Biotech companies hope that their efforts to use modern genomics to identify new therapies for human diseases are on the verge of paying off. That's still a big if, however

Mining the Genome for Drugs

The construction crews have put the finishing touches on the maze of rooms housing the tubes, ducts, and silver-colored vats needed for production to commence. In the foyer, the large bronze of Mercury carrying a caduceus, a symbol of healing, serves to announce the task at hand. This 7000-square-meter, state-of-the-art facility is being prepped to mass-produce what may be the first drugs to emerge from the rush to find all human genes.

The company that built the $45 million factory, Human Genome Sciences Inc. (HGS) of Rockville, Maryland, plans to use it to manufacture two human proteins and one human gene now in clinical trials. The molecules are meant to heal severe wounds, grow new blood vessels to circumvent damaged ones, and protect the blood-forming cells from the often lethal effects of cancer chemotherapy. If all goes as HGS intends—and that's a big if—these molecules will help establish the credibility of a revolutionary new approach to drug development, one of several that makes use of the growing knowledge of genes.

In the past, biotech company scientists looking to develop new therapies for human diseases had to start with a protein already known to be a key player in the disorder, insulin in diabetes, say, or human growth factor in dwarfism. They would then clone the corresponding gene, and with it manufacture the protein to use in therapy. Now, HGS and other companies are mining large databases of human gene sequences, looking for previously unknown proteins that might have therapeutic value. Once promising genes are identified—often by their structural similarity to known molecules—company scientists screen the genes' protein products in cells and animals for medically useful effects.

HGS has a leg up in this game. "HGS was first out of the gate in amassing [genomic] information. It looks like they've built the scientific infrastructure for the next step—developing pharmaceuticals," says Bill Boyle, a top genomics researcher at another biotech firm, Amgen Inc., in Thousand Oaks, California. But other companies, including Amgen, are also taking the plunge. Researchers at Amgen, for instance, have fingered a bone-building protein from their own gene database that is now in human trials as a potential treatment for osteoporosis and other bone-thinning ailments. At Seattle-based Immunex Corp., researchers have nabbed a tumor-killing compound from a public gene database that they, now in collaboration with Genentech Inc. of South San Francisco, plan to bring to the clinic next year. And plenty more genomics-derived drug candidates are very likely under wraps at those companies and others.

SOME HUMAN PROTEINS MOVING TO THE CLINIC

Company	Gene or protein	Condition targeted	Stage
Human Genome Sciences	MPIF-1	Protect bone marrow during cancer therapy	Early human trials
Human Genome Sciences	KGF-2	Enhance wound healing	Early human trials
Human Genome Sciences	*VEGF-2*	Enhance blood vessel growth to heart/limbs	Early human trials
Amgen	OPG	Strengthen bones	Early human trials
Immunex/ Genentech	TRAIL	Kill tumor cells	Preclinical

The success of these efforts is not assured, however. The hope is that because proteins have been designed by nature to work in the body, they can be developed for clinical use years faster, and far more cheaply, than synthetic chemical drugs can. The human protein drugs identified by more conventional means do include some blockbusters: erythropoietin, a protein used to treat anemia, reaped more than $2 billion in sales last year. But some other protein drug candidates have not panned out. For one thing, proteins often have more widespread effects than the drug developers count on: Tumor necrosis factor (TNF), for example, was touted as a potential cancer cure, but turned out to kill many normal cells as well.

And no one knows whether the genomics approach to finding potential therapeutic proteins will be any more successful than the more traditional approaches. "There is nothing magical about molecules derived from genomics methodologies," says Doug Williams, head of discovery research at Immunex. "You still have to do the biology to find out if you have a product candidate." Indeed, for all of the genomics-based drugs, the hardest biological tests are yet to come: the ones conducted in large numbers of people.

Gathering genes

One reason HGS leads the pack in the search for genomics-based drugs is its early association with The Institute for Genomic Research (TIGR), founded by biologist J. Craig Venter. In the early 1990s, Venter, then working at the National Institutes of Health, along with Mark Adams and their NIH colleagues, devised an efficient way of finding genes. Instead of taking the Human Genome Project's tack of spelling out every letter of DNA's code—97% of which is not genes—Venter's group simply plucked out the molecular footprints active genes leave in cells. These are messenger RNAs (mRNAs) copied from the genes as the first step in protein synthesis. Venter's team would copy the mRNAs back into DNAs and then spell out a part of each gene to create what are called expressed sequence tags (ESTs), which could be later used to find the entire gene.

