

OLIGOSACCHARIDE RESEARCH

U.K. COMPANY MOVES INTO COMPLEX SUGARS

OXFORD—For many biotechnologists, the carbohydrate portions of glycoproteins are of considerably more nuisance than interest. In particular, they preclude the use of bacterial expression systems for proteins that cannot function properly without glycosylation. But it is the carbohydrates that are of consuming interest to a group of Oxford University scientists, whose technology is now ripe for exploitation.

As Raymond Dwek, director of the Oxford Glycobiology Unit, is fond of pointing out, the oligosaccharides occupy a considerable portion of the surface area of glycoproteins. More to the point, they come in a bewildering variety. For the past five years, Dwek's unit, which is part of the university's biochemistry department, has been developing high-tech sys-

logical activity of glycoproteins; consequently, some glycoforms of, for example, tissue plasminogen activator (tPA), may be of more pharmaceutical value than others.

Oligosaccharide analysis is demanding in time, reagents, and chemical expertise. The general strategy is to use trypsin to fragment a highly purified glycoprotein into a number of glycopeptides that are then separated by high-pressure liquid chromatography. The oligosaccharides are released from the column by hydrazinolysis and fractionated either by high-voltage electrophoresis, or (after neuraminidase digestion) by gel-filtration, which determines the number of sugar units in each oligosaccharide. Finally, the chemical structure of the sugar units released by sequential ex-

major source of income will be oligosaccharide sequencing equipment, which the company will develop and assemble. Selling the glycosidases needed in the analytical procedure and the oligosaccharides that serve as standards will also generate income. Dwek's group has developed techniques for purifying both types of

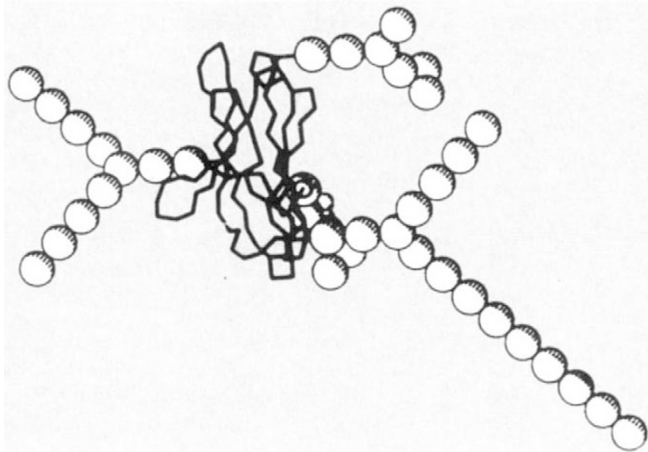
OTHER PLAYERS

- Carbohydrates formed a part of the initial portfolio of British Bio-technology Ltd (Oxford), which has recently announced a second-stage private placement of £8 million. The company has not followed through with its plans to market synthetic oligosaccharides but is exploring the possibility of a synthetic carbohydrate-based vaccine against meningococcal meningitis.

- Carbohydrates International (Arlov, Sweden), a member of the Volvo Group and a spin-off from Sockerbolaget, Sweden's only sugar-producing company, sells over 100 oligosaccharides—mostly O-linked—that are made by chemical synthesis or biosynthesis.

- Biocarb (Lund, Sweden) also sells oligosaccharides—a spin-off from carbohydrate research at Lund University and Karolinska Institute.

- ChemBioMed (Alberta, Canada), a private company wholly owned by the University of Alberta, is developing monoclonal antibodies as diagnostics for sugar-typing blood group antigens. The company is also synthesizing complex carbohydrates as potential human and veterinary therapeutics.



Molecular model of Thy-1, a glycoprotein on the surface of thymocytes and brain cells. The model points out the relative sizes of the polypeptide chain (black line) and the three attached carbohydrate groups (each sphere represents a sugar unit).

tems for analyzing N-linked oligosaccharides, with the financial backing of Monsanto Co. (St. Louis, MO). Oxford Glycosystems Ltd. is ready to commercialize some of these systems.

Dwek also likes to emphasize that any glycoprotein exists in several "glycoforms"—varieties determined by the oligosaccharides. A typical glycoprotein will have several glycosylation sites and a heterogeneous population of oligosaccharides on some or all of the sites, even within a single tissue. Other tissues may have yet another range of glycoforms. It is largely an act of faith on the part of those who go to the trouble of analyzing glycoforms that variations in oligosaccharide can influence the bio-

oglycosidase digestion is determined.

The Oxford group has attempted to take some of the pain out of the process by automating and computerizing the analytical processes, particularly so that natural mixtures of glycoforms can be profiled. Monsanto has provided great assistance in developing both hardware and software; it pumps £1.5 million a year into the unit (and has to give five years' notice if it wishes to pull out) in exchange for first patent options. Monsanto is exploring possible carbohydrate-based methods of diagnosis and treatment of arthritic diseases, as well as the use of particular tPA glycoforms as fibrinolytic agents. The patents relating to instrumentation and analytical reagents, however, are licensed to Oxford Glycosystems.

The new company's start-up is financed by venture capital, led by Advent Ltd.; Advent's Jerry Benjamin forecasts a turnover of £25 million within 5 years. He anticipates that the

reagents to the degree necessary for sequencing; the highly purified reagents can fetch up to £100,000 a gram.

Another source of income will be contract work from customers who want complete oligosaccharide analyses of their glycoproteins. It may require an investment of £5 million before Oxford Glycosystems can break even, guesses Benjamin. Oxford University will hold 25 percent of the initial shares in the new company, and both Monsanto and Dwek will also become shareholders.

—Peter Newmark