GILDER
BIOTECH
REPORT

November 2002
Vol. 2, No. 11

By Scott Gottlieb, M.D.

Published by Gilder Publishing, LLC

A New Millennium

The current knock on drug companies is that pipeline productivity just isn't measuring up to historical standards. Critics look at all the innovative new technology that's being brought to the task of discovering new drugs and ask: Where are the results?

As evidence of industry-wide malaise, critics cite the declining number of "new molecular entities" coming to the market. These are drugs that are without precedent—the sort of breakthrough compounds considered to be different than any others currently on the market. Indeed, the annual number of these new compounds approved by the FDA went from an all-time high of 53 in 1996 to 24 in 2001. By the end of this September, the number of new molecular entities approved was only 11—a pace that could result in the lowest yearly totals since the 1980s.

Temporary blip

Don't read too much into those results. We think the slowdown is a temporary blip, brought about by a combination of regulatory skittishness on the part of the FDA and the clumsy integration of some new technology on the part of big drug companies. On the regulatory front, the FDA has dramatically increased the rigor of its statistical standards that it uses to rate new drugs. In other words, the numerical bars that clinical trials must surmount have been raised in recent years. The result is that drugs that would have been swiftly approved five years ago are being held up pending additional studies, or they are simply rejected outright. The tougher standards and longer approval times have also prompted some companies to withhold drugs from FDA filing or, in other cases, abandon some programs altogether. The renewed regulatory rigor is infecting thinking throughout drug companies, all the way down to the laboratory bench.

On the technology front, drug companies were faced with a mountain of new technology that they quickly tried to integrate into their discovery programs, from antibodies to antisense on the drug-design front, to proteomics, genomics, and in silico biology among other new tools. These transitions are never smooth, as old researchers are forced to learn new tricks. And the big drug companies haven't had an easy time of it. They are just becoming comfortable with this new technology. Given the long cycles between the acquisition of new technology and the realization of its promise, investors shouldn't expect to see the deluge of innovative drugs that will eventually spring from these new techniques for still many years to come.

But even if the deluge will be slow to arrive, a steady flow of these novel drugs is already apparent. The productivity of the industry's research is hardly declining. In fact, it's poised to accelerate.

Millennium Pharmaceuticals

We can cite dozens of companies whose discovery efforts are the embodiment of that accelerating productivity, but to make our point, we really

Dr. Scott Gottlieb

Millennium is known for its highly valued partnerships, licensing deals, research, and drug discovery efforts.

INSIDE:

only have to cite one, **Millennium Pharmaceuticals** (MLNM).

Millennium has been battered down in recent months on a string of disappointing news and a weak market for biotechnology stocks, and it's now trading at a paltry $4 or $5 above its cash value. Don't let the cheap price scare you away. We believe substantial upside lies ahead, based on both accelerating sales of its lead drug, Integrillin, as well as some promising clinical candidates now in the company's growing pipeline. Critics who contend that the drug industry is having a hard time absorbing all the new discovery technology that has sprung up in the last decade should take a close look at Millennium, one of the industry's top technology integrators. So should investors.

In our original meeting with **Curagen** (CRGN) almost a year-and-a-half ago, Curagen's CEO commented that he saw his company as an early Millennium. We believe that's a good place to begin our discussion, because Millennium is in many ways what Curagen aims to become—a company built on a core expertise in genomics that is able to rapidly acquire drug development expertise, to turn itself into a full-functioning biopharmaceutical company. Today, Millennium is one of the industry's best technology integrators—leveraging its genomic platform with expertise in gene identification, drug-target validation, high throughput screening proteomics, and pharmacogenomics—to build a broad and sustainable pipeline. Most recently, Millennium has expanded its research expertise into cardiovascular medicine and endocrinology (including diabetes and obesity). We believe this is an opportune time to by into one of the most productive research organizations and one of the industry's most interesting pipelines at a bargain price.

GILDER BIOTECH REPORT

Editor Scott Gottlieb, M.D.
Managing Editor Marie Lavinio
Art Director Charles Bork
Editorial Director Richard Vigilante
Chairman George Gilder

Gilder Biotech Report is published monthly by Gilder Publishing, LLC. Editorial and Business address: 291A Main Street, Great Barrington, MA 01230.

