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Cracking the Body Code: Cellular Signals Short-Circuit Disease

Forecast: a cascade of wealth creation, as *in silico* companies shift from treating surface symptoms to targeting the body's molecular roadmap.

A few years ago a patient of mine, call her Sally, developed a deadly blood cancer called chronic myelogenous leukemia. Sally was just 42 years old, so we treated her aggressively with the standard battery of powerful chemotherapies then available. It worked. The cancer receded. Hooray for the docs, right?

But the potent cocktail killed the healthy cells in her body as well as the bad, leaving Sally with a badly depleted immune system dangerously vulnerable to infection. She caught a particularly nasty one and died, her cancer well treated.

Losses like that are hard on doctors, and ever harder (naturally) on patients and their families.

I think of Sally when I look at the amazing advances now taking place in understanding the cellular pathways of diseases. Soon losses like hers will be a thing of the past. Today, biodigital tools are enabling doctors and drug companies to understand medical maladies in terms of their molecular machinery rather than surface symptoms. The key advance is abundant processing power, enabling huge genomic data sets linking gene sequences to body functions and dysfunctions. The new bioinformatics has researchers searching for molecular on and off signals that trigger deadly diseases. For patients this means a wealth of new life-saving treatments. For companies that understand and exploit the new biodigital possibilities, it means vast new wealth-creation. For investors, of course, it means major new opportunities.

The key to this profitable new creative outpouring is the technology that unlocks the secrets of cellular messaging. Every day our bodies are performing complex miracles of messaging, transmitting critical signals to, say, kidneys on how to rid the body's toxins, or to nerve cells on how to make an arm move.

How critical? Consider a game of telephone. With each transmission from person to person, the message gets corrupted until, when it reaches its destination, it is unrecognizable. Pass the salt, please, becomes: pat the salty peas. Hilarious as a kids' game, not so good for cellular messaging. So our bodies have devised remarkable systems capable of faithfully passing information down cellular pathways. Exact copy, of exact copy, of exact copy. The result? Healthy body.

Or sometimes not. Cells use chemical signals such as hormones to make decisions about whether they're supposed to proliferate, rest, or die. When cellular signals go awry, a host of diseases are born. Dysfunction of these regulatory mechanisms can, for example, cause cancerous transformation of cells, as well as a host of other diseases from diabetes to arthritis to lupus.

INSIDE:

Selected Kinase Inhibitors in Clinical Development

Company	Drug	Indication	Target Kinase	Status
Genentech/Roche	Herceptin	Breast Cancer	EGFR(Her-2)	Marketed
Novartis	Gleevac	CML	Bcr-Abl	Marketed
AstraZeneca	Iressa	Solid Tumors	EGFR	Phase 3
Eli Lilly	LY333531	Diabetic Retinopathy	Proteing Kinase C	Phase 3
Imclone Systems	IMC-C225	Solid Tumors	EGFR	Phase 3
Pharmacia/Sugen	SU-6668	Solid Tumors	PDGF	Phase 3
Genentech/Roche	Anti-VEGF (Mab)	Solid Tumors Cancer	VEGF	Phase 3
OSI Pharmaceuticals	Tarceva (OSI-774)	Solid Tumors	EGFR	Phase 2
Pharmacia/Sugen	SU-5416	Solid Tumors	VEGF	Phase 2
Cephalon/Lundbeck	CEP-1347	Parkinson's Disease	Mixed lineage kinases	Phase 1
Cephalon/Lundbeck	CEP-701	Prostate Cancer	Nerve growth factor kinase	Phase 2

Cellular Signaling

The key to transferring all this intricate information is receptors, sophisticated biological monitoring devices perched on the cell surface. The signals travel down through the cell membrane, along a series of intermediate molecules floating in the watery cytoplasm, eventually reaching the cell's nucleus.