In 1992, Venter received $70 million, to be paid over 10 years, from venture capitalist Wallace Steinberg to create TIGR as a nonprofit gene-finding research institute. Steinberg asked William Haseltine, then a Harvard virologist, to head a for-profit company—HGS—that would help find genes, patent and license promising ones, and spin some into drugs on its own. The partnership eventually soured, as the goals of the two companies diverged, and Haseltine and Venter's personal relations broke down (*Science*, 7 February 1997, p. 778). In the end, HGS and TIGR formally split (*Science*, 27 June 1997, p. 1959), but the collaboration helped HGS create its own enormous EST database, which Haseltine now estimates

The Man Who Would Spin Genes Into Gold

A stoic young man in gilded black armor sits astride a white horse. The fists of the warrior, the young St. George, clench a long sword, ready to dispatch the snarling winged monster clawing at his feet. The tableau—painted some 500 years ago by Raphael—now symbolizes the modern ambitions of William Haseltine, CEO of Human Genome Sciences Inc. (HGS) of Rockville, Maryland, the company in the forefront of efforts to use modern genomics to develop new drugs (see main text). It appears in HGS's latest annual report. "We see St. George as human hope fighting the dragon of disease," says Haseltine.

This choice of symbol echoes Haseltine's own style—brash, aggressive, and vigorously self-promotional. His urgency was sparked long ago, he says, in part by his mother, Jean, who seemed constantly ensnared by the dragon's claws, suffering a chronic skin condition that made her hands blister and bleed and also from detached retinas. Doctors twice had to surgically remove her eyeball to repair it. And Bill himself developed a heart condition that left him bedridden for months as a child.

Spurred by those illnesses, Haseltine enrolled at the University of California, Berkeley, planning to pursue a medical career until he was diverted by a passion for science. Berkeley chemist George Pimentel selected him and 14 other freshmen for a summer science program in which Haseltine read about, and met, several Nobel laureates. "It was fabulous," he recalls. "What you could see from all those guys is that they really loved what they're doing. So I thought: 'Well, I should be a scientist.' "

As a scientist at Harvard, Haseltine conducted groundbreaking research on retroviruses and was one of the first to champion the idea that HIV, the AIDS virus, is a retrovirus. Another pioneer of that notion, Robert Gallo, who now directs the Institute of Human Virology at the University of Maryland Biotechnology Institute in Baltimore, remembers Haseltine as "brilliant" and a tremendous asset to the collaboration. "We went faster because of Bill Haseltine, and that's what I call a good scientist," Gallo says.

Indeed, Haseltine went on to discover many HIV genes and proteins and to start several biotech companies before being asked in 1992 to lead HGS. Now, his hopes rest on a stash of frost-covered vials inside tall freezers that occupy a room in one of HGS's cluster of red brick buildings. Together, these vessels may contain something close to all human genes. The genes, Haseltine believes, hold the secrets that will allow humanity to remake its own tissues when they become frail or diseased. HGS has three potential therapies based on those genes wending their way through clinical testing.

Some attribute Haseltine's success to his practical bent as much as his scientific sense. He likes to explore potential uses for scientific advances, they say—and does so aggressively. "He goes after what he wants with great tenacity," says his former collaborator, virologist John Coffin of Boston's Tufts University School of Medicine. Still, Coffin says he sometimes found Haseltine "challenging" to work with due to his hard-driving style. And Haseltine's eagerness to promote his own accomplishments has grated on a few nerves. Many people engage in self-promotion, Gallo points out, "but Bill does it with more pizzazz."

Haseltine has also ruffled feathers of fellow gene researchers. In addition to his difficulties with biologist J. Craig Venter during his company's partnership with Venter's institute (*Science*, 7 February 1997, p. 778), Haseltine has sharply criticized the stated goals of the Human Genome Project, describing the effort as "a technofolly" and "more about our aspirations to explore the unknown than about anything practical." In May of last year, Haseltine argued in *The New York Times* that the $3 billion in federal funds devoted to sequencing the entire human genome—including the intervening "junk" DNA as well as the genes—should be spent in other ways. At a congressional meeting held shortly thereafter, Francis Collins, the project's director at the National Institutes of Health, said "not to consider that particular point of view as representative of the mainstream of scientific thought, either public or private."

Dragon slayer? As HGS CEO, William Haseltine wants to find new drugs to wage war against the dragon of disease.

Haseltine calls such statements "inappropriately dismissive," considering his expertise in the area. But others, such as Harvard Nobel laureate Walter Gilbert, agree with Collins. "Bill is wildly wrong about that," Gilbert says, referring to Haseltine's opinions about the federal project's limited medical value. Gilbert, who was Haseltine's thesis adviser at Harvard, nevertheless applauds his former student's efforts at HGS.