Awaiting Velcade's results

One caveat: Millennium is poised to announce important results with one of its lead compounds, Velcade, at the annual meeting of the American Society of Hematology, one of the most closely followed medical meetings of the year, held in Philadelphia from December 6-10. While the stock could enjoy some upside—on the order of 10 to 20 percent—if these results are better than expected, we believe most of the positive news is already factored into the stock price, so the downside risk from disappointing news is in excess of any potential upside. Therefore, if you're buying Millennium for its technology lead and plan to stay in the stock for a while, the best time to buy might be after this week's announcement, when its stock price settles out.

Millennium's technology lead is increasingly evidenced in its clinical pipeline, which currently comprises eight clinical candidates in the areas of cardiovascular disease, inflammation, metabolic disorders, and cancer (and should grow to ten drugs by next year). The company's lead clinical candidate, Velcade, recently advanced into phase 3 trials for multiple myeloma. Assuming favorable results from this trial, Velcade is expected to launch in 2005.

The news that Millennium will announce this week is the final result of a phase 2 study of Velcade in patients with advanced multiple myeloma. Positive results from the first 78 patients enrolled in this study were reported at the American Society of Clinical Oncology meeting last May. So at this week's meeting, Millennium will report the results from the remaining 124 patients enrolled in the study. And, yes, the expectations are for positive results that will confirm the findings from ASCO.

Through its acquisition of **COR Therapeutics** in February 2002, Millennium obtained its lead marketed drug, Integrillin, which is widely used for the reduction of complications during angioplasty and for the treatment of acute coronary syndrome (ACS). Sales of Integrillin should continue to grow at a healthy clip, driven by an increase in market share, market expansion—especially for the treatment of acute coronary syndrome—and some new indications. More importantly, the COR acquisition gives Millennium a critical chunk of intellectual property in cardiovascular medicine that gets this technology leader into an entirely new, and lucrative, therapeutic area.

Enlightened experimentation

As we've mentioned before, one of Millennium's key assets has been its ability to integrate new technology into its drug discovery processes. Part of that is a result of a culture of young and aggressive researchers who are recently trained and are therefore able to work easily and quickly with the

new tools of drug discovery. The result is an integrated platform that incorporates key technologies, enabling factory-like automation that can generate and test drug candidates in minutes or seconds, compared with the days that more traditional methods require. Gaining information early on about, say, the toxicological profile of a drug candidate significantly improves Millennium's ability to predict the drug's success in clinical testing and, ultimately, in the marketplace. Unpromising candidates are eliminated before hundreds of millions of dollars are invested in their development. In addition to reducing the cost and time of traditional drug development, the new technologies also enhance Millennium's ability to innovate, since the company has greater opportunities to experiment with more diverse potential drugs, including those that may initially seem improbable but might eventually lead to breakthrough discoveries.

A recent article in the *Harvard Business Review* referred to this process as "Enlightened Experimentation," and practiced by companies like Millennium, it means the incorporation of key processes, especially computational tools, thereby moving drug development up the technology curve. As the cost of computing continues to fall, all sorts of complex calculations are made faster and cheaper. As new technologies such as in silico drug discovery and combinatorial chemistry emerge, companies that incorporate these tools have a greater capacity for rapid experimentation to investigate diverse concepts.

The *Harvard Business Review* article notes that the ability to experiment quickly is integral to this kind of innovation: as developers conceive of a multitude of diverse ideas, experiments can now provide the rapid feedback necessary to shape those ideas by reinforcing, modifying, or complementing existing knowledge. Experimenting with many diverse—and sometimes seemingly absurd—ideas is crucial to innovation. When a novel concept fails in an experiment, the failure can expose important gaps in knowledge. Such experiments are particularly desirable when they are performed early on (or their results are readily recognized) so that unfavorable options can be eliminated quickly and people can refocus their efforts on more promising alternatives. Rapid experimentation, however, often requires the complete revamping of entrenched routines, and many companies that didn't grow up with the new technologies don't easily make the transition. This is what's got the big pharmaceutical companies stuck in a funk. As the *Harvard Business Review* notes, when certain classes of experiments become an order of magnitude cheaper or faster, organizational incentives may suddenly become misaligned, and the activities and routines that were once successful might become hindrances. Building the capacity for rapid experimentation in early development also means rethinking the role of failure in organizations. The key is to fail early and often, but to avoid mistakes.