Scientists call this process "signal transduction": it is how all cells transfer biological information—how pancreatic cells tell muscle cells to take up sugar from the blood for energy, for example, how the immune system instructs antibodies to attack invaders, or how cells of the nervous system fires messages to and from the brain.

But sometimes these pathways go awry, triggering disease. Sometimes the diseased cells have devised their own information tools to override the body's code. These are the pathways, for example, that tell cancer cells how to grow or viruses how to replicate.

As our knowledge of these molecular signals grows, so does the opportunity for dramatic new treatments for some of our most stubborn, deadly diseases. Take cancer, for example. Conventional chemotherapy and radiation treatments such as Sally's assault all cells—cancerous and healthy alike—causing severe side effects; the new chemicals target only disabled, defective or mutated genes' marching orders. "This is the dawn of the future of cancer therapy," says Richard Klausner, director of the National Cancer Institute. J. Michael Bishop, a Nobel laureate in cancer research, says: "For the first time in my life, I believe we will eventually be able to conquer cancer."

Which sorts of signals offer the most promising new avenues towards cancer cures? Some of the best-studied signals are generated by enzymes called kinases, which catalyze the transfer of phosphate groups from adenosine triphosphate (the body's cellular store of energy). Phosphate transfers are the cells' hand-off signal. Think of it as an ingenious kind of parallel processing chemical computer in which genes are continuously turning one another on and off in some vastly complex network of interaction, in this case by the addition and subtraction of phosphate groups.

Scientists have been struggling to figure out the intricacies of cellular signaling for more than 20 years. So why all the optimism now? The key to cracking the body's digital code is the huge increase in processing power. Until recently, biologists searching for cellular signals were wandering in the dark, randomly testing thousands of natural chemicals for therapeutic activity, hoping for a hit. Even when they found one, they didn't know why the chemical worked. They lacked the tools to look at multiple cellular changes at once—the key to understanding how these complicated switches work. The transformation of medical research into a branch of information science is changing all that.

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First, structure-based design techniques have allowed researchers to construct 3-D computer models of molecular receptors. Instead of randomly testing millions of molecules, scientists now digitally design molecules and test only the most likely possibilities in the wet lab. Rational design cuts drug development time by at least half over conventional random testing.

A second major biodigital advance? Huge new genomic databases stuffed with cellular signaling information. Powerful supercomputers only now have the power to unscramble cellular pathways (composed of millions of possibly linked sequences). Using bioinformatic tools to identify some of the defective genes at work, scientists have been able to find places to disrupt them—tossing a chemical monkey wrench into the machinery of diseased cells.

Another key tool in this new war on disease is DNA chips (aka microarrays, or gene chips). One kind of DNA chip, protein chips (manufactured by companies such as Ciphergen (CIPH), LumiCyte, Sense Proteomic, Aspira Biosystems, and Zyomyx) are making it easier to determine whether and how genes activate different disease pathways. Proteins chips are important, because it is proteins that do the bulk of the work of molecular messaging: enzymes are proteins, for example, so are hormones.

Equally important are powerful new computer models developed by companies such as Physiome Sciences, Genomatica, Entelos, and LION Biosciences (LEON). These in silico models combine physiological data and biochemical data to develop virtual maps of cellular signaling cascades, which can be used to uncover cellular functions, find new drugs, and predict an individual patient's response to treatments.

Consider a gene that signals the growth of breast cancer. If you can make a molecule or antibody that neutralizes it or blocks the cell receptor to which it binds—bang! New cancer drug. Just by teasing out the intricate circuitry in and around a medically relevant gene, you've expanded the number of targets at which new drugs can aim.

Short-Circuiting Cancer

In the United States, one out of every four deaths is from cancer. This year alone, 550,000 Americans—more than 1,500 a day—will die from it. The market for better cancer drugs is not only vast, it's highly predictable. Oncologists are early adopters. They deal with dying patients daily and are willing to experiment. Promising cancer therapies leap from lab to clinic in no time at all.

