20. Genzyme scientists are also removing and replacing carbohydrate side-chains of recombinant glycoproteins—to improve therapeutic efficacy through longer serum life-times and specific cell targeting. Genzyme's proprietary remodeling technology, for which a patent application has been submitted, is the result of a joint effort with scientists from MIT. MIT's patent (to which Genzyme has an exclusive license) covers both the remodeling technology itself and the new carbohydrate structures that will result from the use of the technology.

Genzyme's remodeling technology is being used to alter the carbohydrate side-chains on recombinant proteins produced by lower eukaryotic cells, such as yeast and insect cells. Henri Termeer, president and chief executive officer, says that it should also prove useful for therapeutic proteins that are produced in animal cells; altering their glycosylation patterns might improve activity levels. He adds that, at least for some proteins, the Genzyme technology might enable scientists to circumvent mammalian cell systems.

Their approach, according to Blair, is to clip back the oligosaccharide chain until a single N-acetylglucosamine residue remains. It is this residue that attaches the carbohydrate chain to the protein backbone, via an N-glycosidic linkage to asparagine. (There are also O-glycosidic linkages to serine, threonine, hydroxy-lysine, and hydroxy-proline.) After the scientists expose the first sugar moiety, they begin building the chain back up, adding galactose and sialic acid, for instance. (Mannose and fucose are two other building blocks for these oligosaccharide chains.)

Blair says that, in cases where it is desirable to extend a protein's serum half-life, scientists cap the oligosaccharides with sialic acid. Sialic acid is a charged molecule, and this property prevents it from being filtered through the kidneys, thereby improving the protein's life-time in the circulation. Another advantage of capping carbohydrate chains with sialic acid, according to Blair, is that there are no cell-surface receptors that will bind circulating glycoproteins bearing terminal sialic acids.

Genzyme has already used its technology to modify glucocerebrosidase (GCR) for treating Gaucher's disease. This genetic disease, which affects Jews of Eastern European descent, is caused by a deficiency of this enzyme; symptoms include bone erosion and enlarged liver and spleen, with early death. The product is currently in clinical trials; if they are successful, the Food and Drug Administration will approve GCR as an orphan drug.

Gaucher's disease is caused by improper storage of lipid in bone, macrophages, and other locations. Blair says Genzyme scientists have modified the oligosaccharide chains on naturally occurring GCR to expose mannose residues. According to Blair, these mannose residues target specific receptors on the macrophage, and, indeed, macrophages take up modified GCR five-fold better than the natural enzyme.

For some proteins, having the wrong sugar groups may not matter. Rademacher predicts that incorrect carbohydrate side-chains may not interfere with short-term biological effects, and that if therapeutic effectiveness is reduced, the dose might be increased. But, he cautions, for any protein where the sugar groups are needed for biological activity (such as is the case with human chorionic gonadotropin), not having the correct residues present will destroy the activity of that product.

—Jennifer Van Brunt

CHRONICLE

Clinical progress. Amgen (Thousand Oaks, CA) reported success using recombinant human erythropoietin in treating the anemia associated with chronic renal disease in patients undergoing kidney dialysis. Although the results are preliminary, erythropoietin caused significant increases in the percentage of red blood cells in the blood of patients who received the drug in trials at the Northwest Kidney Center (Seattle, WA). In other projects, the Food and Drug Administration (FDA) approved the use of Endotronics' (Coon Rapids, MN) Acusyst-P cell culture instrumentation for interleukin-2 trials against human cancer underway at the University of Minnesota. Also, FDA gave Sandoz (Basel, Switzerland) and Genetics Institute (Cambridge, MA) the go-ahead to test granulocyte-monocyte colony stimulating factor against blood cell deficiencies in humans.

Lawsuit updates. In the latest spate of biotech-related litigation, Jeremy Rifkin and his Foundation on Economic Trends (Washington, D.C.) sued the U.S. Department of Defense (DOD), charging violations of the National Environmental Policy Act in the conduct of DOD's biological defense research and development program. In the Rifkin-motivated suit against the University of California over the field-testing of recombinant bacteria, however, an out-of-court settlement was reached. Under the agreement, the university will conduct an environmental analysis; actual tests probably will not occur before next spring.

New financing. Biotech companies continue to tap the public markets for funding. Most recently, Bio-Response (Hayward, CA) sold $22 million in convertible subordinated debentures, while Life Technologies (Gaithersburg, MD) filed a registration statement with the Securities and Exchange Commission for its initial public offering.

New agreements involving biotech companies include:

- Genetics Institute and Wellcome Biotechnology Ltd. (London) will form a joint venture in New England called WelGen Manufacturing to produce recombinant pharmaceuticals. Both collaborative and proprietary products will be made at the 100,000-square-foot, $30-million facility.
- T Cell Sciences (Cambridge, MA) signed a three-year agreement with Pfizer (New York, NY) worth $4.5–7.0 million for the development of therapeutic products for the treatment of rheumatoid arthritis and type I diabetes.

Edgar Ribi, 65, chairman and chief executive officer of Ribi ImmunoChem Research (Hamilton, MT), died on August 31 when the small aircraft he was piloting crashed in northern Idaho. He built his company on pioneering research into adjuvants and immune regulators, staking out unique niches in both biotechnology and veterinary pharmaceuticals. His son, company president Nils A. Ribi, is running Ribi ImmunoChem until a successor is named.