MILLENNIUM'S CLINICAL PIPELINE

PRODUCT	CLINICAL STATUS
Integrill	marketed for angioplasty and ACS
Velcade	phase 3 for multiple myeloma
MLN-591	phase 1 for prostate cancer
MLN-518	phase 1 for acute myeloid leukemia
MLN-576	phase 1 for solid tumors
MLN-02	phase 2 for inflammatory bowel disease
MLN-519	phase 1 for stroke
MLN-01	phase 2 for stroke
MLN-977	phase 1 for asthma (inhaled version)
MLN-4760	phase 1 for obesity
Factor Xa inhibitor	late preclinical
PDGF receptor kinase inhibitor	late preclinical

Millennium is also a leader in speeding wet lab processes and in incorporating new technologies to move even test-tube experimentation up the technology curve, where they can be integrated with computational tools. For example, Millennium has become a leader in using lab-on-a-chip technologies (called microfluidics). The automation from microfluidics allows Millennium to shorten development times, reduce per-sample costs, and increase its data quality values.

Millennium's Vision

To hear Millennium's Chief Executive Officer Mark Levin tell it, the company's vision has been very consistent: identifying genes and proteins, thereby understanding the pathways that trigger human diseases, and developing the ability to define products that are directly targeted to the underlying causes. Millennium's goal is to leverage its early lead in genomics and pharmacogenomics to develop personalized medicines that are highly efficacious because they are directed, generally with a molecular diagnostic, to highly specific patient populations. In that respect, Millennium shares our longtime vision for the paradigm that we believe the entire drug industry will eventually evolve into. Diagnostics, transformed by molecular medical technology and protected by drug-like patents, will play a fundamental role in medicine and in the profit potential of research-based drug and diagnostics companies. Biotechnology companies will sell tests to probe for a disease and then have drugs to treat it. A host of diseases that are currently classified as one entity—small cell lung cancer, asthma, Parkinson's disease—will each be redefined into perhaps dozens of distinct clinical entities based on different biological markers that trigger specific processes. Diseases that look the same will turn out to be fundamentally different. This is already happening for some pediatric cancers, which represent the low-hanging fruit of this paradigm, since pediatric tumors often turn on a single molecular change. One of the things that has soured the big drug com-

panies on this kind of vision is the idea that personalized medicines will only sell to niche markets rather than to the blockbuster markets to which the big drug companies are addicted. Big Pharma looks at the advance guard of this kind of medicine, i.e., a drug like Herceptin, that only sells to 30 percent of breast cancer patients who over express a certain molecular marker called Her2, and they see only a tiny market. Millennium, on the other hand, sees the future.

Something else has soured the big drug companies to targeted treatments and the idea of marketing drug and diagnostic tandem: the diagnostic tests rarely command premium prices. Diagnostic tests are mostly commodities that sell for pennies. But Millennium's vision is that the diagnostics business will be transformed into a high-margin business in the same way that the vaccine industry was transformed about a decade ago. We believe they're right. In the vaccine business, those who didn't leverage new tools such as recombinant technology in creating new vaccines fell by the wayside. On the other hand, those companies that survived and successfully incorporated the new technology ended up with patent-protected vaccines that have pharmaceutical margins. The same process can take place in diagnostics, where companies like Millennium are prepared to leverage their pharmaceutical technologies in uncovering important new diagnostic markers that represent unique intellectual property and can be protected by patents.

SELECTED PRECLINICAL RESEARCH AT MILLENNIUM

CAB-2 complement inhibitor for reperfusion injury
Tyrosine kinase inhibitor for treatment of glioblastoma
Growth factor receptor antagonists for restenosis
Small molecule drugs for bacterial disease
Therapeutics targeting GC-C and its related ST ligand
Dual topoisomerases inhibitors for cancer

Millennium's first diagnostic test, called Melastatin, is currently available in select medical centers and will be broadly available by the end of the year. It's being co-marketed with **Becton Dickinson** (BDX). Melastatin, a protein expressed in human pigmented skin cells called melanocytes, is considered one of the two best prognostic markers, along with tumor thickness, for the skin cancer, melanoma. Because loss of melastatin is an indicator of tumor aggressiveness, detection of melastatin in patient tissue samples can help determine whether a patient with melanoma has, or is at risk for developing, metastases (aggressive tumor spread). The diagnostic test Millennium created probes for the particular gene responsible for melastatin production. When the gene is inactive in a melanoma skin cancer, the protein is absent, and the tumor is more likely to spread throughout the body. Today, doctors predict whether melanoma tumors will spread by measuring a tumor's thickness, but that's crude and is accurate only 85 percent of the time. Millennium's test, when combined with thickness measurement, may raise the accuracy of the combined profile to about 95 percent.

