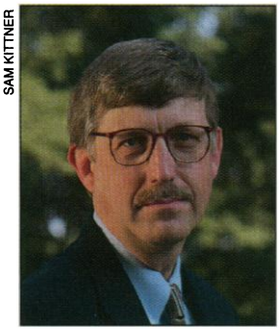
Snipping Away at Genome Patenting

A group of researchers is urging NIH to create a public database of single nucleotide polymorphisms, or "snips," genome markers that are becoming hot commercial property

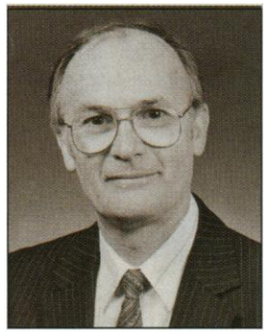
On 28 July, Abbott Laboratories of Abbott Park, Illinois, announced that it had entered into a deal with the genomics company Genset of Paris. The sum involved was relatively modest, but it sent a tremor through the academic genome community. Many saw it as evidence that a powerful new tool for pinpointing genes involved in multigene diseases was about to be locked up behind patent claims and proprietary secrecy.



SAM KITTNER

If [SNPs] get caught in "a tangled mesh of patents and licenses, then we are really in a mess."

—Francis Collins



Merck opposes patenting genetic data because it "noticed that royalty claims were stacking up" on its products.

—Alan Williamson

Abbott announced that it will invest up to $20 million of equity in Genset over 2 years and support up to $22.5 million worth of Genset research over the next 18 months. In return, Genset, which in 1996 hired French scientist Daniel Cohen as its genomics chief, agreed to create two sets of "bi-allelic markers." One will be a specialized set for use in constructing genetic profiles, or "genotypes," of patients in a clinical trial for an unnamed Abbott product. The other will be a broader set of markers that Abbott and Genset hope to market to other drug companies for use in their own clinical studies. It's just the latest example of a trend toward proprietary claims on such markers that Stanford University geneticist David Cox says could become "a nightmare" for companies and basic researchers alike—and that Francis Collins, head of the National Human Genome Research Institute (NHGRI), and others would like to head off.

The markers at the heart of this controversy are a type of variation known as "single nucleotide polymorphisms," or SNPs (pronounced "snips"). A SNP is simply a common alteration that occurs in a single nucleotide base in a stretch of DNA. Some human SNPs may be involved in a disease process; the vast majority probably are not. What they do offer, however, are unique and efficient signposts that can be used by researchers scanning an entire genome for significant mutations. They are piling up in growing numbers as government-funded research centers churn out more and more human DNA sequence in an effort to decipher the entire human genome by 2005.

Fears that this promising new technology might be tied up in commercial claims came to a head last week at the advisory council to the NHGRI, which was attended by many of the nation's top genome researchers. In a session on 11 September moderated by Alan Williamson, vice president for research strategy worldwide of Merck & Co., of Whitehouse Station, New Jersey, the group discussed waging what Williamson called a "preemptive strike" against the commercialization of SNPs. Some panelists wanted NHGRI to issue a manifesto aimed at discouraging such patents. But the majority said that NHGRI shouldn't waste its breath pleading: It should just go ahead and assemble a new repository of human genetic SNPs and release them to the public, no strings attached. Collins agreed that this would be "very desirable." He added that in early September, at a retreat of all the institute heads at the National Institutes of Health (NIH), he had already begun soliciting pledges to help create such a repository.

Researchers have started to collect SNPs because they expect they will be more useful than earlier markers for pinpointing the exact location of disease genes. SNPs are thought to be old and stable mutations, and therefore more reliable for large studies than so-called microsatellite markers or "stutter" repeats, which can alter significantly in a few generations, says geneticist Pui-Yan Kwok of Washington University in St. Louis. In addition, Kwok says, SNPs are widely and evenly distributed throughout the genome. Kwok's review of recently produced human DNA sequence suggests it should be possible to find one SNP per 1000 bases of DNA.

Moreover, says Cox, their brevity and simplicity make them easy to use in digitized genetic diagnostic systems. This makes them valuable for use in automated scans in which researchers analyze the complete genome of many individuals for genetic profiles associated with the disease under investigation—the kind of analysis that will be needed to track down multiple genes that contribute to common diseases.

As a result, pharmaceutical companies are making huge investments in developing SNPs, raising concerns in the academic community—"big time," according to Cox. Indeed, Cox says he was in a dilemma himself about what to do with his own lab's polymorphism data—whether to release it to the public or find some way of protecting it. In a phone interview, he said "one hears rumors" that other researchers are privatizing their data, but he would rather create a public SNP repository available for use by everyone.

The Abbott-Genset deal, says Cox, caught everyone's attention because it could potentially involve huge numbers of SNPs. Genset spokesperson Deborah Smeltzer says Cohen hopes to accumulate 60,000 SNPs from his large set by the end of 1998. According to Smeltzer, "all of the markers Genset is identifying will be proprietary." She notes that "after Genset has filed patents on the markers, and has protected the intellectual property underlying the markers and the high-density map [of the human genome], these markers will be made available publicly." Most genetic information generated by NIH-funded U.S. researchers and shared among academics,

Smeltzer observes, "has been patented and has intellectual property rights attached."

