he believes Gore and Chernomyrdin may make a vague but positive statement about Mars exploration that would leave the door open for a 1998 launch.

Clarke says the 1998 date could be saved if Russia comes up with the money, but that, in the meantime, NASA must press on with its own program. "We are very sympathetic to their plight, and we don't want to do anything to undercut them," he adds.

The demise of a 1998 Mars Together effort won't halt exploration of the planet, however. In December 1996 NASA intends to launch the $170 million Mars Pathfinder mission. When it reaches Mars, a small scientific package outfitted with meteorological instruments and spectrometers will parachute to the ground in the Chryse Planitia region and open up like a flower petal to expose solar arrays to the dusty Martian sunlight. A tiny 35-pound rover will roll off the spacecraft to explore the surrounding terrain. Meanwhile, a U.S. global surveyor mission launched in November 1996 will orbit above, gathering topographical data for planetary scientists. A second surveyor and a lander could also be sent to the planet in 1998.

Russia, for its part, intends to launch a spacecraft in 1996 carrying a host of Russian, European, and U.S. scientific instruments. An orbiter would circle the planet and drop two small robotic stations as well as missile-shaped penetrators that would bore into the ground and relay back data. "The Russians have told us that Mars '96 will go off on schedule," says Clarke. One European official, however, is skeptical of that timetable. "That and 50 cents will get you a cup of coffee," he says, adding that he expects Russia will postpone the mission. The mission was originally set for launch this year before budget problems forced a delay.

At the Moscow meeting, Gore and Chernomyrdin were also expected to agree to set up a space biomedical research center run by Moscow State University and the University of Houston. "The idea is to have a mechanism to bring medical technology developed in space down to Earth," says Clarke. "We'll use this center as an incubator for private industry in Russia and to give our medical community better access to Russian data and technology."

The two leaders also have plans for closer cooperation in Earth observation. NASA wants to give Russian scientists access to its information system containing remote sensing images in exchange for Russian agreement to distribute data widely and at a low cost. Russian scientists would also be encouraged to contribute their data sets. In addition, Russia would launch upgraded versions of first the U.S. Stratospheric Aerosol and Gas Experiment and, a few years later, the U.S. Total Ozone Mapping Spectrometer.

–Andrew Lawler

HUMAN GENOME SCIENCES

The Company That Genome Researchers Love to Hate

Sitting in an office with an expansive view of old farms and meadows that are rapidly being chopped up into research parks, William Haseltine, chair of Human Genome Sciences Inc. (HGS) of Rockville, Maryland, isn't modest about his company's achievements. "We are the Balboa of human genes," Haseltine says. "We are the first to see this new horizon," he continues, describing a landscape surveyed by HGS that, in his estimate, contains 50,000 to 70,000 genes.

Over the past 2 years, Haseltine's company has pursued an aggressive search for DNA expressed in human tissue, and now, he says, it has filled its data banks with sequences representing about 85% of the entire suite of human genes. Haseltine believes HGS has laid its hands on the main prize of human genetics: sequences that can identify most of the expressed genes and the means to locate those genes on the chromosomes.

You might think that these achievements would be hailed by the genome community as a major advance toward the goals of the Human Genome Project. But that's not so. In fact, HGS and its nonprofit partner, The Institute for Genomic Research (TIGR), are widely viewed as the bad boys of genetic research. Many academic researchers dismiss the science done by HGS and TIGR, calling it "cream skimming." They view it not so much as exploration but as land grabbing. And TIGR's director, J. Craig Venter, is still feeling the bruises from a public disparagement in 1992 by James Watson, then director of the federal genome program. Watson quipped that "virtually any monkey" could obtain gene sequences by the methods Venter and Haseltine have adopted, although Watson later said he regretted that remark.

More recently, HGS caused a furor by insisting that researchers who plan to use information from HGS-TIGR data banks sign over to the company commercial rights to any discoveries that result (*Science*, 14 October, p. 208). This move could impede public-private collaborations on one of the goals of the Human Genome Project—construction of a map of the genome that pinpoints the location of genes. HGS and TIGR are offering information that could help build such a map, but academic researchers are leery of the terms (see box on p. 1802).

Indeed, feelings are running so high in the genome community that a move is afoot—encouraged by federal officials—that would undermine the value of HGS-TIGR's work by duplicating it and making it public. And this possibility isn't so far-fetched, because the Patent Office has ruled that the type of data HGS-TIGR has amassed—sequences of gene fragments—is not patentable. Already, several academic researchers and companies are chipping away at HGS-TIGR's monopoly by depositing sequences in public data banks, and the Merck Pharmaceutical Co. announced in October that it plans to bankroll a public sequencing venture (see letter on p. 1790). Some observers, including Harold Varmus, director of the National Institutes of Health (NIH), say it's only a matter of time before the commercial value of HGS's data is eroded. This puts HGS under the gun to promote its database and get outside help in identifying patentable ideas.