One of Millennium's other recent forays into the diagnostic test market was the launch of a wholly owned subsidiary, Vitivity Inc., which will sell genetic information directly to consumers. Millennium seeded the new venture with $10 million in start-up capital. The premise behind Vitivity is to provide a filter for healthcare information, so-called "medical-you-can-use" data that will be peddled directly to consumers who have specific health questions and needs. All of the information will be tailored with an eye toward a particular person's genetic map. To be sure, the bricks and mortar of the operation will include a genetic testing and sample collection and storage facility. We'll be the first to say that Millennium isn't the first biotechnology company to venture into this space, but we can say that it's the first time an already successful biopharmaceutical company has established this kind of business under its own umbrella. This moves Millennium farther down the technology curve, where companies won't be marketing just products, but a whole range of services all bundled together, including diagnostic tools coupled with drugs and test kits to measure prognosis. This is the essence of personalized medicine.

Historical perspective

Millennium is delivering on this promise through its current products as well, evidenced through the productivity of its researchers and its proprietary pipeline. The company's lead clinical compound is Velcade (MLN-341), currently in a phase 3 clinical trial for multiple myeloma.

Velcade is a small molecule that causes apoptosis (aka self-destruction) of cancer cells. Multiple myeloma is a plasma cell tumor, which is a disease in which certain cells in the blood (called plasma cells) become cancer. Plasma cells are made by white blood cells called lymphocytes. The plasma cells make antibodies, which fight infection and other harmful things in the body. When these cells become cancer, they may make too many antibodies and a substance called M-protein is found in the blood and urine. Only they make just one kind of antibody, at the expense of all the other normal antibodies that people need to fight infections and to carry on other normal body processes. As a result, patients become particularly susceptible to bacterial infections. While there are several types of plasma cell neoplasms, the most common type is multiple myeloma. In multiple myeloma, cancerous plasma cells are found in bone marrow. The disease currently affects 50,000 people in the United States, and as many as 14,000 new cases are diagnosed every year. And so far, standard of care has

included high-dose chemotherapy plus stem cell transplant, chemotherapy with thalidomide, and high dose steroids. But these are all shotgun treatments, killing healthy and harmful cells alike. They represent the old paradigm of cancer care. There aren't any effective and targeted treatments, and if Velcade clears phase 3 trials, oncologists would adopt it quickly. We estimate that the market potential for Velcade in this indication could top $200 million, admittedly a niche market. But sales for the drug could be substantial if it's eventually approved in other indications. In addition to the phase 3 trial examining Velcade in the treatment of multiple myeloma, the drug is also in 28 different trials, including four phase 2 clinical trials for the treatment of solid and certain blood tumors, including chronic lymphocytic leukemia.

Proteasomes: Millennium's core expertise

Velcade springs from one of Millennium's top research programs and from a core expertise of the company—proteasomes. What's a proteasome, you ask, and how does it treat cancer? It's a complex of proteases, which are basically enzymes for breaking down proteins. As we've discussed previously, proteins carry out the nuts and bolts of managing bodily processes. Hormones are proteins and so are antibodies and enzymes. Proteins are the regulatory messages that cells send and receive, turning metabolism on and off, keeping our hearts beating, and transmitting instructions from our brains to our muscles and organs. In human physiology, the right protein is everything. Normally to produce a protein like insulin, our body first scans for the gene that contains the code for manufacturing insulin and then copies it out from the DNA into an intermediate set of instructions called messenger RNA (*mRNA*). The process of copying the gene is called *transcription*. Another set of molecules, ribosomes, uses the mRNA as templates to manufacture proteins. Proteins are thus the "business end" of genes, the final products that carry out all the DNA instructions. So many drug researchers are not just mapping the genome, they are plumbing the proteasome—concentrating on identifying and targeting modifications made to proteins manufactured from mRNA templates. Add Millennium to that pioneering list.