Indeed, there is little that is understated about Haseltine, except perhaps his attire, which features dark fashionable suits, thin-rimmed circular glasses, and a simple wedding band. Beyond that, his taste is more elaborate. His condominium at the posh Pierre Hotel in New York City has the air of a palace—with its colorful, paisley couches, art from many cultures and eras, and ornamental furniture.

His dreams may be even bolder than the decor. He looks beyond the kinds of gene-based therapies now being developed at HGS to an era when older tissues can be transformed into young ones by setting back their genetic clocks. "I think we can get to a stage, perhaps 100 years from now, where we can keep people young and dramatically extend human life," says Haseltine, with a daring worthy of St. George. **–I.W.**

CREDIT: HGS

contains tags representing more than 95% of all human genes, although that figure is difficult to verify independently.

To start with, Haseltine's team looked for membrane-bound proteins, including receptors for growth hormones, neurotransmitters, and the immune system regulators known as cytokines, that might serve as targets for chemical drugs to be developed by HGS's first corporate partner, SmithKline Beecham, and later by other partners. In addition, HGS scientists kept an eye out for proteins that might make good drugs themselves—proteins such as hormones, growth factors, and cytokines that are secreted by cells into the bloodstream. They identified such proteins by their structural similarity to known, secreted protein classes. By 1996, HGS scientists had found about 300 genes that appeared to encode new members of these classes. At that point, company researchers began making the proteins and testing them for activities that might help combat disease.

Wound-healing was an inviting target. So-called "chronic wounds" fail to heal normally because of underlying medical prob-

lems such as poor blood circulation due to diabetes and other conditions. The only medication currently available to treat chronic wounds is Regranex, a gel containing platelet-derived growth factor that is marketed in the United States by Ortho-McNeil Pharmaceuticals Inc. Regranex is approved to treat persistent ulcers on the feet of diabetics. Although the drug clearly helps, it doesn't solve the problem. In a large clinical trial, Regranex completely healed the wounds of half the patients who received it, compared to 35% of patients who received a placebo treatment.

In search of a better wound healer, HGS researchers tested the ability of their proteins to spur the growth of skin cells called keratinocytes in culture. Of those that did, only one didn't also cause other cell types, such as fibroblasts, to grow—a potential disadvantage because fibroblast growth is associated with scarring. The researchers began animal tests of that protein, called keratinocyte growth factor 2 (KGF-2), and this past February, HGS's Pablo Jimenez and Mark Rampy reported in the *Journal of Surgical Research* that in rats, it fosters the healing of linear cuts similar to wounds humans receive during surgery.

Research in press in the *Journal of Pathology* by plastic surgeon Tom Mustoe at Chicago's Northwestern University Medical School and his colleagues suggests that KGF-2 also works on chronic wounds. They found, for example, that in animals it closes open wounds that, like many chronic wounds in humans, have an insufficient blood supply.

Mustoe describes KGF-2 as "generally promising." Still, no one knows yet whether it will work in humans. Clinical trials were launched several months ago to test KGF-2's potency against venous ulcers, persistent leg sores that afflict some patients with vascular disease. Results aren't expected until sometime early next year, and because these tests are small, and chronic wounds are highly variable from one person to another, experts won't have confidence in the compound until it's been successfully tested on hundreds of patients. They are all too aware that other proteins, such as epidermal growth factor, looked promising in animal tests of wound healing but later failed in human efficacy tests.

KGF-2 isn't the only prospect HGS is testing, however. Also entering clinical trials is a chemokine, a protein that regulates immune cell function, called myeloid progenitor inhibitory factor (MPIF-1). In cell culture experiments published in 1997, an HGS team led by Vikram Patel found that the protein reversibly stops the proliferation of several types of bone marrow stem cells, the cells that give rise to mature blood cells, including those of the immune system. Thus, the researchers reasoned, the protein might help protect the bone marrow of cancer patients from the toxic effects of chemotherapy, which preferentially kills rapidly dividing cells. Available drugs can boost blood-cell numbers after a round of chemotherapy, but there are no approved ways to protect such cells from being killed in the first place.

MPIF-1 does seem protective in mice. In as yet unpublished work, Patel and his HGS colleagues injected the protein into mice before administering repeated rounds of chemotherapy. After several rounds, they found, both clot-forming platelets and disease-fighting white blood cells rapidly returned to normal levels in the MPIF-treated mice but remained suppressed for several more days in the control mice.

