MEETING BRIEFS

Chemical Society Hosts Biotech Gathering

Last week more than 1200 scientists attended the Ninth International Biotechnology Symposium sponsored by the American Chemical Society (ACS) in Crystal City, Virginia. The conference, held every 4 years, ranged from basic science topics (such as finding structural motifs in protein data banks) to applied work (including the latest advances in making human proteins in transgenic animals).

Finding a Motif in a Haystack

Everybody knows about the false positives in medical testing—in the AIDS test, say. But medical testing isn't the only area of science plagued by false positives. Take the computer software that searches for protein "motifs"—short stretches of amino acids that fold up into particular shapes that play a key role in a protein's function. For protein chemists, identifying the same motifs in different proteins is a hot area of research because that information can provide a guide to what the proteins do. But because many different amino acid sequences may give rise to the same motif, computer programs that search sequence databases for these motifs may turn up a wealth of false positives. Recently, for instance, a standard weight-matrix method turned up 8000 false positives and only 250 true positives in a search for the so-called helix-turn-helix motif in a large protein database.

Douglas Brutlag, a biochemist at the Stanford University School of Medicine, wants to do a lot better than that, as he told a session on "bioinformatics" at the ACS symposium. And, with graduate student Tod Klingler, Brutlag has come up with software he claims could do the trick, generating far fewer false positives. By way of comparison, their system, based on a principle called a "belief network," searched the same database (the Brookhaven National Laboratory's Protein Data Bank) for the helix-turn-helix motif and turned up only 80 false positives in the course of coming up with 280 true positives.

The secret of the belief network's success is its ability to account for chemical interactions—such as disulfide bonds or salt bridges linking oppositely charged amino acids—between amino acids at different positions in a motif. After identifying all possible interactions, Brutlag's belief network (a name borrowed from a logic scheme engineers use to depict relationships between objects) eliminates the false positives by ruling out sequences that may appear to fold up into particular motifs based on amino acid sequence alone—but don't, in fact, because of chemical interactions between nearby amino acids. And that's the reason for its success compared to such methods as a weight matrix, he says.

Some scientists in the field are cautiously optimistic about Brutlag's method. "It's a novel idea, and all kinds of new ideas should be fostered," says Samuel Karlin, a Stanford biomathematician familiar with Brutlag's work. But until Brutlag gets more data, Karlin cautions that "it's a little too early to evaluate" the belief network. After Brutlag publishes his method, he plans to make the program available to other researchers, he says.

Pigs as Protein Factories

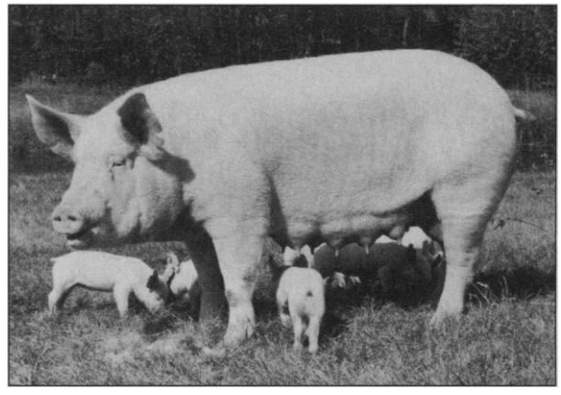
Almost any protein the human body produces can also be made in other animals, if their genes are programmed correctly—which gives goats, pigs, cows, and other mammals the potential of being turned into "bioreactors," or, in essence, drug factories. And several research groups and biotech firms are hot on the trail of mammalian protein factories.

Until now, many of the problems in creating these bioreactors have been technical, such as getting the right genes in place and getting the protein expressed at high enough levels for commercial success. Many of these problems remain, attendees at one session of the symposium heard, but several companies say real progress has been made and that they're only a few years away from testing their proteins in human clinical trials. The problems that remain, attendees were told, have as much to do with the legal arena as with the scientific one.

"All of us have filed patents, and the main battle still has to begin," says Rein Strijker, a molecular biologist at Genepharming Europe BV, a Leiden, Netherlands-based subsidiary of GenPharm International. Genepharming is developing transgenic cows that will produce human lactoferrin, an antimicrobial protein, in their milk. Strijker's concern, like that of other players in the field, has to do with who owns key processes needed to create transgenic mammals. Ian Garner, head of molecular biology at Pharmaceutical Proteins, in Edinburgh, also worries about patent issues, though he thinks most disputes will be worked out peaceably: "I think generally there will be more deals than litigation." His company is aiming to get human alpha-1 antitrypsin (a protein that helps to keep cells elastic), made in sheep's milk, into clinical trials in 1994.

Patents aren't the only issue troubling the makers of these interspecies factories. The other is uncertainty about what guidelines the Food and Drug Administration (FDA) is going to lay out for approving proteins made this way. Chemical engineer William Velander of Virginia Polytechnic Institute says his group has already begun an "informal dialogue" with the FDA to find out what the agency will require in its Investigational New Drug applications for the transgenic proteins. Velander's group is collaborating with molecular biologist William Drohan and colleagues at the American Red Cross to develop Protein-C (a clotting factor that may be helpful in patients after surgery) in pigs. Potential regulatory concerns may include the degree of genetic modification an organism undergoes and its potential threat to the environment, as well as the potential for impurities such as viruses or agents that could cause scrapie.

All this talk about legal and regulatory hurdles tended to overshadow innovative science at the session. But that doesn't mean there aren't a lot of intriguing new developments coming along in transgenic animals. One development that piqued interest at the meeting was the possibility of getting goats to produce CFTR, the transmembrane protein that is defective in cystic fibrosis, in their milk. Scientists hope to use the bioengineered protein to replace defective CFTR in cystic fibrosis patients, says Harry Meade, a molecular biologist at Framingham, Massachusetts-based Genzyme Corp. He says that Genzyme can now produce only microgram quantities of CFTR in milk—but within a decade they hope to scale up and produce clinical quantities.



VIRGINIA POLYTECHNIC INSTITUTE

Going to market. A sow genetically engineered to produce Protein-C (a clotting factor that could help patients after surgery) in her milk.

–Richard Stone