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The Focus Factor: Why Bigger Isn't Better

As Big Pharma transitions into marketing and distribution, OSI and Vertex show the way toward real innovation

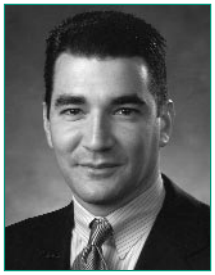
Time Warner was a publishing powerhouse until it tried to own the Internet, and AT&T was a solid telephone service provider before it failed to execute its strategy to aggregate cable. Even New York City's budget was perpetually in the black before it bit off the Bronx.

Big isn't always better, one reason why the Pfizer-Pharmacia [PFE] merger announced last month was received with such cool odium on Wall Street. Market movers read the entrails of the new beast and didn't like what they saw. A week after the announcement, Pfizer had lost $40 billion in market capitalization—roughly 20 percent of its value.

The merger creates a pharmaceutical behemoth with leading products in every therapeutic category. The new entity will be a marketing and sales powerhouse. Pfizer-Pharmacia is a one-stop shop for drugs and a seductive marketing partner for small biotechnology companies. With a sales force of more than 13,000 reps making about 2 million details on doctors every year, Pfizer-Pharmacia will become the partner to have in just about every therapeutic category. That was the point.

But big pharmaceutical companies are net consumers of intellectual property. They are not net producers, and as such, are increasingly dependent on the biotechnology industry for new product ideas. Pfizer-Pharmacia is no exception, one reason management from both companies focused on innovation and R&D when explaining the rationale of their merger to Wall Street at a closed-door meeting with analysts.

The talk rang hollow. Peter Corr, Pfizer's senior vice president of Science and Technology, promised the assembled analysts that Pfizer would file 20 significant new molecular entities (NMEs) over the next five years, an unparalleled level of productivity. Pharmacia Chairman and CEO Fred Hassan was only slightly more cautious: "We do believe that the combined company can lead the way in increased R&D productivity, but one must also be realistic that the major outcomes from the many new technologies, including



Dr. Scott Gottlieb

"Big pharmaceutical companies are not net producers of intellectual property. They are net consumers"

INSIDE:

TARCEVA ONGOING CLINICAL TRIALS

Phase	Indication	Trial Sponsor	Results
3	NSCLC	Genentech	4Q03
3	NSCLC	Roche	2004
3	NSCLC	OSIP	Late 2003
3	Pancreatic Cancer	OSIP	Late 2003
2	Refractory NSCLC	OSIP	Early stage
2	Ovarian CA	OSIP	Early stage
1b	Solid Tumors	OSIP	Early stage

Note NSCLC = Nonsmall-cell lung cancer.

genomics, are five to ten years away for most companies."

The engine of growth in this industry remains product innovation. To take full advantage of the new technology that is driving drug development (i.e., genomics, proteomics) companies should be getting more focused by structuring themselves around specific diseases and families of molecular targets. Instead, driven largely by regulatory and economic imperatives, pharmaceutical companies keep getting bigger. But size, and marketing clout, will never supersede the need for innovation. The drug companies can't grow their way out of their declining research productivity.

Some big drug companies are coming to grips with this reality. As Eli Lilly's [LLY] John Lechleiter recently told Roger Longman, a writer from the respected drug industry magazine *In Vivo*: "I don't think anyone understands the right levers to pull in the innovation business. GlaxoSmithKline [GSK] is at least publicly asking 'how do you manage a $4 billion R&D budget?' The industry may have grown faster than our ability to manage R&D." So companies like Lilly, Bristol-Myers Squibb [BMY], Merck [MRK], and one of our former favorites Elan [ELN], are orienting themselves around areas of therapeutic expertise, bringing focus and synergies to their research efforts. Lilly concentrates on diabetes and neurology, Bristol Myers on cancer, Merck on vaccines and neurology—among other areas, and Elan on neurology.

