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# Helping Cancer Patients to Heal Themselves

**Rationally designed therapeutic vaccines are about to enable a new medical strategy that puts the power of the body's self-healing abilities to work and creates a new area of opportunity for investors.**

Lisa was recently diagnosed with breast cancer. In some ways, she was fortunate. Her tumor was diagnosed early, before it spread to the lymph nodes in her arms and chest. And unlike many of my patients, hers was one of the 30 percent of all breast cancers driven by the overexpression of a receptor called HER2, a receptor that produces a particularly aggressive form of cancer, but also one susceptible to **Genentech's** [DNA] powerful drug Herceptin. She's got options.

Herceptin is an artificially produced model of a naturally occurring immune cell called an *antibody*, designed to hone in on those HER2 receptors, binding and disabling them, effectively shutting down the signals that instruct cancers to grow. So for the last six weeks, Lisa has gone to her oncologist's office to get the 30-minute infusions of the miracle drug. She, like many such patients, has an excellent shot at a cure.

Herceptin is one of the best selling cancer drugs—the vanguard of a group of tiny Y-shaped medicines known as monoclonal antibodies. Like tiny divining rods, these molecules hunt down diseased cells and disable them, avoiding the shotgun approach to cancer treatment that was the hallmark of older drugs.

This kind of target selectivity is one of the main reasons why two of the top moneymaking cancer drugs are monoclonal antibodies: in addition to Herceptin, there's **Idec's** Rituxan, which was approved by the Food and Drug Administration in 1997 for the treatment of low-grade non-Hodgkin's B-cell lymphoma, a cancer that affects some 250,000 Americans and is notoriously difficult to treat. The cancer cells divide too slowly for chemotherapy to have much effect. (We'll be discussing Idec as well as other cancer treatment companies in the next issue of the *GBR*). The highly effective arthritis medicines Enbrel and Remicade are also mono-

Dr. Scott Gottlieb

"The key to cancer vaccines is antigens that can stimulate the production of disease-fighting immune cells."

## INSIDE:

clonal antibodies. Antibodies have been one of the extraordinary drug stories of the 1990s.

Herceptin and Rituxan are first-generation drugs, at the forefront of a plethora of treatments that will exploit elements of our body's own immune system to conquer cancer. When the immune system perceives a potentially harmful invader, it unleashes a variety of responses. Two of the most effective anti-tumor immune responses are achieved by stimulating T-cells (the cellular arm of the immune system) which can recognize and kill tumor cells directly, and B-cells (the humoral arm of the immune system) which can produce long-lasting immunity by unleashing the production of antibodies just like Herceptin and Rituxan.

It was once thought that the immune system actively prevented cancer by being constantly "on patrol." When cancer took hold, it was assumed that this surveillance had broken down, with the immune system losing the ability to distinguish between normal and cancerous cells. Since the immune system is primed to recognize foreign molecules called *antigens* but doesn't recognize cancer cells, researchers reasoned that cancer cells must not produce any antigens that can be seen by the body's immune cells. Today, however, we know that tumor cells do express antigens. With the right priming, they can be recognized readily by our immune system.

No longer are the immune cells regarded as bumblers that overlook a proliferating, but otherwise passive, enemy within. More likely, cancer grows because our anti-tumor immune responses are difficult to generate, regardless of the state of the immune system. Scientists now believe cancer cells employ strategies that actively throw immune cells off-track. No one knows for certain how these strategies work, but they range from camouflage and smoke screens to subversion and bait-and-switch.

The immune system's monumental task is to differentiate between normal cells and those infected by bacteria, virus, or cancer. It must have the ability to attack abnormal cells, but tolerate those that are normal. When that system fails and attacks normal cells, the results are nasty autoimmune diseases such as diabetes, Crohn's disease, and Lupus. To our immune system, cancer differs from normal cells in small ways—too small, it seems, to be marked for destruction.

