Monoclonal Antibodies Search Out Disease

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When monoclonal antibodies were first developed just over ten years ago, the inventors had no idea how useful they would be. Even five years ago few could have predicted the explosion in monoclonal technology that is now taking place.

This is partly illustrated by the fact that Dr Cesar Milstein and Dr Georges Kohler, inventors of the technology, were not awarded a Nobel prize for their work until 1984, nine years after the event.

Now laboratories and commercial companies are making up for lost time. The particular qualities that monoclonal antibodies (MABs) possess are revolutionising the fields of diagnostics and purification, and every day inventive researchers are finding more ways of using them, for example, in cancer therapy.

Antibodies are normally made by white blood cells or lymphocytes and act like the immune defences' alarm system. They are large molecules designed to recognise foreign material in our bodies and, when they encounter something like bacteria, they notify the rest of the immune system that there is an intruder.

Problem Solved

Scientists started to use antibodies in the laboratory in the early 1960s when it was recognised that they could identify foreign material outside the body.

Unfortunately, these "polyclonal" antibodies needed to be purified straight from immunised animal blood and samples tended to contain a mixture of different antibodies. It was impossible to purify them down so that there was only one type of antibody.

Then in 1975, Kohler and Milstein at the Medical Research Council's Laboratory of Molecular Biology in Cambridge, eastern England, invented a technique that solved this problem.

They started by immunising mice against the material they were interested in. The animals' lymphocytes immediately began producing antibodies to cope with the intrustion.

These antibody-producing lymphocytes were then removed and fused together with a strain of immortal myeloma or cancer cells. The result was a special hybridoma cell line that went on continuously reproducing itself like cancer but also produced antibodies like lymphocytes.

Since one lymphocyte produces only one type of antibody, these hybridoma cells, when isolated and allowed to reproduce, produced large quantities of one type of antibody instead of the usual polyclonal mixture - they were monoclonals.

Production Multiplied

Eleven years on there are a number of companies making large quantities of MABs. Celltech of Slough, near London, is the world's largest producer. The company has one 1000 litre fermenter and is about to start up a second, as well as having a considerable number of smaller fermenters.

In these vats, the hybridoma cells are grown in large quantities. The environment is kept at the same temperature as blood, and air is bubbled through to supply oxygen to the delicate cells.

After the fermentation mixture has been purified, Celltech produces between five and ten kilograms of antibodies a year.

Damon Biotech hopes eventually to exceed this rate by building a large MABs production facility in Livingston, Scotland.

The company has patented a technique called Encapcel for fermenting large quantities of MABs. One of the problems of growing hybridomas in fermenters is that they are delicate and tend to stick together so that the cells in the middle suffocate.

Detecting Cancer

The Encapcel method manages to isolate small groups of hybridomas in the porous polymer coat. Inside a protective sphere, they can grow and produce antibodies but are prevented from clumping together in larger groups and can stand up to a fair amount of bubbling without breaking apart.

Now that the means exist to make MABs by the kilogram, research institutes, commercial companies and medical schools all over the United Kingdom are taking advantage of the full potential of them.

Work is proceeding at laboratories such as those of the Royal Marsden Hospital and the Imperial Cancer Research Fund in London to use them in cancer treatment. MABs have been developed to search out cancer cells. The aim is to attach markers to these cancer-specific antibodies so that once they are injected into a patient the presence of cancerous lesions can easily be detected.

Alternatively, poisons such as the A chain of ricin can be attached to the MABs. When injected the poison-antibody partnership moves harmlessly around the body until it reaches a cancer cell. Then, as the antibody attaches itself,the poison molecule slips free and kills the cancer.

Diagnostic Kits

But it is in the field of diagnostics that the major impact is currently being made. Most clinical laboratories now have a range of MABs to detect different diseases.

An agreement between Boots, the pharmaceutical company, and Celltech has produced one of the largest organisations making diagnostic kits for use in laboratories - such as the test for chlamydia.

However, MABs make these tests so much easier to handle that they are no longer limited to laboratories. Unipath, a division of the Unilever group, is now selling a pregnancy test called Clearblue through retail chemists. It uses MABs immobilised on to the tip of a sampler stick. The stick's ability to identify minute amounts of the pregancy hormone HCG provides a simple, reliable test which can be carried out shortly after conception.

One major aim is to move more of the routine tests that clinical laboratories have to do into the family doctor's office. This would make diagnosis quicker and cheaper.

Industrial Application

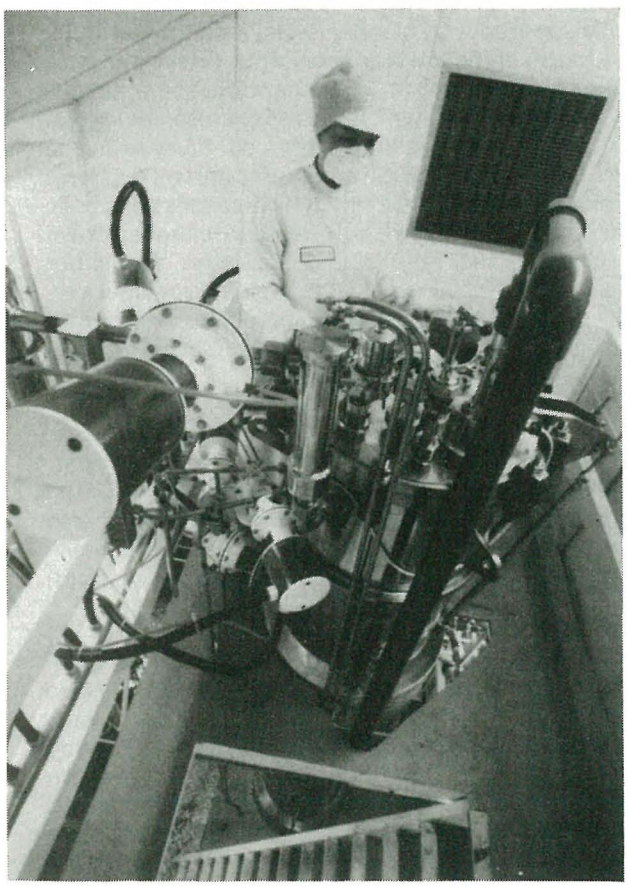
P.A. Technology, a science consultancy near Cambridge, is working on a generic diagnostic kit. Within three years the company hopes to provide doctors with a simple desk-top device that complements a range of MAB test sticks. So, depending on what the doctor needs to test, whether it is pseudomonas, staphylococcus or streptococcus, he can select a stick, take a sample, and the machine will give him the answer.

This field of biosensors has been given a boost by the durability and reliability of MABs.

Monoclonals have also helped with the purification of minute amounts of precious biological materials from mixtures of substances. Interferons, for instance, can be picked out of pints of donated blood much more easily now that immobilised-MABs-to-interferon is available. It is only since MABs came along that scientists have discovered how many forms of interferon there are.

Medicine, however, is not the only area to benefit from these highly specific natural labels. Plant and zoological researchers and the chemical industry have used them, for instance.

As more and more MABs are produced they will slowly become cheaper and so be available for use in other areas outside medicine.



Celltech's 1000 litre fermenter is mass producing monoclonal antibodies.