Why does size stifle? At the scientific level, focusing on a specific disease area, or even on a single molecular target or receptor family, allows scientists to become adept at mapping the key interactions that mitigate a disease, identifying new genes or therapeutic targets, uncovering new regulatory elements, or characterizing responses to different drug candidates. The goal is to integrate all the "omics" (i.e., proteomics, genomics) and come up with some meaningful model for drug discovery. A discrete biological function can only rarely be attributed to an individual molecule, in the sense that the main purpose of hemoglobin is to transport gas molecules in the bloodstream. In contrast, most biological functions arise from interactions among many components.

Intellectual island

Possessing a little island of intellectual property around one receptor or drug lead might give you a single drug but misses all the other receptors in between that make equally attractive targets. Taking the approach of looking at the entire receptor family or more broadly, a class of therapeutic targets, provides the opportunity to own outposts along the way, where many equally attractive drugs might be concealed. This approach requires a critical mass of know-how and a set of infrastructure to pursue it.

By maintaining far-flung research operations in dozens, if not hundreds, of different diseases and target families, big drug firms are prevented from developing the core expertise that's required. No matter how much money a big company throws at its drug development problems, it's doubtful it can maintain enough key scientists and own enough intellectual property to be adept in every therapeutic area. Firms that don't focus their R&D in specific diseases are just spinning their wheels and wasting their money.

At a business level, owning a critical mass of intellec-

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tual property in a particular therapeutic area also gives a company a firm stake, forcing late comers to have to pay up to patent around their position or form a favorable alliance. Elan, if it can survive its accounting woes, is years ahead of competitors in some of neurology's most attractive new targets. Assuming Elan doesn't sell its IP to raise cash, competitors are going to have to pay homage to its patent portfolio, or settle for second.

The benefits of focus are one of the reasons we remain fans of Vertex Pharmaceuticals [VRTX]. It tops our list of stock picks.

Vertex still on top

Vertex follows a format toward which every drug company aiming to innovate will have to evolve, by focusing its discovery efforts around specific therapeutic areas (principally drugs that treat autoimmune diseases and inflammation, neurological disorders, and infections). Within these areas of therapeutic interest, Vertex organizes another layer of specialization around specific categories of molecular targets and gene families. By focusing in this way, it's easier for Vertex's researchers to leverage each other's discoveries.

Among the molecular targets where Vertex toils are kinases, neurophilin ligands, protease, caspase, and the enzyme inosine monophosphate dehydrogenase. Vertex looks for specific families of molecular targets that act as sentinels or regulators in processes that are at the crossroads of fundamentally important pathways. This allows scientists to identify biochemical connectivity.

We believe that general "design principles"—profoundly shaped by the constraints of evolution—govern the structure and function of the body's molecular machinery. Since the body is highly conservative—using a finite number of redundant molecular systems to run all of its different networks—the science becomes simple once you zero in on the key regulatory nodes that are at the nexus of many different molecular circuits. If you find the right node and come up with the right compound to bind to it, you can have a drug that works in a lot of different diseases.

Take the TNF inhibitors Enbrel and Remicade. These drugs—antibodies that mop up the inflammatory protein Tumor Necrosis Factor—were originally designed to treat rheumatoid arthritis. But we've learned that TNF isn't only a culprit in RA, but a broad selection of disease from Crohn's to psoriasis, and maybe even heart failure. The same inflammatory pathways regulating RA are at work in other ailments.

By focusing on nodes at the intersection of different molecular systems, Vertex looks for drugs that could alleviate a broad swath of human suffering. The end result is evident in Vertex's product pipeline.

Take protease inhibitors. You can look simply at viral proteases (those that target HIV or hepatitis C). But this narrow orientation makes it hard to understand the mechanics of the target or appreciate its other therapeutic opportunities.

Vertex looks at proteases as a gene family, so it sees all the other places where targeting them can yield therapeutic benefits. For example, Vertex is studying the role of proteases in preventing the plaque build-ups believed to cause Alzheimer's disease. "You can see the scientific cross-talk and synergy by comparing similarities of proteases from a gene target or gene family point of view," said Vertex's director of research John Thompson. "Starting with an understanding of the target helps you understand its utility and find additional opportunities and synergies."

