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Battle of the Bugs

A patient of mine, I'll call her Lauren, was admitted to the hospital recently to have her arthritis-wracked right knee replaced with an artificial joint. It's a fairly common procedure, done thousands of times each year. She had even been through it before. Lauren had her first "total knee"—on her left side—five years earlier. She was looking forward to walking with less pain again, but this time the procedure didn't go smoothly.

When bacteria embedded themselves in the area around the new metal joint, the ramifications were hardly routine. Lauren found herself on what has become the shaky outer edge of medicine's ability to deal with microbial disease. Her new joint was infected with a form of resistant staphylococcus bacterium that thwarted attack from almost all of our medicines. Lauren's routine operation became a herculean struggle.

Two weeks after her original surgery and without ever leaving the hospital, Lauren went under the knife a second time to have her wound reopened and drained of the pus that had accumulated inside. Then she was put on the antibiotic of last resort, called vancomycin. It worked, but barely. Before the antibiotic finally managed to knock out the invading organism, the bugs first spread to her other organs. She spent two weeks in the medical intensive care unit and nearly died.

Two decades ago, the drug industry was lulled into a false sense of security that infectious diseases were under control. The big drugmakers began shifting their resources away from creating new antibiotics into other areas like AIDS and cancer. The space was ignored, left to be picked over by start-up biotechnology outfits, many of which never had much traction. But now new antibiotics are in much demand. Antibiotic research is fashionable once again on Wall Street.

Dr. Scott Gottlieb

"Antibiotic research is fashionable once again on Wall Street."

Fearing the enemy

The need for new antibiotics is being driven by the spread of resistant bacteria just like the bug that nearly claimed Lauren's life. Among the diseases caused by drug-resistant bacteria are once ordinary pneumonias, tuberculosis, ear infections, sexually transmitted diseases, diarrhea, and bloodstream and wound infections. Infections due to drug-resistant bacteria result in significantly higher mortality rates, prolonged hospitalizations, and higher healthcare costs. In the hospital, it's one of the most talked about topics. Where doctors once prescribed antibiotics without much consideration, now they must carefully target their drug regimens to make sure that they're covering all the resistant microbes that might be at play. Serious infections are our most feared enemy.

Indeed, by now, it is common knowledge that microorganisms are becoming resistant to drugs that used to kill them quickly. MRL Pharmaceutical Services Inc. of Reston, Virginia, has been tracking antimicrobial resistance data since 1994, through The Surveillance Network Database. More than 100 participating U.S. institutions now send electronic files of the organisms they are seeing each day to

INSIDE:

MRL. Currently, the database contains the results of more than 425,000 patients treated with different antibiotics. And the results are sobering.

MRL Pharmaceutical Services reports that some 40 percent of staphylococci, the bacteria most commonly associated with hospital-acquired infections, are now resistant to methicillin, the first-line drug that used to combat these microbes. Antimicrobial resistance is not just a problem in hospitals but affects the general population as a whole. The rates of penicillin-resistance among strains of Streptococcus pneumoniae, the most common cause of bacterial pneumonia and meningitis in the United States, are rising. In 1994, 35 percent of the strains of this organism were resistant to penicillin. By 1997, 44 percent were resistant. Even ordinary urinary tract infections are becoming resistant to the two main drugs that are used to treat them, Bactrim and Cipro.

Vancomycin-resistant enterococci (VRE) are likely the most feared resistance problem in hospitals: the same multidrug resistant strain that infected Lauren. The VRE microbe can kill patients with weakened immune systems if it enters their bloodstreams. This nasty bug has been causing problems for more than five years and is growing ever more prevalent. Yet the armamentarium capable of treating it has remained largely static. Some new drugs have been used, but none are very good. They are either too weak to knock out the infection reliably, or they are plagued with side effects. There's plenty of room for something much better.

