Media communiqué

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Bioprocess increases vaccine yield

Vaccines from the bioreactor

Vaccinations are the most effective weapons in the fight against infectious diseases. However, developing novel vaccines alone is not sufficient to win the battle and the development and manufacture of economically priced vaccines in sufficient quantities represent real research challenges. Empa researchers, working together with the ETH spin off GlycoVaxyn AG, have developed a new bioprocess which increases the vaccine yield by a factor of fifty compared to conventional techniques..

Empa researchers have managed to adapt a process for manufacturing certain vaccines for use in bioreactors, with the result that the yield is enhanced enormously. In this technique, antigens in the form of sugar chains (oligosaccharides) are chemically linked to carrier proteins in a complex process known as glycosylation. Conjugate vaccines already available are among the most effective and safest preventive agents against dangerous bacteria such as Haemophilus influenzæ. The vaccination of infants against this disease is recommended since it causes serious infection in the nose and throat, and can result in potentially fatal meningitis.

Designer bacteria instead of chemical processes

A more elegant way, however, is to allow this task to be performed by specially designed, non-toxic *Escherichia coli* bacteria, which are normally present in the human gut. For this purpose GlycoVaxyn has developed an enzyme-based *in vivo* method. The *Escherichia coli* bacteria were genetically modified, so that they glycosylate certain proteins – in order words, they generate vaccine material. Unfortunately, however, the yield in the GlycoVaxyn process was too low. The vaccine manufacturer needed the help of specialists to upscale their process so it could be used in bioreactors. Their search came to an end in Empa's «Biomaterials» laboratory, where both the necessary know-how and the bioreactors were at hand.

From cell culture to bioreactor

"This is a classic biotechnology «scale-up-problem». It is not simply a question of multiplying everything by a hundred," explains Empa expert Julian Ihssen ."On a large scale everything becomes more difficult. At higher cell densities many factors change." For example, *Escherichia coli* bacteria begin to produce acetic acid. The oxygen supply is also no longer optimal. This makes the results very difficult to predict.

The Empa researchers discovered that the production of the glycoconjugate, i.e. the vaccine itself, was influenced by both the type of culture medium used as well as the way the process steps were controlled.

Several different process sequences were tried out, with the best turning out to be a «fed-batch» strategy involving the periodic addition of glycerol as the main nutrient.

A significantly higher vaccine yield

The novel bioprocess resulted in a forty times increase in the biomass concentration – that is, the bacterial cell density – compared to the previously employed shaken flask technique. At the same time each individual bacteria produced on average somewhat more vaccine than before, so that all told the yield in purified conjugated vaccine rose from 0.6 to over 30 milligrams per liter of culture medium, an increase of about a factor fifty. “The results using a three liter bioreactor were very promising. Now we are hoping to be able to scale up the principle even more to the industry standard level,” says GlycoVaxyn co-founder Michael Wacker.

The same process can very likely be used to manufacture various conjugated vaccines, for instance against certain diarrhea producing organisms. This would above all offer a glimmer of hope to developing countries, where often vaccination campaigns fail because of the high price of vaccines.

Further information

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Empa researchers have successfully scaled-up a new method of producing vaccines to enable the use of a bioreactor.