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Defending Against Biowarfare and Disease

A patient of mine, I'll call her Lisa, would have died if it were not for a relatively old drug called Acyclovir. She had a rare autoimmune disease that obligated her to a lifelong regimen of drugs that depleted her natural immune system. The drugs kept her disease at bay, but they also set her up for the worst kinds of infections. And as a second grade school teacher, there was no shortage of contracting illness from the many contacts in Lisa's life. So, when she came in to the hospital at ten in the evening complaining of a headache, fever, and nausea—with small blisters all over her body and her face—I knew what I was looking at. Lisa had chickenpox.

Acyclovir wasn't designed to treat chickenpox, any more than it was designed to treat smallpox. But the best drugs often share this kind of versatility. Acyclovir, and a host of other antiviral agents, would all be available to us in the event of an attack with a viral bioweapon like smallpox. That's the good news. With the ready availability of these drugs, many of which have shown excellent activity against smallpox in test tube studies and even in live animals, we can expect the death and suffering from a deliberate attack to pale in comparison to that which older generations had to contend, when doctors could offer patients little more than supportive care.

The bad news is that these antivirals aren't magic bullets. They weren't designed to target smallpox. It just so happens that they work. Since most bugs turn on a few basic mechanisms, a wrench in one bug invariably hits some of its cousins. But there's a growing awareness in Washington that we need to design treatments deliberately for these diseases to couple with our vaccines. New legislation that dangles carrots before private industry to find cures could, in time, create a viable market and an inescapable opportunity for companies that own the right technology.

Where are these treatments likely to originate? In the case of smallpox, some of the same drugs designed to treat AIDS, like Cidofovir, developed by Gilead Sciences [GILD], seem to work. Newer versions, targeted specifically for smallpox, could be even better. And consider anthrax, where antibiotics like Cipro are usually little help after a patient has become seriously ill, since it doesn't neutralize the deadly toxin that the bug releases. This toxin is the bug's real killer, triggering systemic inflammation, eventually suffocating its victims by causing fluid to build up in their lungs. Cipro needs to be given before the bacteria release the toxin. Last October we got lucky since we knew who had been exposed. Cipro was handed out early to the victims, yet five of the eleven people with full-blown anthrax still passed away.

An effective antidote would disable the toxin as it coursed through a victim's blood, turning anthrax into a nuisance, not a killer. Metalloenzyme inhibitors failed as experimental cancer drugs but

Dr. Scott Gottlieb

"Antibody drugs have the potential to treat an enormous range of diseases, from cancer to heart disease and arthritis."

INSIDE:

Therapeutic Antibodies on the Market

DRUG NAME	MAKER	INDICATION	SALES($MIL.)
Campath	ILEX	B-CLL	$27.0
Herceptin	Genentech	Metastatic Breast CA	$346.6
Mylotarg	Wyeth	CD-33+ AML	N/A
Orthoclone	Ortho Biotech	Renal transplant rejection	N/A
Remicade	Centocor/J&J	RA, Crohn's	$721.0
ReoPro	Centocor/Eli Lilly	Acute Coronary Syndrome	$431.0
Rituxan	IDEC/Genentech	Relapsed NHL	$818.7
Simulect	Novartis	Renal transplant rejection	N/A
Synagis	MedImmune	RSV	$516.0
Zenapax	PDL/Roche	Renal transplant rejection	$69.6
Zevalin	IDEC/Schering AG	Relapsed NHL	N/A

appear to disable the toxin. These drugs are currently sitting on the laboratory shelves of a number of biotechnology companies including British Biotech [BBIOF.PK]. So are some monoclonal antibodies drawn from the same technology that turned medicines like Remicade and Enbrel into arthritis cures. Antibodies are also being targeted against other feared bioweapons, such as the Ebola and Marburg viruses by biodefense drugmaker EluSys Therapeutics, Inc. But all of these drugs remain on laboratory shelves, unavailable if we're attacked with biowarfare. That could change quickly if incentives now being considered in Congress become law.

