


# “This Vaccination Should **Benefit every Country**”

Chronic hepatitis B infections often lead to cirrhosis and cancer of the liver. There is currently no known cure for the disease. However, a cure is precisely what Prof. Ulrike Protzer and her team of researchers are striving to develop with the help of a therapeutic vaccination to drive the virus from liver cells.

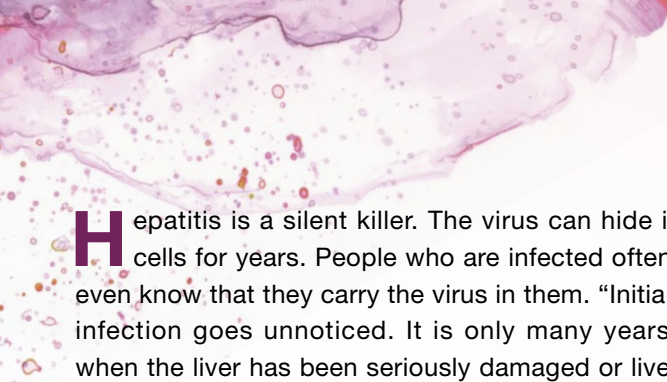
*Kurzfassung · Langfassung: [www.tum.de/faszination-forschung-25](http://www.tum.de/faszination-forschung-25)*

**„Diese Impfung soll allen Ländern  zugutekommen“**

260 Millionen Menschen weltweit sind chronisch mit Hepatitis B (HBV) infiziert. Das Virus existiert in ihren Leberzellen. 890.000 Todesfälle pro Jahr sind die Folge der Infektion. Bisher gibt es nur Medikamente, die das Virus in Schach halten. Prof. Ulrike Protzer hat einen neuen therapeutischen Impfstoff entwickelt, der Hepatitis B tatsächlich heilen könnte. Er stimuliert ganzheitlich das körpereigene Immunsystem und versetzt es in die Lage, das Virus effektiv zu bekämpfen und zu eliminieren. Die Prime-Boost-Methode läuft in mehreren Phasen ab. Zunächst erhalten die Patienten zwei Mal einen Proteinimpfstoff. Das stimuliert die B-Zellen: Sie bilden Antikörper gegen HBV. Auch die T-Zellen werden bereits alarmiert. Dann folgt eine weitere Impfung mit einem eigens entwickelten, komplexen MVA-Impfstoff. Der aktiviert vor allem die T-Zellen, welche die Virus-DNA aus den Leberzellen entfernen und infizierte Zellen zerstören. Die klinische Prüfung soll Anfang 2021 starten. □

Link

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**H**epatitis is a silent killer. The virus can hide in liver cells for years. People who are infected often don't even know that they carry the virus in them. "Initially, the infection goes unnoticed. It is only many years later, when the liver has been seriously damaged or liver cancer develops, that the virus becomes evident," explains Prof. Ulrike Protzer, Director of the Institute of Virology at TUM and the Helmholtz Zentrum München.

If you come into contact with the hepatitis B virus (HBV) as an adolescent or an adult, your immune system will be able to keep it in check. Although the immune response will trigger a liver infection, in most cases your immune system will be able to fight and eliminate the virus, and only five to ten percent of all patients develop a chronic infection. The situation for babies and young children is much more dramatic. Their immune systems are not yet fully matured and lack the defense mechanisms required to fight off HBV. Consequently, the virus is able to settle in liver cells in 90 percent of cases in this age bracket – where it remains for the rest of the individual's life.

Around 260 million people suffer from a chronic infection with the virus. Most of them are unaware of this – and those who are aware often hide it due to the stigma attached to it. People with a hepatitis B infection often face accusations of drug abuse, despite the fact that there are many other origins of infection. Liver cirrhosis and liver cancer are common long-term consequences of a chronic HBV infection. The hepatitis B virus kills around 890,000 people every year as a result of such complications, putting it among the most deadliest diseases. And, while the number of deaths caused by malaria, HIV and tuberculosis show consistent declines, deaths from hepatitis B continue to rise. A prophylactic vaccination for hepatitis B

has been available for almost 40 years; in Germany, all children receive the vaccine within the first 12 months of life. In other parts of the world, however, the situation is quite different. Mothers infected with the virus can easily transmit it to their newborn child. In such cases, the vaccination must be administered within 24 hours of a child being born. In geographically remote areas of Africa and Asia, that is simply not feasible.

