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The Anthrax Chronicles

Yes, biotech beats bioterror, but smart investors focus on the real biodigital bonanza: new antibiotics and antivirals.

The same day I rolled into San Diego's Burnham Institute, the news broke that anthrax had claimed another victim in New York City—a hospital worker. The Burnham Institute is a premier nonprofit cancer research center located not far from La Jolla beach (and right next to General Atomics, maker of the Predator drone now combing so sweetly through Afghanistan). I was there to see Robert Liddington, the Brit who has just become the first man to successfully crystallize the protein structure of so-called "lethal factor," a.k.a. the business end of the anthrax toxin.

The receptionist wore rubber gloves as she sorted mail. But Liddington—the principal of all of the Institute's recent attention—showed no anxiety. As we sat at a shaded outdoor table for more than an hour, he sipped hot tea, pausing laboriously between long sentences to catch his breath. "I have a terrible chest cold. I can't breathe well," he told me. "Anthrax?" I worried, half-jokingly. But he demurred. "I called my doctor and he said I didn't need Cipro." I had a blank prescription in my wallet. He didn't care.

Liddington has cause to be bold. He is a central actor in the development of biotechnology that will eventually neutralize anthrax, and perhaps a host of other bioterrors. While FBI agents scour the ground for low-tech terrorists, Liddington and other biodigital researchers are scouring the genome for the knowledge that will allow us to fight not only bioterrorism, but a host of other more deadly natural scourges.

If there are any more lurking anthrax terrorists, Liddington's achievement will translate into saved lives. Lying like dormant eggs, inhaled anthrax spores germinate one to six weeks later into living bugs. Within days they replicate wildly, dumping their deadly toxin into the blood. It wasn't the anthrax bacteria, but the poisons they released that killed Kathy Nguyen and the other anthrax victims. The lethal factor causes body organs literally to decompose; patients often bleed into their own lungs and drown. At that point, antibiotics won't work; killing the bugs after they've dumped toxins is just too little, too late. By the time doctors suspect inhalation anthrax, what we really need is an antidote, giving antibiotics time to kill the bacteria.

But what kind of antitoxin? This is where Liddington's work—and the new *in silico* tools that make it possible—come in.

By pinpointing the molecular structure of the lethal factor, Liddington saved researchers years of trial-and-error search. Instead of floundering around testing random compounds, for example, researchers (peering into the lethal factor's crystalline structure) suddenly remembered something potentially crucial: an old, failed anticancer drug developed a few years ago (called a metalloprotease inhibitor) targets a molecular on/off switch embedded in the lethal factor. Bingo! Trials are underway to test its ability to inhibit the anthrax toxin. Structural Bioinformatics, another San Diego in silico start-up, is using Liddington's 3D structure of the anthrax toxin to digitally design a drug that can, say, mop up the free-floating toxins in the blood or prevent the toxin from binding to human organs and doing damage.

INSIDE:

This is the promise of structure-based or rational drug design. Bioterrorists are dependent on bugs like anthrax that have been around for ages. Even the most advanced weaponized anthrax spores were made using technology developed by governments a generation ago. It is a characteristic of what President Bush calls evil-doers that they must borrow from free, creative societies to work their terrible acts of destruction. Could a bin Laden hiding in the caves of Afghanistan build, much less invent, a Boeing 757?

Beating bioterror is a small niche compared to huge new markets for antibiotics

Fear not. Biotechnologies of freedom will beat bioterror every time. The bioterror boomlet has boosted a number of biotech stocks. But beating bioterror, in itself, is only a small niche compared to the huge market for drugs that treat naturally occurring viruses and infections. Fortunately, the same techniques now garnering market attention as weapons against bioterror have a far larger application—and market—in defeating some of the most common, and increasingly deadly, bugs among us.

The antibiotic bottleneck

Not long after the first anthrax attacks I got a call from a big-city journalist friend of mine, call her Jane. She visited the ER with all the symptoms of flu—or early-stage inhalation anthrax. But at the hospital doctors refused to give her a prescription for Cipro or doxycycline, or any of the other antibiotics known to kill anthrax.