Just how serious is VRE? According to the CDC, the incidence of VRE rose from 0.3 percent in 1989 to 14.2 percent in 1996 among patients who had enterococci infections during hospital stays. What makes VRE so significant is that vancomycin is not the first drug of choice to treat the microbe, but the last. Not only is VRE resistant to vancomycin, it is usually resistant to all other drugs commonly used to treat it.

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Antibiotics: Opportunities for Small-Caps

Across the country, researchers are competing furiously to uncover the private lives of bacteria like these, probing their genes to learn which are necessary for survival and which are involved in infecting people, and what mechanisms the microbes use to survive antibiotics. The edge is going to the biotechnology companies that have stuck with it for the last ten years. Some of the Big Pharma companies have long since lost their intellectual edge, and they're having a hard time building it back up again.

As a result, antibiotics are an increasingly lucrative opportunity for smaller companies. They are already the third largest-selling class of drugs. Worldwide sales totaled about $26 billion in 1996, about $7 billion of that in the United States alone. Given the failing potency of existing treatments, market demand for new and better compounds is bound to be high.

There are also few barriers to drug development as preclinical tests of antibiotics in test tubes and animals yield excellent predictive information of how likely they are to work in people. And the clinical endpoints of most antibiotic treatments are clear—create a compound that kills the bug without hurting the patient. Clinical endpoints aren't nearly so precise in trials for psychiatric drugs or a new treatment for Alzheimer's. That makes the latter inherently more risky. As a regulatory hurdle, antibiotic trials are generally more straightforward and easier to predict than, say, cancer trials.

Consider, too, the fact that existing antibiotics automatically make themselves obsolete after they've been on the market for a number of years, thanks in part to the ability of microbes to develop mechanisms of resistance. And no totally new antibiotic has come to the market in the past twenty years: that's a lot of drugs growing old. According to a recent survey in the industry publication *In Vivo*, all of the 150 antibiotics approved in the United States are derived from the same 15 compounds. So there's ample room for new entries.

New Approach to Killing Bugs

Because of advances in molecular biology and genomics, it's possible for scientists at some of the smaller biotechnology firms to have a decided edge when it comes to developing entirely new classes of drugs. Size doesn't matter. It doesn't take a big-cap pharmaceutical firm to devise new antibiotics. New methods are yielding drug targets and candidates that were overlooked or

unheard of even a few years ago; as a result, some of the most innovative products are in the pipelines of small-cap companies. While most of the products that will enter the market in the next several years are basically better versions of drugs we already have, a new generation of radically different antibiotics—being developed by biotechnology companies—is not that far behind.

For many years, new antibiotics were discovered by randomly screening samples found in nature. Microbes have existed in the soil since the creation of the earth. As a result, many antibiotics were found by sifting through soil samples, where these chemical compounds had been used by competing bacteria and organisms to fend off one another. Drug developers screened libraries of these natural products against organisms cultured on petri dishes, hoping that one of the extracts would kill the bug and announce itself as a raw candidate ready for further refinement.

There's probably still some mileage to be gained from this rudimentary approach, especially given the industry's ability to refine compounds to make them better. But to combat resistant organisms with drugs that have broad spectrums—meaning they're able to kill many different kinds of bacteria simultaneously—will require some fundamentally new mechanisms and points of attack. Tinkering with the known chemicals—tweaking them to make them a little stronger—will only get us so far. We need a radically new approach to killing bugs.

Thanks to the convergence of information and biological sciences, and the ability to rapidly discern the molecular machinery of the smallest microbes, these techniques are finally at hand. Of particular interest to the pharmaceutical industry are the fully sequenced genomes already available for several bacteria. Craig Venter, the former chief executive officer of Celera (CRA), estimates that the biochemical codes for up to 40,000 new microbial genes already exist in public databases. Researchers will discover as many as 500,000 more genes in the next decade, mostly in microbes. Now, says Venter, industry must winnow its interest to the few that will make the best drug targets.