So proteasomes work by essentially preventing the production or function of proteins implicated in causing certain diseases. Take Velcade. It prevents a protein called NFK-B from migrating to the nucleus of cancer cells, where it is responsible for stimulating the release of certain growth factors that instruct the tumor cell to continue dividing. Proteasomes is a core expertise for Millennium, in much the same way that Vertex has staked claims in specific gene families. Millennium has another proteasome drug in clinical development—its MLN-519, which is an oral proteasome inhibitor in phase 1 studies for the treatment of stroke. MLN-519 may be able to reduce tissue damage from a stroke if it's used within the first two hours of being stricken. It works by blocking the activation of certain inflammatory molecules that cause some of the tissue destruction experienced by the brain during a stroke.

Proteasomes aren't without some controversy, although we believe it's overblown. Millennium's lead drug Velcade—as well as the company's stock price—took a hit last month with the publication of a report from scientists studying brain-wasting diseases linked to mad cow, which warned that proteasome inhibitors like Velcade could have the potential to set off similar brain deterioration. We believe the findings aren't a cause for concern. First, they were generated by testing proteasome inhibitors (not Velcade) on cells from mouse brains that were suspended in Petri dishes—hardly the most efficient model for the behavior of these drugs in humans. Also, Velcade isn't able to cross into the brain, so even if the drug did cause some effect on brain cells, it wouldn't be able to reach them. The only downside we see from the report is the interest it piqued inside the National Cancer Institute and the FDA. Previously, there was speculation that the FDA might approve Velcade if the results from the phase 2 trial to be released this week were particularly strong. But with limited safety data and the suggestion that the drug could have some untoward side effect on the brain, we expect the FDA to require Millennium to complete the full phase 3 trial before approving the drug. (Indeed, after learning of the possible risk, the NCI held several meetings during the summer with experts in prion disease and with the FDA, and the researchers walked out of the meeting saying that they would require more thorough neurological evaluation of patients.)

Millennium initiated its phase 3 trial of Velcade in the treatment of multiple myeloma in June of 2002. The trail will enroll 600 patients with advanced disease who have failed one of three prior therapies. The study will be powered to look for a 30 percent improvement over an estimated time-to-tumor progression of 12 months. Secondary endpoints include clinical benefit, quality of life, survival, and response in certain surrogate markers for cancer such as tumor size and M-protein levels. As we mentioned earlier, in May 2002, Millennium presented results from the first group of 78 patients from its phase 2 trial of Velcade. The drug was tested on patients with relapsed or refractory multiple myeloma. About 77 percent (54 of the 70 evaluable patients) showed stable or reduced protein levels (an indicator of tumor burden) after Velcade therapy for up to 24 weeks. Specifically, 20 percent showed a greater than 90 percent reduction in the tumor marker, while another 47 percent had at least a 25 percent reduction. The results that will be presented this week comprise the rest of the 202

patients enrolled in this trial, as well as longer-term data on the 78 patients whose results have already been reported.

Not a one-trick pony

The current buzz on Wall Street is that the data is going to be positive, but as we mentioned earlier, we see Millennium as a good, long-term stock pick and not a near-term trading play. We would advise investors to tread carefully this week if they're inclined to buy this stock. Positive news has already been factored into Millennium's stock price (which curiously has been up sharply over the past two weeks). As a result, the downside from disappointing results from the Velcade trial will be far larger than the near-term pop that the stock is likely to experience if the results are surprisingly strong.

Clearly, Millennium's near-term performance is riding on the success of Velcade, but the company is hardly a one-trick pony. The company has three other cancer compounds in phase 1 clinical trials as well as two drugs in phase 2 clinical trials for different inflammatory diseases (in addition to MLN-519 for stroke). The company also recently put a compound in phase 1 trials for obesity and expects to move at least two preclinical candidates into trials for cardiovascular diseases.

KEY RECENT COLLABORATIONS (Entered into during 2001)

ABBOTT: Exclusive five-year alliance entered into in March of 2001, where the companies agree to develop drugs, diagnostics, and pharmacogenomic products for metabolic diseases, including diabetes and obesity. Abbott will purchase $250 million in Millennium stock over two years. The companies will share profits worldwide.

ROCHE: Three-year, exclusive collaborative agreement to develop diagnostic products for rheumatoid arthritis. Roche has marketing rights worldwide. Millennium will receive a licensing fee, funding for research, milestone payments, and royalty fees.

PROTEIN DESIGN LABS: Millennium has a five-year agreement to obtain up to three humanized antibodies under Protein Design's technology. Millennium will pay Protein Design an upfront fee and royalties on net sales.