Why? Her doctors weren't worrying about Jane's health in particular. They were worrying (as doctors increasingly do) about public health, about antibiotic resistance. Many antibiotics no longer work against bugs they once slaughtered. Over time, bugs develop crafty ways to resist our current drug crop.

Yet most firms that make antibiotics are far behind the emerging in silico technology curve. The major pharmaceutical companies sink billions into information technology upgrades to develop "high throughput" robotic systems that speed the antiquated random drug-design model, helping Ph.D.s synthesize and survey increasing numbers of chemical compounds per week. In random testing, volume is everything. The more compounds you test, the more chances you have of stumbling onto a hit. But technological upgrades to conventional random drug design only boost productivity marginally, compared to rational drug design.

Conventional pharmaceutical companies find new antibiotic leads mostly by blind luck. They mix millions of different chemicals against Petri dishes seeing which ones kill infections, with little clue as to how they work in the human body. Scientist see what Petri dish do. Problem is, no matter how many times you stumble onto a hit, the Petri dish doesn't get any smarter. So conventional drug researchers keep making small changes to existing antibiotics, hanging a few atoms here and there and then retesting to see if the kill-ratio improves. The whole process wastes time and money. And even when they succeed, researchers always have to start from scratch. Why does this particular drug work? The petri dish can't say, and so neither can the scientist.

Big Pharma is married to this flawed process—especially in antibiotics. All known antibiotics are aimed at the same 30 molecular targets. Most are found by sifting through soil to find bacteria or fungi that naturally kill rival microbes, so even the very latest antibiotics are familiar to some bacteria. It's becoming far harder to find new compounds this way, or to find new ways to make the old drugs work better. Conventional drug companies are losing the race against bacterial evolution. Doctors, remembering the bad old days when people died en masse from common infections, are terrified.

In a local Asian community in Queens where I practice, more than a quarter of urinary track infections are Cipro-resistant. Not long ago, patients with bladder infections would have been reflexively prescribed Cipro, but not in Queens, not anymore. (That's why doctors are afraid to prescribe Cipro even for people like Jane who have reasonable anthrax anxiety: they fear mass use will create more Cipro-resistant bacteria—but for a vast variety of common infections).

I recently treated an 18-year-old diabetic girl who came in with pyelonephritis, or an infection of the kidneys from an ordinary urinary track infection that goes untreated. After three days of Cipro, she wasn't any better. On the fourth day, we finally got back the blood tests: her kidney infection was a

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Cipro-resistant strain of *E. coli*. A one-day hospitalization turned into five. That's the last time I used Cipro in Queens.

As antibiotic-resistant genes pass from bacteria to bacteria like sniffles in an elementary school, the list of effective antibiotics is getting shorter and shorter. Meanwhile, the drug industry hasn't introduced a significant new antibiotic in almost 40 years. Even allegedly new, patented antibiotics like Cipro are only slight modifications of older antibiotics.

Fig. 1. Mechanisms of Antibiotic Resistance.
Common antibiotics and some mechanisms of antibiotic resistance

Antibiotic Class	Representative Drug	Site of Action	Mechanisms of Resistance
Glycopeptides	Vancomycin	Cell wall synthesis	Altered target of antibiotic
Betalactams	Penicillin G	Cell wall synthesis	Enzymatic inactivation of antibiotic
Aminoglycosides	Gentamicin	Protein synthesis	Enzymatic modification of drug & altered target
Macrolides	Erythromycin	Protein synthesis	Altered target of antibiotic
Quinolones	Ciprofloxacin	DNA synthesis	Altered target or decreased intracellular accumulation of antibiotic
Tetracyclines	Tetracycline	Protein synthesis	Decreased intercellular accumulation of antibiotics

I was calling attention to this problem over a year ago, declaring in the *Wall Street Journal* in June of 2000 that there was a "relative dearth of new antibiotics in the pipeline during much of the 1990s, particularly those with novel modes of action that would be more difficult for bacteria to circumvent."