But finding optimal drugs hasn't been easy. Cancer cells do not go quietly when they have outlived their usefulness. Normal cells go through *apoptosis*, or preprogrammed cell death. They self-destruct when they are damaged. But cancer cells seem to lack this off switch. They just keep on replicating.

Scientists are just beginning to uncover the many reasons why. Each cell cooks up its own blend of regulators: cyclins, kinases, phosphatases, inhibitors, and oncogenes. When these regulators fail, cancer often results. A mutation in the growth-inhibitory pathway (a tumor suppressor gene) or in a growth-promoting pathway (an oncogene) causes a cell to proliferate madly, outgrowing its neighbors. Many of the most promising new cancer drugs in development target one of two mutations in growth-promoting pathways: receptor tyrosine kinases or the ras pathway.

Market Sizes for Some Common Cancers

Tumor Type	Total Cases	1999 New Cases	1999 Deaths
Lung Cancer	397,308	171,600	158,900
Colorectal Cancer	1,232,998	129,400	56,600
Ovarian Cancer	191,029	25,200	14,500
Renal Cancer	204,004	30,000	11,900
Pancreatic Cancer	24,334	28,600	28,600

Unlike conventional chemotherapy which poisons unhealthy and healthy cells alike, this new class of drugs targets only cancer cells. So unlike conventional chemotherapy, which can cause nausea, vomiting, hair loss, infections, and a long list of other unpleasant and even deadly symptoms (like Sally's), side effects should be minimal.

Take protein kinases, which regulate growth and reproduction in normal cells. A mutation causing overproduction of kinases prompts cells to keep dividing when they should stop. For example, Vascular Endothelial Growth Factor-2 (VEGF-2) is a human protein that stimulates the proliferation of both blood and lymphatic vessels. Researchers recently discovered that VEGF-2 is associated with both metastasizing breast cancer and malignant melanoma (aka skin cancer). Human Genome Sciences (HGSI), among others, has developed a human antibody that recognizes and inactivates VEGF-2. Clinical tests are planned on a wide range of solid tumors.

Protein kinases come in two major classes: as receptors on the cell surface or as free-floating molecules in the cell's cytoplasm. One type of protein kinase called tyrosine kinases works through a process called "phosphorylation"—by sticking phosphate molecules onto, and off, various proteins. Cells respond to these signals by turning on and off still other regulatory nodes. Kinases thus work as microscopic on/off switches triggering complicated signaling cascades. Tyrosine kinase inhibitors jam the signal.

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, the same cancer Sally had. The disease strikes about 6,000 Americans each year, many in the prime of their lives. (Gleevac is also being used as an experimental drug for other cancers that have failed to respond to conventional treatment). It is a landmark advance for drug developers, dispelling the long-held myth that selective inhibitors of key cell-signaling molecules cannot be safe and effective medicines.

Cynics snicker that drug development is more serendipity than science. No more. Gleevac proves that rational drug design leads to smarter drug design. Understanding cellular signals is the key. The potential profits are huge. Gleevac alone has beat expectations, racking up $36 million in sales in the first quarter of 2001.

Among the companies working on new tyrosine kinase inhibitors: Cephalon with its drug CEP-701 in a phase 2 trial for the treatment of prostate cancer; AstraZeneca (AZN) with its drug Iressa in a phase 3 trial for the treatment of non-small cell lung cancer; Sugen with its drug SU-6668 in a phase 3 clinical trial for the treatment of solid tumors; OSI Pharmaceuticals (OSIP) with its drug Tarceva in a phase 3 clinical trial for the treatment of breast, lung, and pancreatic cancer; and Imclone (IMCL) with its drug IMC-C225 in a phase 3 clinical trials for the treatment of solid tumors.

Mutant Proteins

Tyrosine kinases aren't the only juicy targets among the cascades of cellular messages. Another class of cell-proliferating mutations is called oncogenes. 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 tiny molecular shift radically changes its function. Oncogenes play major roles in triggering a wide range of human cancers, continuously misinstructing the cell to divide when it should rest.