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Vertex, he says, sees itself polarized on both ends: specializing in therapeutic areas on one and target families at the other. They develop gene family platforms that are universal to a variety of diseases, giving them a greater multiplicity of new drug opportunities—taking advantage of the wisdom that comes with specialization. Some areas Vertex is looking to grow into are neurology, particularly stroke and neurodegeneration. Another is oncology, where Vertex hopes to roll out some new compounds from its program in kinases, where Vertex's collaboration with Novartis is among the very largest integrated drug discovery programs anywhere.

Enzyme targets

One of the interesting molecular targets Vertex is looking at is the enzyme inosine monophosphate dehydrogenase, a family of metabolic enzymes that serve as gatekeepers of many different processes. The enzyme is essential for production of nucleotides, the building blocks of RNA and DNA.

Vertex's drug candidate, VX-148, is aimed at treating autoimmune diseases by inhibiting IMPDH in cells believed to be responsible for the overactive immune response produced in patients with these diseases.

Inhibiting IMPDH blocks DNA synthesis, which is essential for lymphocyte proliferation (part of the immune response).

Vertex is also targeting the same enzyme to treat hepatitis C, showing the synergies of focusing on molecular targets that cut across a variety of diseases. The compound merimepodib (another inhibitor of inosine monophosphate dehydrogenase), is in Phase 2 clinical trials for treatment of HCV infection.

Another one of the target families on which Vertex focuses is caspases. These molecules play integral roles in both programmed cell death and inflammation and are implicated in a variety of diseases.

From Sepsis To Cancer

Take sepsis, a severe, life-threatening bacterial infection in the bloodstream that overwhelms the body's immune system. It affects nearly 700,000 people in the United States each year and an additional 1.2 million in Europe and Japan. Vertex is conducting preclinical studies with VX-799, a potent small molecule caspase inhibitor and potential sepsis treatment. Another of Vertex's lead clinical compounds, Pralnacasan (VX-740), is an inhibitor of ICE, an enzyme that regulates a stop along the same molecular pathway. Building upon expertise gained in the discovery of inhibitors of ICE (AKA caspase-1) for inflammatory diseases, Vertex is extending its research efforts to additional targets within the same target family.

Caspases are becoming a big target for new drugs precisely because they're implicated in so many different diseases. The goal is to discover, develop, and commercialize caspase inhibitors that block or reduce apoptosis (programmed cell death), which has been implicated in cell and tissue damage in everything from stroke to myocardial infarction and a range of neurodegenerative diseases. Vertex has determined the three-dimensional atomic structure of four different caspases, one from each subfamily of the target, and more than 50 enzyme and inhibitor complexes. By holding a lot of IP in this area, Vertex's scientists are able to identify all of them. Some turn out to be good for treating sepsis, some for autoimmune diseases, and some perhaps for cancer.

Caspases are becoming a big target for new drugs precisely because they're implicated in so many different diseases.

Or consider again Vertex's expertise in kinases. It's a vast target area because there are so many kinases, and picking the right one can be tricky. But as a drug target, it's already been confirmed. Genentech's cancer drug Herceptin targets the HER-2 transmembrane tyrosine kinase receptor, and Novartis AG's Gleevac inhibits three different tyrosine kinases.

Many kinases have different isoforms that are each involved in different diseases. Often one drug won't target all the different isoforms, but by understanding how kinases work, you can tweak the drug you have in order to make it hit the right target. This takes know-how that Vertex has acquired in large measure because of its orientation around molecular families. Vertex looks at kinases as a category of targets rather than focusing on just a single kinase aimed at a single disease.

This year, Vertex initiated a Phase 1 clinical study with VX-702, targeting the treatment of inflammatory diseases, including rheumatoid arthritis (RA). VX-702, one of Vertex's second-generation p38 MAP kinase inhibitors, emerged as the result of focused efforts to discover and develop multiple drug candidates directed at p38 MAP kinase. Phase 2 clinical data from the first-generation compound, VX-745, provided the first demonstration of a clinically relevant anti-inflammatory effect in rheumatoid arthritis with a p38 MAP kinase (MAPK) inhibitor.