Consequently, it will not be possible to eradicate hepatitis B through prophylactic vaccination. Medications have so far only been able to control the infection. What efforts to fight hepatitis B actually need is a way to remove the virus from liver cells once infected.

### **A therapeutic vaccination heals**

It is hoped that a new treatment developed by Ulrike Protzer called TherVacB will be able to cure hepatitis B infections. With the help of a therapeutic vaccination, the treatment aims to strengthen the immune system, enabling it to fight the virus and drive it from the body. In preclinical models, the novel concept behind TherVacB outcompetes other vaccine candidates currently in clinical trials. To understand how it works and why it may be superior, however, we first need to look at how the hepatitis B virus works.

When a person becomes infected with the virus, it circulates in their blood until it reaches the liver cells. Once there, it is smuggled into cells by one of the cells' own transporters, which are actually tasked with transporting bile acid, and then imports its tiny genome into the cell's nucleus. This genome is just 3,200 base pairs long, circular and only double-standard in sections. By way of comparison, the human genome is a million times larger; even a herpes virus has 50 to 70 times more DNA. ▶

# 1,500,000

people died in 2017 of viral hepatitis and its consequences



1

## Cardiovascular disease

is the top health cause of death globally

2

## Cancers

claim the second most lives

3

## Respiratory diseases

rank number 3 in death rates across the world with nearly 4 million deaths

4

## Lower respiratory infections

are responsible for 2.6 million deaths per year globally, the fourth-largest number

5

## Dementia

claims about 2.5 million lives each year

6

## Digestive diseases

cause the death of 2.4 million people a year

7

## Neonatal disorders

claim the lives of 1.8 million babies each year

8

## Diarrheal diseases

rank eighth and lead to the death of 1.6 million people per year

9

## Liver diseases and acute hepatitis

kill 1.5 million people each year

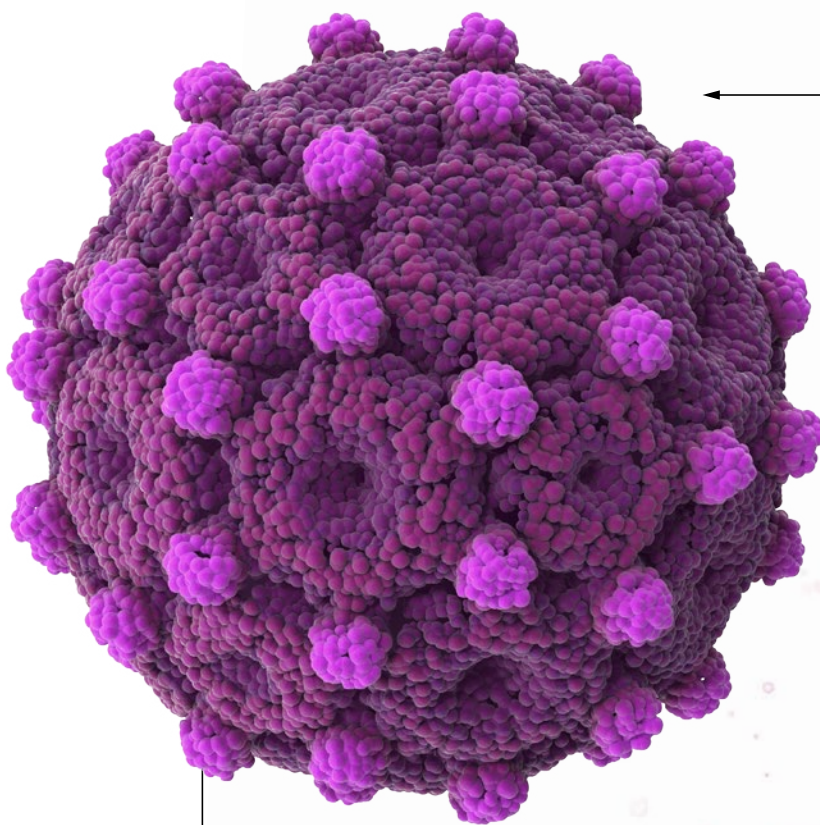
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## Diabetes