The criticism may be driven partly by envy, however, for HGS and TIGR have put together a formidable research tool. Haseltine rattles off examples of the advances the database has already made possible. One is the well-known discovery last spring of a human DNA repair gene involved in colon cancer, identified through a rapid search of HGS's data by in-house and academic geneticists, including Burt Vogelstein of Johns Hopkins University. Another discovery, not yet published, came about when Tomas Lindahl of the Imperial Cancer Research Fund in London dipped into the data. With the company's help, Lindahl may have located another DNA repair gene involved in a lethal immune disorder.

And this is just a glimmer of what lies ahead, according to HGS biologist Kenneth Carter. He says HGS staffers have already identified 10 human DNA repair genes and mapped six of them to megabase-long regions on human chromosomes. Carter and his colleagues say they are identifying thousands of DNA sequences never described before: keys to new proteases, kinases, phosphatases, transcription factors, and others.

In an interview with *Science*, Haseltine sought to counter impressions that HGS is attempting a power grab by appropriating genetic sequences. He says that, just because "we were the first" to see many genes "doesn't mean that we own everything we see." Furthermore, Haseltine recognizes that "we are not alone" in the use of the research tactics that amassed the sequence data. (HGS and TIGR extract messenger RNA from human tissues, reverse copy it into strands of complementary DNA [cDNA], grow these fragments in clones, and sequence the clones.)

But "we blazed the trail," Haseltine says, and HGS will have the first chance to survey the landscape and identify targets that may lead to medical products. Moreover, although Haseltine and Venter say they will share sequences and clones with others, they are not about to give away their proprietary rights.

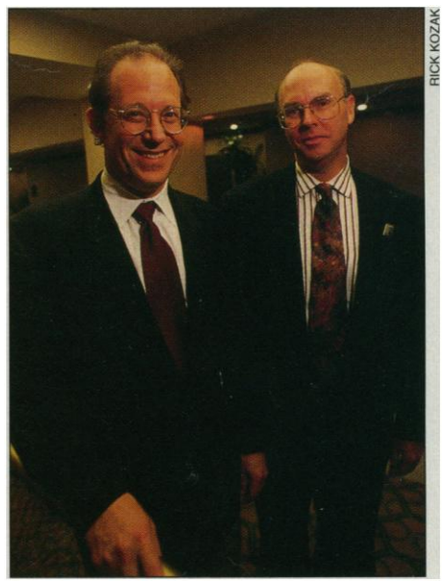
NIH misses the boat

The controversy swirling around HGS-TIGR is nothing new. Venter, who began sequencing cDNAs in the late 1980s as a staff scientist at the National Institute of Neurological Disorders and Stroke, says the genome community has never welcomed his efforts. Academic scientists objected that the cDNA capture technique would be slow, redundant, and wasteful, and they disliked the industrial approach Venter planned to use. According to *Gene Wars*, a history of the genome project by Robert Cook-Deegan, NIH officials repeatedly delayed Venter's proposals, subjecting them to bureaucratic holds and deferring to extramural academics who argued Venter's work was too weak to deserve support. In addition, Venter says, "several people told me they viewed what I was doing as a threat to the genome project."

Perhaps some researchers did feel threatened, but Venter protests that he was only trying to find the quickest route to a master list of human genes. He adds: "I wasn't the first to see the value of the cDNA approach." He counts Sydney Brenner of Britain's Medical Research Council Laboratory of Molecular Biology in Cambridge, U.K., and Paul Berg of Stanford University as two early champions. They were "shouted down" on theoretical grounds, Venter says. But as the debate went on, Venter obtained enough support from sources other than NIH's genome program to begin to assemble a small cDNA database. The initial 7300 human gene fragments he collected while he was on the government payroll have now been put into the public database at the National Center for Biotechnology Information (NCBI). Venter's donation remains the second largest batch of human cDNAs put into the public domain. The largest (11,730, including 8000 donated last month) came from Charles Auffrey of France's Généthon.