Abgenix to the Rescue

Abgenix, Inc. [ABGX] is among a handful of companies working with the U.S. Defense Department to develop antibodies to the anthrax toxin. We're longtime fans of Abgenix, the leader among companies in the antibody space, and, indeed, among its industry peers. It could remain newsworthy in the next year for a variety of clinical programs. This is an opportune time to take a closer look.

Abgenix has been able to leverage its core expertise in the production of humanized monoclonal antibodies to earn near-term licensing revenue from other companies seeking to develop antibodies to their own disease targets. At the same time, Abgenix has entered into a series of agreements in which it extracts intellectual property from other companies in exchange for making its antibody-producing mice available to them.

One of these deals is with CuraGen Corporation [CRGN], another company whose stock is down due to overall market sentiment, but for which we have high hopes. The two companies have joined to commercialize genomics-based antibody drugs using the Abgenix XenoMouse technology and CuraGen's suite of functional genomic technologies. The goal of the collaboration is to develop antibody therapeutics against CuraGen's most promising antibody drug targets.

Antibodies are the essence of highly targeted molecular medicine. Like tiny divining rods, monoclonal antibodies hunt down diseased cells and disable them directly, avoiding the shotgun approach to cancer treatment that was the hallmark of older drugs. Antibody drugs have the potential to treat an enormous range of diseases, from cancer to heart disease and arthritis—with fewer side effects than traditional medicines. They put our own immune system to work instead of blasting the body with drugs that affect the whole system. This kind of selectivity for their targets is why two of the top money-making cancer therapies are monoclonal antibodies: in addition to Herceptin for breast cancer, there's Rituxan, which fights low-grade non-Hodgkin's B-cell lymphoma, affecting some 250,000 Americans and notoriously difficult to treat (the cancer cells divide too slowly for chemotherapy to have much effect). The highly effective arthritis medicines Enbrel (by Immunex, now part of Amgen, Inc. [AMGN]) and Remicade (by Centocor, Inc. [CNTO.PK] now part of Johnson & Johnson [JNJ]) are also monoclonal antibodies.

Harnessing the powers of the body's disease-fighting immune system has long been a goal in the world of medical science. When the immune system perceives a potentially harmful invader, it unleashes its own variety of antibodies—substances that have a unique way of finding and attacking the invader. Scientists Georges Kohler and César Milstein created the first genetically engineered antibodies in 1975. Nearly a decade later they won a Nobel Prize for their work. They first created an immune reaction in mice; then they cloned the immune cells from those mice that

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contained antibodies, fusing the immune cells with cancer cells (so they'd become immortal), producing endless streams of highly targeted antibodies.

Room to Run

While we believe a far more elegant approach to generating antibodies is through the administration of therapeutic vaccines, stimulating the body to produce them itself, there are many clinical circumstances where this isn't possible. For example, patients with depleted immune systems probably can't mount an effective antibody response. Sometimes it's also impossible to create the right mixture of immune-stimulating antigens for a vaccine. In these cases, the only way to deliver the antibodies to a patient is to administer them intravenously.

Antibodies are also the low-hanging fruit of genomics—it's generally easier to make an antibody drug than a small molecule that can be taken in the form of a pill. Eventually, medicine will turn away from antibodies—they're expensive and difficult to administer—since they need to be given intravenously. But these marvelous medicines still have a lot of room to run before they become obsolete. And some of them, for reasons we still don't understand, seem as if they'll never be supplanted by small molecules. The pills just don't work the same way.

The first therapeutic antibodies were called monoclonal because, unlike the cocktail of antibodies our body creates, these antibodies all do the same thing and react the same way to a particular *antigen*—a piece of protein or carbohydrate on the surface of an "invader" cell. Best of all, scientists could make lots of them. This is not an overnight success story: researchers spent more than 20 years doing the underlying work that led to the arrival of monoclonal antibodies in the marketplace.