The basic principle of realizing synergies by focusing on particular diseases—and indeed specific molecular targets—are especially true in cancer. In contrast to this apparently impenetrable thicket of complexity, several lines of investigation indicate that the emergence of all cancers from normal precursor tissues is governed by a common set of mechanisms that are limited in number.

The economies to be drawn by building a core expertise in cancer, and in the most attractive therapeutic targets, bring us to another favorite company: OSI Pharmaceuticals [OSIP].

The OSI opportunity

OSI focuses almost exclusively on cancer and has consummated a number of deals in the past two years to shed itself of peripheral business and acquire additional cancer research capabilities. The company has a well-balanced clinical development program with six anti-cancer products in various stages of human clinical trials: two products are in the middle-to-later stages of development, and four are in early stages.

OSI's lead product, Tarceva, has been developed to disrupt the signal transduction of a well-known thera-

peutic target, epidermal growth factor receptor (EGFR). It's estimated that more than 700,000 cancer patients in the United States alone are diagnosed with tumors that are known to overexpress EGFR.

We like OSI for Tarceva, but equally important, the company's singular focus on cancer and, increasingly, on particular families of targets. Like Vertex, OSI is directing its efforts where it aims to excel—in this case, cancer—and building the requisite know-how around a handful of the most highly valued targets.

Any discussion of OSI must begin with Tarceva. Enthusiasm for the class of drugs to which Tarceva belongs recently received a setback on news from AstraZeneca [AZN] that its EGFR candidate, Iressa, when given with standard chemotherapy, failed to improve the survival rate of 2,000 lung cancer patients in two large, late-stage clinical trials. AstraZeneca hasn't released the actual results as of press time for this report, but said that two Phase 3 clinical trials showed that Iressa, taken as a pill, did not provide improvement in survival when the drug was added to a standard chemotherapy treatment. (We expect full results to be released at the European Society for Medical Oncology meeting in October and at AstraZeneca's FDA hearing for Iressa, scheduled for September.)

Blockbusters no more?

Based on these results, Wall Street is assuming that the class of epidermal growth factor (EFG) inhibitors will be relegated to use in patients with refractory (untreatable) disease, a significantly smaller market than their prior assumption (that these drugs would be used in both early- and late-stage patients). As a result, OSI Pharmaceuticals dropped 58 percent the day AstraZeneca unveiled its disappointing news (it has drifted up ever since.) The perception on Wall Street was that none of these drugs would turn into the blockbusters once envisioned. Since OSI Pharmaceuticals was seen as being most dependent on the success of its EGFR candidate, investors assumed it was also the most vulnerable.

Last May, however, AstraZeneca presented results that showed Iressa as highly effective when used alone (or as monotherapy) in patients with advanced lung cancer who have run out of other medical options. The FDA is currently reviewing the approvability of Iressa used in this way, and the drug was slated for discussion at an upcoming FDA cancer drug advisory panel meeting in September.

The new trials showed only that Iressa didn't work as an adjunct to chemotherapy in lung cancer.

OSI DRUGS IN CLINICAL TRIALS

Product	Drug Type	Status	Collaborator
Tarceva	EGFR Inhibitor	3	Genentech/Roche
OSI-211	Liposomal Lurtotecan	2	OSI-owned
OSI-7836	Gemzar analog	1	OSI-owned
OSI-754	Farnesyl Transferase	1	OSI-owned
CP-632	VEGFR	1	Pfizer
OSI-7904L	Liposomal Thymidycate	1	OSI-owned

AstraZeneca's setback hardly spells doom for Tarceva or the drug's class, making OSI's sell-off an unprecedented buying opportunity.

The truth on Tarceva

For one thing, Tarceva is a different molecule than Iressa, and we believe a better drug. It is more potent and selective and has different pharmacokinetic properties.

