HGS launches "first" genomics product in clinic

Thirteen days before the end of 1997, Human Genome Sciences (HGS; Rockville, MD) kept a bold promise that its chairman and CEO, Bill Haseltine, made in the summer of 1996—that the company's genomics effort would produce a clinical candidate within 18 months. On December 18, 1997, HGS announced the filing of its first investigational new drug (IND) application and was preparing to begin clinical testing of a chemokine called myeloid progenitor inhibitor factor-1 (MPIF-1) for the treatment of cancer patients to allow more potent doses of chemotherapy. According to HGS, MPIF-1 is the "first genomics-derived therapeutic product candidate to enter clinical trials."

By inhibiting the proliferation of stem cells, MPIF-1 should help protect cancer patients' bone marrow from the toxic effects of chemotherapy, allowing white blood cell counts to rebound more quickly after treatment. It could be used either instead of, or to potentiate, drugs like erythropoietin or granulocyte–macrophage colony stimulating factor. According to Haseltine, MPIF-1 may have "a potential billion dollar market in the US alone."

MPIF-1, one of the 23 novel beta-chemokines sequenced by HGS, illustrates the company's drug development strategy of trying to identify, at an early stage, the best candidate protein following an exhaustive search based on sequence comparison and expression profiling. The search for full-length proteins began in earnest in the summer of 1994. Before that, HGS researchers had focused their efforts largely on compiling a substantial database of partial cDNAs corresponding to 85–90% of all expressed human genes.

The route to MPIF-1 started with the identification of four putative chemokines by searching the HGS database of cDNA fragments for the repetitive cysteine motifs characteristic of the chemokines that were then known. The sequence searches were then refined by looking for new similarities in the expanded set of known and novel chemokines. The first round of the refined search identified another eight novel chemokines, and a subsequent refinement identified another eight

HGS identified further chemokine genes without recourse to sequence homology. It looked instead for tissue-specific gene expression in lymphoid tissues and the presence of leader "signal" sequences—the signature of secretory proteins. According to Craig Rosen, HGS's senior vice president of research and development, one chemokine was fished out merely on the basis of its exclusive expression in the thymus. He says that HGS's exhaustive approach both maximizes the chances of finding the right protein to match a particular therapeutic requirement and decreases the chance that a competitor will subsequently come up with a superior protein product.

By 1995, HGS had 50 candidate proteins for subsequent testing in an extensive range of high-throughput cellular assays. Other candidates were active, but MPIF-1 showed the greatest selectivity, the least inflammatory properties, and the best protective activity against a wide range of chemotherapeutics in over a 100 primary human cell lines. "We picked it out very early on and it simply turned out to have the best activity and side effect profile," says Rosen. By the following year, MPIF-1 had moved into animal testing with "impressive results." In mouse models, it reduced the severity of neutropenia, prolonged stem cell survival, and rapidly reverted white blood cell counts to normal following successive rounds of chemotherapy.

Haseltine says an additional benefit of HGS's strategy is the ability to select proteins that have large markets in indications with clear clinical end points in order to make clinical trials less complex and shorter. In the case of MPIF-1, HGS will be the sole sponsor of the phase I/IIa trial, and on completion, first Schering-Plough (Madison, NJ), and then SmithKline Beecham (King of Prussia, PA), will have an option to codevelop the protein in later trials. "If neither wish to develop the molecule, then other collaborations can be pursued," he explains.

For Haseltine, the MPIF-1 IND is more than a milestone in HGS's transition from gene discovery company to full-blown drug company. It is a vindication of his vision of genomics-driven development of medicines: "When Craig [Rosen] and I first left research in 1992, it was not to set up a company providing a sequencing service for pharmaceutical companies. . .We left our jobs because we saw a huge opportunity to go about making drugs using a completely new paradigm... People thought we were nuts!"

Now, more than 5 years later, HGS has one protein in the clinic and another (keratinocyte growth factor-2 [KGF-2]) expected to enter trials in the next few months. Four other proteins (MPIF-2, monocyte colony inhibitory factor, monocyte attractant protein, and fibroblast growth factor-10) are in the pipeline. Moreover, HGS still has a potentially rich stream of royalty revenue from its pharmaceutical partners for whom HGS has identified proteins as small-molecule development targets.

Andrew Marshall

A brief history of Human Genome Sciences.

June 1992	Company founded.
October 1992	Gets exclusive license to discoveries using technologies from the Institute for Genomic Research (TIGR; Rockville, MD), committing $85 million over 10 years.
January 1993	Research commences at Rockville facility. HGS constructs cDNA libraries and purifies the DNA; TIGR carries out sequencing and analysis.
May 1993	$125 million, 3-year agreement signed with SmithKline Beecham to develop and market diagnostics, small molecules, and other therapeutics based on HGS discoveries.
December 1993	IPO raises $27 million.
April 1994	TIGR stops sequencing human DNA; HGS facility takes over.
September 1994 to March 1996	Smaller deals with Genetic Therapy (9/94; gene therapy), Isis Pharmaceuticals (1/95; antisense), Takeda Chemicals (6/95; human therapeutics), MedImmune (7/95; vaccines), Pioneer Hi-Bred (1/96; corn genome), and Hoffmann-La Roche (3/96; *Streptococcus pneumoniae*).
September 1995	Secondary offering raises $61 million.
March 1996	Further offering raises $105 million.
June to July 1996	>$90 million deals over 5-year period with Schering-Plough (6/96), Synthelabo (6/96), and Merck KGaA (7/96).
October 1996	Deal with Pharmacia & UpJohn to develop antimicrobials against *Staphylococcus aureus*.
June 25, 1997	TIGR agreement prematurely terminated.
November 10, 1997	Participates in formation of gene therapy company, Vascular Genetics (Boston, MA).
December 18, 1997	IND filed for MPIF-1 as chemoprotectant.
December 29–30, '97	INDs filed for KGF-2.

As Nature Biotechnology *went to press, HGS had filed two new INDs for KGF-2, one as an oral treatment for chemotherapy-induced damage to the gastrointestinal lining, the other as a topical preparation for the treatment of a variety of open wounds.*