For these reasons, the immune system has been a bit player in the fight against cancer, and scientists have been perplexed to find ways to bring it into the ring. We've had to settle for endogenous infusions of immune system elements. That's what Herceptin is, after all, a bagful of antibodies infused into a patient's blood—not because his body doesn't have all the machinery to produce the same antibodies on its own, but because we haven't figured out a good way to prime that machinery to bring it to the fight.

Treatments to boost the immune system to combat cancer can be broken down into two basic elements. Herceptin is an example of the first, dubbed passive immunotherapy, or the administration of antibodies directed against elements on the surface of particular tumor cells called antigens. "Passive" means the antibodies are produced in the lab rather than within the patient's own immune system. The good news is that monoclonal antibody therapy can work even if the patient's own immune system is too weak to produce antibodies on its own. The bad news is that these treatments need to be administered continuously and are costly and difficult to produce.

Such antibodies are called monoclonal because, unlike the cocktail of antibodies our body creates, they all do the same thing and react the same way to a particular antigen, which is nothing more than a piece of protein or carbohydrate on the surface of an "invader" cell. Once attached to its target cell, mon-

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oclonal antibodies can be engineered to either flag the diseased cell for destruction by a person's own immune system, or kill the cell outright by interfering with its growth or by punching holes into it.

Researchers spent more than 20 years doing the underlying work that brought monoclonal antibodies to the marketplace. The first monoclonals were produced in mice. But those drugs triggered rejection from human patients' immune systems, often resulting in life-threatening immune reactions.

By the 1980s, researchers had begun replacing parts of the mouse antibody with human antibody (replacing at least half of the mouse DNA) to ensure that the engineered antibodies would be better tolerated in humans. The first "humanized antibody" to reach the market, in 1994, was **Centocor Inc.'s** ReoPro, a clot-busting drug that reduces the risk of death during coronary angioplasty by 57 percent. ReoPro, half-mouse, half-human, is low-tech by current standards. Genentech's Herceptin, which came to market four years later, is 5 percent mouse, 95 percent human. And better versions are on the way.

Yet for all their potency, monoclonal antibody treatments are still a rather crude construct, infusing people with frequent and costly bags of antibodies that start breaking down the minute they enter a person's blood, requiring constant new infusions.

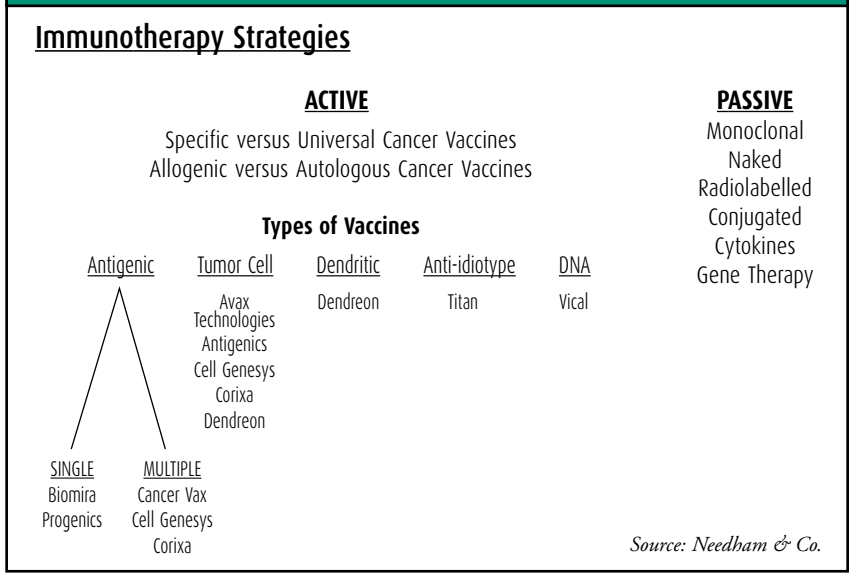
Why not simply teach the body's immune system to produce the same molecules on its own?

