Just saving the world

HIV research: optimists in search of an effective vaccine.

By Sonja Kastilan
Frankfurter Allgemeine Sonntagszeitung, 06.12.2015

“We are trying something that has never been done before, at least not in this form.” Mark Feinberg chooses these words to describe not an attempt to climb Mount Everest via a new, daring route – which would probably be an easier feat than what he has set out to do – but his goal to conquer HIV, the virus that causes AIDS, which was discovered in 1983 and has since spread all around the world. Feinberg, a physician, has been working on this unique pathogen since he studied medicine at Stanford.

The World Health Organization (WHO) estimates that globally more than 36.9 million people globally are currently infected with the human immunodeficiency virus (HIV), and about 1.2 million people died from it in 2014. European public health authorities recently reported the highest number of new infections since the disease first broke out, with 142,000 new cases recorded last year. Modern antiretroviral combination therapy has advanced sufficiently to allow almost 16 million people to live with the disease, and drugs are also available to prevent infection. However, Feinberg is certain that the spread of the pandemic can only be halted if a safe and effective vaccine is found, and many of his peers agree. In September, Feinberg was appointed President and CEO of the International AIDS Vaccine Initiative (IAVI), an organization that has been driving research into a vaccine at all levels for almost 20 years. IAVI takes the position that “the very best research at each and every link of the R&D chain” is essential if this goal is to be achieved. HIV presents a rich target for innovation, and the biology of this lethal virus is as fascinating as it is challenging for researchers.

“We must always be better than the natural immune response if we want to develop a vaccine,” Feinberg emphasizes during our interview. As a rule, the human body has been unable to rid itself of the virus without external intervention, because HIV is a retrovirus, meaning that it embeds itself into the genome of its host and is also capable of hiding from immune system agents inside certain types of cells. The infection usually persists chronically and can even go through different permutations, as the virus is astoundingly changeable and people carrying one type of HIV are not protected against other variants. There are not only several sub-groups of HIV-1 and HIV-2, but also numerous different strains which any vaccine would need to protect against; similar to a broad-spectrum antibiotic, but at a prophylactic stage. Attenuated HIV cannot be used for this purpose, as the risk of an insidious mutation developing – as happened with the polio vaccine – would appear to be too great.

The first vaccine studies, carried out in the late 1980s according to conventional patterns, were sobering. Researchers were, for example, unable to provoke a protective antibody response to the envelope protein on the surface of the virus – something that other vaccines commonly achieve. The virus kept perplexing and frustrating vaccinologists, who at the same time felt increasing pressure from the growing HIV pandemic, as Anthony Fauci and Hilary Marston recently pointed out in *Science*.

However, research has made great advances over the past three decades: “HIV has taught us more about the human immune system than any other pathogen,” Feinberg says. “We needed to understand the virus, its biology and the human body’s response to it.” What answers does he have to offer? What role do the various immune cells play? Which antibodies are produced when? How can the viruses be kept under control and prevented from embedding themselves? Each answer raises new questions that have spurred more scientific investigation. “Even our laboratory methods and technologies are so much better now than they were even five, ten or fifteen years ago,” Feinberg adds. That sounds as if scientists are now well equipped to head straight from base camp to the summit, and a number of research teams have indeed set out to experiment with variations on conventional approaches or entirely new technologies.

Above all, they had to identify so-called vectors for vaccines, which allow the human immune system to be efficiently exposed to certain features and protein structures of the AIDS virus that are prone to attack. Scientists have experimented with naked DNA, for example, to enable the body to build its targets independently, and with small protein snippets and viral helpers containing relevant genetic information. They have tested repeated injections and the so-called prime-boost vaccination strategy. “The systems developed from this research now help fight other diseases, including Ebola, and several current vaccines are based on vectors initially identified for HIV,” says Feinberg, who is thoroughly familiar with this area of research, having worked in academic settings, for the US National Institutes of Health and, most recently, for the pharmaceutical industry. As a researcher for Merck, Feinberg was tasked with the development and testing of the Ebola vaccine rVSV-Zebov, for example.

Feinberg now wants to apply his experience to extending the IAVI network. To do so, he envisages a scientific community that involves both the public and the private sector, particularly to ensure that more clinical studies can be launched and vaccine candidates can be tested more quickly. Even if some results may be disappointing, concepts may then be updated to take the most promising approaches further.

Hendrik Streeck, the head of the HIV Research Institute at Essen University Hospital, pursues a similar goal with his plan to network German HIV researchers within a consortium to boost the development of a vaccine in Germany. “So far, it’s been everybody on their own, but we’ll make better progress if we work together, especially when it’s about organizing costly clinical studies.” Streeck hopes to receive funding from the German Ministry of Education and Research, saying that “we wouldn’t need a large budget to bring existing competences together.”

“You could compare it with a shared dinner, where everybody brings a plate, and it ends up costing not very much. After all, Germany has always been strong on vaccine research,” adds Nelson Michael, Director of the US Military Research Program

(MHRP). He is interested in cooperating with the consortium and travelled to Essen in mid-November, together with Merlin Robb, who is responsible for clinical research within the MHRP.