The best understood example comes from the *ras* family. Ras proteins are the master controller switch in a large network of signaling pathways controlling the differentiation of cells. How does ras work? In the early 1990s, scientists learned that the epidermal growth factor (EGF) receptor and the ras protein are terminals on the same chemical relay system. Growth hormones secreted by other organs signal the EGF receptor it is time for cells to divide. EGF relays the message to ras, which dispatches it to the cell nucleus.

Ras, in turn, activates a cascade of intracellular protein kinases, culminating in the activation of the extracellular signal-regulated kinase pathway (ERK). Once inside the nucleus, ERK phosphorylates and activates proteins that are involved in the transcription of genes into messenger RNAs. These mRNAs may then be translated into protein, altering the composition of the cell and leading to changes in the cell's function.

Ras mutations have been identified in approximately 30 percent of all human cancers, including 50 percent of colon cancer, thyroid cancers, leukemia, multiple myeloma, cancers of the urinary tract and bladder, and almost all pancreatic cancers. (See figure). A cancer drug that disables ras mutations would thus have a huge potential market.

But how can the mutant protein be inactivated? One approach is directly inhibiting ras protein by chopping their genes into small bits using enzymes called ribozymes or inactivating them by binding short strips of DNA to them, called antisense oligonucleotides. A second strategy is to prevent ras from binding to cellular membranes in the first place, or inhibiting the gene's downstream messengers.

The antisense approach received a boost after the technology's pioneer, Isis Pharmaceuticals (ISIP), received a sizable investment from Eli Lilly (LLY). The drug giant agreed this August to buy a nine percent stake in Isis and commit more than $200 million in funding. In October, Isis raised an additional $100 million in a secondary stock offering.

Isis currently has three antisense compounds in development: ISIS 3521 (a PKC alpha inhibitor in phase 3 trials for lung cancer that could be marketed as early as 2003); ISIS 5132 (a c-ras kinase inhibitor now in phase 2 trials for prostate, colorectal and ovarian cancer); and ISIS 2503 (a ras inhibitor which is currently in phase 2 trials for pancreatic cancer). Isis may also get a boost from the new bioterrorism initiative, developing germ-warfare remedies that could treat bacteria that have been genetically altered to resist antibiotics.

The leader in the alternate ras-inhibiting ribozyme technology, Ribozyme Pharmaceuticals (RZYM), has several products in development. Angiozyme, for example, which inhibits the formation of blood vessels (angiogenesis) in tumors, is in phase 2 trials for multiple tumors, including colorectal cancer. A second product, Herzyme, is in phase 1 trials for ovarian cancer, and preclinical studies for breast cancer.

There is also a third way to disable mutated ras. To carry out its work, ras needs to burrow deep into the inside of the cell membrane. This process is called *farnesylation*. Farnesyl transferase inhibitors (FTI), which block this process, are remarkably specific for cancer cells, minimizing side effects. Because the FTIs have been shown experimentally to work even better when combined with cytotoxic agents such as Taxol, patients probably would take several pills in combination.

Among the companies developing farnesyl transferase inhibitors are AstraZeneca with its AZD 3409 for the treatment of solid tumors, Merck (MRK) with L-778123,

NuOncology with Arglabin-DMA, and LG Chem with LB 42708 and LB 42908 being tested for the treatment of colon cancer. The list of companies pursuing such inhibitors also includes Aventis Pharma, Hoffmann-La Roche, Bristol-Myers Squibb (BMY), Parke-Davis, Genentech (DNA), Glaxo Wellcome (GSK), Pharmacia Corp.(PHA), Sugen, ImClone Systems, British Biotech (recently purchased by ISI Pharmaceuticals and Cell Pathways (CLPA).