How big would a market for some really good new antibiotics be? Consider just one serious category of infections, hospital-acquired or "nosocomial" infections, which often occur after surgical procedures. Of the 40 million people admitted to hospitals each year, roughly 5 percent, or about two million each year, get one. Nosocomial infections are associated with about 100,000 deaths each year, according to the Centers for Disease Control. The price tag? The average infection prolongs a hospital stay by four to six days, and costs $1,500 per patient to treat, or $3 billion annually. Because nosocomial infections occur in hospitals filled with very ill patients, bacterial resistance can spread fast and threaten lives. A really good new antibiotic would have a large, rapid market. Not only are doctors deeply aware of and concerned about antibiotic resistance, but any would-be technology-laggers would surely face enormous liability costs.

In U.S. hospitals, more than 20 percent of all enterococcus infections (including infections of the gastrointestinal tract, heart valve, and blood) are now resistant to vancomycin, the antibiotic of last resort. Even more worrisome, insensitivity to vancomycin is showing up in the dangerous common family of staph infections. A recent study in the *Journal of the American Medical Association* found that about 20 percent of the 500,000 cases of ordinary pneumonia diagnosed in the hospitals is caused by bacteria resistant to one or more antibiotics.

Resistance is futile

The good news for patients and investors: biodigital medicine is tipping the battle of bug v. drug back in favor of the humans. Where conventional drug design is rooted in randomness, rational drug design starts from the opposite assumption: we can learn at the molecular level, what good drugs look like and begin the testing process on promising compounds. Genomic techniques are revealing the underlying structures of both disease and health. Good drugs, we know, must be good binders to their newly uncovered cellular targets. They must possess significant structural similarity to the receptor at which they're being aimed.

You can't get that from a Petri dish. But you can get it from powerful computer algorithms that solve the 3D jigsaw puzzle of digitally docking chemical fragments into the active sites of target proteins.

How do bacteria resist antibiotics? Before structure-based drug design, the answer was: well, no clue really. How do you know how bugs develop resistance to drugs if you don't even know how the drugs work? Take, for example, the class of antibiotics that includes clindamycin, chloramphenicol, and erythromycin. For years, scientists believed these antibiotics targeted a piece of the bacterial replication machinery called ribosomes, but how? New genomic research published last month in *Nature* has at last unveiled the mystery. Turns out, they don't affect ribosomes at all. Instead, their target site is a cavity on the ribosomal instruction sets called RNA. This is no mere academic triumph: discovering this cavity, called "peptidyl transferase," gives scientists a brand new target for brand new classes of antibiotics.

These structure-based studies also revealed another crucial common molecular fact about these antibiotics. What helps them bind to bacteria? A single magnesium ion. Thanks to this kind of biodigital knowledge, researchers looking to slaughter antibiotic-resistant bacteria know now to search for a new drug with a magnesium ion in the right orientation. As we move beyond the surface effects of drugs to understand their structure and function at the molecular level, a whole new world of medical (and investment) possibilities opens up. Human intelligence will beat not only backwards bioterror, but blind bacterial evolution.

High-throughput crystallography

Genomic tools help map the cellular pathways that regulate different bacterial functions. One key is *high-throughput crystallography*, which allows researchers to rapidly screen millions of drug compounds against targets. Rational drug designers can take a drug that binds poorly and chemically refine it to make it work better (called *lead optimization*). Here's how conventional drug design works: you make small changes in an existing antibiotic in the chemistry lab and then go back to your tests tubes. Do they work any better? If not, then back to the chemistry lab to make another random change, and then back to the beakers to test it, and so on, and so forth, in endlessly serial fashion. Rational drug designers, by contrast, use computers to check drug leads against their targets to see whether they stick or which stray molecules hang over target sites. With these structural maps, scientists can also find target sites common to all strains of the bugs. For antibiotics and antivirals, good target sites on bacteria and viruses are usually active regions on enzymes important to their growth and reproduction or the protective proteins that the bugs coat themselves in.