Monoclonal antibodies were produced in mice because it was comparatively easy to do so. But the drugs triggered rejection from human patients' immune systems, which recognized them as foreign proteins. The result was that patients who received them often suffered life-threatening immune reactions. By the 1980s, researchers had begun to humanize the antibodies by replacing parts of the mouse antibody with human antibody, which ensured that the engineered antibodies would be better tolerated in humans. In effect, scientists re-engineered the antibodies to look more familiar by replacing at least half of the mouse DNA with human DNA.

Mighty Mouse

The first of these "humanized antibodies" to reach the market, in 1994, was Centocor's ReoPro, a clot-busting drug that reduces the risk of death during the coronary procedure angioplasty by 57 percent. ReoPro—which is half-mouse, half-human—was still low-tech by current standards. Genentech's [DNA] Herceptin, which came to market four years later, is 5 percent mouse, 95 percent human. And better versions are on the way. Currently, there are nine monoclonal antibodies on the market generating sales of more than $2 billion.

MONOCLONAL ANTIBODIES ARE BEING ENGINEERED TO ADDRESS THE CELLULAR IDIOSYNCRASIES OF DIFFERENT CANCERS—DESIGNER DRUGS TAILORED TO THE UNIQUE PROFILE OF A PERSON'S TUMOR

The innovation that Abgenix brought to the industry was a better way to make these antibodies fully human. Abgenix effectively shares a duopoly on transgenic mice that makes human antibodies with Medarex Inc. [MDRX]. Both firms license their technologies on an antigen-by-antigen basis, but they are building more value by deploying the methods on their own behalf in proprietary drug development programs and through 50/50 deals with companies willing to share targets and development costs. But the early lead Abgenix had, its integration of an in-house genomics effort to discover novel targets, and its savvy at striking the best deals to get its hands on the most interesting ones have made it a market leader in its space.

Selected Deals to the Abgenix XenoMouse Technology

COMPANY	MAXIMUM POTENTIAL PAYMENTS ($MILLIONS)
Abbot Labs	$7-$10
Agensys, Inc.	$175-$250
Amgen	$15-$25
AVI Biopharma	$7-$10
BASF	$7-$10
Biogen	$105-$150
Celltech	$17
Centocor	$20-$30
Chiron	$15-$25
Corixa Corp	$5-$10
Corvas International	$20-$30
CuraGen	$7-$10
Diabetogen Biosciences	$15-$20
Dyax Corp	$7-$10
Elan Corp	$7-$10
Genentech	$120
Human Genome Sciences	$15-$25
ILEX Oncology	$7-$10
Immunex	$15-$20
Lexicon Genetics	$10-$20
MDS Proteomics	NA
Millennium Cell	$100
Pfizer	$100
Schering-Plough	$7-$10
GlaxoSmithKline	$7-$10

The company's core technology is its engineered mouse called the XenoMouse that's capable of producing 100 percent human antibodies. To create the mouse, all the genes in the mouse genome for producing mice anti-

bodies are disabled and replaced with human antibody-producing genes. The XenoMouse is a kind of mouse factory for producing human antibodies. The widespread belief is that these human antibodies will have a higher affinity for their cellular targets and won't elicit the immune responses that doomed earlier generations of monoclonal antibodies.

As the technology improved, each generation of monoclonal antibodies became more powerful, lasting longer and becoming increasingly selective for its target—destroying only diseased cells while leaving healthy ones alone. As a result, monoclonal antibodies are being engineered to address the cellular idiosyncrasies of different cancers—designer drugs tailored to the unique profile of a person's tumor. "You can go from gene discovery to therapeutic candidate in just a few months," says R. Scott Greer, founder and CEO of Abgenix.