One of Genset's goals, says Smeltzer, is to enable companies to target drugs to the patients whose genetic profile indicates they are most likely to benefit. At the same time, Genset will use genetic markers to identify and eliminate patients who seem likely to experience bad side effects, says Smeltzer.

A similar collection of SNPs is being put together at the Massachusetts Institute of Technology's (MIT's) Whitehead Institute for Biomedical Research with corporate support. Last April, three companies—the pharmaceutical giant Bristol-Myers Squibb of New York City, the biotech firm Millennium Pharmaceuticals Inc. of Cambridge, Massachusetts, and Affymetrix of Santa Clara, California, the maker of digital genetic analysis "chips"—pledged an investment of $8 million a year for 5 years to develop a set of genetic markers for use in pharmacology. The project will be led by MIT gene mapper Eric Lander.

According to one geneticist who asked not to be identified, Lander and Affymetrix are hoping to announce a proprietary digital diagnostic tool called the "poly2000 chip" that can simultaneously monitor 2000 SNPs in a single DNA sample. Lander could not be reached for comment. Affymetrix Chief Executive Officer Stephen Fodor, a speaker at the 11 September NHGRI meeting, confirms that his company is developing the technology for this project. He adds that he was uncertain about the intellectual-property claims on SNPs that might be used on this chip and had often wondered, "Can we put them on a chip and sell it [with reasonable property-rights agreements]?"

During last week's council meeting, Collins said he was concerned that such private claims might make it hard for researchers to get unconditional access to SNPs or other new types of markers—such as a set of single nucleotide changes that create errors in protein coding, which he dubbed "misSNPs." If these get caught in "a tangled mesh of patents and licenses," Collins warned, "then we are really in a mess."

Council member Jeanne Lawrence of the University of Massachusetts Medical Center in Worcester suggested that NHGRI issue a statement saying that SNPs were so "obvious" scientifically that they shouldn't be patentable. Another suggested that Collins and his staff should conduct a series of seminars to educate the U.S. Patent and Trademark Office (PTO) about the need to avoid SNP patents. An NHGRI staffer replied that PTO officials "have not welcomed" such offers in the past. Indeed, the PTO declined to take part in the 11 September discussion, the staffer said. Cox then urged NHGRI to assemble "a ton" of SNPs and make them public.

Members of the panel asked company executives attending last week's session whether their businesses would be "threatened" by such a move. Williamson indicated that Merck's would not. He said the company had become accustomed to paying royalties on many small patents that went into each pharmaceutical product, but recently Merck "suddenly noticed that royalty claims were stacking up" on each product to an unacceptable degree. Over the past 5 years, Merck has invested tens of millions of dollars in efforts to publish and share basic genetic data—for example, creating a public database of "expressed sequence tags" (ESTs) from human DNA that can be used to identify human genes—to avoid this layer-cake effect. Affymetrix's Fodor said he was chiefly concerned about the continuing uncertainty over who owns SNPs, but he did not oppose a public SNP repository. And Incyte Pharmaceutical's vice president David Bailey said that "we were not threatened at all" by Merck's release of EST data, which simply "added value to our database." The same, he felt, would apply to SNPs.

Collins concluded the discussion by noting that it would be too expensive and possibly controversial for NHGRI to try to go it alone in creating a SNP repository. He noted, however, that some NIH institute chiefs have already expressed interest in helping. For example, Richard Klausner, director of the National Cancer Institute, is ready to contribute. Queried by e-mail, Klausner says: "Francis and I have discussed this for months, and I believe that this is a very important resource for us to begin to assemble." The NHGRI session closed with staffers promising to look into costs and logistics. Soon the institute will decide whether to take the plunge and fund another big genomics project.

–Eliot Marshall

GENETIC ENHANCEMENT

From Science Fiction to Ethics Quandary

Newspaper readers across the United States got a jolt last week. Full-page ads announced: Children made to order. The ad offered a checklist of traits—including musical ability, athletic prowess, and protection against premature baldness—for parents to choose for their offspring. And it provided a toll-free telephone number and a Web site for readers to set up an appointment. Tiny type at the bottom of the page provided the only giveaway: The ad is promoting a science fiction movie called *GATTACA* (a clever play on the letters of the genetic code), set to open in late October. Get ready for a few weeks of hype about using genetic manipulation to enhance individual qualities.

Coincidentally, the day before the ads ran, a group of leading gene-therapy researchers was discussing exactly that issue—and they concluded that the possibilities aren't entirely in the realm of science fiction. At the first Gene Therapy Policy Conference sponsored by the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH), scientists predicted that within 2 years, a researcher will propose a gene-therapy experiment that, although initially aimed at curing disease, could eventually be used to enhance a trait in healthy people. "It's going to happen," pediatrician and gene-therapy researcher W. French Anderson of the University of Southern California in Los Angeles told the conference. "It's going to happen pretty quickly, and it's going to happen in the guise of something else."

Panelists pointed out, for example, that research teams are already working on genetic treatments to restore lost hair and to strengthen muscles. Researchers are likely to propose the first tests of such therapies in chemotherapy patients or those with muscular dystrophy, but if they prove effective, it would

End of the slippery slope? *GATTACA*'s fictional world.