Structural pictures of these key proteins can be digitized. Software tools, called docking programs, test different chemical structures against binding sites, looking for snug fits. Computers linked to massive databases play a central role, instructing chemists which small changes will diminish toxicity or increase absorption. Syrrx Inc., the envy of many biotech execs we meet, has industrialized and automated the process using sophisticated robotics borrowed from automobile manufacturing. (We visited Syrrx recently. More on these guys as they get ready for a public offering.)

Fig. 2. Gilead Sciences 2001-2002 Upcoming Milestones

24-Week data from study 907 for Viread at ICAAC	Dec 2001
Phase III Cidecin data in skin and soft tissue infections at ICAAC	Dec 2001
Results from a comparative study of Viread to Zerit	Q1 2002
European approval of Tamiflu for influenza (treatment)	Q1 2002
European launch of Viread for HIV	Q1 2002
Regulatory filings for adefovir for hepatitis B	H1 2002
European filing for Cidecin for bacterial infections	H2 2002
European approval of Tamiflu for influenza (prophylaxis)	2002
Japanese approval of Tamiflu for influenza (prophylaxis)	2002

How can biodigital techniques defeat antibiotic resistance? Once again the key is new genomic knowledge that allows us to discover how resistance develops. Bad bugs survive by creating elaborate pumps to eject penicillin or slightly changing the structures to which current antibiotics bind. Using 3D pictures computers design new molecules that will bind to these restructured proteins in ways that the bugs won't be able to evade. Conventional drug designers sift the soil for compounds that are natural antibiotics, slight variations on existing drugs. Structure-based drug designers invent whole new compounds, molecule by molecule, based on what we now know a good antibiotic should look like. The resulting products are usually compounds that don't exist in nature. Guess what that means? *None* of the bad bugs will have ever seen them before.

Skeptics argue that the pharmaceutical industry has spent decades screening every compound under the sun, searching for even trivial antibacterial and antiviral activity. Somebody would have found any really good new drugs after almost 60 years, they say. But 60 years of random testing is no substitute for systematic, rational drug design. We've learned that even small changes in a compound's molecular structure can have huge implications. Many rationally-designed compounds may have antibacterial and antiviral activity, while close cousins lurking in nature have none, merely because a few carbon rings were arranged the wrong way. By designing the template of what a good drug will probably look like first, researchers not only slash costs and increase hits—they also look beyond the drugs contained in known databases to design entirely new antibiotics and antivirals that don't exist in nature.

This is how Gilead Sciences (GILD) designed the new antiviral drug Tamiflu, which jams the molecular machinery the flu virus uses to infect your respiratory tract. Older flu treatments such as amantadine and ranitidine only managed to inhibit one of the two major types of flu. Gilead Sciences wanted to know why.

Genomic comparisons between the two flu strains revealed that older flu drugs target a receptor found only on type A influenza. They also discovered one receptor-molecule, neuraminidase, on the surface of both influenza A and B. So researchers spliced out the gene for the protein receptor, synthesized, and then crystallized it. Using digital models of neuraminidase's structure to guide their computational chemistry, Gilead scientists were able to intelligently design a compound that would block both influenza A and B. In this case, structure-based tools not only found a drug that traditional techniques overlooked, it did it in less than half the time and therefore a fraction of the cost. While many drug companies are moving to adopt in silico techniques, Gilead Sciences is the only public company to exploit fully the in silico paradigm in the development of new antivirals. More on them later.

Best of all, drug companies that adopt the in silico paradigm boost their own learning curve exponentially. Unlike random drug designers, each time a structure-based research team finds a new drug, they learn something valuable at the molecular level about what a good drug should look like. Even failures produce valuable increases in knowledge about molecular function and drug design. Each year petri dishes remain, well, Petri dishes. But each year smarter

software algorithms, better genomic databases, and leaps in processing capacity increase the power of biodigital teams to locate and create new drugs. Each year the capacity of in silico companies increases at an explosively faster rate than conventional scientists incorporating digital tools only into the same old laborious, trial-and-error wet lab.