"It's a very exciting and important area," says Hal Broxmeyer, an experimental hematologist at the Walther Oncology Center and Indiana University School of Medicine in Indianapolis who has studied MPIF-1 in cell culture. Broxmeyer cautions, however, that a related agent failed to provide much protection for blood cells in a trial of cancer patients conducted last year. "I'm just not sure one chemokine is going to work better than any other," he says, adding that combining chemokines with other agents might ultimately be necessary to protect against anticancer drugs.

House of dreams. HGS hopes that the genes and proteins to be made at its new plant, shown here, will help cure human diseases.

CREDIT: DAN CUNNINGHAM

A verdict should soon emerge about what MPIF-1 can do alone. After a successful safety study, doctors at several U.S. medical centers are now testing its ability to protect the stem cells of patients receiving chemotherapy for breast and ovarian cancers.

A third prospect HGS is testing, as part of a joint venture called Vascular Genetics Inc. (VGI), is a gene, rather than a protein, that might provide help to patients whose severe atherosclerosis has resulted in blockage of blood vessels supplying their hearts or legs. About 4 years ago, HGS identified the gene for a protein called vascular endothelial growth factor 2 (VEGF-2) that promotes blood vessel growth. When company scientists presented a poster on VEGF-2 at a gene-therapy conference in 1997, it caught the eye of cardiovascular gene-therapy pioneer Jeffrey Isner of St. Elizabeth's Medical Center in Boston. Isner had seen vascular growth in rabbits after delivering the gene for VEGF-1, a previously discovered protein with similar effects, and he was interested in testing the *VEGF-2* gene as well.

Isner and HGS decided to collaborate, forming VGI, and so far the animal results look promising. In work described last August in the *American Journal of Pathology,* Isner's team injected the *VEGF-2* gene into rabbits in a hindlimb that was deprived of blood by tying off one of the arteries that feeds it. They found that capillary density and other measures of vascular growth improved in the animals' legs as a result. They are using the gene because it's easier to produce than the protein and, because it's more stable, it may have longer lasting effects.

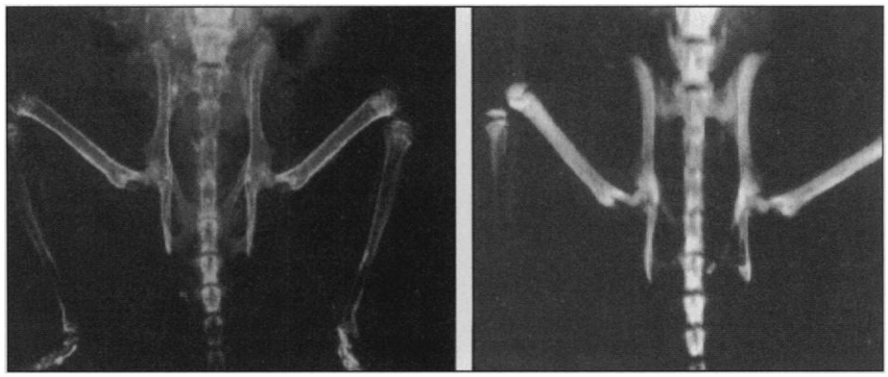
Isner's team has recently begun testing the gene therapy in a small number of patients with critical limb ischemia, or persistent pain in their legs due to insufficient blood flow. Additional trials are now also under way in patients with coronary artery disease. The approach has many clinical hurdles to cross before it becomes therapy, and plenty of competition, too. Various companies are testing forms of the *VEGF-1* gene, and scientists at Chiron Corp. in Emeryville, California, have just begun controlled human trials of fibroblast growth factor for fostering blood vessel growth in diseased hearts.

HGS has a lot at stake in these trials. Although the Maryland Economic Development Corp. (MEDCO) floated a bond to finance the construction of the Rockville plant, including the equipment inside, the company must pay property taxes, as well as cover rent and the cost of operating the facility. And, of course, the company, presumably with the help of pharmaceutical and fi-

nancial partners, must finance the clinical trials of each protein—which Haseltine estimates will cost up to $100 million per drug by the time they are through. Still, Haseltine feels the money will be well spent. "These drugs are designed to meet major medical needs," he says. "Each and every one has the potential to be a blockbuster."

Saving bones

HGS is not the only firm to find the risk worthwhile. In 1994, Amgen's team plucked out a gene from their company's cDNA database for a protein that looks like a receptor for TNF, the failed cancer therapy—except for one feature. It has no section that would allow the protein to stick into cell membrane, as a true receptor would. That indicated that it floats outside a cell. "That was really interesting," Amgen's Boyle says. "It suggested the compound was acting as a sponge or a neutralizing factor" for whatever binds to it, which was then unknown.