Understanding which genes, and therefore which proteins, make a bacterium function is essential to learning how to fight it. Having complete genomes permits entirely new forms of analysis. With a whole genome at your disposal, you have in a sense a closed world. You can analyze an organism in terms of biochemical pathways, for example, and be assured that you'll have every possible biochemical reaction represented in your database. Among some of the pure plays in this field are GPC-Biotech (GPCBF), Elitra Pharmaceuticals, Pathogen Genomics, Microcide Pharmaceuticals and its subsidiary Iconix Pharmaceuticals, and SIGA Technologies (SIGA). But these techniques aren't exclusive to these biotechnology firms. They're being employed by a broad range of drug discovery firms, including one of our favorites, Versicor (VERS).

CALENDAR OF UPCOMING EVENTS

EVENT	EXPECTED DATE
Dalbavancin phase 3 initiation for soft tissue infections	4Q02
Anidulafungin phase 2 data fro candidemia expected	4Q02
Anidulafungin initiation of phase 3 in candidemia	4Q02
Completion of merger between Versicor and Biosearch	1Q03
Anidulafungin phase 3 data for esophageal candidiasis	1Q03
Anidulafungin FDA filing	2Q03
Dalbavancin phase 2 data for bacteremia expected	1H03
Oxazolidinone initiation of phase 1 study	1H03
Deformylase inhibitor phase 1 initiation	2H03
Anidulafungin FDA approval	2Q04

Versicor's Versatility

Versicor has in-licensed "me-too" drugs from other companies. But it has also used its equity to invest in radically new technology that we believe can yield entirely novel antibiotics—the kinds of drugs we need to combat the lingering threat from resistant microbes. In our view, Versicor represents the ultimate risk-reward profile: near-term revenues from improved versions of existing products that have a low-risk profile, combined with the potential for long-term upside from innovative research into the development of entirely new antibiotics. Versicor is an attractive pure play on antibiotics.

Versicor was founded in 1995 as a subsidiary of Sepracor (SEPR) to exploit the application of combinatorial chemistry (a new discipline of organic chemistry) to the creation of new anti-infectives. Versicor was the only company with broad expertise in chemistry that devoted itself entirely to the development of new antibiotics. The company's two lead products, Anidulafungin and Dalbavancin, are licenses from Lilly (LLY) and infections Biosearch Italia (BOSHF), respectively. Versicor has worldwide rights to Anidulafungin and North American rights to Dalbavancin. In addition, Versicor has a number of novel antibiotics that it's developing for its own.

Both of Versicor's lead products are for the relatively focused, hospital-based infectious disease markets. That limits the revenue that each drug will eventually generate, but means that Versicor will most likely sell the drugs with its own home-grown sales force of about a hundred people. The hospital-based market is a fairly specialized niche that can be easily penetrated with a sales force this size.

Selling inside the hospital is also an ideal way for Versicor to get its feet wet while it develops completely novel antibiotics. The balance of Versicor's early pipeline is filled with

oral antimicrobial drugs targeted for the community-based market. Selling antibiotics to community-based doctors is the bread-and-butter of the industry and requires a large sales force. But it's also where the most money is. Versicor can't sell these kinds of mass-market products alone and currently has two partnerships with Pharmacia (PHA) and Novartis (NVS), with such a goal in mind.

Versicor's lead compound, Anidulafungin, is an antifungal drug that targets a novel component of the fungal cell walls known as glucan. The drug is designed to treat hospital-acquired fungal infections. Many of these infections occur in patients with suppressed immune systems; for example, organ transplant recipients who are receiving immunosuppressant drugs such as cyclosporine to prevent their body from rejecting their new organs. Fungal infections are also common in patients with end-stage AIDS and in those with autoimmune diseases who might be receiving immunosuppression with drugs such as steroids (prednisone). There are about 200,000 hospital-acquired fungal infections in the United States every year, at an average treatment cost of about $4,000 per infection.