Engineering Antibodies

How do monoclonal antibodies work? The concept of using an antibody as a drug is fairly simple. 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. The next step is to generate large quantities of the antibody that represent the particular antigen you're after. Manufacturing costs are often a negligible part of the price, but occasionally they can eat up as much as 20 percent of the retail take if you're dealing with a "replacement" antibody, the kind that needs to be infused into patients in large quantities to work. This is a problem that Immunex faces with Enbrel, which needs to be infused in patients in pints.

Once attached to its target cell, monoclonal 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. Other monoclonal antibodies are turned into delivery trucks for toxic payloads such as radiation-laden molecules or anti-cancer drugs. These substances are dumped into the diseased cell once they find it. They can be used to destroy the cell outright, in the case of chemotherapy, or mark the cell for destruction with a second medicine the patient takes. Cambridge, Massachusetts-based ImmunoGen Inc. [IMGN] has developed one such drug, using monoclonal antibodies as a transport vehicle for a toxic payload. Once the antibody finds and attaches itself to a cancer cell, the anti-cancer drug naytansine is released, delivering the drug directly and only to the cancer. This approach is quite different from the carpet-bombing technique of current cancer therapies such as chemotherapy and radiation. These therapies cause destruction all over the body and still may not rout the enemy. In contrast, monoclonal antibodies target only diseased cells.

Bioterrorism isn't a reason to own Abgenix, but we believe the application validates the technology. It also speaks to the very same reasons why antibody drugs pose fewer risks to investors than, say, the small molecule drugs that comprise the pills most people are accustomed to taking. They can be developed, and deployed, more quickly than small molecules. The pills usually need to pass through the liver to be metabolized into their active form. This is where things usually go wrong. Sometimes the drugs are metabolized too quickly. We believe this is what happened to Iressa, the highly touted cancer drug developed by AstraZeneca PLC [AZN] that recently failed to show any benefit in two phase 3 studies with lung cancer patients. Sometimes the drugs aren't metabolized at all; sometimes they end up destroying the liver. With antibody drugs, there are fewer questions since the drugs aren't dependent on the liver. They're injected in their active form directly into the bloodstream of patients. They either bind to their targets or they don't. There are fewer organs to get in the way, so there's less serendipity.

So is Abgenix the best technology for producing fully human monoclonal antibodies? We think so. There are technologies competing with the XenoMouse, including phage-display technology championed by Cambridge Antibody Technology [CAT] and Dyax Corporation [DYAX], as well as techniques for configuring human antibodies on computers from pieces of different antibodies, a process developed by Protein Design Laboratories [PDL]. While we're fans of companies that move experimental techniques onto computers, harnessing the accelerating processing power we enjoy, the technology is becoming a commodity that all companies, including Abgenix, now have. As for phage display, the jury is still out. It hasn't been used for any approved medicines. Clinical trials of antibodies produced with phage display are currently underway.

Phage-Display Technology

Because many readers have been inquiring about these technologies, they deserve some discussion. Phage display is a novel method of displaying proteins and peptides on the outer surface of a small bacterial virus known as a phage. Viruses have the capacity to display a gene product, or protein, on its surface. By engineering the sequence of a phage to include that of a specific protein, the protein becomes expressed on the outside of the bacterial virus (phage). Scientists can then use this system to select proteins that

bind to a specific target. For example, phage libraries can be constructed to screen the surface proteins against biological targets. Once these proteins are found, they can be grafted into antibodies. Bingo, you have an antibody engineered to precisely bind to the target you started out with.

The positive buzz about phage-display technology is that it's a fast way of generating antibodies that can be used to validate targets quickly and to create a starting point for developing a drug. That's a marketplace perception Cambridge Antibody Technology relishes, and one its competitors would like to dispel. On the downside, there's a belief that while the technology is a good research tool, it doesn't readily generate antibody fragments that are easily druggable. Phage display has been around for eight or nine years and has yielded far fewer drug candidates than transgenic mouse technology. Another criticism of CAT is that phage-display technology generally results in lower-affinity antibodies. They don't stick to their targets as well as the mouse antibodies do.