In silico companies start way ahead of the game. But each year they also leap light years ahead in knowledge compared to companies stuck in the rut of conventional random drug search. Don't count on Big Pharma to stay that way, unless they adapt their corporate culture (difficult to do) to exploit fully the power of biodigital techniques. Meanwhile, many currently tiny companies that understand the power of the in silico paradigm will be rewarded with bulging pipelines of powerful and profitable new drugs. Ten years from now, expect the names on the top ten lists of America's drug companies to change dramatically.

It is hard to exaggerate how crucial the current moment and how dramatic the coming change is. Even three years ago, the complete DNA sequences for the 50 most important infectious bacteria just hadn't been mapped. In just the next few years, all known bacterial DNA sequences will be completed. (Much of this work was done gratis and deposited in public databases by the Institute for Genomic Research, Craig Venter's old outfit before he left to found Celera.)

By themselves, DNA maps don't tell much. But when the sequence information is loaded into large databases which can be mined with sophisticated algorithms, brand new targets for antibiotics or other drugs emerge. By the end of this year, for example, sequencing of the bacteria that causes inhalation anthrax will be available.

How big a difference do the new in silico techniques make? Liddington's efforts to crystallize the single anthrax protein took ten years spanning two continents at three different labs. Today, researchers at Syrrx are able to accomplish in a week what took Liddington years, crystallizing and digitalizing 100 protein structures every week.

Quorex, et. al.

One interesting company attempting to exploit the power of biodigital medicine is Lexington, Massachusetts-based Cubist Pharmaceuticals. Through its acquisition of TerraGen Discovery, half of Cubist's efforts focus on screening natural compounds for antibacterial and antifungal activity. They combine this old method with a twenty-first century core competency in cheminformatics and synthetic chemistry that enables them to map entire molecular pathways, modify existing compounds, or design entirely new ones with the information they've gleaned.

Cubist also uses structure-based techniques in collaboration with Syrrx to develop new antibiotics. Cubist identifies and generates novel proteins essential in bacterial life cycles. The company then hands the genes off to privately-held Syrrx, which synthesizes and crystallizes the corresponding protein.

Fig. 3. Gilead Sciences Product Portfolio

Name	Indication	Stage
AmBisome	Systemic fungal infections	Marketed
Vistide	CMV retinitis/AIDS	Marketed
DaunoXome	Kaposi's Sarcoma/AIDS	Marketed
Tamiflu	Influenza treatment & Prophylaxis	Marketed
Viread	HIV/AIDS	Marketed
Adefovir	Hepatitis B Virus	Phase III
Cidecin	Gram-Positive Bacterial Infections	Phase III
NX1838	Age-Related Macular Degeneration	Phase III
Small Molecule Drugs	HIV/AIDS	Research

A lot of companies now try to bill themselves as structure-based drug designers. Companies such as Micrologix Biotech, Inc. (MGIXF) and Demegen, Inc. (DBOT) use structure-based techniques to refine antimicrobial compounds they found in nature. But Cubist also uses them to design drugs de novo, using docking programs to find novel antimicrobial compounds. Cubist and Syrrx load the structures into supercomputers and run them against a library of 2.7 million digitalized compounds, sharing hits, with each company keeping half for further development. "We're looking at all the stuff bacteria require to stay alive," Syrrx Associate Director of Protein Chemistry Kenneth Goodwill, Ph.D. told me. "All of them are pharmaceutically naïve targets. Nobody has tried them before."

Should you invest now? In ten years, Cubist hasn't yet brought any products from its own research efforts into clinical trials. Its two lead products, Cidecin and oral ceftriaxone, were licensed from other companies. Cubist has been aggressively transitioning into the in silico paradigm and is now brimming with preclinical candidates. We do not want to add Cubist to the list, however, until the company's in silico division has actually developed new drugs and moved them into clinical trials. We want proof that Cubist not only aspires to, but can execute, the in silico paradigm. Watch and wait.

