

Top-Level Service Monoclonal Antibodies Ready-to-Measure

Established by the immune system for millions of years, antibodies have long become an indispensable tool in research and therapy. Making good antibodies, however, is a task reserved for specialists – and not all institutions have the excellent possibilities of the GSF. With its Research Platform Monoclonal Antibodies it is an important interface in the network of health and environmental research.

It was back in the early eighties that Dr. Manfred Eulitz, then a scientist at the GSF Institute of Immunology, who established a group producing monoclonal antibodies. The basic idea of this group was that any GSF scientist interested could acquire the knowledge required to be able to develop the monoclonal antibodies he/she wanted.

But it soon turned out that the logistic requirements were too much for most laboratories. This is why the group was converted to a service facility. Today Dr. Elisabeth Kremmer heads the Research Platform Monoclonal Antibodies at the GSF Institute of Molecular Immunology.

Large-Scale Production

“Today our working group can continuously produce the antibodies exactly matching the requirements of the requesting scientists,” Kremmer explains. “Under the new service concept we have been producing high-quality monoclonal antibodies ready-to-measure very quickly since 1995, approx. 300 different antigens per year, with a rising tendency.” At the same time Kremmer’s group is extremely flexible: together with the client they discuss which antigen is best suited for the production of the requested antigens. “Some proteins cause no or only a very weak immune response, they are not immunogenic,” Kremmer explains. “No antibodies against them can be made. Together with the partners we then look for more suitable antigens.”

When an immunogenic substance has been found, an immune response against it is produced in the animal model. The B cells of the bodily defense activated in this process and directed against the antigen will be extracted and fused with a tumor cell line, a so-called myeloma cell line. “When this happens, the desired property of the B cell to produce a specific antibody is transferred to the myeloma cell and a so-called hybridoma is produced,” Kremmer explains. This will now be reproduced in the cell culture, the antibodies secreted into the medium will be withdrawn and added to the antigen. “If the antibody binds specifically and strongly to the antigen introduced, it has the desired high affinity and specificity. The antibodies are sent to the partners for further characterization,” says Kremmer.

Producing good antibodies is a task reserved for specialists – and the service unit of the GSF has them: with their experienced eyes the scientists see which cells have grown so well that they are worth testing. “We examine all growth media and reagents for their suitability for the production of hybridomas,” says Kremmer. “This saves time.” It is not so much the laboratory equipment as it is this skill, diligence and the many years of experience together with a subtle feeling for whether, e.g., a culture needs an additional change of medium, which guarantee the high



quality standard of the service unit.

High Efficiency Without High-Tech

“We are particularly efficient, although or maybe just because we work without any special devices, such as a pipetting robots, freezing machines and bioreactors,” says Kremmer. “With just four people we produce approx. 30 different hybridomas per week, which we propagate in culture bottles.” It would be much too complicated to charge a bioreactor for the small quantities of antibodies requested. Apart from that, if a culture bottle is accidentally contaminated with bacteria, this one culture can quickly be disposed of, while all others can continue to grow. “A bioreactor would have to be cleaned completely in this case, and all cells in it at this point in time would be useless at once,” says Kremmer.

Together with her colleagues Dr. Martin Lipp and Dr. Reinhold Forster from the Max-Delbrück-Center of Molecular Medicine as well as Dr. Eckhard Wolf from the Gene Center of the University of Munich the physician was awarded the Erwin Schrödinger Prize 2000 for the exceptionally high quality of the antibodies. The fact that, apart from GSF scientists, scientists from many universities and research institutions throughout the world have their antibodies made by the GSF platform is also owed to the special support after

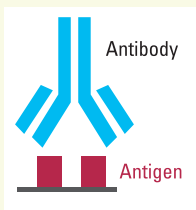
Scientists from all over the world have their antibodies made by the GSF Antibody Platform. With just four people Dr. Elisabeth Kremmer, head of the Platform, produces approx. 300 highly specific antibodies a year. Apart from the high quality standards the clients particularly appreciate the service platform for the intensive support provided even long after the production.



With their experienced eyes the specialists of the Antibody Platform see which cell lines have grown so well that they are worth testing for antibody production. The many years of experience are more important here than any high-tech laboratory equipment.

Detectives for Research

Antibodies are complicated protein structures which can react with chemical structures of many different kinds due to the variation of amino acids in certain sections of the protein chains. The ability of the organism to react to noxae which have entered by forming antibodies developed over many million years. Predecessor structures of the antibodies have been found in cartilaginous fish. The fact that they can bind many different chemical structures with high specificity makes the antibodies, together with immunological detection methods, such as radio and enzyme immunoassays "RIA" and "ELISA", unique detectives in research.



The normal antibody response of the body after contact with an antigen, however, has one disadvantage: it is inhomogeneous, because it consists of a mixture of specifically and less specifically binding antibodies. It takes a lot of time and effort to isolate high-purity molecules from this, and this is often not even crowned with success. Thanks to Georges Köhler's and Cesar Milstein's work those antibodies

can be selected from the multitude of possible antibodies today, which bind the desired antigen with high specificity. For this hybridoma technology published in 1975 the two scientists were awarded the Nobel Prize for Medicine in 1984. Those cells are selected as the end product of this process, which produce only one antibody of the required specificity.



The ability of the organism to react to foreign substances which have entered by producing antibodies developed over millions of years. Predecessors of the classical Y structure of antibodies which can bind a large number of chemical structures are found in cartilaginous fish, such as the nurse shark.

delivery: even many years later the working group can supply more of any antibodies once ordered, because all hybridomas ever made are clearly marked and kept in liquid nitrogen. Apart from this the employees of the GSF support their partners in the subsequent detailed characterization of the antibodies, e.g., by providing so-called secondary antibodies for labeling the originally used proteins. It is these and other services which eventually result in such high-quality products.

"Monoclonal antibodies identify the desired proteins so accurately, because the antigen-antibody system is very old and has been made more and more perfect by nature over time," Kremmer concludes. "This is why the methods developed with their help work so well and are transferred more and more from research to clinical applications."

To Clinical Applications With High Accuracy

This may also soon apply to the antibody which recognizes a deletion mutant of the protein E-cadherin. E-cadherin is a protein which is partly responsible for maintaining the contact of the cells. Deleted E-cadherin, which is only found on cancer cells, particularly frequently with diffuse gastric cancer, is recognized by a monoclonal antibody. If α -radiators are coupled with the antibody, only the cancer cells will die, because the antibody binds to them exclusively. What can already be done at the laboratory, will hopefully also soon cure cancer patients in the clinics.



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