Ultimately, phage display is a far more scalable tool than developing antibodies in mice, but it's also become something of a commodity tool. Abgenix and Medarex [MEDX] both own some IP in the space and do their own phage-display experiments in-house to validate and refine their antibody products. For now, CAT hasn't been as adept at leveraging its tool to strike deals for good targets. It hasn't fully grown up yet into a drug discovery engine: it's still a tool company. Both Medarex and Abgenix continue to license their technologies to partners that will pay royalties, but their focus is also on their own products or on partnerships that allow them to keep more of the value they help to create. CAT is regarded as being further behind: its technology has been used more frequently for discovery-stage target-validation programs rather than for product development.

That's another reason to own Abgenix: it's the partner to have for companies with good targets to make antibodies for. So Abgenix ends up profiting from some of the industry's best deals. We believe that the antigen is the key to the success of an antibody in the clinic. Evidence is emerging that the mechanism of how antibodies achieve their therapeutic effects is far more complex than previously suggested. The more we know about an antigen target, the higher the probability that an antibody drug will succeed. Another good reason to own Abgenix is that it has its own in-house genomics discovery engine. As Abgenix gears up and gets smarter, a greater portion of its antibody drug candidates will come from targets it discovers itself.

Abgenix's Strategy

Abgenix has embarked on a three-pronged strategy to create value for investors. To compensate for its lack of clinical development expertise in some therapeutic areas and also to share clinical development costs and risks, Abgenix has entered into several co-development partnerships with biotech companies. This is the nature of its deal with CuraGen. Abgenix also has deals with Immunex and SangStat Medical Corporation [SANG].

In addition, Abgenix licenses its XenoMouse technology to pharmaceutical and biotechnology companies that use it to generate antibodies to their own proprietary targets. This allows Abgenix to collect licensing revenue as well as milestone payments or royalties if the products make it onto the market. Typically, Abgenix provides a licensee with engineered mice so the client can immunize the mice with their antigens to produce antibodies specific to these targets. Occasionally, Abgenix also takes clients' antigens and does the immunization and screening for additional fees. So far, the company has established a total of 30 licensing agreements with a variety of companies. (On average, it's likely to take 30 months to bring a drug to human clinical trials, and another eight years to bring a drug to the market.) But in 2001, Abgenix started to sign more co-development deals like the one with CuraGen, reflecting a change in the company's business strategy.

The third strategy involves the development and commercialization of its own proprietary antibody drugs. Abgenix has established a product pipeline that contains three humanized antibody drugs from cancer and autoimmune diseases, its two therapeutic areas of focus. Abgenix intends to take these products through phase 2 clinical trials and then partner them to pharmaceutical and larger biotechnology companies to get help with regulatory approval and commercialization and marketing muscle. It's also anticipated that Abgenix will file at least two additional new drug applications in the next two years with some of its preclinical compounds.

Abgenix is currently working with 50 different targets that have emerged from its own discovery efforts

The company's lead compound continues to be ABX-EGF, which it is developing in collaboration with Amgen Inc. [AMGN]. This monoclonal antibody is designed to inhibit the epidermal growth factor receptor. It's the same kind of drug as ImClone's [IMCL] Erbitux and similar to OSI Pharmaceutical's [OSIP] Tarceva and AstraZeneca's Iressa.

The EGFR receptor is over-expressed in a wide range of solid tumors, including colorectal, pancreatic, lung, prostate, kidney, and head and neck cancers. We believe the Abgenix drug could be more potent than Erbitux. For one thing, ABX-EGF works via a different mechanism than ImClone's Erbitux. It binds to a different epitope (or part) on the receptor. It's also demonstrated to be safe in the clinical trials that have been conducted so far with no serious problems to report. ABX-EGF is currently in five phase 2 trials for four tumor types: kidney, non-small cell lung, colorectal, and prostate cancers. Abgenix is conducting kidney and prostate trials and Amgen is handling the remainder.

