

Bayer researchers build customized protein molecules for the treatment of serious diseases

On the way to finding a top candidate

Biologics are a group of medicinal products with very special characteristics. They are based on endogenous proteins and amongst other things can support the human immune system in its fight against diseases such as cancer or multiple sclerosis. Researchers at Bayer HealthCare are using high throughput technologies to optimize the molecular structure of these therapeutic proteins until they have all the desired therapeutic characteristics.

They are modern prospectors for gold: pharmaceutical chemists, biotechnologists and chemists searching for valuable nuggets in the form of new medicinal products. By the time they create a potential active substance, numerous other candidates will have been tested and rejected. Dr. Wayne Coco, Head of Biologics Research Cologne/Wuppertal in Bayer HealthCare's Bayer Schering Pharma division, is one of them. Together with a team of

specialists, he sifts through substances which have the potential to become top drug candidates. "We select suitable active substance candidates from certain protein families and tailor them for very specific functions or characteristics," explains Coco.

The Bayer researchers are searching for biologics – a class of substances that includes antibodies and other therapeutic proteins. Biologics are rather like optimized versions of endogenous sub-

stances. For example, they intervene in the immune response and have a very specific effect on the disease process. Experts rate medicinal products in this substance class as the fastest growing market segment in the pharmaceutical industry. "Antibodies are important defense molecules in the human body. They act against intruders almost like the body's own police force," explains Dr. Beate Müller-Tiemann, Head of Biologics Research in Wuppertal. For



Talent scouts: Alexander Korseska and Nina Habrich (photo left, left to right) use robots to test up to 80,000 protein variants every day. Dr. Wayne Coco (above) then uses them as the basis for new medicines.

Promising candidates: in the search for new biological and pharmaceutical active ingredients, Bayer scientists like Dr. Carsten Baumchen use state-of-the-art screening technology and have access to a huge reservoir of mainly human protein molecules.

patients with diseases such as multiple sclerosis or cancer they are often the only hope. Each protein molecule attacks only one very specific target. For example, it only attacks a patient's cancer cell receptors, not healthy tissue. "Many kill pathogenic cells directly, whilst others mop up the growth factors which cancer cells need to survive and which swim freely in the blood stream," says Müller-Tiemann. "The ability of antibodies to bind specifically to antigens on tumor cells, for example, is what makes them so interesting for cancer research," adds Dr. Heiner Apeler, Head of Molecular & Antibody Biology at Biologics Research in Cologne.

In addition, Bayer's Biologics researchers also use the antibodies as selective carriers for cell toxins, known as immune conjugates. "These chemotherapeutic agents are delivered by the antibody directly to the tumor, thereby reducing side effects during chemotherapy – something which is badly needed in cancer treatment," says Müller-Tiemann. At present, new immune conjugates are being developed in Bayer's Biologics laboratories for the treatment of the most common types of cancer such as breast and lung cancer. "In addition, in the development of new immune conjugates we optimally combine two of Bayer Schering Pharma's core competences: classic medicinal chemistry for the chemotherapeutic agents and protein engineering for the antibodies as highly selective binders and carriers," explains the biochemist.

The Bayer scientists are already on their way to clinical trials with several of their prospective therapeutic antibodies.


Huge gene libraries for protein optimization

Before they reach this stage, however, the proteins have to undergo an optimization process and the technology needed for this is termed protein engineering. "Antibodies and other naturally occurring protein molecules don't usually work in precisely the way we need them to for a specific purpose," explains microbiologist Coco. This is why the Bayer scientists intervene in the construction plan of a protein to alter its structure. "Every day in our laboratory we test about 80,000 different variants of a protein which is to be optimized," says Coco. This is made possible firstly by the fully automated, robot-aided high-throughput process. Secondly, the researchers also rely on a patented protein engineering platform which allows the creation of whole gene libraries which can then be tested with high throughput screening and special assay systems. The people mainly responsible for this at Biologics Research in Cologne are the departmental heads Dr. Ulrich Haupts and Oliver Hesse.

Bayer's protein engineering platform came from the Cologne biotech company Direvo Biotech AG, which was merged with the company's existing biologics department in Wuppertal in April 2009 and is now part of Bayer

HealthCare's Bayer Schering Pharma division. "Together, we can now press ahead with research into biopharmaceutical products even more effectively. Biologics research is one of the mainstays of Bayer Schering Pharma," says Dr. Clive Wood, Head of Global Biologics at the company.

As well as accelerating the screening process, the protein engineering platform also speeds up measurement with a patented laser process, and the optimization and selection of promising candidates. Bayer scientists in Protein Therapeutics are currently testing large numbers of top variants from their research programs which have now been combined. And they have no greater wish than for one of their optimized proteins to prove to be a major success and go into development.

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