

First US patent on TPA for Oxford University

- Patent highlights sugar sidechains
- Other TPA patents expected

Washington

THE University of Oxford plans to announce this week that it has been granted a US patent covering the clot-dissolving glycoprotein known as tissue plasminogen activator (TPA). This development will surprise, but also disappoint, many other groups working towards this prize.

The patent is the first to be awarded for TPA in the United States, and is unique among other patents for proteins in that it specifies exactly the sugar groups attached to the protein's basic amino acid sequence.

It has been expected for some time that the first US patent for TPA would be issued this summer, but most observers had predicted that it would go to Genentech, the Californian biotechnology company that received approval to market TPA as a drug to treat heart attack at the end of last year. Genentech sells a recombinant version of TPA based on the over-expression of the human TPA gene inserted into cell cultures of the Chinese hamster ovary. The company has filed a US patent for TPA which is believed to be nearly as broad as the British patent it held until a year ago, but which was then declared invalid by a British court in a suit brought by the drug company Wellcome plc (see *Nature* 328, 189; 1987).

Genentech's British patent, now under appeal, covered all forms of human TPA produced by recombinant DNA technology, and all means for producing it.

The University of Oxford patent is not based on recombinant DNA technology. Its broadest claim is for human tissue plasminogen activator derived from cultured normal human colon cells, specifically fibroblasts. Further claims describe in detail the oligosaccharide sidechains of two forms of TPA produced by the cultures: one that acts quickly in the bloodstream to break down a blood-clot, and another that acts more slowly.

The Oxford patent is based on the premise that proteins produced by eukaryotic cells may exist in several different forms, differing in physiological activity, according to the type, number and position of the oligosaccharide sidechains added after the protein is assembled from its amino acids. There may be several different "glycoforms" of a protein within the same tissue.

Previous patent claims for either recombinant or naturally-derived proteins with potential uses as medicines have taken no account of the various glycosylation

patterns of the proteins that there may be.

The multinational pharmaceutical and chemical company Monsanto supported the research leading to the Oxford patent. Monsanto, interested in the possibility that the sugar sidechains of proteins may affect their activity as drugs, began supporting the Oxford Glycobiology Unit led by Raymond Dwek in 1983. Under the agreement, Monsanto contributes \$1.5 million a year to Dwek's unit, in exchange for the right of first-refusal to license any patentable technology. Monsanto will license the Oxford patent once it is issued, probably in the third week of this month.

Monsanto's subsidiary G.D. Searle has plans to market a form of TPA under development by Monsanto and the St. Louis biotechnology company Invitron, in which Monsanto holds a controlling interest. Invitron and Monsanto are being sued by Genentech for theft of trade secrets by two Invitron employees who formerly worked in scaling up the production of Genentech's recombinant protein products.

Genentech has charged that Invitron hired away its employees to gain access to information about its proprietary protein expression technology, with the intention of developing competing products. The suit is just beginning, but Genentech is asking for damages in the tens of millions of dollars, and a permanent injunction against sales of any forthcoming Invitron products.

Genentech and the Monsanto-Invitron collaboration are only two of many companies with various forms of TPA under development. Further along with modified, or second-generation, versions of TPA are Genetics Institute and Integrated Genetics. Genetics Institute's approach involves streamlining the TPA molecule by altering some of its domains to give it a longer half-life in the bloodstream, which should prevent clots from reforming after a heart attack has been stopped. The technology for altering the configuration of the sugar sidechains of a recombinant protein after it has been expressed is also being developed by Genzyme, which has filed patents on its technique.

It is believed that many of the roughly 19 companies working on TPA have filed patents covering their methods and formulations. In the United States, filed patents (known as patent applications elsewhere) are confidential until they are issued (granted), so it is difficult to say

Refusniks and *glasnost*

JEWISH "refusnik" scientists in Moscow are planning to test the limits of *glasnost* this autumn by holding an international symposium to which foreign participants will be invited. The organizers, Yurii Chernyak, a physicist, and Igor Uspeski, an entomologist, say that they are in touch with some 60 scientists who are denied permission to emigrate, only 10 per cent of whom have jobs "more or less adequate for their qualifications". This, they say, shows there is no substance to the latest stance of Soviet officials that to permit free emigration would be to connive at a brain-drain.

Although Soviet scientists caught in the limbo between losing their jobs, after applying to leave, and receiving an exit visa have been attempting to organize international meetings since 1972, the authorities have repeatedly intervened since 1974 to prevent them happening.

Those planning this year's meeting hope to work within the terms of the May 1986 decree permitting the establishment of "informal associations and hobby-clubs". But several attempts by Jewish seminar groups to register as "informal associations" have been rejected on technical grounds. V.R.

More research centres

BRITAIN'S Science and Engineering Research Council has invited bids from higher education institutions to host a further six interdisciplinary research centres. The centres will be in process simulation, integration and control; high performance materials; optical and laser related science and technology; surface engineering; polymer science and technology; and application of parallel and novel architecture computing in science and technology. It is hoped that the new centres will start in the autumn of 1989. Meanwhile, the first research centre, in high-temperature superconductivity and based at the University of Cambridge, has appointed its director. He is Dr Peter Duncumb, who before joining the university's Earth sciences department in January was director of an industrial physics laboratory. The centre is to be formally inaugurated by education secretary Kenneth Baker on 21 June. S.H.

how many patents for TPA will emerge, and how broad their claims may be.

Issuing a patent to the University of Oxford will not prevent the US Patent Office from issuing further, perhaps even broader, patents covering TPA. But this development may set a precedent forcing other companies fully to characterize and define the glycosylation patterns of protein products, of which TPA is only one, for which they seek protection.

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