At the meeting of the American Society for Clinical Oncology (ASCO) held in May, Abgenix presented preliminary phase 2 response rate data of ABX-EGF as monotherapy in refractory renal cell (kidney) cancer. A total of 88 patients were given eight weekly infusions of different doses of the drug. Three patients had a partial response; two had a minor response; and 44 patients had their disease stabilized. These are encouraging results, but perhaps the best data on the highest doses are still being compiled. We believe that the results from the second part of the study, where an additional 40 patients will be treated with two higher doses of the drug, will serve as the best indicator of the potential of ABX-EGF in this indication. The drug seems to work better at higher doses. Full phase 2 results are expected in the first quarter of 2003. Abgenix also gains from Martha Stewart's misfortune. The delay in ImClone's Erbitux has closed the timeline gap between the two drugs and provides Abgenix with a clearer development pathway for its own drug.

EGFR Over-Expression in Selected Tumors

TUMOR TYPE	% EXPRESSING EGFR	NEW U.S. CASES IN 2001
NSCLC	40%-80%	140,000
Renal	50%-90%	30,000
Breast	14%-91%	181,000
Ovarian	35%-70%	27,000
Glioma	40%-50%	15,000
Pancreatic	30%-50%	29,000
Head & Neck	80%-100%	30,000
Colorectal	25%-77%	131,000
Bladder	31%-48%	55,000
Esophagus/Stomach	30%-70%	35,000
Prostate	10%	209,000

Also watch for data from Abgenix's pivotal, single-agent, phase 2 refractory colorectal cancer trial, which could be available in late 2004— leading to a Biologics License Application (this is the application a company files with the FDA for approval to sell a new drug; it's commonly referred to as the BLA.) filing in early 2005 and product launch in the first quarter of 2006. Colorectal cancer, you'll remember, was the same indication that ImClone is after. In the United States there are about 45,000 colon cancer patients taking third-line therapy each year (the indication Abgenix is after). That's a market of about $675 million. The company's other initial indication will be kidney cancer. There are about 30,000 new cases of this cancer each year. ABX-EGF would likely be used first in patients who are refractory to more traditional treatments. This comprises a universe of around 15,000 patients annually, representing a market of around $250 million with a worldwide market about twice that size. Data from the phase 2 trial in renal cell cancer are expected by the end of 2005, with approval possible as early as 2006. In the best-case scenario, the product could then be launched for the kidney indication in the first quarter of 2007. In the prostate cancer indication, the phase 2 trial is designed to assess the safety and efficacy of the drug as monotherapy in patients with hormone-resistant cancer without spreading to other organs. The trial will enroll up to 50 patients.

Powerful Marrow

Among the company's two other clinical candidates, ABX-CBL is an antibody against CD147 (also called neurothelin) that is present on the surfaces of many immune cells. It is upregulated in activated B and T cells, which are part of the machinery responsible for immune responses. In bone marrow or stem cell transplant patients, activated immune cells from the bone marrow of donors sometimes attack the various organs in the transplant recipient. This process is called graft-versus-host disease or GVHD. One way to perceive this is that the immune system in the transplanted bone marrow is more powerful than the patient's own immune system. The transplanted bone marrow takes over, then recognizes the recipient as "foreign" and attacks him or her.

Because the binding of ABX-CBL results in destruction of the activated immune cells, the antibody is being developed as a treatment for GVHD in patients who have failed treatment with first-line therapy—which is typically ordinary steroids. The market for acute GVHD is relatively small. Each year in the United States, there are about 8,000 to 9,000 patients receiving allogenic stem cell transplants, and it's estimated that 30 percent of patients receiving stem cells from well-matched donors and 55 percent of patients receiving stem cells from less well-matched donors develop GVHD. However, the incidence of the condition is rising as more transplants are done. Still, the number of treatable patients is likely to be around 5,000 each year, giving Abgenix a total market of no more than $50 million to $75 million to aim for.