Of Millennium's phase 1 cancer drugs, one of the most interesting is MLN-576, an oral inhibitor of topoisomerases I and II being tried in the treatment of solid cancer tumors (Millennium in-licensed this drug from **Xenova** (XNVA). Topoisomerases are enzymes responsible for maintaining the proper DNA configuration so that DNA replication can occur. Like proteasomes, inhibition of these enzymes is designed to lead to apoptosis, or cell death. The company's other cancer compounds include MLN-591, a radio-labeled antibody for the treatment of prostate cancer that Millennium in-licensed from **BZL Bio-Logic Systems** (BLSC) in April 2001, and MLN-518, a small-molecule inhibitor of the FLT-3 receptor tyrosine kinase (RTK). MLN-518 is also very interesting to us. It's a homegrown drug that could eventually emerge as a significant cancer drug. FLT-3 is a gene that makes the enzyme tyrosine kinase, which is believed to be responsible for tumor growth. In AML (acute myeloid leukemia), the FLT-3 gene is stuck in the on position and may cause the defective cell to reproduce without limit. The gene may represent a vulnerable point in the cancer cell that specifically targeted drugs could exploit. In other words, if you can block FLT-3, you might be able to turn off the switch that instructs the cancer cell to keep dividing.

AML is a market in need of this kind of innovative approach. The disease is rapidly progressing, resulting in the accumulation of immature cells in the marrow and blood. The proliferation of these abnormal cells causes decreased production of normal red and white blood cells and of normal disease-fighting antibodies. According to the American Cancer Society, AML represents 90 percent of all adult acute leukemias, with an estimated 10,600 new cases annually in the United States. The overall five-year survival rate for AML is 14 percent, and approximately 7,400 Americans are expected to die from AML this year. AML is usually treated by a combination of cytotoxic drug therapies, and, in some cases, bone marrow transplantation. But approximately 30 percent of patients with acute myeloid leukemia have a FLT-3 gene mutation, which may be involved in the growth and survival of the AML cells. Currently, AML patients who express the FLT-3 mutation represent a group with poor prognoses and few treatment options. The targeted approach to this patient population is consistent with Millennium's often-stated goal of developing personalized medicine based on an understanding of the human genome and the genetic basis of disease. Millennium started the phase 1 trial of MLN-518 at the beginning of 2002. About 40 patients with relapsed AML who are not candidates for conventional remission-induction chemotherapy will be enrolled.

Among Millennium's portfolio of drugs for inflammatory diseases, the compound that's furthest along is MLN-02, which is in phase 2 clinical trials for the treatment of inflammatory bowel disease. MLN-02 is a humanized monoclonal antibody to the alpha-7-beta-4 integrin receptor. In September 2002, Millennium and its partner, **Genentech** (DNA), announced negative results from a phase 2 trial studying MLN-02 in Crohn's disease. The trial didn't achieve statistical significance in its primary endpoint in reduction of disease severity but there was a benefit in inducing remission. Detailed results are expected at the Digestive Disease Week conference in May 2003. Phase 2 trials are currently ongoing in ulcerative colitis, with results expected in the first half of 2003. Millennium may elect to perform additional phase 2 trials.

It should be noted that drugs that target Integrins are another broad area of focus for Millennium. When cells are surrounded by other cells, integrins are proteins on the cell surfaces that attach one cell to another at specific locations. Integrins are so named because they integrate the function of the cell with the outside world. These proteins can be thought of as Velcro on the surface of the cell.

Integrins serve a notably broad range of biologic processes, including platelet aggregation and the mobilization of while blood cells (known in medical parlance as *leukocyte extravasation*). The loss of an adhesion interaction may result in disease, as may the stimulation of excessive adhesiveness. Among the company's other drugs targeting integrins are one for the treatment of inflammatory diseases, known as MLN-01, which is in phase 2 trials for the treatment of the complications of stroke. MLN-01 is a humanized monoclonal antibody against beta-2 integrins, which are adhesion molecules involved in the recruitment of white cells to sites of inflammation. Millennium is collaborating with XOMA on the phase 2 trial that examines whether MLN-01 will help reduce tissue damage after a stroke. Rounding out the other interesting compounds in Millennium's pipeline is MLN-4760 in phase 1 studies for the treatment of obesity. The drug is Millennium's first small molecule against a genomic target for the treatment of a metabolic disease and the first ever to enter clinical trials from Millennium's collaboration with Abbott. MLN-4760 inhibits carboxypeptidase, an enzyme believed to play a role in diet-induced obesity and insulin sensitivity.