That's the basis of "active immunotherapy," wherein doctors administer proteins that "activate" a patient's own immune system. Active immunotherapy is behind all the strategies for developing cancer vaccines. But after two decades of trying, scientists have not brought one product to market. We believe that's about to change, thanks to a confluence of scientific discoveries.

Early approaches to cancer vaccines were plagued by poor science—we didn't have the right molecules that when placed inside a vaccine could trigger an immune response. That's changed with the advent of better scientific tools, particularly recombinant technology.

Recent progress has enabled the testing of 29 compounds by 20 companies for 22 different cancers. The vaccines used in these trials cover 90 percent of the addressable cancer market, and a few of these companies are on the verge of filing for FDA approval to market their products. The result is a potentially lucrative opportunity for investors and a powerful new medical strategy. Give a patient an antibody such as Herceptin through passive administration, and you will treat his cancer today. Teach his body to produce its own antibodies, and you treat his cancer for a lifetime.

**Immunotherapy Strategies: Many Different Approaches are being Studied under the Umbrella of Active Immunotherapy**




## Therapeutic vaccines

Like old-fashioned vaccines, therapeutic ones battle disease by tapping the body's own immune system. Unlike the earlier vaccines, whose mode of action against tumors couldn't be defined precisely, these rationally designed therapeutic vaccines attempt to provoke highly specific immune reactions. Although clinical trials with therapeutic vaccines are currently aimed at amelioration in the form of a few extra years of life rather than a cure, they could nonetheless prove a significant addition to the drug arsenal of the medical community, increasingly focused on the body's self-healing ability.

The key to cancer vaccines is antigens that can stimulate the production of disease-fighting immune cells. Tumor-associated antigens are structures (i.e., proteins, enzymes, or carbohydrates) that are present on tumor cells and relatively absent or diminished on

| Passive Immunotherapy Provides Strengths and Some Limitations | |
|---|---|
| **Benefits of Passive Immunotherapy** | Antibodies provide a speed of administration to achieve protective levels of antibodies. |
| | There is specificity of antibody action toward a tumor-associated antigen (thereby lowering the side-effect profile and increasing the effectiveness profile). |
| | Antibody products already present in the marketplace are well established. |
| **Limitations of Passive Immunotherapy** | There is a need for the therapy to be administered repeatedly, as the antibodies are cleared from the system. |
| | The manufacturing process can be long and costly, and capacity issues exist. |
| | Specificity could be a double-edged sword: if the tumor-associated anitgen (the target for the antibody) becomes "hidden" from the antibody, the therapeutic effects cease to occur. |

*Source: Needham & Co.*

| Active Immunization Provides Strengths and Some Limitations | |
|---|---|
| **Benefits of Active Immunotherapy** | The vaccine persists as a long-term theraperutic, based on the enhanced immune system of the patient producing T-cells and B-cells. |
| | The immune reaction to multiple antigens results in more heightened immune reaction against the patient's tumor. |
| | The vaccine can be either patient-specific (autologous approach with tumor sample from patient) or nonpatient-specific (allogenic approach with cells-in-a-bottle) therapy. |
| **Limitations of Active Immunotherapy** | No cancer vaccine products are currently approved in the market, and historical results have shown varying benefits. |
| | It takes time for the body to develop antibodies (B-cell) and cytotoxic T-cells (T-cell). |
| | The vaccine requires both humoral and cytotoxic response to provide maximum benefit. |

*Source: Needham & Co.*

normal cells, providing targets for the immune system to recognize and destroy. Through a variety of technological advances including recombinant DNA, it's possible to derive many of these antigens for use in vaccines, stimulating the immune system to recognize and destroy them.