In addition, Johnson & Johnson (JNJ) is in phase 3 trials with Zarnestra for the treatment of both pancreatic cancer and relapsed, refractory (difficult to treat), and secondary acute leukemia. The chemotherapy agent, to be marketed by OrthoBiotech, is also in phase 2 trials for ras-dependent solid tumors. Janssen is in a phase 2 trial with FTI inhibitor R 115777 as a potential treatment for malignant melanoma and in the treatment of relapsed and refractory acute leukemias.

Human Genomes Sciences Product Pipeline

Product	Indication	Stage	Next Milestone	Timeline
Repifermin	Venous Ulcers	IIb	Enrollment	2002
Repifermin	Mucositis	IIa	IIa Results	4Q01
Repifermin	Ulcerative Colitis	IIa	IIa Results	2Q02
MPIF	Marrow Protection	IIa	IIa Results	2Q02
BLyS	CVID	I	Compoletion	4Q01
Albuferon	Hepatitis	I	I Results	1H02
Albutropin	GH Deficiency	IND Approved	Start Phase I	3Q01
SB-435395	CAD	I	Ongoing	2001
Anti-CCR5	Inhibits HIV Entry	Preclinical		
FasTR	Immune Regulator	Preclinical		
Anti-Trail	Cancer Growth	Preclinical		
Anti-VEGF2	Vascular Growth	Preclinical		
Lp-PLA2	Plaque Formation	Preclinical		
C#A-mAb	Asthma	Preclinical		
GMAD-466	Diabetes	Preclinical		

OSI Pharmaceuticals also has two promising, orally active FTIs in development: CP 609,754 which is in phase 1 clinical trials for colon and bladder cancer and CP 663,427 currently in advanced pre-clinical development for colon cancer.

Diabetes Destroyer

Many other diseases are caused by defects in cell signaling pathways. Consider diabetes, generating worldwide sales of over $8 billion. Diabetes comes in two forms, type I, arising from insulin deficiency, and type II, arising from resistance (or insensitivity) to insulin. There are 16 million people in the United States who have diabetes, with 2,200 newly diagnosed each day: about 798,000 people will be diagnosed this year alone.

The hallmark of type-II diabetes (the most common form) is a deficit in the body's ability to remove glucose from the blood despite the normal insulin release. Normally, insulin gets released from the pancreas in response to high blood glucose levels. Cellular signals tell fat and muscle cells how many glucose receptors they should add in response to different sugar levels. When there are not enough receptors, the body becomes insulin resistant. The pancreas is producing enough insulin, but the cells' glucose transport system no longer responds normally to the hormonal signal.

New drug development for type-II diabetes zeroes in on the activation of these insulin-signaling pathways. The main insulin receptor is a tyrosine kinase that works by adding phosphate molecules to two other insulin-uptake pathways, setting in motion the signal cascade that leads glucose transporters to transport sugar from the blood into the cell. Much current research concentrates on activating receptors called *peroxisome proliferator activated receptors* (or PPAR). At least nine drugs that target the PPAR receptors are in clinical trials. Two PPAR drugs are currently available: rosiglitazone and pioglitazone. Both work by improving peripheral glucose uptake in muscle and fat and decreasing production of new sugar by the liver, called *hepatic gluconeogenesis*.

OSI Pharmaceuticals is among a group of biotechnology companies pursuing novel strategies. In October 1999, OSI entered into a fully-funded collaboration with the Japanese drugmaker Tanabe Seiyaku to discover and develop small molecule drugs for the treatment of type II diabetes. Defective signal transduction mechanisms or gene transcription processes (which are among OSI's greatest areas of expertise) are believed to be key to development of the disease.

A third approach aims at reducing the collateral damage diabetes does. High blood sugar wreaks havoc with the body's small vessels leading to problems with the kidneys, heart, eyes, and virtually every major organ. Even meticulous glucose control sometimes isn't enough to avoid infections, blindness (retinopathy), kidney failure (nephropathy), nerve damage (neuropathy), and heart disease. Each year, from 12,000 to 24,000 people go blind because of diabetes. More than 56,000 diabetics get amputations as a result of vascular and nerve damage. The total sum: diabetes care costs about $100 billion a year in this country, or about 10 percent of total health care expenditures—astonishing given that diabetics represent only about 2.5 percent of the population.