Millennium's lead compound is arguably Integrillin, which as we've mentioned, is FDA-approved and widely used during angioplasty and in the treatment of acute coronary syndrome. The company acquired the compound through its purchase of COR Therapeutics in February 2002.

Integrillin is what's known as an IIb/IIIa inhibitor. The drug works by blocking a specific integrin called GPIIb/IIIa that's found on the surface of platelets. These surface markers are what cause the platelets to aggregate, sticking together to form clots. In this way, Integrillin works as a blood thinner. In addition to Integrillin, there are two other platelet IIb/IIIa inhibitors on the market: ReoPro, a monoclonal antibody by **Johnson & Johnson** (JNJ); and Aggrastat, an injectable small molecule (which is the same kind of drug as Integrillin). Among the three different drugs, Integrillin has the broadest indications, is priced competitively, and, as a result, enjoys a 60 percent patient share.

We expect Integrillin sales to continue to grow as the drug is expanded into other indications and gains wider use in acute coronary syndrome and broader acceptance as a first-line treatment for unstable angina in the emergency room. Right now, Wall Street is forecasting about 30 percent growth for Integrillin sales to just under $300 million for 2002, with about 20 percent growth in sales in 2003. To increase Integrillin's acceptance as a treatment for unstable angina, Millennium is conducting the CRUSADE trial which is examining the use of Integrillin in the setting of acute coronary syndrome in about 60,000 patients spread over 600 hospitals. Millennium also plans to initiate phase 2 trials on Integrillin in coronary artery bypass surgery (CABERNET) and for heart attacks in combination with TNKase (ADVANCE-MI). We're not very optimistic but the CABERNET trial—surgeons don't like to operate on patients who've been given IIb/IIIa inhibitors because these patients tend to bleed more during surgery. The ADVANCE-MI trial, however, could lead to a new and lucrative indication for the drug.

The Integrillin franchise recently got a little bump from data presented at the recent annual meeting of the American Heart Association on a competing drug called Angiomax, produced by **The Medicines Company** (MDCO). The data showed that Angiomax was as effective as the combination of heparin (another blood thinner) plus a IIb/IIa inhibitor like Integrillin (this latter combination is the current standard of care) in conjunction with elective angioplasty procedures on low-risk heart patients. While Angiomax didn't prove to be more effective than the heparin-IIb/IIa combination, it was less expensive and left patients less prone to bleeding. Therefore, you can say, it has certain advantages. We believe these results will have little impact on Integrillin's primary market, which is in the higher-risk patients—especially patients who roll into the emergency room with chest pain and then go on to have angioplasty or "rule in" for small heart attacks. Consider this: it's estimated that 200,000 elective angioplasty procedures are performed each year. These will comprise the primary market that Angiomax is going to go after. However, this is a population of low-risk patients that represents less than 4 percent of total Integrillin sales. We believe that interventional cardiologists—the primary users of IIb/IIIa inhibitors—are unlikely to extrapolate the data of noninferiority for Angiomax in low-risk patients to their high-risk patients. We can't rule out the possibility that Angiomax may eventually prove beneficial in the high-risk patients as well, but we believe, nevertheless, that there will continue to be an important place in the treatment protocols for drugs like Integrillin.

As a result, we don't expect this to impact sales growth for Integrillin. Integrillin will continue to be a solid earner and could more than justify Millennium's current stock price. Look at it this way. First assume peak sales of Integrillin at around $500 million, which is conservative, and then factor in the 50 percent profit split that Millennium has with **Schering-Plough** (SGP). That means

that the implied value for the drug is about $1.25 billion (assuming that drugs are valued at five times their peak sales, which is the low end of the historical average for that widely accepted valuation metric). Adding in Millennium's net cash of about $1.1 billion, it gets you pretty close to the company's current market capitalization. That means Wall Street is currently valuing Millennium's research capabilities, its intellectual property, its patents, and its product pipeline at zero.