The Iressa trial also wasn't well powered, designed as it were to detect a 35 percent improvement in overall survival—a benchmark that is too high.

Nor do we believe the news from AstraZeneca spells doom for that company's own drug, Iressa. It's possible we will identify a subgroup of tumors that respond best to these drugs based on a particular molecular marker they express (as we did for Herceptin) or that these drugs will be used as maintenance treatments after standard chemotherapy. Or we will identify another chemotherapy agent besides platinum-based drugs (used in the current trial released by AstraZeneca) that these drugs synergize with. As far as mechanism of action is concerned, it's illogical to suggest that these drugs do not have additive effects when used in combination with standard chemotherapy. In its clinical trials in breast cancer, Genentech's Herceptin antibody showed significant results in combination with chemotherapy, and it's in the same receptor family.

Iressa, we're reminded, was also tested in lung cancer, a notoriously difficult disease. Tarceva is being tested in lung cancer, but also in pancreatic, breast, head and neck, and ovarian cancer. It's quite possible these drugs will emerge as effective treatments for one cancer type, but not for others.

AstraZeneca's CEO is reported to have said that while they have no data, their scientists believe that no EGFR drugs will be used successfully in combination therapy. We disagree strongly. ImClone's [IMCL] existing Erbitux data show definitively that this EGFR inhibitor works well in combination with established

chemotherapeutics. The studies looking at Iressa as monotherapy were equally impressive. Clearly these drugs work. Like all clinical questions, figuring out for whom they work best—and how they're best deployed in clinical practice—will take some time to resolve.

UPCOMING TARCEVA MAJOR MILESTONES

Present additional data on Tarceva at the EORTC meeting	2nd half of 2002
Present data on Tarceva in pancreatic cancer at ASCO	1st half of 2003
File Tarceva NDA (new drug application) in pancreatic cancer	1st half of 2003
Phase III data in refractory NSCLC	mid-2003
Phase III data in first-line NSCLC	2nd half of 2003
Launch Tarceva in pancreatic cancer	1st half of 2004
File Tarceva NDA for front-line NSCLC	1st half of 2004

It's all the more reason to get it into the hands of doctors who can start deploying it into their chemotherapy regimens. We're also reminded of the TNF inhibitors, which were also written off many years ago after some mixed results. Those drugs went on to become outstanding medicines. It wasn't until they were approved for a narrow indication, and put in the hands of doctors who began using them for other things, that doctors realized just how broadly applicable and effective they are.

There's more to OSI's story than Tarceva. The company is becoming a major force in cancer drug research given the quality of its small-molecule pipeline. In addition to Tarceva, it is developing improved versions of cytoxic agents and novel targeted therapies.

OSI has enhanced both its pipeline and development capabilities through major transactions. In 2001, OSI acquired three products plus clinical development facilities and personnel from Gilead Sciences [GILD] in exchange for $130 million in cash and 925,000 common shares, as well as the pre-clinical and pilot scale manufacturing facilities of British Biotech in exchange for $13.9 million cash.

OSI now has five anti-cancer drugs in clinical trials, three of which (OSI-211, OSI-7836, and OSI-7904L) were acquired in 2001 from Gilead, and two developed by OSI under its original collaboration with Pfizer (Tarceva and OSI-754). OSI also has other non-oncologic programs, although these remain small and not integral to their core mission to become a leading cancer company.

Looking into OSI's oncology portfolio, we believe the most promise belongs to its work with two receptors: the VEGF receptor tyrosine kinase and farnesyl transferase.

Farnesyl transferase is a key enzyme involved in the regulation of the growth and proliferation of cancer cells. Inhibition of protein farnesylation alters the activity of a number of proteins important in tumor cell proliferation, including the ras family of oncogenes. The most advanced inhibitor in this class is Schering-Plough's lonafarnib, which is going into a Phase 3 trial for the treatment of ovarian cancer.