Privately-held Quorex Pharmaceuticals is another great biodigital company, using sophisticated bioinformatics to design novel drugs that work through a unique approach. Quorex seeks drugs that don't just inhibit a single protein (like most drugs), but interrupt the common chemical "language" that bacteria use to coordinate their activities.

Bacteria, it turns out, do not usually decide to wreak havoc alone. They try to stay under our immune system's radar until they have numbers enough to fight the good fight. Quorex drugs seek to block the communication system that tells the bugs fellow-invaders are close-by. This language has been dubbed *quorum-sensing* because it tells the bac-

teria when enough of them are present to get down to business. Quorum-sensing is involved in numerous processes, such as determining when bacteria exchange genes or release antibiotics to fight off other bacteria or fungi. Quorex aims to rationally design molecules that bind to the bacterial sensors, blocking out signaling molecules.

Quorex also has a parallel effort underway using genomics to identify new protein targets for antibiotics. Quorex computers flag a particular protein as a promising drug target. Researchers will then synthesize it, crystallize it, and run it back through the company's structure-based drug design team to find a new drug.

How big a market can Quorex capture? Antibiotic sales exceed $1 billion.

Some of Quorex's senior scientists come from the top ranks of Agouron Pharmaceuticals, one of the early in silico pioneers. The two-year old Quorex recently raised about $19 million from private investors and venture capitalists. The company's Chief Scientific Officer Jeffrey Stein, Ph.D., told me they expect to file their first investigational new drug application in the next two years and launch another round of private financing next year. Quorex is early-stage and privately held, but it is so committed to the in silico paradigm that we're enthusiastically adding it to our list and will stay in close contact with its management.

How big a market can Quorex capture? The biggest selling antibiotics have sales exceeding $1 billion annually. The world's best-selling antibiotic, Augmentin from GlaxoSmithKline, had sales exceeding $1.8 billion last year, making it the industry's fourteenth-best-selling drug overall, and Cipro had revenue of $1.6 billion in 2000, which doesn't include the anticipated blip in sales as a result of the anthrax scare. Anti-infectives are the fourth largest pharmaceutical market and account for $20 billion in worldwide sales, of which $15.8 billion is anti-bacterial agents ($7.4 billion in the U.S. alone). Each dose of Linezolid, one of the first new classes of antibiotics to come on the market in 35 years, costs approximately $70. It needs to be taken twice a day, sometimes for weeks.

Gilead Sciences

When it comes to antivirals, the established in silico leader is Gilead Sciences, which I recently spent a day visiting. Located in Foster City, about 30 minutes outside downtown San Francisco, Gilead is housed in an industrial park on filled-in marshland adjacent to the San Francisco Bay.

The first thing you see as you enter the glass lobby is a bronzed copy of a Board of Directors resolution passed when one of its members, Donald Rumsfield, left a year ago for better work. Despite the company's close connection to the Pentagon chief, Gilead's communication director insists, as we walk toward the first meeting, that they haven't received any calls inquiring about Gilead's cidofovir, the only antiviral known to work well against smallpox.

What makes Gilead different from other companies seeking to break the antiviral bottleneck? Gilead is the only company to combine genomic tools with a structure-based approach, harnessing the full potential of the in silico paradigm. At the one end of the discovery process, they use supercomputer power to assemble databases that can scan through the genomes of many different bugs, looking for key sites that—if disabled—will kill not just one strain, but all the viruses. They develop a 3D picture of the proteins regulated by these key genes. Then back to supercomputers again, this time to search for the right molecular compounds to disable those proteins. Gilead's approach places the maximum effort onto computers crunching billions of bits of data, taking advantage of the key new abundance in biodigital medicine: awesome advances in analytic power ruled by Moore's and Metcalfe's laws. The result? A bulging pipeline of promising new anti-infectives.

Gilead began life about ten years ago with a dual expertise in nucleoside analogues to treat HIV and structure-based drug design. This dual expertise has paid significant dividends for Gilead, producing among other approved compounds, two for HIV (cidofovir and tenofovir) and one for flu, oseltamivir phosphate (a.k.a. Tamiflu).