In early tumor cells, an antigen is present on the surface. But as the tumor progresses, the antigen levels diminish until the body no longer recognizes the tumor as foreign. Some vaccines mimic the antigen so that the body will still fight the tumor even in its later stages. Another method involves invading the target cells and forcing them to produce more antigens themselves. The theory is that by changing the genetic structure of the diseased cells so that they start producing more antigens, the immune system will be enabled to attack them on its own.

These strategies are complicated by the insidious ability of tumors to hide from or confuse the immune system. Some cancer cells seem to mask the expression of antigens, rendering themselves invisible to the immune system. Others may overproduce antigens, releasing them like a fog that overwhelms the immune cells' detection system. Some malignant cells first produce one antigen, and when the immune system focuses on it, then switch to another. Evidence is also mounting that cancer cells even release substances which suppress the action of the immune system, or that some tumors produce cells that suppress the immune system. It's the task of immunotherapy to bolster the immune system and help it see past the smoke and mirrors.

As we've mentioned, most immune cells fall into one of two main camps: B- or T-cells. B-cells comprise about 25 percent of immune cells. They take their name from the fact that they develop and mature in bone marrow. Their job is to produce antibodies just like Herceptin. If all goes well, they're tailor-made to attach to an antigen on the target cell. Each B-cell can recognize only a single antigen, but once activated, a B-cell begins dividing and producing antibodies, churning out as many as 2,000 antibody molecules a second for several days. The antibodies are carried throughout the circulatory system, binding to their antigens upon contact. In this way, they inactivate and destroy viruses, bacteria, and toxins, or mark the invader for destruction by other immune cells.

There are some limitations. Antibodies, for example, cannot reach viruses that have invaded cells. That's one of the tasks of T-cells, which are capable of directly attacking the invader cells. One type of T-cell called a

natural killer cell releases toxins that punch holes in the invaders. Others engulf invaders and digest them.

It all sounds simple enough, but there's a hot debate among cancer vaccine makers about which of the two arms of the immune system to turn on for the best results—the one that relies on T-cells, which directly or indirectly kill tumors, or the one that banks on antibodies. While some have faith in cell-mediated immunity, a substantial number of scientists are genetically engineering vaccines that primarily produce an antibody response. A leading proponent of this strategy is Philip Livingston of the Memorial Sloan-Kettering Cancer Center. We believe the best vaccines combine a little bit of both.

Cancer vaccines come in two primary forms: allogenic and autologous. Allogenic vaccines represent the mass-produced antigens and can be made relatively cheaply. The hope behind these vaccines is that some commonly expressed antigens—similar to the prostate-specific antigen in prostate cancer—can be found on a large group of cancers and keyed in as a vaccination target.

The second variety is the autologous vaccine, the ultimate in personalized medicine. The vaccine is derived specifically from the tumor itself and produced exclusively for a single patient. Autologous vaccines require a sampling of the cancer from which the vaccine is then derived. Sounds cool, but it's difficult, expensive, and a regulatory black hole. This approach holds promise, but call us back when the FDA gives any indication that it's willing to sign off on these treatments.

**THERE'S A HOT DEBATE AMONG CANCER VACCINE MAKERS ABOUT WHICH OF THE TWO ARMS OF THE IMMUNE SYSTEM TO TURN ON FOR THE BEST RESULTS**

We like the antigenic approach. And more specifically, we like vaccines that try to stimulate both a cellular and an antibody response to a cancer. But before we get into that or our favorite company in this space—**Cell Genesys** (CEGE)—there are many ways to skin this cat, and you should be aware of all of them.

The intellectual property associated with these vaccines is not related to the cancer type, but to the specific way the immune response is stimulated. There are five different approaches being tried: 1) tumor cell vaccines; 2) anti-idiotype vaccines; 3) DNA vaccines; 4) dendritic cell vaccines; and 5) antigen vaccines.

Tumor cell vaccines can be produced using the patient's own cancer cells that are removed, killed, and then injected back into him in the hope that the antigens remaining on the dead cells will be recognized by the immune system, stimulating it to attack the live

**Elan Pharmaceuticals** [ELN] has announced that it will simplify its operations by focusing its resources where it excels: neurology.