Streeck in turn runs a working group within the MHRP in Silver Spring, Maryland, and he wants to research how vaccines work: “We use vaccines, but we do not yet know in detail how immune cells respond to them and what sort of antibody response is necessary so that the body can build up protection.” Once this has been properly understood, he believes that laboratory trials could soon set researchers on the right track. Yet large-scale vaccination studies have shown just how complex this very understanding is in case of the AIDS virus. Clinical trials aimed at presenting three HIV proteins simultaneously to the body via modified adenoviruses failed, for example, as the chosen Ad5 vector seemed to increase the risk of infection. Considerable hope was placed in work with harmless fowlpox viruses, which transported the envelope protein only, but the 2009 RV144 study involving 16,000 participants in Thailand left the MHRP team disappointed, as the vector was only effective in about 31 percent of cases and thus fell below expectations. However, Robb now describes this study as bearing an important message, namely that the vaccination does in fact provide protection. Michael adds that, “If we had limited the period of observation to something shorter than the three-and-a-half year span used in the study, the results would have been much better and the vaccine would probably already have been approved.” After one year, the vaccination still provided 60 percent protection – a level that is enormously significant for HIV/AIDS and its consequences, as it means that lives would be saved, especially in high-risk populations.

Michael, Robb and their teams have been evaluating the data more comprehensively since 2009, and they continue to observe participants in the study. New vaccination strategies have been developed for follow-up studies in Asia and Africa in an attempt to extend the effectiveness of the vaccine with appropriate booster injections. It seems that boosting the formation of certain functional antibodies is a decisive factor for vaccines to provide effective protection. Also, important biomarkers have been identified in blood, which suggest that protection against infection has been achieved: these G-class antibodies act against a specific portion of the envelope protein. The relevant molecule on the virus membrane is a typical target for antibodies, which makes it highly interesting for vaccine research, but as its structure is made up of several components, it is difficult to replicate: the gp120 protein is attached to the membrane via a triple anchor (gp41) and forms a spike protruding toward the outside. “This protein also consists of three parts, and we are working very hard to retain its natural structure,” says Streeck. Yet researchers are optimistic, despite the challenges, as “it seems to be easier to develop a vaccine than to completely cure an AIDS patient,” which is why they keep pursuing a wide range of approaches.

“Some of these could be hit or miss, but others may be successful,” says Michael, who studied with Feinberg and shares his passion for developing an effective HIV vaccine. He believes that it would be only logical if IAVI was to invest in projects incorporating novel mRNA technologies, describing this approach as “a cool line of scientific thought.” Feinberg explains that promising methods and technologies such as mRNA technology will be pursued to help researchers design of suitable vaccine candidates much more quickly and flexibly. This is why IAVI entered into a partnership with CureVac, a German pharmaceutical company, in autumn.

The results that the mRNA approach is capable of delivering are impressively demonstrated during a visit to the CureVac offices in the German town of Tübingen, where the growing start-up has had its headquarters since 2003, nestled in the local technology park between the observatory and unused buildings of the Federal Research Institute for Animal Health. CureVac’s state-of-the-art safety laboratories and special manufacturing facility for medical products make the company seem rather exotic compared to its neighbors, and the company has also attracted international attention: CureVac cooperates actively not only with IAVI, but also with the Bill & Melinda Gates Foundation and pharmaceutical giants including Boehringer Ingelheim and Johnson & Johnson.

“Like everybody else, we originally assumed that RNA would be quickly broken down, but that’s not the case: cells absorb it very quickly and read its information,” explains Ingmar Hoerr, one of CureVac’s founders, on whose Ph.D. thesis the company’s business concept is based. RNA molecules contain copies of genetic information, which cells read and translate into protein structures. Hoerr, a biologist, found in animal studies that foreign RNA can provoke a stronger reaction if it is injected in “naked” form, and he intends to exploit his discovery for clinical use, as this approach would allow any protein in tissue to be produced as desired – at least for some time, as mRNA is broken down after a while.

His approach, which has already been assessed as safe in oncological studies, is now to be used to drive the development of vaccines. “Transcription processes are so important in nature, they can’t really go wrong. We now know how we need to design the relevant sequences, we have the expertise to ensure safe production, and we can quickly enter the clinical phase,” Hoerr says confidently. “A great advantage is that, after an injection, it is the body itself that forms the proteins to which the immune system is to respond. These would be difficult to produce and purify otherwise”, explains Susanne Rauch, who is responsible for HIV vaccines within CureVac. Also, the envelope protein of most interest to IAVI tends to break down into its sub-units, causing it to present protein structures that are able to mislead antibodies.

Preclinical tests of the new vaccine candidate are scheduled for completion in 2016, and Hoerr expects that the company’s RNA vaccine will then be tested in humans in one or two years. “When we then get the first results, we will be able to fine-tune the design within as little as a few weeks.” The resulting vaccines would be versatile and resistant to heat, meaning that they would not even require cooling, which would make their practical use in Africa and Asia much easier.

“Maybe we won’t be able to save the world just as yet,” Rauch says, “but we’d have an approach that would show us how it could be done.”

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