kills 1.4 million people a year around the world

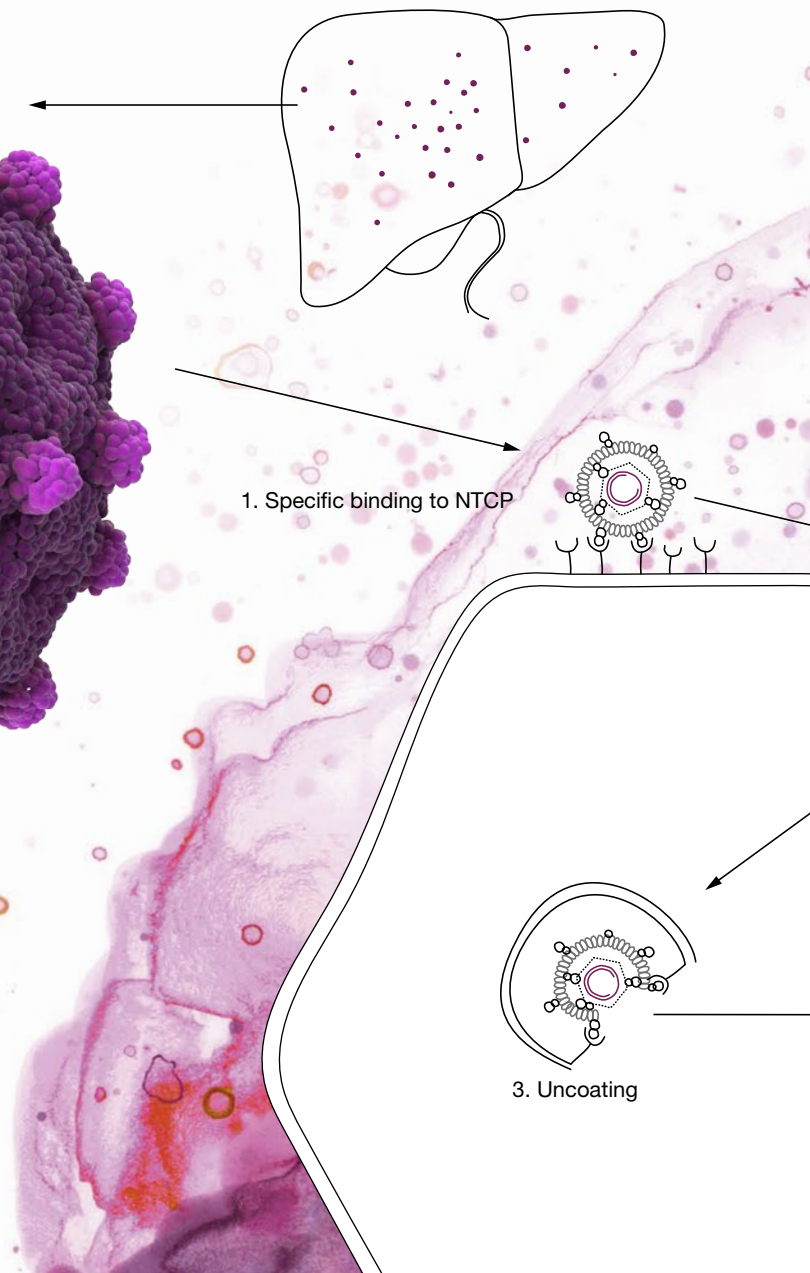
The liver cells' repair mechanisms incorrectly identify this viral DNA as belonging to the cell and thus begin to fill in the shorter DNA string with the corresponding base pairs. This creates what is known as cccDNA, which stays in the nucleus virtually forever. Only once this cccDNA has been created can viral genes be transcribed and proteins produced. One approach, therefore, would be to inhibit replication of the virus by interrupting protein synthesis or RNA transcription. "To date, however, efforts to do so have also damaged cellular functions," explains Ulrike Protzer. An alternative method is known as RNA interference. "By using small interfering RNAs (siRNAs), we can specifically inhibit the production of virus proteins without damaging

the host cell. Unfortunately, that alone is not enough to eliminate the virus." siRNAs are in the early stages of clinical trials and should be available in the near future. The treatment method most likely to cure hepatitis B infections is to teach the immune system to remove the cccDNA from liver cells or to destroy infected cells. The immune system is actually capable of doing so – but the immune response of people with a chronic infection is inadequate to fight off the invader. It is therefore hoped that a therapeutic vaccination will enable the body to expel the virus completely. "The failure of the immune response relates to all of its arms – so our vaccination also needs to stimulate all arms of the immune system," explains Protzer. ▶



Hepatitis B virus

The hepatitis B virus uses liver cells for reproduction.