COMPETITORS' EVENTS TO MONITOR

EVENT	EXPECTED DATE
Cubist's Cidecin U.S. Regulatory filing	4Q02
Fujisawa's potential FDA approval for micafungin	1H03
InterMune Oritavancin phase 3 data from soft tissue trial	1Q03
InterMune Oritavancin begins phase 3 trial in pneumonia	1H03
InterMune Oritavancin files for FDA approval for skin infections	1H03

Anidulafungin belongs to a class of drugs known as echinocandins that break down a substance called glucan, effectively blocking the synthesis of the fungal cell wall. Since the enzyme that these drugs target is common to most fungi, these drugs have broad indications across many different kinds of fungal infections, including Candida that has become resistant to the leading antifungal drug fluconazole, and the aspergilli which are naturally resistant to fluconazole. The only important fungal infections the echinocandins don't target are the Cryptococci species, which usually infect end-stage AIDS patients. Since Cryptococcus is an infrequent infection that is very specific to a small number of health problems. We're not worried that it will alter the future for this class of drugs.

The echinocandins are particularly promising drugs for Candida, where they are fungicidal (they kill fungi) rather than fungistatic (keeping fungi from growing) like the other drugs used to treat this infection; this is significant because most people who get fungal infections are immunocompromised and severely ill. Even if they're taking a drug that keeps a fungal infection from spreading, they'll have a hard time mounting enough of an immune response to kill off the fungi already floating through their blood. So they need a drug that can kill it for them. Anidulafungin fits that bill.

Battle of the Antifungals

Yet despite the promising role these drugs are likely to play in the treatment of Candida, there aren't any echinocandins approved for this indication. Versicor's Anidulafungin should be the first. The only approved drug in this class is Cancidas from Merck (MRK), which is approved only for aspergillus salvage therapy. But Versicor is likely to beat Cancidas to the market for the Candida indication. We view this as an important niche for Versicor, since many of the most promising uses of this class of drugs haven't been claimed by competitors.

What about Merck's Cancidas? Is its first-to-market status going to crowd out Anidulafungin? On the contrary, we believe Merck's drug—and its fairly easy regulatory approval—bodes well for Versicor's Anidulafungin. Moreover, Versicor's drug has significant advantages over Merck's. For starters, it has greater potency according to the clinical data we reviewed. It's also likely to have fewer side effects.

In reviewing the FDA advisory committee's assessment of Cancidas, we believe that Versicor's drug is likely to get broader clinical use than Cancidas. Merck's drug, which received approval in 2001, generated $40 million in sales last year. It hasn't been a major success largely because doctors can't dose it with cyclosporine, an immunosuppressant drug that many patients find themselves on when they succumb to fungal infections. It's cyclosporine use that causes many of the serious fungal infections doctors see in the hospital. So what good is a drug for treating fungal infections that can't be used with cyclosporine? That's our point exactly. The drug is commonly prescribed to transplant patients, for example, who constitute a large piece of the antifungal market.

There's one more drug in this class that's likely to make it onto the market in the next year. That's Fujisawa's (FJSPF) drug micafungin. In April, Fujisawa filed a new drug application (NDA) with the FDA for permission to market micafungin for prophylactic use in bone- marrow transplants and empiric therapy. We believe micafungin will be better than Merck's entry and will be competitive with Anidulafungin. But there are some differentiations that could give Anidulafungin a competitive edge. For one thing, it has a greater volume of distribution (it reaches more tissue), and it also has a longer half-life, meaning it lasts longer in a patient's blood. Doctors will have greater comfort knowing that the Anidulafungin is able to find even hard-to-reach sites of infection. Nevertheless, we expect the two drugs to be close competitors. But Anidulafungin doesn't need to own

the market to be a success for Versicor. Just a piece of it.

Versicor recently announced that it completed enrollment of its Anidulafungin phase 3 trial for esophageal candidiasis and its phase 2 trials for invasive candidiasis. These are two feared infections in hospital-based patients, especially among those with weakened immune systems. Positive results from these trials should support an FDA filing for April 2003. The timely completion of the enrollment phase of the trials also speaks well of the company's operational efficiency.

