Therefore, we find it prudent to dedicate this issue to reviewing the marketplace and identifying some of the key players in this new technology. Even if we advise investors to stay clear of RNAi until these companies mature, the validation of this technology—in our opinion—buoys the case for RNA interference in general, and, especially, for ISIS Pharmaceuticals.

Ribozyme's Potential

As we've mentioned, Ribozyme is one of the leaders in the field of RNA-based therapeutics, and it's the only pure-play, publicly traded company in RNAi. So we'll begin our discussion with its prospects. Ribozyme's shares have fallen almost 95 percent in the past year as investors have shunned high-risk companies with few prospects of making a profit in the foreseeable future. Since then, the company has said it will abandon all its other research, including the eponymous area of ribozymes, to concentrate on developing treatments using RNAi.

The recent agreement Ribozyme struck for the sale of $48 million in company stock and in warrants to a consortium of venture capitalists, comprising The Sprout Group, Venrock Associates, Oxford Bioscience Partners, TechnoVenture Management, and Granite Global Ventures, takes Ribozyme through the end of 2005, and includes getting its first compound into the clinic with a phase 1 study. The deal calls for Ribozyme to sell about 145 million new shares at 33 cents per share. In addition, investors were also able to purchase five-year warrants for about 30 million shares of common stock with an exercise price of 42 cents per share. The venture funds' investment resulted in The Sprout Group taking the lead in the PIPE deal, with an investment of $22.5 million. Venrock backed Ribozyme with a $10 million investment, and Oxford Bioscience provided about $7.5 million. With the completion of this transaction, the company's investor group holds an 85 percent equity stake, according to *The Daily Deal*. All three venture funds now have representatives sitting on the company's board.

Ribozyme is still a start-up and needs more time to move its preclinical candidates along

Ribozyme's focus is on RNA-based drugs, and it currently has RNAi programs in hepatitis C and macular degeneration, with additional targets in diabetes, obesity, cancer, and central nervous system disorders such as stroke. But Ribozyme also has a phase 2 anti-angiogenesis drug Angiozyme for metastatic colorectal cancer in development with partner **Chiron Corporation** (CHIR), of Emeryville, California.

Last spring, Ribozyme reported that its phase 2 trial with Angiozyme against metastatic breast cancer failed to achieve a clinically significant response rate. Ribozyme stated that the RNAi funding doesn't affect the Angiozyme data, which have been submitted to the American Society of Clinical Oncology for presentation during its May meeting. But Ribozyme is reported to be "in discussions" with Chiron about how to proceed with the drug, and it is possible Ribozyme could divest itself of its angiogenesis program to focus squarely on RNAi. Recently, Ribozyme also suspended development of its lead compound, Heptazyme, a treatment for hepatitis C, after a disappointing phase 2

study. The company plans to develop another version of the drug that it believes will be more stable and efficacious, but we'd wait and see what happens.

Ribozyme has a lot of experience working with RNA and a lot of intellectual property in the RNAi space. However, the company has little to show for its expertise so far. In fact, there aren't any major Wall Street investment firms following the company. The last of the sell-side analysts who were covering Ribozyme, Fulcrum Partners, pulled out in August of last year. RZYM recently fell below the minimum requirements to continue its listing on the NASDAQ market so its listing was transferred to the small-caps. Yet all this isn't to knock the company.

On Wall Street, one read of Ribozyme's recent restructuring is that the company, desperate to survive, latched on to the "hot new technology" in order to raise more private capital. We believe that's too cynical. Ribozyme has long had expertise in RNA-based treatments, and RNAi is a relatively new concept that seems to be a natural fit for Ribozyme's scientific expertise. Moreover, there is a long history of biotech companies that refocused their scientific orientation as principles evolved—principal among them is **Gilead Sciences** (GILD), long one of our favorite companies. We believe that's the hallmark of a good, early-stage company. So Ribozyme's restructuring, alone, isn't reason to stay away from the company. But its dearth of clinical candidates is. The truth of the matter is that Ribozyme is still a start-up and needs more time to move its preclinical candidates along. Until it does, the stock isn't likely to move—we'd wait and watch for signs of progress before making any investments.

Alnylam's Buzz

Among the private companies that are furthest along in investing almost entirely in the development of new classes of highly specific drugs based on RNAi are: **Alnylam Pharmaceuticals**, **Cenix BioScience GMBH**, **Intradigm Corporation**, **Nucleonics, Inc.**, **Mirus Corporation**, **SomaGenics Benitec**, and **Ribopharma AG**. Of these private companies, the outfit currently attracting the lion's share of the capital and creating the buzz in scientific circles is Alnylam Pharmaceuticals.