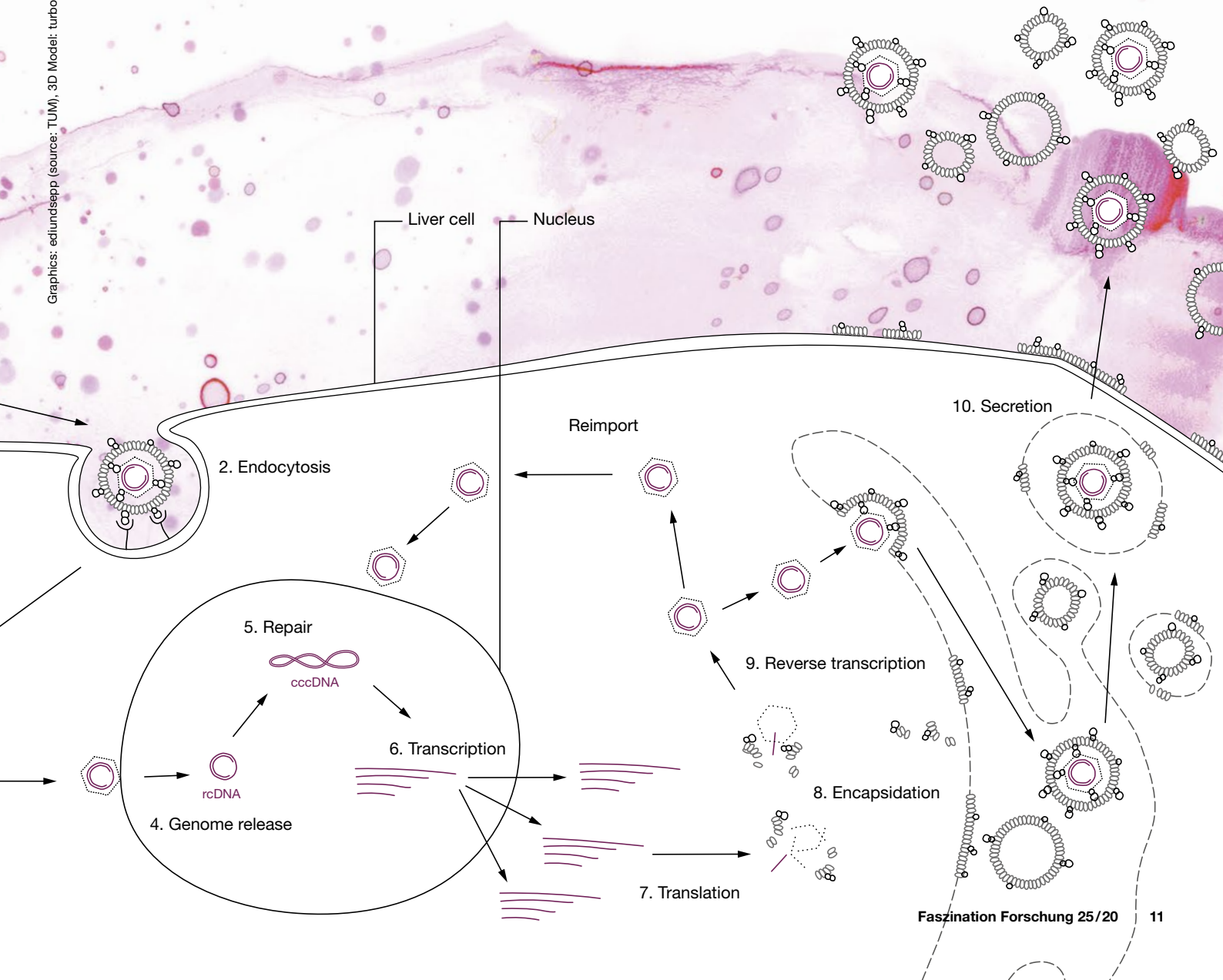




**Prof. Ulrike Protzer**

Ulrike Protzer studied medicine at universities in Erlangen, Basel and Durban (South Africa). She holds specialist qualifications and passed board exams in two areas, namely internal medicine plus microbiology, virology and infection epidemiology. From 2002 to 2007, she led a junior research group at the University of Cologne's Center for Molecular Medicine. She assumed the Chair of Virology at TUM in late 2007 and has since become Director of the Institute of Virology at TUM and the Helmholtz Zentrum München.