Gilead recently sold its oncology pipeline to OSI Pharmaceuticals (OSIP) for up to $200 million, allowing it to focus on what it does best. The company also has a collaboration with Cubist Pharmaceuticals, marketing Cubist's drug Cidecin.

So where's the rub? Turns out, Wall Street likes Gilead almost as much as we do. The stock is trading at a 52-week high. Some analysts have even sheepishly advised clients to take profits. We believe the best time to buy into the in silico paradigm is now. Despite short-term fluctuations based on current market products, Gilead's powerful biodigital engine will keep its drug pipelines producing profitable winners. Despite the recent surge in Gilead's stock price, it is still undervalued relative to the potential market for its target products.

Consider hepatitis B, for which Gilead has a promising treatment in phase III trials, adefovir. More than 2 billion people alive today have been infected with the hepatitis B virus and 350 million of them are chronically infected carriers. Worldwide, hepatitis B kills one to two million people every year. In the United States, the disease claims between 4,000 and 5,000 lives annually among the 1.25 million chronically-infected Americans.

Interferon is the gold standard for chronic hepatitis B infection, but it costs $6,000 per patient, and more than half of all patients do not respond to it, according to the World Health Organization. There's a vaccine for hepatitis B, but many peo-

ple (especially the young, sexually active, who are most at risk) fail to get it. Antiviral agents (including HIV drugs) are being investigated as treatments, but early reports show these drugs work weakly, and in fewer than half of patients. By contrast, one recent study showed 12 weeks of treatment with Gilead's drug adefovir reduced genetic markers for the levels of circulating virus in about 70 percent of patients and resulted in a total loss of markers for the virus in about a quarter of patients. If a 12-week course of the drug, priced at $300 per week, were administered to one-fifth of the chronically infected patients, adefovir alone could represent a $1 billion market.

And that is just hepatitis B. What about hepatitis C? A recent study in the *American Journal of Public Health* estimates that between 2010 through 2019, 165,900 Americans will die from chronic liver disease, running up $10.7 billion in direct hepatitis C expenditures alone. The current care for chronic hepatitis C, (interferon in combination with ribavirin) can cost more than $5,000 per patient, has dangerous side effects, and only works for about 40 percent of patients, according to a November 17, 2001 editorial in the *British Medical Journal*. Imagine how quickly a new antiviral for hepatitis C would spread among the estimated 200 million infected people worldwide?

Not to mention the host of other viruses for which there are no effective treatments, everything from herpes to viral pneumonia to the common cold. Antivirals are a largely unmet need.

Many companies are getting out of the HIV space, worried over the glut of competing drugs (there are currently 15 approved drugs for HIV with aggregate sales totaling $4 billion in 2000) and the growing problem with maintaining patent protection in third-world markets. Why not Gilead? The company is using its structure-based technology to develop a new generation of medications that evade HIV resistance. The market for a new generation of more potent HIV medications that outfox current strains is going to grow rapidly as an older generation of drugs begins to fail. The problem isn't going away: there are approximately 40,000 new HIV infections annually in the U.S., according to the Centers for Disease Control.

Moreover, the ongoing third-world patent encroachment issue shouldn't hit Gilead hard. The market worries not only that those cheap copycat drugs will be sold in third-world countries, but that many will then make their way back into developed nations. Alternatively, markets fear the huge price disparities between knockoff HIV drugs and their patent-protected counterparts in the West will increase political pressures to reduce prices and profits. Gilead's target market niche is different. Because standards of care lag so badly in poor countries, most new cases of HIV in third-world nations, where patent protections are in dispute, respond well to first- or second-generation HIV antivirals. Gilead is in the business of designing third- and fourth-generation drugs to combat resistant strains, not needed in less-developed countries, so they don't expect much competition from patent-infringing copycat generics. Why learn to copy new drugs if the old drugs work?

Much of the run up on Gilead's stock stems from market enthusiasm for the approval of tenofovir. But Gilead's structure-based tools are ideal for creating new generations of antivirals, especially HIV drugs to thwart resistant strains. "The trick is to look at the structure of the proteins and see why the drugs don't bind anymore, what changed when it gained resistance—what's hanging out of the active site," as Norbert Bischofberger, Gilead's executive vice president of research and development, told me.