Oncogenes are mutant versions of normal genes that drive cell growth. The differences between oncogenes and normal genes can be subtle. The mutant protein that an oncogene ultimately creates may differ from the healthy version by a single amino acid, yet the alteration dramatically changes its function.

While oncogenes constitute only a small proportion of the full genetic set, they play major roles in triggering a wide range of human cancers. In their normal configuration, they choreograph the life cycle of the cell—the intricate sequence of events by which a cell enlarges and divides. When they are mutated there is no "off" switch for certain cell signals, resulting in continuous stimulation of cellular proliferation, continuously misinforming the cell, instructing it to divide when it should not.

Molecular switches

The best understood examples—the ras family of oncogenes—are the master controllers of a central cellular signaling pathway. They function as a molecular switch in a large network of signaling pathways, mainly by controlling the differentiation or proliferation of cells. Farnesyl transferase inhibitors "turn off" the signals that are stoking the growth of cancer cells.

OSI's compound, OSI-754, is an orally active inhibitor of the farnesyl transferase pathway. It's being developed for the treatment of bladder cancer, where mutant and overexpressed forms of the h-ras oncogene are known to be present.

Another one of OSI's clinical programs targets a class of molecular receptors known as the VEGF tyrosine kinase. VEGF is a human protein that stimulates the proliferation of both blood vessels and lymphatic vessels. Researchers recently discovered that it is associated with metastasis of breast cancer and malignant melanoma. The receptor that these VEGF blockers target is known as a kinase.

Most kinases exist as two major classes, as receptors on the cell surface or as molecules free floating in the cell's

cytoplasm. Kinases work as microscopic on/off switches inside complicated signaling cascades, called signal transduction. Tyrosine kinase inhibitors jam the signal.

OSI's lead compound in this program is CP-547,632. It's a small molecule inhibitor of this receptor that's currently in phase 1 clinical trials. It was developed through a joint collaboration with Pfizer. If approved, Pfizer will pay OSI a 6 percent royalty on product sales.

Drugs like CP-547,632 inhibit just the catalytic effect of deleterious kinases, leaving the function of other kinases unaffected. The drug blocks the formation of blood vessels required for tumor growth, a process known as angiogenesis. In May, the Food and Drug Administration approved the first small-molecule kinase inhibitor, Novartis's [NVS] Gleevac for the treatment of chronic myeloid leukemia which strikes about 6,000 Americans each year. The drug's discovery and approval was a landmark achievement for drug developers, dispelling the long-held myth that it was not feasible to develop selective inhibitors of key cell-signaling molecules as safe and effective medicines.

All of these drugs, including Tarceva, work by shorting the signals that instruct cancerous cells to grow and multiply. Scientists have been struggling to figure out the intricacies of cellular signaling for more than 20 years. Why is this suddenly a good investment idea?

Bioinformatics the key

Traditionally, researchers studied the manipulation of signaling pathways by analyzing changes in the activity of a single protein, or at most several proteins at a time. They lacked the tools to look at multiple cellular changes at once—the key to understanding how these complicated switches work. Tools of bioinformatics are unscrambling this regulatory network, allowing biologists to use computational and mathematical techniques to look at this complicated circuitry.

Clearly, OSI has a lot riding on the prospects of Tarceva, and we remain optimistic about this drug's potential for all the reasons we noted. OSI has entered into strong commercial partnerships for the drug at attractive financial terms.

The company enjoys sound financing, with about $560 million in cash and investments on hand, with a burn rate this year estimated around $120 million. The company recently raised $200 million in convertible senior subordinated notes with a coupon rate of 4 percent, a maturity in 2009, and a conversion price of $50 per share.

We remain hopeful that Tarceva will be a valuable addition to many cancer arsenals and believe OSI has a powerful discovery engine capable of creating other similarly attractive drugs. Wall Street has overreacted to the Iressa trial and driven OSI's stock at an extremely attractive valuation.