So with all of the competition in this space, how much is Anidulafungin worth? Current worldwide sales for all antifungals total about $3 billion. A little more than half come from two drugs in the azole class: Fluconazole and Itraconozole. Both have the advantage of being administered orally and are fairly well tolerated by patients, the reason they're so often used to outpatient management of less serious fungal infections. That accounts for much of their combined sales. But when it comes to hospital management of serious infections, the azoles are not very effective drugs and are ripe for replacement. We expect Versicor to bite off about 5 percent of the total market for this indication, which represents sales in the $100 million range: a conservative estimate that gets Versicor to a valuation more than double where it is now. We believe Versicor could easily capture more sales.

More from Versicor

Versicor's other lead compound, Dalbavancin, could have even higher peak sales. It's being tested for the treatment of serious gram-positive infections and is expected to launch in 2005. Infections of this type are evading existing antibiotics and becoming a deadly problem inside hospitals. Of the 2.5 million hospital-acquired infections occurring each year in the United States, 64 percent are caused by gram-positive bacteria. More than 95 percent of staph—the most common of the gram-positive infections—is now resistant to penicillin or ampicillin, and more than 30 percent is now resistant to methicillin—the current front-line therapy. Methicillin-resistant staph infections are now treated with vancomycin and Zyvox, a woefully inadequate drug.

Dalbavancin is basically a better vancomycin, and we believe it will compete favorably with both drugs. Dalbavancin is bactericidal (meaning it kills bugs) unlike Zyvox which is bacteriostatic (it keeps bugs from growing). And it has greater potency than vancomycin and a longer half-life, which allows for weekly dosing rather than the daily dosing that's required for vancomycin.

The potency factor is a key attribute, in our opinion, and should spur doctors to switch rapidly to Versicor's drug. If patients only need to get dosed once a week, they won't require indwelling intravenous lines, or sometimes even hospital admissions, thereby cutting the cost of administration and the risk of subsequent infections. They can also be more easily treated as outpatients. Since Dalbavancin remains in the blood for a long period, it maintains its killing power for long stretches, unlike vancomycin that must be dosed daily and probably falls below its peak killing concentration in between doses. So Dalbavancin should be a more potent bug killer.

Worldwide sales of drugs for serious gram-positive infections are currently about $800 million—including worldwide sales of vancomycin of $500 million. Vancomycin is heavily used (1.7 million prescriptions written in 2001), but it's a generic drug and priced at about $40 per day. A premium-priced competitor like Dalbavancin can turn this into a $3 billion market. We expect Dalbavancin to be priced competitively with Zyvox, which has an average wholesale price of about $106 per day, resulting in a total cost of $1,500 for an average 14-day course. Although Dalbavancin's pricing will be a premium to vancomycin, we expect Dalbavancin's ease of administration—and the nursing-cost-savings that comes with weekly dosing—to drive utilization and justify the higher cost.

While Dalbavancin doesn't kill all the resistant bacteria that vancomycin misses, it's bactericidal against some species while vancomycin is only bacteriostatic. The list includes enterococci and some methicillin-resistant strains of staph, which should be an important selling point with doctors, especially for the treatment of immunocompromised patients who will need the drug's added killing-power. It's basically a better vancomycin, and there's plenty of room to justify its higher cost.

Versicor recently reported interim results with Dalbavancin in a phase 2 study. Patients showed a higher response rate to Dalbavancin compared with a variety of current treatments, including Eli Lilly's vancomycin. The

Versicor has used its equity to invest in radically new technology that we believe can yield entirely novel antibiotics

62 hospitalized patients in the study had infections involving abscesses (closed-space infections, essentially pockets of pus), ulcers, and burns. Patients using Dalbavancin showed a 94 percent response rate, compared with 76 percent for patients getting standard care, which involved taking antibiotics daily for up to three weeks. Phase 3 clinical trials for Dalbavancin are scheduled to begin later this year, and the company seems to be on target to reach that goal. It expects

to file an approval application in 2004. Dalbavancin also acts through a mechanism distinct from vancomycin, which should render it less susceptible to the development of resistant microbes. Another important selling point.