Frustrated by the slow pace and chronic infighting of the NIH community, Venter quit the government in 1992 and joined Haseltine and HGS. Just before he left NIH, the Department of Energy (DOE) gave him a $1 million grant to do large-scale cDNA sequencing. DOE was just dipping its toes into these waters, but it soon backed away, says James Sikela, another early cDNA sequencer at the University of Colorado, Denver. According to Sikela, DOE thought there would be no point in duplicating what Venter and Haseltine were planning to do, partly because they assumed the data would be made generally available. The government simply opted out and left HGS-TIGR to pursue the approach on their own. Sikela's own DOE grant was not renewed, and Venter returned his $1 million to DOE. This year, Sikela gave the 3100 human cDNAs he collected to NCBI, placing him third on the public donors list.

Both Haseltine and Venter say that Venter's reason for going private was to find a source that would pay him to do what he had wanted to do at NIH. For that reason, TIGR was created as a nonprofit institute, administratively separate from HGS, focused more on science than applications. TIGR is governed by Venter and an independent board. It directs its own research, plans to share data and clones with outsiders, and publishes independently. Venter's hope is that TIGR will collaborate with academics in the pursuit of pure science, and it will oversee extramural use of the shared HGS-TIGR database. HGS, in contrast, is a profit-making venture—with the guarded mentality that sometimes characterizes the private sector. For example, HGS recently linked its three buildings in Rockville with fiber optics, in part to prevent computer lines from leaking signals that might be monitored by a competitor. Both TIGR and HGS are funded by a $125 million investment from SmithKline Beecham of Philadelphia, and both must give the first option for any commercial development of discoveries to SmithKline.



RICK KOZAK

Surveying the genome. HGS's William Haseltine *(left)* and TIGR's Craig Venter.

Genes in the bank

Haseltine says HGS and TIGR believe the first phase of their search is nearly complete. From emergency rooms and pathology labs they have collected material from more than 120 human bodies, representing 248 different tissues and various disease conditions and stages of human development. They have extracted mRNA, converted it to cDNA, and cloned these fragments into 380 well defined *E. coli* bacterial "libraries." For example, 41 of the libraries are devoted to genes expressed in cancerous tissue. With HGS doing the bulk of the labor, they have sequenced 380,000 gene fragments and grouped them into 92,000 contiguous assemblies or "contigs." Based on correlations between HGS-TIGR data and genes identified in the past, Haseltine says he anticipates finding a gene for every 1.5 to 1.7 contigs. This means HGS now has over 50,000 genes in hand. Already, HGS has identified about 500 health-related "projects" worth exploring.

At HGS, computer specialist Michael Fannon oversees an electronic network that keeps track of the test samples as they wend their way through the laboratory and also runs an analytical database for the staff. Fannon's software allows a scientist to run almost instantaneous comparisons between new sequences from the HGS lab and those deposited in the HGS-TIGR data banks or in public databases, chiefly NCBI. To simplify the task, arcane search commands have been reduced to icons on the screen.

Fannon illustrates the system for a visitor by clicking on a "gene name" search, then asking for chemokines. The computer returns a list of HGS-TIGR human gene fragments automatically assigned to this category by the computer based on similarity to known genes. Fannon picks one, then clicks on another icon to translate the sequence into proteins according to six possible reading frames. The computer reaches out over the Internet to NCBI and brings back lists of proteins compiled by researchers around the world, comparing the HGS sequence with all existing knowledge. When the comparison is done—in a matter of seconds—the computer ranks the more significant "hits" in order of the quality of the match. With another click, a scientist can scrutinize the amino acid sequences of the six potential proteins with those of real proteins in the public database. A closer look revealed something interesting: a match-up of two amino acids at parallel

Terms for a Dip Into TIGR's Database

Researchers are eager to get a look at a trove of complementary DNA (cDNA) fragments amassed by two private concerns—Human Genome Sciences Inc. (HGS) and The Institute for Genomic Research (TIGR)—because those fragments may be useful in identifying disease genes and mapping active sites on the human genome. But many academics don't like the legal terms the companies have proposed.

For example, Harold Varmus, director of the National Institutes of Health (NIH), says he advises scientists "to think very carefully before they get in bed with those who would tie them to intellectual property agreements" in return for cDNA data. Varmus explains: "I'm worried about having hundreds of investigators all tied up in negotiations, because there's no time limit to the obligations" in HGS's contracts. Varmus also envisions a nightmare scenario 10 years down the road in which second-generation users of the data end up in court over claims tied to a point on a gene map. This would be "intolerable," he says.

