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HGS–TIGR splits, opportunity knocks

The June 25 split between The Institute for Genome Research (TIGR) and Human Genome Sciences (HGS) received scant mention, but for those who want to make their fortunes on the fruits of genomics research, the implications of this split are worth careful consideration.

Over the past two years, reported disputes between TIGR and HGS over the direction of their collaboration and intellectual property have escalated. Craig Venter, head of TIGR, says HGS's threat to get a court injunction to prevent TIGR from going to press with the sequence of the *H. influenzae* genome demonstrates how bad the situation had become. HGS's CEO Bill Haseltine says that none of this occurred.

To many, the terms of the settlement suggest that HGS got the lion's share. The company pockets the $38 million it still owed TIGR over the next five and one half years, retains its rights to patent any data TIGR has generated to date, and secures a noncompete agreement on the 10 therapeutic proteins it is presently developing. If, during the next two years, TIGR independently develops peptide drug leads, the settlement entitles HGS to a healthy share of the licensing and royalty fees. With its partners, its business plan, and now its freedom, HGS's only obstacle to achieving Haseltine's vision of making the company into a fully integrated pharmaceutical company lies in the difficulty of making peptides—and their small molecule analogs—into drugs.

Why would Venter give up $38 million of guaranteed cash and forfeit all intellectual property? Haseltine suggests that Venter had painted himself into a corner and had to do something because he was running into conflicts with other organizations that were funding non-HGS research at TIGR: They also wanted intellectual property rights for the expressed sequence tags (ESTs)—short sequences that uniquely identify full-length genes—they had funded. But according to Venter, this has never been an issue. He says that TIGR's grants—totaling $12 million annually—had no intellectual property strings attached.

His explanation for walking away from the cash? "I decided I would rather fail on my own than be locked into an ongoing situation during the genomic era that I helped create," says Venter. "In the future, the fact that I walked away from $38 million will either be viewed as smartest or the dumbest move I ever made."

Venter says that he is not interested in the patenting of strategic ESTs. This is surprising, because it appears that the US Patent and Trademark Office (PTO) is actively moving to allow companies to do just that. According to John Doll, director of the PTO's biotechnology patent examining group, since January 1997, the PTO has been asking inventors who hold the 350 patent applications containing approximately 500,000 ESTs to select 10 ESTs in each of their applications for PTO review. The PTO will then review these 10 ESTs based on the approximate $1,000 filing fee they initially paid. Additional ESTs from their application may be reviewed, in groups of 10, by filing divisional applications—and paying the filing fee each time. Doll says that inventors will be willing to do this because when their patent is granted—and the PTO has decided it will patent ESTs—the inventor will have the dominant patent for the gene containing the EST.

What this means for drug development is that once the full-length sequence of a gene is determined, its function is established, and a patent granted to the inventor, a company that wants to develop that gene into a license will be forced either to cross-license or to pay a royalty to all holders of patents for ESTs whose sequences are contained in that gene.

This suggests that for companies with the wherewithal to afford $100 an EST—plus attorney's fees—the PTO has opened the door to a lucrative sequencing and patenting business. But since no one—including HGS—has enough money to pay for patenting all the ESTs, the trick will then be to pick out the strategic ones and patent only those. Bioinformatics will be the key to picking those sequences. As no one has established a clear lead in this area, small academic groups working on discovering a gene might do well by convincing their academic institutions—and their drug development collaborators—to put something away for a rainy day by filing for patents on these short sequences.

With HGS executing its business plan, and TIGR claiming to be disinterested in ESTs, it appears that the demise of this collaboration has brought opportunity in its wake.

EuropaBio's regulatory niche

Outsiders are often mystified by European rules and regulations governing genetic engineering. But that legislation—technology based and obstructive to market entry—has evolved into the niche that corporate interests left for it.

By being mousy and indecisive about what they wanted, European companies have allowed the voices of other lobby groups—environmentalists, consumers, farmers, protectionists, for instance—to sound more loudly and more clearly in the ears of legislators and politicians. By speaking with many voices—one for the large companies, one for each and every industrial sector influenced by biotechnology, and one for each national group of small companies—the message from those developing biotechnology was garbled and confused. The pleas of the small companies and the research communities were particularly timid and highly diluted.

All is not lost, of course. First, Europe's biotechnology regulations do not hurt most of its industrial biotechnology. That still takes place mainly in big companies. Large, complex multinational companies like large, complex multinational markets. They don't mind much that small innovative companies—potentially invasive agents—need to come to them to reach these markets. Indeed, difficult market access may strengthen their negotiating stances in their dealings with R&D suppliers like biotechnology companies. Tricky regulations favor large companies with preadapted regulatory affairs departments.

Second, there is now EuropaBio, the long-sought single voice of commercial biotechnology in Europe. EuropaBio can be the single lightning rod that conducts the "will" of European biotechnology concerns. It can be the single channel through which to communicate that will. And it can bring the industrial muscle and financial resources of large and powerful companies to bear on the matter. EuropaBio will doubtless be effective in making biotechnology's voice heard by legislators. But that still leaves an important question. Whose voice will be heard within EuropaBio?