In Versicor's 52-patient phase 1 trial with Dalbavancin, all doses of the drug in both the single and repeated dose groups were well tolerated, something seen across all of Versicor's trials with the drug. It appears to be safe, and that will be a key factor in driving its sales. There were no patient withdrawals due to adverse events at any dose level, and the drug was safe even at higher doses. Even vancomycin couldn't match that track record. In fact, Dalbavancin may be the safest drug in this category.

Two other drugs coming onto the market will be competing in the same space as Dalbavancin: Cubist's (CBST) Cidecin and Intermune's (ITMN) Oritavancin. However, Dalbavancin should not be viewed as their direct competitor. Dalbavancin will be used as a vancomycin replacement. Both Cidecin and Oritavancin are active against certain vancomycin-resistant bacteria known as enterococcus. Dalbavancin is not. But that's not necessarily a negative. The overwhelming majority of infections are gram-positive infections sensitive to Dalbavancin (enteroccocus is gram negative, having to do with the structure of the bacterial wall). Cubist's and Intermune's drugs are likely to be reserved mostly for resistant enterococcus infections in the same way that Synercid and Linezolid are reserved for these infections now. Dalbavancin is likely to pick up a piece of everything else.

Versicor's Collaborations

Versicor and Biosearch Italia recently signed a definitive merger agreement. The reason for the merger was primarily strategic as the two companies, which had ongoing collaborations in place for several years, will be in a better position to commercialize their existing products. They each have complementary technologies for bringing new products into their pipeline. From a tecnhological standpoint, the merger makes good sense. The combined entity will have about $190 million in cash and no significant debt. Biosearch Italia also adds an additional late-stage clinical compound, Ramoplanin, to the combined entity.

Anidulafungin and Dalbavancin will provide Versicor with near-term revenue and underwrite the formation for the company's sales force and the growth of its research operation. We expect sales of Dalbavancin to be a significant fraction of vancomycin sales, but even a conservative estimate of about 10 percent of vancomycin sales gets us to our valuation for Versicor that is more than double its current price.

As enthusiastic as we are that Dalbavancin and Anidulafungin represent tangible improvements over existing drugs, it's the early-stage portion of the company's pipeline that could provide Versicor with its most dramatic growth over the long term.

In its collaboration with Pharmacia, Versicor is discovering second- and third-generation antibacterial compounds in the oxazolidinone class, which have a broader spectrum of activity and greater potency than first-generation compounds in this class such as Zyvox. Oxazolidinone drugs are a new class of antibiotics that act by blocking protein synthesis in the bacteria at a very early stage. As a result of its mode of action, oxazolidinone antibiotics are expected to be bacteriostatic—they kill bacteria rather than just check its growth. Development of better versions of these drugs is extremely competitive, with Versicor, Pharmacia, Astra Zeneca (AZN), Johnson & Johnson (JNJ), Bayer (BAY), and Synthon Chirogenics all vying for a piece of the action. Versicor recently entered the clinic with a new oxazolidinone as part of its collaboration with Pharmacia.

Few details are public about Versicor's entry into the oxazolidinone category, but unless Versicor is able to reduce some of the side effects associated with the first-generation oxazolidinone, Zyvox, we're not excited about any new entry. We'll continue to press the company to see if their candidate avoids some of the side effects that plagued Zyvox, principally bone-marrow suppression. Versicor has indicated that it has some preclinical candidates that have improved profiles over Zyvox, but we're not sure if they're referring to safety, potency, ease of administration, or some combination of those three elements. We'll assume that Versicor knows what we know about the Zyvox safety problems and the reluctance of doctors to prescribe that drug for precisely these reasons. We'll keep you posted if we learn anything new.