In addition to its patents, Alnylam has some of the biggest names in RNAi research on its team

Alnylam is in its seedling stages: it had fewer than a dozen employees as of this past summer, but its founders claim exclusive license to develop therapeutic applications of RNAi patents filed by one of the leading research institutions in this field, MIT. Sources reported to the industry publication *In Vivo Start-up* that Alnylam filed a patent application on March 30, 2000, claiming use of RNA molecules of 21 to 23 bases pairs in length, synthesized or isolated from cellular extracts, and reintroduced to other cells for the purposes of inducing gene inhibition. The technology was reportedly taken in by Waltham, Massachusetts-based, Polaris Venture Partners and Atlas Venture Partners. Alnylam's interim CEO was Polaris Venture Partners' general partner Christoph Westphal, who built the team and helped raise a total of $17 million in venture capital from a group of venture firms. MIT and the company decline to say precisely what they've patented, but if they hold the kind of patents that are rumored, they'd be in a commanding IP position. Alnylam is focusing from the outset on developing therapeutics, using an approach that revolves around direct delivery of small interfering RNAs (called *siRNA*s) to block the coding sequences in genes that turn different pathologic states on and off—in other words, to thwart disease-triggering genes.

In addition to its patents, Alnylam has some of the biggest names in RNAi research on its team. Principal among them is Nobel Prize winner Philip Sharp. In July, researchers in his laboratory announced that they could slow down HIV at every stage of its life cycle by exposing cells with the virus to special siRNAs that they had cooked up. Paul Schimmel, an infectious disease expert who was a founder of **Alkermes** (ALKS) and **Cubist Pharmaceuticals** (CBST), is also with the start-up, as are three professors who've been pioneers in RNAi: Thomas Tuschl of the Max Planck Institute; Dave Bartel of MIT; and Phil Zamore, now of the University of Massachusetts Medical School and formerly one of the postgraduate students who Sharp set to working on RNAi. The team plans to develop drugs for oncology, infectious diseases, inflammatory disorders, and other conditions where it is possible to deliver RNA directly to specific tissues.

The history of drugs based on these so-called "naked oligos," essentially bits of DNA and RNA, is that they are very hard to deliver. The body has devel-

oped elaborate systems for recognizing foreign DNA and RNA and for destroying it. That's one of the questions that remains about RNA-based drugs—can they be taken systemically and reach their target tissues? For the most part, the RNA needs to be coated in something to protect it from being rapidly degraded. That's going to be the challenge for Alnylam, Ribozyme, and for many of the other companies working in this area. Not surprisingly, almost a dozen companies have sprung up to supply the technology for precisely this purpose. Many are similar to **Protiva Biotherapeutics**, which uses lipids to coat RNA and to increase its circulation time, theoretically allowing for the systemic injection of these products.

To see if bits of RNA can be turned into drugs, we'd keep an eye on developments at **Genta** (GNTA), which has its lead RNA-based cancer drug in phase 3 clinical trials, as well as on ISIS. Both focus on antisense drugs, and their general principles are similar. Thus, there could be some information gleaned from antisense drugs that would provide insights into RNAi, i.e., whether RNA-based drugs can remain stable long enough to carry out their therapeutic effect and whether they can reach a target of interest. Another drug to keep your eye on is an anti-VEG-F product by Eyetech Pharmaceuticals that's currently in phase 2 and 3 trials. The drug is essentially bits of chemically synthesized, short strands of RNA that are designed to inhibit VEG-F, a protein that causes abnormal blood vessel growth (angiogenesis). VEG-F is found in elevated quantities in the eyes of patients with age-related macular degradation and diabetic retinopathy. It's thought that leaky vessels lead to blurred vision, and the hope is that inhibitors of the protein will improve patients' vision.

Update on ISIS

Finally, we'd be remiss if we didn't take the opportunity in this RNA-focused report to update you on ISIS Pharmaceuticals. While Wall Street is focused, rightly so, on the company's lead drug Affinitak and its impending phase 3 trial results in nonsmall-cell lung cancer, investors should not lose sight of the fact that the company's broad product pipeline resulted in five positive phase 2 clinical trial results in 2002.

Indeed, ISIS has a total of ten drugs in development, nine clinical trials underway, and remains on track in its key programs. Some upcoming milestones this year include results from: the phase 2 trial of Affinitak in lung cancer; the use of ISIS 2302 (Alicaforsen) in ulcerative colitis; a phase 2 study of ISIS 2503 (an inhibitor of h-ras) in the treatment of several cancers; ISIS 104838 (a second-generation antisense inhibitor of tumor necrosis factor) in the treatment of rheumatoid arthritis and psoriasis; and the phase 2 trial of ISIS 14803 (an inhibitor of hepatitis C mRNA). ISIS also plans to initiate three phase-1 clinical trials this year for: ISIS 13650, an inhibitor of c-raf, for the treatment of diabetic retinopathy; ISIS 113715, a second-generation inhibitor of PTB-1B for the treatment of type 2 diabetes; and ISIS 10 107248, a second-generation inhibitor of VLA-4 for the treatment of multiple sclerosis.