Among OSI's other portfolio products are some better formulations of old-style chemotherapy drugs that while less exciting from a new technology standpoint, warrant mentioning. While early-stage products, these could eventually generate significant sales: OSI-211, to treat a range of cancers, including lung and ovarian; OSI-7904L, for colorectal and metastatic breast cancer; and OSI-7836, for nonsmall-cell lung cancer.

OSI recently announced that it's accelerating the conclusion of its research alliance with Anaderm Research (a wholly owned subsidiary of Pfizer), focusing on novel treatments for skin and hair conditions. These were cosmeceuticals. We're encouraged by this deal. It signals that OSI is serious about focusing on oncology.

On our subscriber web site, we recently wrote about what it will take to bring biotech out of its funk. There is a historical rationale for biotech dutifully following a pharma upswing. It's based on the idea that investors only migrate into growth stocks once they become secure in their safe havens. A rising pharmaceutical market provides that kind of safety net for biotechnology stocks.

OSI HAS ENHANCED BOTH ITS PIPELINE AND DEVELOPMENT CAPABILITIES THROUGH MAJOR TRANSACTIONS AND NOW HAS FIVE ANTI-CANCER DRUGS IN CLINICAL TRIALS.

But there's also a strong argument why this kind of thinking may no longer be appropriate. As the big pharmaceutical companies morph into marketing and distribution powerhouses, it's doubtful they will continue to enjoy the same pipeline productivity they did during the past two decades.

If the pharmaceutical companies don't experience a sharp snapback, does that mean biotechnology is destined to a similar fate? The real question is whether investors will notice and whether biotech can dissociate itself from Big Pharma. Given the earnings news of the last two months, it should be hard for investors not to see that biotech is in much better shape than pharma.

As biotech and Big Pharma move in different directions, and biotech embraces the technology while pharma grows too fat to benefit from it, the innovation gap—as

well as the earnings' disparities—will become increasingly apparent. On Wall Street, some hedge fund managers are openly asking whether the enormous R&D budgets at the pharmaceutical companies would be better-spent by taking advantage of the advances of the biotechnology companies. This represents the ultimate capitulation. Wall Street is waking up to the reality that the biotech companies, not the big drug makers, will be the real innovators.

Companies like OSI Pharmaceuticals, and especially Vertex, which have focused their discovery efforts at pockets of expertise, are in the best position to take advantage of new tools of drug discovery. Vertex is far along that path; OSI is just beginning this journey. We believe each is poised to capitalize from the genomic and molecular information—the new currency of drug discovery.

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August 27, 2002

BIOTECH COMPANIES

Company	Technology Leadership	Reference Date	Reference Price	7/31/02 Price	52-Week Range	Market Cap
Cell Genesys (CEGE)	Cancer Therapeutics	6/10/02	13.24	12.13	10.48 - 25.02	435.9M
Cogent Neurosciences (none*)	Neurogenomics	5/2/02				
CuraGen (CRGN)	Cellular Signalling	3/13/02	17.67	6.51	4.50 - 25.88	324.5M
Gilead Sciences (GILD)	Rational Drug Design	12/05/01	33.88**	30.47	22.85 - 39.00	5.93B
Human Genome Sciences (HGSI)	Cellular Signaling	10/26/01	43.97	17.33	10.03 - 53.51	2.21B
Isis Pharmaceuticals Inc. (ISIS)	Antisense Therapeutics	7/9/02	7.30	8.85	6.10 - 27.15	482.1M
MDS Proteomics (none*)	Proteomics	2/05/02				
Nanogen (NGEN)	BioChips	10/2/01	4.95	2.11	1.80 - 10.13	45.7M
OSI Pharmaceuticals (OSIP)	Cancer Therapeutics	8/27/02	16.16	29.96	13.52 - 50.94	586.9M***
Quorex (none*)	Rational Drug Design	12/05/01				
Sequenom (SQNM)	Pharmacogenomics	1/09/02	9.00	2.34	2.31 - 11.44	90.0M
Triad Therapeutics (none*)	Rational Drug Design	4/9/02				
Vertex (VRTX)	Rational Drug Design	9/17/01	28.60	19.74	12.67 - 43.37	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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