Versicor also has a two-part collaboration with Novartis to develop entirely new classes of antibiotics. The first part of this collaboration involves antibacterial assay development. Essentially, Versicor is using its expertise in chemistry to develop tools to aid Novartis's internal antibacterial development efforts. This is more than fee-for-service business. Versicor gets to keep a piece of the discoveries that are a result of the collaboration. In this deal, Versicor is developing assays that can then be used to test whether any compounds contained in the drug libraries at Novartis might make good antibiotics.

The second part of the collaboration is aimed at developing a completely new class of antibacterial agents known as deformylase inhibitors which are active against an essential enzyme found only in bacteria. Since the enzyme isn't found in human cells, chances are low that it's going to be toxic to people—just bacteria. These drugs called peptide deformylase inhibitors (PDF) is one of a group of so-called

metallo-enzymes, because they contain small amounts of a metal, such as iron or cobalt. About 4 percent of the enzymes produced by bacteria fall into the group, and many of them are essential for the life of the microbe. Since PDF is needed for bacterial proteins to mature and function, blocking the action of PDF inhibitors essentially jams the microbe's cellular machinery and causes it to die.

Versicor's leading preclinical candidate in this category, VRC-4887, is being developed as an oral drug for the treatment of upper respiratory pathogens, including drug-resistant strains of pneumonia. According to early reports, the drug is completely effective against bacteria that have developed resistance to conventional antibiotics, including multidrug resistant Staphylococcus aureus (MRSA), a lethal microbe that is the bane of hospitals throughout the world. The drug is less than one year away from being moved into clinical trials. Versicor is not alone in this space, but it's keeping close pace with its nearest competitor, British Biotech (BBIOF), which formally announced this month that it started a phase 1 trial involving BB-83698, its own entry into the PDF-inhibitor class. Many independent medical experts familiar with the pace of research into PDF inhibitors believe Versicor is the leader in this category.

Future Endeavors

Versicor is also developing several other new classes of antibiotics. Since these projects are early, company insiders are reluctant to talk about them. One of them is a broad-spectrum bactericidal antibiotic for hospital-based infections called VRC-3950. The details of this compound are still unreported, but the drug class has been identified as inhibitors of protein synthesis that kill bacteria rather than just check their reproduction. The company has said that the drug candidate shows no cross-resistance to existing antibacterial drugs and has a low frequency of resistance development in the laboratory. The drug is probably two years away from making it to the clinic.

One of the reasons we like Versicor is that the company remains committed to developing its core technology even while it advances its two lead products through clinical trials and onto the market. Versicor started its life as a leader in the application of combinatorial chemistry to the development of antibiotics. In fact, Versicor was one of the only companies to have such extensive chemistry expertise devoted entirely to antibiotics. But since its start, Versicor has used the cash and equity it was able to earn from its two lead compounds to grow its technology base and to build out its product pipeline. In other words, some companies get fat by in-licensing products of other companies and taking them to the market. Versicor in-licensed its share of products, but used the money it made to continue investing in its own technology platforms.

One of those technology platforms is dubbed gene-to-screen. The platform is based on the premise that a drug's target becomes more sensitive to the presence of a drug when that target is expressed at very low rather than high levels. Any response to a candidate drug therefore becomes easier to detect. The platform allows Versicor to vary the amount of the drug target that is being expressed in a cell (for example, an enzyme like PDF that's made by the bacteria but can be blocked by a drug) and then see how much of the drug it takes to kill or fully saturate it. This helps Versicor more quickly identify promising antibiotics. It's one more example of the kind of tools in which the company is investing in order to develop new generations of antibiotics.