The upshot: ISIS is more than just the results of Affinitak—although clearly much is riding on those results, not the least of which is ISIS's rising stock price. We expect the results of the phase 3 trial to be announced this month. It will be viewed on Wall Street as a litmus test for antisense, and, perhaps for RNA-based drugs in general. As you may recall from our previous July 2002 issue focusing on ISIS, Affinitak is designed to block a specific gene from producing a protein believed to play a role in cancer cell development and growth. Major drug firm **Eli Lilly & Company**'s (LLY) 2001 decision to co-develop the drug and commit $200 million in funding to Isis was regarded as a long-awaited stamp of approval for the field. But scientists have continued to debate whether antisense drugs can actually work by silencing gene activity. If the drug doesn't work, ISIS will take a significant hit in the public markets. Moreover, some recent reports have been spreading rumors that the trial has failed.

In the final analysis, we remain upbeat at the prospect for RNA-based drugs, but like all new technologies, we believe this one will take time to mature

The results are just weeks away. However, even if the trial fails, all is not lost. A more promising drug could be the company's antisense compound for Crohn's disease, for which a second round of phase 3 results are expected early next year.

In the final analysis, we remain upbeat at the prospect for RNA-based drugs, but like all new tech-

nologies, we believe this one will take time to mature. ISIS has taken that time and worked out some of the problems of its early antisense drugs. RNAi companies are just getting started down that long and bumpy road.

Scientists will have to work the kinks out of RNAi, and more than a few drugs are bound to fail along the way. Such is the story of biotechnology: new scientific concepts become hot long before they fully mature, only to find investors cool to the idea at the precise moment when new therapeutics are finally at hand.

Antisense: The Moment Has Arrived

We believe that the moment has arrived for antisense, a decades-old concept that was once the hot idea on Wall Street, but then cooled off considerably at the exact time when other interesting drugs appeared on the horizon. To the chagrin of early investors, this is the story of many investment paradigms. But the moment has not yet arrived for RNAi; it will remain an investment fad long before it becomes a successful drug. Follow the RNAi-focused companies closely, though, because the science is sound, and we believe it will one day bear fruit. There are bound to be a few busts along the way, but if you are willing to wait, there will be better times to buy this new paradigm.

Scott Gottlieb, M.D.
March 7, 2003

BIOTECH COMPANIES

COMPANY	TECHNOLOGY LEADERSHIP	REFERENCE DATE	REFERENCE PRICE	3/6/03 PRICE	52-WEEK RANGE	MARKET CAP
ABGENIX (ABGX)	ANTIBODY THERAPEUTICS	9/30/02	6.61	6.00	4.52 - 21.77	525.5M
CELL GENESYS (CEGE)	CANCER THERAPEUTICS	6/10/02	13.24	7.66	7.50 - 18.02	275.9M
COGENT NEUROSCIENCES (NONE*)	NEUROGENOMICS	5/2/02				
CURAGEN (CRGN)	CELLULAR SIGNALLING	3/13/02	17.67	3.60	3.20 - 18.40	177.5M
GILEAD SCIENCES (GILD)	RATIONAL DRUG DESIGN	12/05/01	33.88**	34.14	26.08 - 40.00	6.7B
HUMAN GENOME SCIENCES (HGSI)	CELLULAR SIGNALING	10/26/01	43.97	6.50	6.31 - 25.77	836.9M
IMPATH (IMPH)	GENOMIC DIAGNOSTICS	12/20/02	19.48	13.80	9.98 - 44.40	225.3M
ISIS PHARMACEUTICALS INC. (ISIS)	ANTISENSE THERAPEUTICS	7/9/02	7.30	4.44	4.22 - 18.00	244.8M
MDS PROTEOMICS (NONE*)	PROTEOMICS	2/05/02				
MILLENNIUM PHARMACEUTICALS (MLNM)	TARGETED DRUGS	11/29/02	10.01	6.73	6.24 - 25.55	1.9B
NANOGEN (NGEN)	BIOCHIPS	10/2/01	4.95	1.01	1.01 - 5.20	22.2M
OSI PHARMACEUTICALS (OSIP)	CANCER THERAPEUTICS	8/27/02	16.16	13.90	11.50 - 43.58	506.6M
QUOREX (NONE*)	RATIONAL DRUG DESIGN	12/05/01				
SEQUENOM (SQNM)	PHARMACOGENOMICS	1/09/02	9.00	1.62	1.25 - 7.66	63.8M
TRIAD THERAPEUTICS (NONE*)	RATIONAL DRUG DESIGN	4/9/02				
VERSICOR (VERS)	ANTI-INFECTIVES	10/29/02	10.00	10.85	7.65 - 20.30	286.2M
VERTEX (VRTX)	RATIONAL DRUG DESIGN	9/17/01	28.60	10.25	9.97 - 32.45	782.8M

* 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.