This is what we predicted in the last issue of the *GBR*, and while the change was heralded even faster than we anticipated, we believe this is an overwhelmingly positive development. It bodes well for Elan's long-term prospects.

Elan announced that it will now focus its drug discovery efforts on pain management and traditional neurology like Alzheimer's, as well as multiple sclerosis. The company is also divesting certain noncore assets. Elan, which is under SEC investigation for its accounting practices, stated that the moves are in an effort to regain "its credibility with shareholders and other stakeholders."

Bravo. Elan also plans to acquire marketed products with a potential of greater than $100 million for the U.S. market and $50 million for European markets, but said their acquisition program will be tempered by their "objective to retain maximum financial flexibility and liquidity." Translation? They plan to hoard their cash.

While stock investors typically prefer that company's swing for the fences, we think Elan's newfound discipline and focus will serve its long-term interests well.

This should give renewed confidence to Wall Street investors who are concerned that any debt Elan carries could force the company into a cash crisis later this year. Husbanding cash will give them more flexibility to deal with it. One Wall Street investor we know who has a large position in that debt responded to this news by buying more of it. B

cancer cells as well. In an anti-idiotype vaccine, the administration of an antibody to a tumor antigen causes the immune system's B-cells to produce its own antibodies that should recognize the tumor cells. In a DNA vaccine, portions of DNA from parts of the patient's cancer cells are injected into the patient, which code for the creation of certain antigens found on those cancer cells. The immune system is supposed to respond to the ensuing antigen load by making T-cells that will attack the original cancer cells. Some other twists on this approach involve cloning known antigens into viral vectors or cloning them to be used as naked DNA vaccines.

**Cell Genesys Cancer Portfolio**

| Product | Status | Market (# of Patients) |
|---|---|---|
| GVAX Prostate | Phase II | 1 million |
| GVAX Pancreatic | Phase II | 30,300 |
| GVAX Lung | Phase I/II | 135,000 |
| GVAX Myeloma | Phase I/II | 50,000 |
| GVAX Leukemia | Phase II | 30,800 |
| CG7060 Oncolytic Virus (prostate) | Phase II | 1 million |
| CG7870 Oncolytic Virus (prostate) | Phase I/II | 1 million |
| CG7890 Oncolytic Virus (colon) | Preclinical | 107,000 |
| CG8900 Oncolytic Virus (liver) | Preclinical | 16,600 |
| CG8840 Oncolytic Virus (bladder) | Preclinical | 56,500 |

The fourth approach focuses on the role of the dendrite. This immune system cell is found in small numbers in the body, but it's recently been discovered to be a main player in the immune response. Dendrite cells work by breaking off the antigens from the cancer cells and digesting them into smaller pieces. These pieces are then processed and presented to other cells that comprise the immune system. The end result is the stimulation of the T- cells, which go on to destroy cells containing the same antigens. T-cells can be nasty, hunting down cancer cells and secreting a toxic substance that eats it into little pieces. Because dendrite cells work by showing the T-cells the antigen they should go after, they're often called "antigen presenting cells."

The stimulation of T-cells, which can directly recognize and kill tumor cells, provides one of the most effective defenses. But the T-cells don't do all of the killing themselves. They also activate the B-cell side of the immune system, which eventually stimulates the production of an antibody response. This is what gives us long lasting immunity to the viruses we encounter. The T-cells clear the infection, but they leave behind a pool of B-cells capable of producing antibodies at a moment's notice should our body encounter the same virus again. Some of these B-cells, dubbed memory cells, can last decades—remaining on guard to secrete a deadly load of antibodies if they ever encounter the same pathogen again.