The company's third drug, ABX-MA1 is a humanized antibody against a cell-surface molecule called MUC18, or Mel-CAM (melanoma cell adhesion molecule). MUC18 is a protein belonging to the super-family of immunoglobulins that are present in aggressive, metastatic melanoma cells and prostate cells, as well as in smooth muscle and vascular wall linings. While its normal function is not well understood, it's been closely correlated with enhanced tumor growth. Disruption of MUC18 either physically, through the addition of an antibody to its surface, or functionally, through chemicals that alter the protein's enzymatic activity or shape, seem to prevent melanoma cells from becoming aggressive and metastatic, thereby stopping cancer development. Abgenix began a phase 1 trial in February 2002 in melanoma patients. Data from the trial should become available at the end of 2003.

Abgenix has also invested heavily in its own development programs to generate proprietary products. We believe this is a validated model that other biotechnology companies have successfully used—develop a core expertise (in this case production of fully human antibodies) and then use that technology edge as leverage in order to develop a proprietary pipeline of novel drugs. Abgenix is currently working with 50 different targets that have emerged from its own discovery efforts and 20 targets that it has captured from the public domain, in addition to its collaborations. The status of these programs has not yet been disclosed, but the company says it intends to move two additional drug candidates into human trials by the end of the year.

One of these preclinical candidates is a human antibody against the CD45 RB antigen, a form of the CD45 antigen that is found only in activated immune cells. Because activated immune cells are frequently invoked in autoimmune diseases, the antibody could be developed as a treatment for a broad range of autoimmune diseases from Crohn's to psoriasis to arthritis. Abgenix has said that it's in the late stages of preclinical development with this drug and could move it into the clinic by the end of the year, probably as a potential treatment for transplant rejection and inflammatory diseases. The company's other preclinical candidate is an antibody against the complement protein properdin. It's a potential treatment for cardiovascular and inflammatory diseases and is similar to drugs being developed by the biotechnology company Alexion Pharmaceuticals [ALXN]. The drug candidate was licensed from Gliatech, Inc. [GLIAQ.PK].

The CuraGen and Abgenix Arsenal

Throughout their five-year alliance, CuraGen and Abgenix intend to develop and test up to 250 fully human antibody therapeutic candidates, expanding upon their original agreement to develop up to 120 candidates. The antibodies are intended to treat a broad range of diseases, including metabolic diseases, cancer, inflammation, and autoimmune disorders. Under the agreement, CuraGen will work exclusively with Abgenix to develop selected antibodies. In exchange, Abgenix made an equity investment in CuraGen totaling $50 million. In addition, each company expects to eventually invest an additional $100 million to support the collaboration.

Abgenix Product Pipeline

DRUG	STATUS OF DEVELOPMENT
ABX-EGF	Phase 2
ABX-CBL	Phase 3
ABX-MA1	Phase 1
Anti-CD45 RB	Preclinical
Anti-Properdin	Preclinical

There's a risk worth noting: one of the reasons we like the company so much—its work on an EGFR inhibitor——is also its Achilles heel. Abgenix has a lot riding on that single drug, and so does its stock price. We figure the company would take at least a 30 percent hit if the EGFR paradigm faces a serious setback from here on out. Keep in mind, OSI Pharmaceuticals also has an EGFR blocker in development (Tarceva), so if you own OSI and Abgenix, you're betting big on this class of drugs. That's a bet we'd make. We're bullish on this class of drugs, for all the reasons we outlined in the August report. If you're looking to play the EGFR paradigm as an antibody drug, we believe the Abgenix drug trumps ImClone's. If you're looking to play it as a small molecule, we believe OSI Pharmaceutical's drug Tarceva trumps Iressa from AstraZeneca. Since Abgenix will be later to the market than AstraZeneca and perhaps OSI, it has less upside unless its drug proves to be more efficacious, but it also faces lower development risk. Another risk: Cell Genesys [CGEN] owns about 9 million shares of Abgenix, so if you're an owner of both stocks, beware that you have twice the exposure.