How big a problem is HIV resistance? Patients infected with HIV now take at least three drugs a day to completely block the virus. It is called triple-combination therapy and has greatly reduced the death rate due to AIDS. Unfortunately, over half the patients in the United States have already failed at least one round of therapy due to growing drug resistance. Gilead's tenofovir specifically targets drug-resistant viruses.

Gilead's approach maximizes computers crunching billions of data bits

Of the 350,000 Americans on treatment for HIV, 26 percent are on second-generation agents and 29 percent on salvage therapy because they already failed first- and second-line drugs. This latter population will be Gilead's target market. Priced at $340 for a monthly supply of 30 tablets, tenofovir translates into an annual cost of $4,135. Gilead is predicting initial sales of $10 million to $15 million, and Wall Street is forecasting peak sales of around $300 million.

Wall Street is valuing Gilead largely on future sales of tenofovir and its pipeline of approved drugs, whose 2005 revenue estimates run around $800 million, with a net income of $300 million. Imagine Gilead as taking a tenth of the market share for a discounted treatment for hepatitis B, which could easily increase their revenue by 50 percent. Add a breakthrough in another major viral area that they're researching, such as hepatitis C, and it's easy to see Gilead trading at well above its current levels.

Infectious disease specialists are aware of the new drug, tenofovir, and eager to incorporate it into the regimens of difficult-to-treat patients. Everyone from the Centers for Disease Control to the World Health Organization now argue that the way to restrain resistant microbes and viruses is to withhold our most powerful drugs from patients who don't desperately need them. This strategy of scarcity, will at best, only delay the fast-approaching day when current antibiotics and antivirals no longer kill many common (deadly) infections. What everyone from the CDC to Wall Street hasn't yet really taken into account is the powerful advantage

BIOTECH COMPANIES

Company	Technology Leadership	Reference Date	Reference Price	11/30/01 Price	52-Week Range	Market Cap
Vertex (VRTX)	Rational Drug Design	9/17/01	28.60	25.30	15.50 - 84.50	1.9B
Human Genome Sciences (HGSI)	Cellular Signaling	10/26/01	43.97	42.51	26.41 - 89.50	5.0B
Nanogen (NGEN)	BioChips	10/2/01	4.95	6.32	3.00 - 17.00	135.5M
Gilead Sciences (GILD)	Rational Drug Design	12/05/01	67.72		24.87 - 73.67	6.6B
Quorex (none*)	Rational Drug Design	12/05/01				

* Pre-IPO startup companies.

NOTE: This list of Gilder Biotech companies is not a model portfolio. It is a list of technologies in the Gilder 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.

of the in silico paradigm: as new strains mutate in response to this and other HIV drugs, companies like Gilead and Quorex that are going to be in the position to respond with new anti-infectives.

The solution to antibiotic and antiviral resistance won't be found by withholding our best drugs, but by designing even better ones. Neither the bugs nor the bioterrorists are unlikely to outsmart us for long.

This confluence of technological innovation will position companies such as Gilead and Quorex for a new growth curve, soaring upwards on the exponential pace of Moore's law and our growing ability to digitalize bioinformation to take advantage of abundant new processing power. By itself, the bioterror boomlet won't last. But the same companies and biotechnologies beating agents like smallpox and anthrax will, even more importantly break open the antibiotic bottleneck, leading to successive generations of truly new antibiotics and antivirals.

What stirs the imaginations of evil people who would spread infections as weapons is not a utopian vision, but rather a dystopian delusion. No wonder the Liddingtons of the world laugh in the face of anthrax anxiety. Liddington's confidence stems from his vision. He's not only seen the future, he's helped build it. He knows biotechnologies of freedom can conquer bioterrorism.

This is how a society progresses, how civilizations express their optimism in the face of crisis, how man not only survives, but prevails. Through acts of creation, ultimately, our inner values are stamped on the world.

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