Bone strengthener. A mouse making large amounts of the protein osteoprotegerin *(right)* has much denser bones than a control animal *(left)*.

CREDIT: AMGEN INC.

To find out what the protein does, Boyle and his colleagues engineered mice to make huge amounts of it. The mice appeared healthy, but x-rays revealed that their bones were virtually solid, lacking the marrow-filled core of normal bones. In contrast, mice in which the gene had been deleted developed severe osteoporosis that mimics the human form "right down to the hump in the spine," Boyle says. "We concluded that the amount of [this protein] in the body correlated with bone density and strength."

Other tests indicated that the protein, which the company named osteoprotegerin or OPG, meaning "protector of bone," might be useful in treating or preventing osteoporosis. Osteoporosis risk rises in women at menopause or after removal of the ovaries, when estrogen levels drop. And company researchers found that in rats whose ovaries had been removed, OPG injections blocked the bone loss that would otherwise occur.

Cell culture studies provided a mechanism for OPG's protective effects. They showed that the protein inhibits the maturation of cells called osteoclasts, which chew up bone, apparently because it blocks a molecule on other bone cells that are required for osteoclast development. Because osteoporosis is caused by too many osteoclasts, OPG seemed capable of directly attacking the cause of the disorder.

Steven Teitelbaum, a bone cell biologist at Washington University School of Medicine in St. Louis, calls the OPG story "the most important thing that's happened in bone biology in the past decade." But proteins such as OPG, he notes, are far from ideal treatments for osteoporosis because they must be injected, and many women won't tolerate shots to stave off a disease that has yet to produce any symptoms.

Boyle agrees that a pill would be better, but says that if OPG shots are required only infrequently and the protein is safe and effective, it may be an option for women at risk for osteoporosis who experience unpleasant or dangerous side effects from oral drugs such as supplemental estrogen. Safety trials in people have just been completed successfully, and the company is gearing up for the next phase of clinical trials, which are likely to include women who already have osteoporosis.

Immunex, meanwhile, has been investigating a possible cancer therapy based on a gene its computers picked out from a public database based on its similarity to the *TNF* gene. The Immunex team hoped this new protein would be more specific and thus less likely to cause the side effects that derailed TNF itself.

It seems to be—both in cell culture and now in mice. In last February's issue of *Nature Medicine,* Henning Walczak, David Lynch, and their Immunex colleagues reported that the protein, called tumor necrosis factor apoptosis-inducing ligand (TRAIL), strongly suppresses the growth of tumors induced in mice. It also shrank and, in some cases, eliminated established tumors. Most remarkably, none of the treated mice showed any evidence of damage to the liver, brain, or any other tissue or organ. "With TNF, there wasn't a selective effect on tumor cells. With TRAIL, there seems to be," says Immunex's Williams. It's not clear why TRAIL might be so selective, but one possibility is that normal cells, but not susceptible tumor cells, have proteins that suppress the cell-death programs TRAIL would otherwise trigger.

Although TRAIL has not yet entered tests in people, the researchers hope it may someday be used along with chemotherapy to enhance tumor killing, or even used alone. But results in mice are often not replicated in people, so no one knows whether TRAIL will be a breakthrough in cancer treatment or another disappointment.

Given such uncertainties, these companies are spreading their bets across a number of compounds. An HGS team led by David Hilbert, for instance, has just now reported finding a novel cytokine they call BLyS for B lymphocyte stimulator, which promotes the growth and activation of antibody-producing cells called B lymphocytes in cell culture and in mice. They suggest that the factor might be used to treat ailments of the immune system such as AIDS or autoimmune disorders (*Science*, 9 July, p. 260).

In addition, over the past 2.5 years, HGS researchers have cloned some 14,000 genes for secreted proteins and others—up from hundreds in 1996—that they think might be good drugs or drug targets. Last year, HGS scientists began screening these proteins on a massive scale for their effects on many different cell types.

At least some of these proteins should prove valuable, predicts Daniel Cohen, chief genomics officer at Genset SA in Evry, France, which has a secreted protein project of its own as part of a collaboration with Genetics Institute, a unit of American Home Products in Cambridge, Massachusetts. "There were 2000 secreted proteins known before genomics, and 10 of them were blockbuster [drugs]," he says. "So the assumption is that in the next 2000, there will be another 10."

For Haseltine, christening any of these new compounds as drugs would be a realization of plans laid long ago, when HGS was first founded. "For me, this is like a butterfly emerging from a cocoon. There is a deep sense of satisfaction in seeing this program unfurl," he says.

–INGRID WICKELGREN