Part of the reason that Wall Street has soured to Millennium's stock is the recent bad news over its Crohn's drug, as well as a drug in development for asthma. We believe these are the usual set backs and represent "business as usual" for a pioneering biotechnology company. For every product that clears clinical trials, as many as ten will fail. Millennium was amply demonstrated that it is capable of coming up with promising leads, and we believe more than one of its current crop of clinical candidates will make it through, more than justifying the valuation that the entire pipeline is now being assigned. The company has enough cash on hand to fund its operations for another three to four years. This should be more than enough time to allow one or more of its clinical candidates to progress to the point where it will be able to raise additional capital.

Millennium is a technology leader and a pioneer in the development of genomically targeted drugs. With a burgeoning pipeline, Millennium will certainly have some hits to go with its recent misses. The company's product portfolio, and its stock price, will finally reflect the realization of its original promise.

Scott Gottlieb, M.D.
November 29, 2002

BIOTECH COMPANIES

COMPANY	TECHNOLOGY LEADERSHIP	REFERENCE DATE	REFERENCE PRICE	11/29/02 PRICE	52-WEEK RANGE	MARKET CAP
ABGENIX (ABGX)	ANTIBODY THERAPEUTICS	9/30/02	6.61	9.27	5.16 - 38.16	811.8M
CELL GENESYS (CEGE)	CANCER THERAPEUTICS	6/10/02	13.24	13.03	9.32 - 25.02	469.4M
COGENT NEUROSCIENCES (NONE*)	NEUROGENOMICS	5/2/02				
CURAGEN (CRGN)	CELLULAR SIGNALLING	3/13/02	17.67	5.34	3.40 - 25.88	261.4M
GILEAD SCIENCES (GILD)	RATIONAL DRUG DESIGN	12/05/01	33.88**	39.42	26.08 - 40.00	7.8B
HUMAN GENOME SCIENCES (HGSI)	CELLULAR SIGNALING	10/26/01	43.97	10.66	8.15 - 47.31	1.37B
ISIS PHARMACEUTICALS INC. (ISIS)	ANTISENSE THERAPEUTICS	7/9/02	7.30	8.63	6.10 - 27.15	475.8M
MDS PROTEOMICS (NONE*)	PROTEOMICS	2/05/02				
MILLENNIUM PHARMACEUTICALS (MLNM)	TARGETED DRUGS	11/29/02	10.01		7.13 - 36.25	2.88B
NANOGEN (NGEN)	BIOCHIPS	10/2/01	4.95	2.05	1.50 - 6.99	45.0M
OSI PHARMACEUTICALS (OSIP)	CANCER THERAPEUTICS	8/27/02	16.16	21.59	11.50 - 50.94	784.1M
QUOREX (NONE*)	RATIONAL DRUG DESIGN	12/05/01				
SEQUENOM (SQNM)	PHARMACOGENOMICS	1/09/02	9.00	2.19	1.25 - 11.44	86.3M
TRIAD THERAPEUTICS (NONE*)	RATIONAL DRUG DESIGN	4/9/02				
VERSICOR (VERS)	ANTI-INFECTIVES	10/29/02	10.00	11.29	7.65 - 25.40	297.8M
VERTEX (VRTX)	RATIONAL DRUG DESIGN	9/17/01	28.60	18.58	12.67 - 32.45	1.42B

* Pre-IPO startup companies. ** Split-adjusted price.

NOTE: This list of Gilder Biotech Report companies is not a model portfolio. It is a list of technologies in the biotech paradigm and of companies that lead in their applications. Companies appear on this list only for their technology leadership, without consideration of their current share price or the appropriate timing of an investment decision. The presence of a company on the list is not a recommendation to buy shares at the current price. Reference Price is the company's closing share price on the Reference Date, the day the company was added to the table, typically the last trading day of the month prior to publication. The author and other Gilder Publishing, LLC staff may hold positions in some or all of the companies listed or discussed in the issue.

References

Almond, J. B. and G. M. Cohen. 2002. The proteasome: a novel target for cancer chemotherapy. Leukemia 16:433–443.
Hood, J. D. and D. A. Cheresh. 2002. Role of Integrins in Cell Invasion and Migration. Nature Reviews Cancer 2:91–100.
Kloetzel, P. M. 1998. The proteasome system: a neglected tool for improvement of novel therapeutic strategies? Gene Therapy 5:1297–1298.
Zwierzina, H., et al. 1999. Endogenous FLT-3 ligand serum levels are associated with disease stage in patients with myelodysplastic syndromes. Leukemia 13:553-557.