But HGS's president, William Haseltine, claims the terms of data sharing are no worse—are more generous, in fact—than those of pharmaceutical companies. The main conditions for anyone wanting to see the more valuable HGS-TIGR data, called "level II" access, include the following:

- The HGS-TIGR database may be used only for noncommercial scientific research. To regulate demand initially, each researcher will be allowed to withdraw only 50 sequences per year.
- The researcher must notify his university or other licensing office 30 days in advance of releasing any publication that uses HGS-TIGR data; the licensing office must notify HGS within 10 days.
- If no patentable material is found, publication may occur 30 days after the researcher's licensing office has been notified, assuming HGS seeks no delay. If HGS wishes, it may impose an additional 30-day delay for a more complete patent review.
- Researchers may share or publish actual sequences from HGS-TIGR only under certain conditions: if they obtain written permission from HGS, if the sequence has already been published, or if they add new knowledge. The last category includes such things as completing a partial cDNA sequence, explaining the function of an anonymous gene, or adding some other "substantial scientific contribution."
- If patentable material is found, the first option for exclusive commercialization goes to HGS, and HGS agrees to exercise or surrender the option within 60 days.
- The terms on which a discovery will be licensed are to be negotiated between HGS and other parties to "fairly reflect the relative contributions of the parties to the invention." The inventors may take up to 6 months to negotiate the license, or longer if both parties agree.

–E.M.

locations, signaling a new member of an important gene family.

Using tools such as these, Haseltine says, HGS will spend the next 5 to 6 years mining its data for potential medical products. Among the first goals may be a better test for prostate cancer, based on gene expression. Haseltine says HGS has identified "a handful" of genes that appear to be turned on only in cancerous prostate tissue. The same strategy for developing diagnostics is being pursued by nearly a dozen companies in the United States and several in Japan and Europe—none of which has accumulated a cDNA database as extensive as HGS-TIGR's.

Public vs. private

Venter says he was "stunned" by the furor that arose earlier this year in academic labs over the terms of the HGS-TIGR data exchange contract, because unlike most commercial ventures HGS-TIGR is willing to allow outsiders to collaborate with them. The intense opposition may be melting, however, in light of the value of HGS-TIGR's wares. Already, about 100 nonprofit researchers have signed HGS's restrictive terms, and six major universities are experimenting with the database. Haseltine declines to name the schools. Not everyone has gone along yet, however. One major player—NIH—has not negotiated an agreement that would permit its intramural scientists to collaborate.

The biggest problem, everyone agrees, is figuring out how to use the HGS-TIGR cDNAs as markers on a public map of the human genome. Such a map would be extremely useful, helping pinpoint genes that cause genetic disease and possibly speeding the development of cures. And Francis Collins, director of NIH's National Center for Human Genome Research, says he is encouraging researchers to use such data whenever possible to mark locations on the maps they build. But it would be difficult to incorporate HGS's sequences in a public map, because HGS insists the data must remain confidential. Haseltine suggests that markers using his gene fragments be referenced by a code. Scientists who had signed a data exchange contract with HGS would then be permitted to use the code to retrieve the sequences. The academic community isn't enthusiastic about this idea.

Some academic researchers are hoping that the impasse over use of the HGS-TIGR data in constructing a transcript map can be broken by duplicating their sequences in a public venture. Merck has already taken a step down this road by offering to pay for sequencing of some public-domain cDNAs, which might be used to make such a map. But it will require more money than the roughly $5 million Merck has committed to the project—and more directed management than has been evident so far—to bring the project off. Nevertheless, several groups of public-spirited map builders will be meeting in London on 24 January under the aegis of the international Human Genome Organization to discuss which technical approaches might be the best to follow.

While they may dislike the contract terms stipulated by TIGR and HGS, scientists don't stint their praise for the companies' technical accomplishments. The database is "tremendously valuable," says Eric Lander, director of the genome center at the Massachusetts Institute of Technology. "TIGR and Venter have done a wonderful job," and their data are of high quality, Lander says. Adds Varmus: "I wish we had pushed for getting someone to do [a similar] database in the public domain some years ago." And Collins, responding to a question about NIH's slowness to recognize the value of DNA transcripts, says it's wrong to think "that we've been asleep at the switch and hadn't thought about this." In fact, Collins argues, it is only "in the past 3 months" that technical tools have become available that would enable scientists to build a genome map based on cDNAs.

These developments—and a recent surge of corporate interest in human genome science—have raised feelings of excitement in the map-making community to a high level. But unless a major institution, such as NIH, Britain's Medical Research Council, or some philanthropy offers to bankroll the development of cDNA-based analytical tools, HGS-TIGR will continue to hold the key cards for several years. The result is likely to be that, for the time being, the most comprehensive picture of the genes expressed in human tissue will remain the closely held property of the genome's Balboas.

–Eliot Marshall