Washington planners know that the best time for a rogue regime like Iraq to use its bioweapons arsenal would be before we go to war, so Saddam Hussein can terrify the American people. Hussein's gamble would be that he could disrupt our systems enough to destabilize our effort. That's the near- term threat. But that threat won't go away when Saddam does. It will remain with us for many years, a realization Washington is warming to, and a reason why companies with the technology to combat these agents will have an important role in our national defense.

Milestones Expected in Next 12 Months

TIME	EVENT
1Q03	ABX-EGF Phase 2 renal cancer trial analysis
1Q03	ABX-EGF Phase 2 colon cancer results
1Q03	ABX-CBL Phase 3 results
2Q03	ABX-EGF Phase 2 prostate cancer results
3Q03	ABX-EGF Phase 2 NSCLC results

In its collaboration with the U.S. Army Medical Research Institute of Infectious Diseases, Abgenix is also developing fully human monoclonal antibodies against filoviruses, which include the Ebola and Marburg viruses. These pose a potential threat to U.S. security since they can be used as biological weapons. Recent data show that antibody therapy may be a viable means of treating a filovirus infection, including data from an outbreak in Zaire in 1995 that suggest an experimental antibody treatment may have helped save seven of the eight individuals who received whole blood from recovering patients who survived an infection of Ebola hemorrhagic fever. Doctors believe the antibodies lurking in the donor blood helped cure the infections.

Bioterrorism isn't the reason to own Abgenix, but we believe the Pentagon's interest in antibodies validates the best aspects of the technology: its broad applicability and its quick development cycles. Abgenix won't rise and fall on government grants for bioterrorism work. But its work in this field continues to demonstrate its technology lead and why antibodies will remain an important part of the medical arsenal.

Scott Gottlieb, M.D.
September 30, 2002

BIOTECH COMPANIES

Company	Technology Leadership	Reference Date	Reference Price	8/30/02 Price	52-Week Range	Market Cap
Abgenix (ABGX)	Antibody Therapeutics	9/30/02	6.61	6.49	5.61 - 38.16	577.5M
Cell Genesys (CEGE)	Cancer Therapeutics	6/10/02	13.24	11.57	10.48 - 25.02	413.0M
Cogent Neurosciences (none*)	Neurogenomics	5/2/02				
CuraGen (CRGN)	Cellular Signalling	3/13/02	17.67	5.81	4.50 - 25.88	284.4M
Gilead Sciences (GILD)	Rational Drug Design	12/05/01	33.88**	32.08	22.95 - 39.00	6.29B
Human Genome Sciences (HGSI)	Cellular Signaling	10/26/01	43.97	15.06	10.03 - 49.18	1.94B
Isis Pharmaceuticals Inc. (ISIS)	Antisense Therapeutics	7/9/02	7.30	10.12	6.10 - 27.15	549.5M
MDS Proteomics (none*)	Proteomics	2/05/02				
Nanogen (NGEN)	BioChips	10/2/01	4.95	2.16	1.56 - 10.13	47.4M
OSI Pharmaceuticals (OSIP)	Cancer Therapeutics	8/27/02	16.16	15.68	13.52 - 50.94	569.5M***
Quorex (none*)	Rational Drug Design	12/05/01				
Sequenom (SQNM)	Pharmacogenomics	1/09/02	9.00	2.43	1.71 - 11.44	91.4M
Triad Therapeutics (none*)	Rational Drug Design	4/9/02				
Vertex (VRTX)	Rational Drug Design	9/17/01	28.60	19.90	12.67 - 39.67	1.51B

* Pre-IPO startup companies. ** Split-adjusted price. *** Market cap as of 8/27/02.

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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