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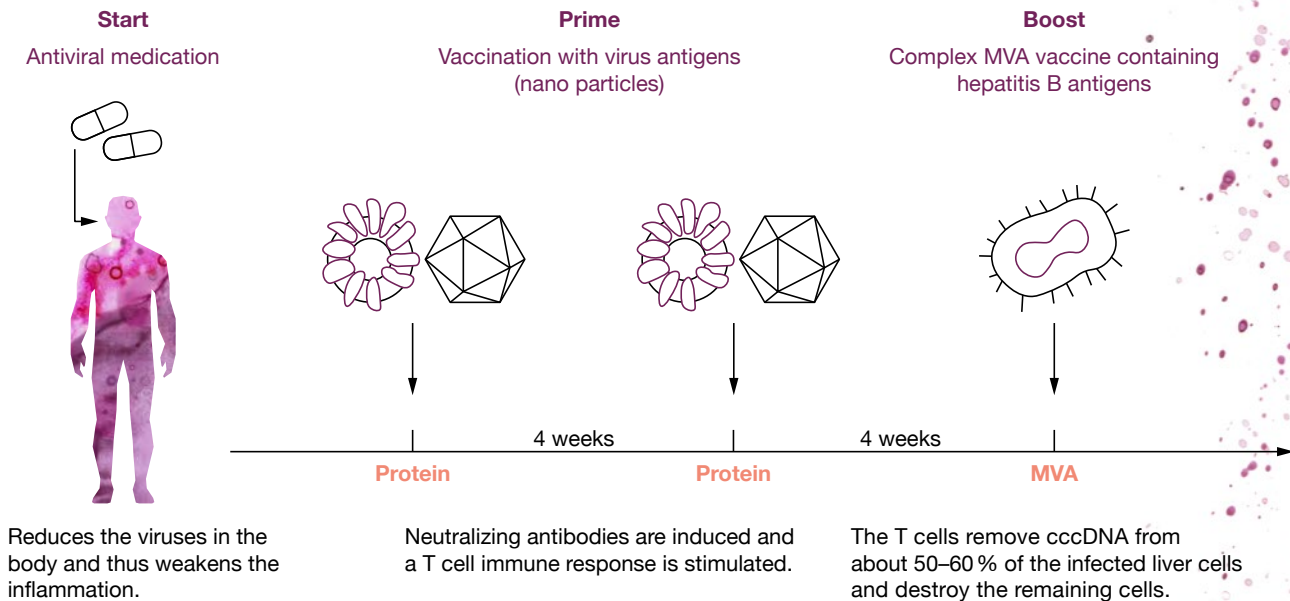


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*The failure of the immune response relates to all of its arms – so our vaccination also needs to stimulate all arms of the immune system.*

Ulrike Protzer





**The phases of the therapeutic vaccination** that can heal hepatitis B (TherVacB).

### Several vaccination phases

The vaccination is administered in several stages in a process the virologist has dubbed “prime-boost”. The first step effectively lays the groundwork by giving patients antiviral medication that inhibits replication of the virus’ DNA in their liver cells. As soon as siRNAs are clinically available, they will replace this as the first step. Next, for the prime stage, the patients receive two vaccinations four weeks apart containing different virus antigens, thereby stimulating the T helper cells and warning the T cells that an intruder will soon arrive. In parallel, this activates B cells in the patients’ immune system. Neutralizing antibodies are then formed that prevent the virus from spreading further. After another four weeks, the treatment moves on to the next step – the boost. Patients are given a vaccine that shows the T cells the antigens of the hepatitis B virus, which the T cells would not otherwise be able to identify in the liver. At this stage, the T cells have two tasks. First, they release cytokines that instigate a complex signal cascade and degrade the cccDNA in liver cells. This removes virus DNA from around 50 to 60 percent of infected liver cells. The remaining infected cells are then destroyed by T killer cells.