While we think most of the approaches being taken with the dendrite cells are clumsy (they require doctors to take out your dendrite cells, manipulate them, and then re-infuse them into your body) we do like the idea of stimulating both arms of the immune system. For these reasons, we like the fifth approach, antigen vaccines. We are particularly fond of a company called Cell Genesys, which has technology that combines elements from both antigenic and tumor cell strategies to create vaccines that stimulate the full complement of the immune response.

Under the antigenic approach, patients are injected with some of the original antigen found on the surface of cancer cells, inactivated, of course, so it won't cause any more disease. Sometimes it's a synthetic copy of the antigen. Sometimes it's the real thing. This same crude concept underlies many of the childhood vaccines to which we've become accustomed.

## Promising phase 2 results

Cell Genesys's vaccines are created for the treatment, not the prevention of cancer. Their flagship products, their line of GVAX cancer vaccines, are made up of lethally irradiated tumors cells that are genetically modified to secrete an immune stimulating protein known as *granulocyte-macrophage colony stimulating factor* or *GM-CSF*. The immune response that the vaccine generates is meant to persist following surgery, radiation therapy, or other cancer treatments. The goal? Maintain remission and prevent new cancers following more traditional treatments.

Cell Genesys recently reported outstanding results with one of those vaccines at the recent meeting of the American Society of Clinical Oncology—a phase 2 study of GVAX in prostate cancer (70 percent survival at the 2.5 year mark, compared to standard of care of approximately 12-month survival). The data represented the third set of positive results for the prostate cancer vaccine. Patients not only lived longer cancer-free, they mounted an effective T-cell and B-cell response to

the cancer, suggesting the vaccine works as advertised. That's welcome news for the one million men in the United States suffering from prostate cancer.

Recently, the company also began a phase 2 trial with its GVAX vaccine in the treatment of pancreatic cancer, the fourth leading cause of cancer death in the United States, not because it's common, but because it's so universally fatal. An estimated 30,300 Americans will be diagnosed with pancreatic cancer in 2002, and 29,700 will die from the disease. In a phase 1 trial, the vaccine showed prolonged, disease-free survival in three of eight patients treated with high doses of the vaccine. Admittedly, it was a small trial, so it's difficult to draw any definite conclusions. But these were patients with highly aggressive, end-stage tumors. All should have died years ago, and three are still alive.

Given all these results, Cell Genesys is starting to generate some well-deserved attention on the Street. All totaled, the company has seven products under clinical development for the treatment of lung cancer, prostate cancer, pancreatic cancer, leukemia, and multiple myeloma. Moreover, Cell Genesys has $230 million in cash and about 9 million shares of Abgenix stock valued at more than $100 million. That should be more than enough cash to support multiple phase 3 trials over the next year, and puts Cell Genesys among the growing number of companies that are trading near cash value.

Cell Genesys also has some other products in its portfolio besides the GVAX line, including a gene therapy program that uses viral vectors to attack cancer, and an early-stage autologous cancer vaccine program. We believe some of these are interesting technologies, but we're not assigning them any value just yet. According to some institutional investors we spoke to, neither is Wall Street, for that matter. In the near term, the company's valuation will clearly rise or fall with its results from the trials of its lead vaccine in prostate cancer.

Not a believer? We can't blame you. So far, there's been a lot of money spent on cancer vaccines with little to show for it. Many doctors are skeptical, too. The other day I was treating a patient with metastatic kidney cancer who was having a piece of his tumor removed so doctors could make him a personalized cancer vaccine. Another doctor mumbled to me: "Doesn't work, you know." In the wake of spectacular blow-ups like Biomira and Corixa, many of the believers have been shaken out of the marketplace. So prices are also low.