More than 60 percent of that that $100 billion is due to long-term complications. Companies that find ways to block complications of diabetes are going to find a huge market for their products.

One promising strategy? Protein kinase C inhibitors may provide a so-called golden bullet for the small vessel disease (microvascular) caused by glucose toxicity, offering major advances in the medical management of diabetic blindness, nerve damage, and kidney failure. Pfizer (PFE) has a protein kinase C inhibitor in phase 2 clinical development in the U.S., and is expected to file for European marketing approval in 2001. (Filing for FDA approval is not expected until 2003). Pfizer's would be the first oral compound for treating diabetic retinopathy, a leading causes of diabetic-related blindness.

Eli Lilly has another protein kinase C-beta inhibitor in phase 3 trials for the treatment of diabetic macular edema and diabetic retinopathy that the company predicts could top $1 billion in annual sales if it gains FDA approval (the company says, by 2003).

The biotech company Isis Pharmaceuticals recently received a patent on another protein kinas C inhibitor for treating diabetic complications, licensed to Merck for further development. A protein kinase C inhibitor was also at the heart of the previously mentioned $400 million deal struck between Isis Pharmaceuticals and Eli Lilly at the end of August. Lilly was after Isis' antisense cancer compound, ISIS 3521, a selective inhibitor of protein kinase C-alpha expression that is in a phase 3 trial for the treatment of non-small-cell lung cancer.

Blizzard of Wealth-Creation

How to pick winners among this blizzard of companies? Well I do think there are some ways to do that and I'll get to them in a moment. But what we also need to realize is that the advances that will happen in drug research through the in silico paradigm mean over all a huge shift in value added, and thus revenues, within the health care industry, away from some of the most inefficient treatment practices and toward the biotech drug sector as a whole. As health care dollars massively shift toward biodigital diagnoses and drug treatments and away from hospital stays and other capital and labor intensive modes of treatment, one terrific strategy is to buy into a broad swathe of companies headed in the right direction.

To see why this is so, think for a moment again about Sally, the patient we saved from cancer and lost to the cure. Precisely because we did not have the right drugs, the cost of Sally's treatment, like that of anyone you know who has been through a severe course of chemo, did not come mostly from the drugs we pumped into her. The biggest costs were in supporting her body—and spirit—through the course of treatment, an effort which ultimately failed. More than 85 percent of the hospital stays or clinical visits of patients like Sally are driven not by the few hours it took to administer the drugs, but by the effort to control the damage done by the drugs themselves.

Less safe or effective drugs are literally less valuable because they mean more resources spent on all other aspects of treatment to compensate for the drugs' shortcomings. But armed with highly targeted drugs that kill cancer cells and not healthy cells, most of the resources we now spend in coping with chemo (as well as the pain and suffering we create) vanish. The value in treatment shifts to every company within the drug sector that effectively adopts the in silico paradigm.

Nevertheless, I do think there is at least one company that will be a particularly powerful player in the cellular signals game.

Human Genome Sciences

In the early 1990s, Human Genome Sciences got its start by mapping human genes and selling that information to pharmaceutical companies for their drug discovery efforts. But since then, Human Genome Sciences has shifted from selling bioinformatics to discovering and developing its own drugs. HGS has five products in clinical testing—the most advanced therapy being Repifermin, a wound healer used to mitigate some of the effects of today's anti-cancer agents. The company says its systems, which rely heavily on bioinformatics, has shortened the 14-year drug-development process by four or five years, allowing HGS to get drugs into human clinical trials for one-tenth of the costs shouldered by large pharmaceutical companies. The company now plans to bring three to five new drugs to the clinic each year and expects to have 10 to 15 ongoing trials by the end of 2002.