This vaccine is a complex MVA vaccine developed by Protzer herself. “MVA is the perfect vaccination vector as it boosts B and T cells in equal measure,” outlines Protzer.

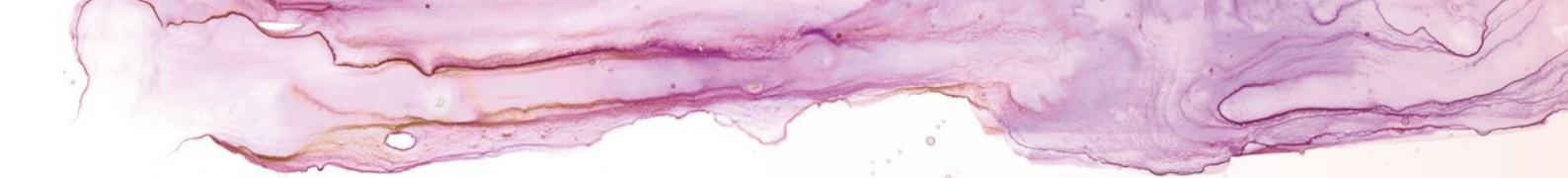
### A specifically developed vaccine

MVA is the abbreviation for Modified Vaccinia Virus Ankara, an attenuated virus from the poxvirus family. Although it can infect human cells, it is not able to reproduce in these cells and does not elicit any symptoms. The genome of the MVA virus serves as the backbone of the vaccine. Researchers in laboratories can then introduce new gene sequences that code for the antigens of other viruses and thus trigger an immune response against these antigens.

In principle, it should be possible to use this technique to produce all manner of vaccines. A clinical study of an MVA-based influenza vaccine is currently underway. Efforts to test the viability of a coronavirus vaccine using this system are also underway.

In most cases, only one new gene is built into the MVA backbone. Sometimes two. Yet, Ulrike Protzer wanted her hepatitis vaccine to be effective against almost all hepatitis B strains, all around the world. One or two genes were not enough to achieve this; Protzer needed to use five. “I’m not sure whether anyone has ever been crazy enough to pack five new genes in there,” she laughs. Many simply did not believe it would work – but it has. However, another hurdle lay in the researchers’ path. They needed to find a suitable adjuvant – an agent to intensify the initial immune response. “There are, in effect, no freely available adjuvants,” says Protzer. ▶