**Cell Genesys's Upcoming Milestones for 2002**

Initiate second phase 1/2 trial for GVAX pancreatic cancer vaccine
Initiate lung cancer GVAX vaccine phase III trial
Report data from the phase 1/2 GVAX myeloma vaccine study
Report preclinical cancer data from oncolytic virus program at AACR
Initiate phase 1/2 trial for CG7060 for prostate cancer
Initiate phase 1/2 trial of CG7870 in combination with taxotere
Complete construction of two manufacturing facilities in California and Tennessee

Eventually one of these vaccines is going to work spectacularly and redefine the way we treat cancer. We believe it might just be a vaccine developed by Cell Genesys. The results have been more than encouraging. Their phase 2 data is unusually strong. And while blow-ups in phase 3 trials have been common, this technology represents the future of cancer care.

Also remember that most of these vaccines are being tested on end-stage cancer patients who already have depleted immune systems. So it's particularly hard to jump-start them. But once marketed, real users of these vaccines will be patients with early cancer, who have stronger immune systems and are much more likely to mount a strong response to a vaccine. For these reasons, we believe the results for a vaccine that eventually makes it to the market could be revolutionary.

We're also reminded of antibody therapy, which got its start in the 1970s with some research breakthroughs in academia. However, it was marred by some disappointing results that sunk more than a few companies in the 1980s and didn't make it to commercial success until the late 1990s. Cancer vaccines have gone through their own fits and starts for more than a decade now. This is the nature of biotechnology. But we now know that antibodies effectively combat cancer, and for this reason we also know that immunotherapy in cancer care works. The first companies to strike gold will be those like Cell Genesys that are developing vaccines to effectively generate both a cellular and an antibody response.

So look to the future. Because the immune system is more likely to be overwhelmed and ineffective when matched against a large number of tumor cells, vaccines are probably best used in combination with

traditional chemotherapy, with the vaccine used to prevent new malignant cells from forming.

Increasingly, cancer will be treated not as an acute event to be dealt with just one time, but as a chronic illness. Antibody therapy patients like Lisa will have to return every few weeks or months for hour-long infusions of the cocktail. That's twentieth-century medicine. The twenty-first-century alternative is a cancer vaccine by Cell Genesys that jump-starts both arms of the immune system, enabling the body to fight its own disease. Lisa comes in once every four months for a simple injection. It's cheap, it's quick, and it's going to redefine the way we treat this disease.

Scott Gottlieb
June 10, 2002

## BIOTECH COMPANIES

| Company | Technology Leadership | Reference Date | Reference Price | 5/31/02 Price | 52-Week Range | Market Cap |
|---|---|---|---|---|---|---|
| Cell Genesys (CEGE) | Cancer Therapeutics | 6/10/02 | 13.24 | | 11.75 - 25.02 | 459.1M |
| Cogent Neurosciences (none*) | Neurogenomics | 5/2/02 | | | | |
| CuraGen (CRGN) | Cellular Signalling | 3/13/02 | 17.67 | 8.09 | 6.76 - 41.34 | 332.9M |
| Elan Corp. (ELN) | Neurogenomics | 5/2/02 | 11.15 | 9.86 | 8.75 - 65.00 | 3.6B |
| Gilead Sciences (GILD) | Rational Drug Design | 12/05/01 | 33.88** | 35.66 | 22.85 - 39.00 | 6.7B |
| Human Genome Sciences (HGSI) | Cellular Signaling | 10/26/01 | 43.97 | 17.25 | 13.85 - 77.00 | 1.94B |
| MDS Proteomics (none*) | Proteomics | 2/05/02 | | | | |
| Nanogen (NGEN) | BioChips | 10/2/01 | 4.95 | 3.05 | 2.60 - 10.60 | 60.6M |
| Quorex (none*) | Rational Drug Design | 12/05/01 | | | | |
| Sequenom (SQNM) | Pharmacogenomics | 1/09/02 | 9.00 | 4.89 | 3.91 - 18.70 | 155.3M |
| Triad Therapeutics (none*) | Rational Drug Design | 4/9/02 | | | | |
| Vertex (VRTX) | Rational Drug Design | 9/17/01 | 28.60 | 19.73 | 15.50 - 52.25 | 1.4B |

* 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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