The key to HGS's competitive advantage is actually one of biotech's most comprehensive genomic databases specifically designed to uncover how cellular pathways operate.

Human Genome Sciences Milestones for 2001-2002

Initiation of Phase I trials with Albutropin
Results from Phase II trials for Repifermin in Mucositis
Results of Phase I trials for BLyS in Immunodeficiency
Initiation of Phase I trials for BLyS in Autoimmunity
Initiation of Phase I trials for VEGF-2 in Cancer
Results of Phase II trials for Mirostipen in Chemoprotection
Results of Phase II trials for Repifermin in Ulcerative Colitis

HGS has spent the last eight years sequencing genes, intensively studying the proteins they code for and simultaneously identifying potential drugs. This bioinformatics bonanza gives HGS a powerful edge over potential rivals. The company is focusing on the 10,000 genes known to code for proteins found on the outsides of cells, so-called secretory proteins that include hormones, receptors, immune-system messengers and enzymes. The result is an early pipeline rich with a new generation of highly targeted anti-cancer agents.

Protein-based drugs have one disadvantage. Proteins are large molecules that readily degrade in stomach acid. So they need to be intravenously infused, rather than swallowed as pills. The trade-off is the fast discovery of powerful medicines, since the proteins are generally easier to develop.

Another advantage of HGS's platform? Chemical drugs in phase 1 and 2 and 3 trials and after submission of a New Drug Application (NDA) have a 20 percent, 30 percent, 60 percent, and 70 percent chance of final FDA approval, respectively. However, biological drugs which file for a Biologics License Application—the kind of drugs HGS develops—have an improved chance of FDA approval. Because HGS's entire expertise and product line is biotherapeutics, it's in a better position to successfully bring more of its products to the market.

Human Genome Sciences was party to a six-way contract signed in 1993 that gave five drug firms scattered across the globe access to HGS's trove of genes. That exclusive access—dubbed the Human Gene Therapeutic Consortium—expired in July.

In principle, Human Genome Sciences could now go into the information business again, competing with companies that sell big genomic databases. But HGS prefers instead to cut more limited deals that may give a particular drug company access to a single piece of important genetic information in exchange for payments and commercial rights. This strategy allows HGS to earn cash off compounds it cannot develop and still retain the bulk of its digital intellectual property.

In September of 2000 HGS acquired Principia Pharmaceuticals which specialized in technology called albumin-fusion proteins. HGS can now link its protein medicines to albumin, a common blood protein (and the protein found in egg whites). These fused molecules resist breakdown in the body, enabling albumin-fused protein drugs to exert disease-fighting activities for days versus mere hours for normal protein drugs. The benefits? Drugs linger longer and patients require fewer transfusions. From both a marketing and therapeutic standpoint, albumin-fusion puts both new and existing protein drugs on a more equal footing with small-molecule drugs, which can be taken orally and last longer. The first such albumin-fusion product, a form of the immune booster called alpha interferon, is in clinical tests to treat hepatitis C.

Many of the protein drugs in both HGS's and other companies' pipeline could be embellished through the fusion technology. HGS's new fusion technology can thus not only create new drugs but enhance existing drugs "increasing opportunities while decreasing risk," says Haseltine. "You don't generally hear about biotech companies talking about reducing risk. But it's good work if you can get it."

OSI Pharmaceuticals

Another, possibility (which you should know about, but we aren't yet ready to add to the list) is OSI Pharmaceuticals. OSI has used a traditional, wet lab biotechnology platform to develop a strong emerging pipeline of cell-signaling drugs including its lead cancer drug, called Tarceva (OSI-774). The drug is in two phase 3 trials right now, for certain (non-small cell) lung cancers. Tarceva is being pursued in collaboration Genentech (DNA) and Roche, who are helping to offset the costs of trials.