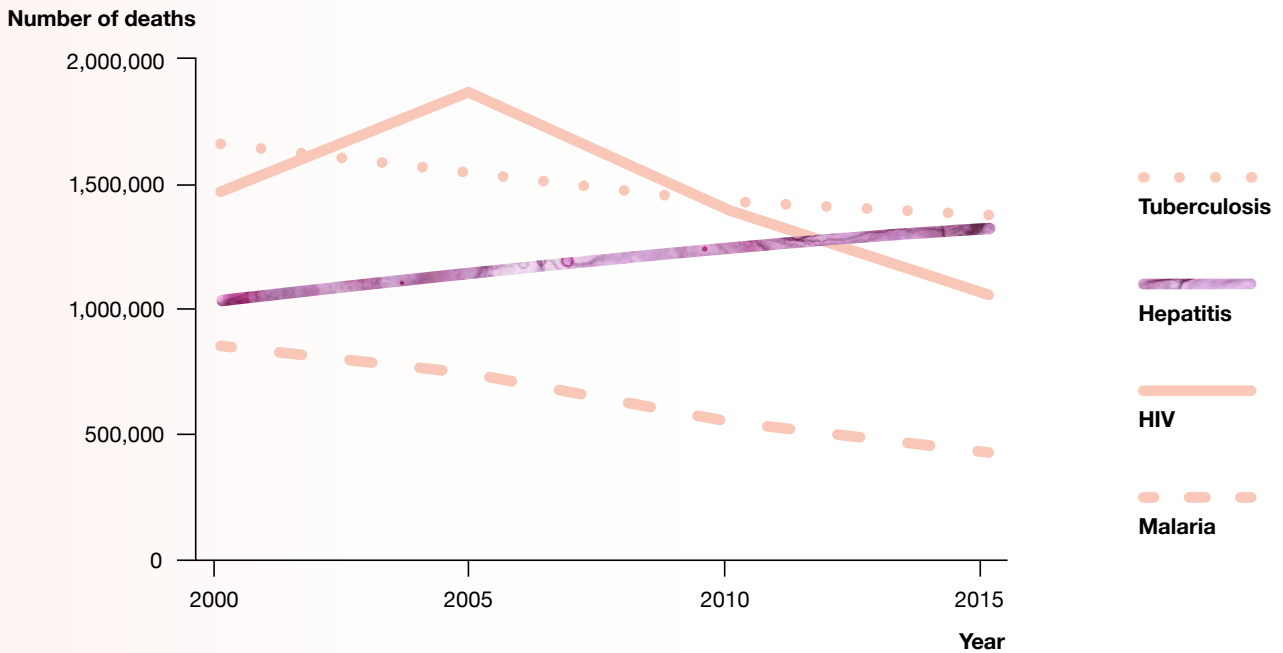
“The patents are almost all held by a single pharma company.” The company did make a product available – but wanted all patent rights to Protzer’s new TherVacB vaccine in return. She turned the deal down. Ultimately, the researchers still found what they needed and can now rely on CpG 1018, an adjuvant already employed in a prophylactic hepatitis B vaccine and therefore approved for use. In preclinical mouse models, Protzer has successfully demonstrated that the immune system reacts as she had hoped to the prime-boost vaccination. The hepatitis B antigens disappear from the blood and are replaced by numerous antibodies against the virus. The T cells do the rest – and cure the liver completely. “We are convinced that the principle we have developed would also be suitable for a vaccine against the novel SARS coronavirus,” she says.

The task now is to produce the vaccine in accordance with Good Manufacturing Practice (GMP) regulations. This will be followed by toxicity tests on mice and rats. A phase 1a clinical trial on human subjects is then scheduled to start

early next year (see box). The first step in this trial will be to vaccinate healthy subjects and determine the best combination of agents for the prime-boost technique. It is extremely rare for a clinical trial in the academic sphere to proceed without the involvement of the pharmaceutical industry. “We’re only able to do so on this project because we are working hand in hand with Klinikum rechts der Isar, LMU Munich and our partners throughout Europe,” explains Protzer. “Otherwise, it simply would not be possible.”

The researchers have already obtained close to €20 million funding for the project, all of which is from public funds – a fact of which Ulrike Protzer is particularly proud. “It means we’re independent of investors, who not only pursue humanitarian interests but also want to make money,” she says. “Ultimately, we hope our vaccine will one day benefit patients in all parts of the world.”

■ *Claudia Doyle*



**Hepatitis B and C diseases are an increasing concern globally.** While the number of deaths caused by malaria, HIV or tuberculosis is falling, the curve is continuously rising in the case of hepatitis.

**Clinical studies – From the lab to the hospital**

All medications have a long road to travel from the lab to being used in hospitals. First, a potential agent is usually tested on cells in a petri dish. If it takes effect, tests are then carried out on animal models that reconstruct the illness as accurately as possible. “Only then can the first clinical trials take place with humans, divided into four phases,” explains Christoph D. Spinner, senior physician and infectious disease specialist at TUM. Working together with Germany’s Federal Institute for Drugs and Medical Devices, the scientists involved in a trial have to determine how many patients need to be included for the results to be significant.

Phase 1 of a clinical trial examines the safety of a substance. “The aim is to exclude the risk of completely unexpected reactions occurring in the complex human organism,” explains Spinner. Consequently, these trials are usually conducted on healthy subjects. Phase 2 serves to identify the correct dosage and involves a small group of patients. In phase 3, the efficacy and safety of the agent are examined on the trial subjects. If the results are again positive, the substance can be approved for use. Phase 4 is therefore also referred to as a post-authorization study. The purpose is to highlight any side effects or long-term effects not identified to date.

TUM is very well positioned to facilitate studies of this type. “We can activate the infrastructure at our disposal overnight,” says Christoph Spinner. “This has enabled us to work intensively on the development of medications to combat COVID-19 since early this year.”