Versicor's balance sheet was given a boost by the recent sale of 2.9 shares of newly issued common stock to selected institutional investors for gross proceeds of about $44.9 million. The sale brought Versicor's cash position to about $100 million. It's matched against a burn rate of about $35 million a year. That figure is likely to go up in the coming years as Versicor undertakes more clinical trials and builds its sales force, but it will then be offset by product revenue. Versicor's cash burn is expected to be closer to $50 million at the end of this year, and Wall Street is figuring that the company might have to raise money again near the end of 2003.

Positive News, Much Promise

Versicor's stock received a small boost during the recent Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). Versicor had a strong showing at this closely watched infectious disease meeting, presenting a number of positive results with its two lead drugs. Experts attending the meeting were generally upbeat about the prospects for the echinocandins antifungal agents, predicting a major role for them in treating serious fungal infections. Versicor also got a boost on positive news about PDF inhibitors. During an ICAAC symposium on these drugs, one expert not affiliated with any company said that the most convincing work in this area is coming out of Versicor.

On the Dalbavancin front, Versicor didn't present any new data at the ICAAC meeting, but we were more intrigued by the noticeable absence of InterMune from the conference. InterMune, as you'll recall, is developing Oritavancin, which promises to be a close competitor to Dalbavancin. The company didn't even have a booth at the meeting's conference hall. Also, an abstract at the meeting presented data that showed that Oritavancin caused a lipid storage disorder in cultured rat embryo fibroblasts. While the clinical relevance of this finding is

unknown, its overall safety will be closely watched.

In the future, doctors will need better versions of the drugs they currently have, but also entirely new classes of drugs that they are just now envisioning. Versicor fires on both of those fronts. The company's second- and third-generation variations of existing antibiotics promise to be an improvement over what we have. And Versicor's pipeline is filling up with completely novel drugs. It's a slow search that's been marked with painful failures in the past. But Versicor can buffer any bumps with the revenue from its two lead products: in our opinion, this represents the ultimate risk-reward profile in the anti-infective space.

Many experts bemoan the growing number of resistant microbes. They try to scare doctors into holding our best drugs in reserve while patients denied good drugs suffer needlessly. We have a better solution. Doctors should be using our best antibiotics without hesitation when good medical practice calls for it. And when resistant bugs emerge, we'll make better antibiotics. Man is smarter than bugs. And so is Versicor.

Scott Gottlieb, M.D.
October 30, 2002

BIOTECH COMPANIES

Company	Technology Leadership	Reference Date	Reference Price	9/30/02 Price	52-Week Range	Market Cap
Abgenix (ABGX)	Antibody Therapeutics	9/30/02	6.61	6.49	5.61 - 38.16	567.0M
Cell Genesys (CEGE)	Cancer Therapeutics	6/10/02	13.24	12.05	10.48 - 25.02	430.1M
Cogent Neurosciences (none*)	Neurogenomics	5/2/02				
CuraGen (CRGN)	Cellular Signalling	3/13/02	17.67	4.22	3.82 - 25.88	206.6M
Gilead Sciences (GILD)	Rational Drug Design	12/05/01	33.88**	33.53	26.08 - 39.00	6.57B
Human Genome Sciences (HGSI)	Cellular Signaling	10/26/01	43.97	12.06	10.03 - 47.70	1.55B
Isis Pharmaceuticals Inc. (ISIS)	Antisense Therapeutics	7/9/02	7.30	9.86	6.10 - 27.15	535.4M
MDS Proteomics (none*)	Proteomics	2/05/02				
Nanogen (NGEN)	BioChips	10/2/01	4.95	1.72	1.51 - 10.13	37.7M
OSI Pharmaceuticals (OSIP)	Cancer Therapeutics	8/27/02	16.16	16.97	11.50 - 50.94	616.3M***
Quorex (none*)	Rational Drug Design	12/05/01				
Sequenom (SQNM)	Pharmacogenomics	1/09/02	9.00	1.54	1.71 - 11.44	57.9M
Triad Therapeutics (none*)	Rational Drug Design	4/9/02				
Versicor (VERS)	Anti-Infectives	10/29/02	10.00		7.65 - 25.40	263.3M
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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