Market Opportunities for Some of Human Genome Sciences Product Portfolio

Disease	Population Worlwide	Estimated Market (millions)
Ulcerative Colitis	515,000	$1,370
Mucositis	548,000	$274
CVID	7,000	$70
Hepatitis C Infection	200,000,000	$3,750
Neutropenia	363,000	$1,300
Venous Ulcers	1,300,000	$2,030
Diabetic Ulcers	5,300,000	$1,870

OSI's plan now for Tarceva is to establish value by targeting different cancers such as lung, breast, and pancreatic cancer (which kills almost all of the 28,000 or so patients diagnosed with the disease each year). Pancreatic cancer does not respond well to conventional chemotherapy. That spells a certain market opportunity. The FDA looks more favorably on new treatments targeting fatal diseases for which no other options currently exist. For pancreatic cancer victims, the journey from diagnosis to death is now, on average, just four months. Available treatment can extend life by only a paltry two months. Pancreatic cancer is also the target of ImClone's product, but that compound—a monoclonal antibody—is only offered intravenously, while Tarceva is can be taken as a once-a-day pill. Other OSI compounds in clinical trials (including several partnered with Pfizer) include new

BIOTECH COMPANIES

Company	Technology Leadership	Reference Date	Reference Price	10/26/01 Price	52-Week Range	Market Cap
Vertex (VRTX)	Rational Drug Design	9/17/01	28.60	25.75	15.50 - 99.25	1.6B
Human Genome Sciences (HGSI)	Cellular Signalling	10/2/01	31.95	43.97	26.41 - 106.85	5.6B
Nanogen (NGEN)	BioChips	10/2/01	4.95	8.15	3.00 - 20.43	174.6M

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

treatments for colon cancer, an anti-angiogenesis drug that would inhibit tumors by restricting blood vessel growth.

If OSI has used traditional wet-lab techniques instead of biodigital platforms to identify its lead compounds, why are we so interested? Because they're making a full court press to adopt the best of in silico technology to expand their drug discovery process and speed the testing of promising agents. In the next year the company plans to move from 100 percent wet lab techniques, to a more balanced, 50 percent wet-lab, 50 percent computational approach. OSI's Executive Vice President, Global Research Arthur Bruskin told me. "I think the big advantage of using molecular modeling at least in next three to five years is it will be giving us access to targets we weren't able to access. We'll learn to identify our old mistakes and new compounds. That's the holy grail."

OSI has among the industry's best wet-lab platforms. In silico tools don't entirely displace bio tools; they enhance their efficiency and value. No matter how good a company's in silico tools are, they still need to do conventional biological testing on the front and back end of any drug discovery program. I think it bodes well that OSI, which has developed some fantastic compounds using purely wet lab techniques, is now moving aggressively to adopt the in silico paradigm. One big caveat though: companies sometimes find it harder to change a successful organization than an unsuccessful one. OSI may find it hard to teach big bio-guys to fully exploit the power of in silico tools. We feel more comfortable waiting to see how that transformation goes before jumping into the company. On the other hand, if successful, the addition of in silico techniques to OSI's fabulously successful wet labs would slash costs and drug development time. Early investors would stand to reap the biggest gains. We will be keeping an eye on OSI.

Targeting the body's molecular roadmap opens up a whole new world of drug development, disrupting disease without all the unintended, costly consequences of yesterday's shotgun therapies. The result will be radically cheaper and better medical treatments for some of today's most deadly (and costly) diseases. HGS is one of the early adopters of this new cell-signalling science. OSI is an expert in these older techniques, but is embarking on an aggressive effort to adopt in silico tools that we believe would enable them to continuously enrich their bulging product pipeline. For that reason we are adding Human Genome Sciences to our list, and watching OSI's operations closely.

By learning the language that cells use to speak to one another and to their internal "workers," we will be able to listen in on their conversations and, ideally, find ways to intervene when the communications go awry and cause disease. Companies like Human Genome Sciences are reducing body language to a precise science.

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