touching base

Embarrassment of Riches

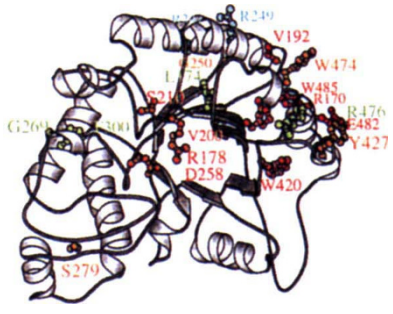
Concerned that they were generating more gene-based pharmaceutical opportuntities than they could realistically handle, Human Genome Sciences, Inc. (HGS) and their corporate partner, SmithKline Beecham Corporation (SB), have agreed to license the rights to the HGS cDNA database to other pharmaceutical companies. As reported in the May issue of *Nature Genetics*, SB bought the exclusive rights to the HGS database in May, 1993, enabling the pharmaceutical giant to develop therapeutic drugs based on novel genes identified in HGS' screens of hundreds of cDNA libraries. But HGS founder William Haseltine says that HGS and SB "have created more opportunities to develop pioneer pharmaceutical products than either company can develop on its own" — hence the decision to share the spoils with other companies. Among the new agreements is a five-year deal with Schering-Plough Corporation for $55 million, and a deal with the large French drug company, Synthélabo, for $35 million. HGS and Schering-Plough are also collaborating to develop gene therapy products based on HGS sequences. Haseltine believes that "this is a new paradigm for cooperation amongst drug companies in which companies collaborate in pre-competitive research." Curiously, perhaps, stock prices for the companies involved dropped on the news.

Screening for Prostate Cancer

Among the news emerging from the recent General Motors Cancer Research Foundation conference (June 19–20, National Institutes of Health) was a new collaborative project to map genes involved in prostate cancer. Almost half of all men who develop prostate cancer before age 55 are estimated to carry an inherited predisposition to the disease, which is becoming a major public health issue in the United States, claiming nearly as many lives each year as breast cancer. The new effort is being spearheaded by Francis Collins and Jeffrey Trent, at the National Center for Human Genome Research, and urologists Patrick Walsh and William Isaacs from Johns Hopkins University School of Medicine. The researchers have already assembled 64 families with multiple affected members, and are looking for others. Several candidate regions have been excluded, and the team is now trawling through 300 markers across the genome, hopefully to be completed before the end of this year. Meanwhile, at the University of Utah in Salt Lake City, Lisa Cannon-Allbright and colleagues are performing linkage analyses in more than 30 families, some containing as many as 20 affected individuals. The work, which began concentrating on a few families in 1992, has yet to detect significant linkage.

A New Take on Tay-Sachs

A new structural model of chitobiase, published last month in *Nature Structural Biology*, not only sheds light on the mechanism by which the bacterial enzyme degrades chitin, the second most abundant polysaccharide on earth, but also has some important insights for human genetics. Chitobiase is a member of the same family of glycosyl hydrolases as the hexosaminidases, including the enzymes defective in Tay-Sachs (HEXA) and Sandhoff (HEXB) diseases. Despite only 26% sequence identity between chitobiase and HEXA, Tews *et al.* produced a three-dimensional model of HEXA based on their 1.9 Å crystal structure of chitobiase (see right). One group of the severe, infantile mutations (shown in red) including those at Arg 178 and Asp 258, are clustered in the active site, although a second group are far removed. Juvenile-onset mutations (orange) lie in the protein core, but further from the active site. By contrast, most adult (green) and benign (blue) mutations lie on the enzyme surface (Tews, I. *et al. Nat. Struct. Biol.* **3**, 628-648; 1996).



Weaver Winds On

The identification last year of the putative mutation in *weaver*, an important mouse neurological mutant strain, left a ripple of surprise in the community. Patil *et al.* identified a Gly-to-Ser missense mutation in the pore-forming region of Girk2, a G-protein coupled, inwardly rectifying potassium channel (*Nature Genet.* **11**, 126–129; 1995), which did not immediately explain how a defect in a channel with widespread expression in the brain should produce a defect as specific as cerebellar granule cell differentiation. A recent series of papers has begun to clarify the effects of this mutation on the functional properties of the channel. In oocyte expression studies, Patil, Cox, Jan and colleagues have shown that the mutation reduces current through heteromeric channels at low expression levels, and abolishes ion selectivity at higher levels (Slesinger, P. *et al. Neuron* **16**, 321–331; 1996). Two more recent studies present evidence for loss of beta-gamma regulation and show that a basally active, G-protein insensitive sodium current may kill the granule cells before they have a chance to differentiate (Kofuji, P. *et al. Neuron* **16**, 941–952; Navarro, B. *et al. Science* **272**, 1950–1953; 1996). As Hess points out (*Neuron* **16**, 1073–1076; 1996), it is not uncommon that neurological defects arise from extremely cell-specific flaws in relatively widely expressed genes.

Brca1 Revisited

Earlier this year, Koller and colleagues (Gowen, L.C. *et al. Nature Genet.* **12**, 191-194; 1996) produced the first description of homozygous mice lacking the mouse equivalent of the hereditary breast cancer gene, *Brca1*. The mice, possessing a deletion of the large exon 11, died between days 10 and 13 of embryonic development, suffering from a variety of neuroepithelial defects. A recent report by Hakem *et al.* (*Cell* **85**, 1009-1023; 1996) describes a new strain of homozygous mice for a putative *Brca1* null mutation produced by a targeted deletion in exons 5 and 6. These mutant mice are more severely affected, dying earlier in embryogenesis at about day 7.5 with no signs of mesoderm formation and reduced cell proliferation. There were also strong signs of disrupted cell cycle regulation via altered levels of gene expression. While the differences are intriguing, Koller points out that the chimaeras in the two studies were bred to different strains, making it harder to pinpoint whether it is the nature of the mutation, alternative splicing or genetic background responsible for the altered survival. Meanwhile, Hakem *et al.* report that after about one year of age, their *Brca1* heterozygous female mice show no evidence of cancer. Likewise, Koller's group has also been unable to detect tumours in its one-year old heterozygotes.

The Secret of Area 51

The blockbuster film *Independence Day* and the cult television show, *The X-Files*, have popularized the mysterious region in the Nevada desert known as Area 51, which paranormal enthusiasts are convinced is the site of top-secret investigations into UFOs and alien remains. Comedian Kevin Murphy has a different idea of what goes on there: "All those socks from all those dryers get sucked through your dryer vents into a porthole, and they end up in Area 51. The government scrapes some of your DNA off the socks to get a genetic encoding. It then puts it into a huge computer so that it always knows what you are doing. Of course, I might be just a little paranoid."