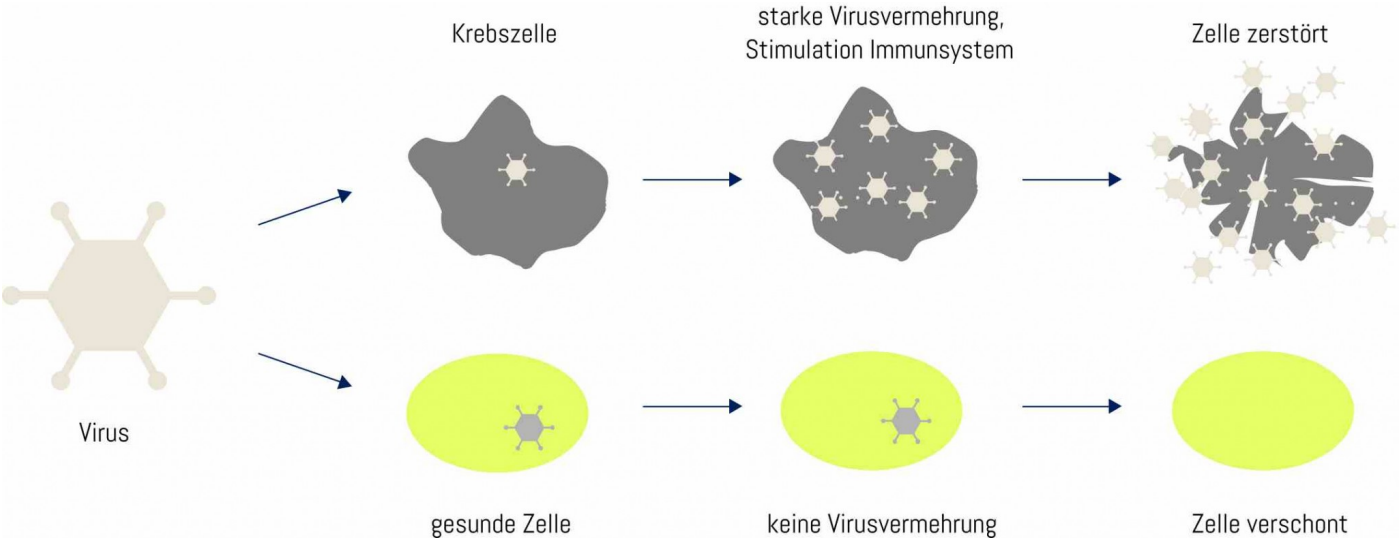
Healthcare industry BW

Ad-O-Lytics – a new biotech start-up from Ulm

Unexpected difficulties sometimes require unusual solutions that may in turn open up totally new opportunities. This is exactly what happened to Florian Kreppel. A few years ago, Kreppel developed a therapeutic approach that combined genetic vaccines with molecular address labels. It worked quite well, but the resulting product did not have the anticipated immunising properties and was put on the backburner. Now Kreppel's group of researchers is nearing completion of another project. The researchers plan to use a patented virotherapeutic platform technology for cancer treatment to establish a company called Ad-O-Lytics GmbH in 2017. Once preclinical development of the drug candidate is complete, the virotherapeutic approach will be tested in a clinical trial involving human subjects in cooperation with a pharmaceutical partner. This is expected to happen in around two to three years' time.

Reaching the target unseen - protected by a molecular swim cap



Ad-O-Lytics' platform technology is based on the principle of oncolytic viruses, which can destroy cancer cells by infecting them, multiplying inside them and making them burst. This simultaneously activates the immune system, which further promotes the healing process.
© Ad-O-Lytics

Ad-O-Lytics' innovative platform technology is based on the well-known infective mechanisms used by oncolytic viruses. Oncolytic viruses can destroy and kill tumour cells. Upon infection, the viruses multiply inside the tumour cells, which are eventually destroyed by oncolysis. This results in the release of new infectious virus particles, which will then infect and kill other tumour cells. In addition to destroying the tumour cells directly, oncolytic viruses also stimulate the host's anti-tumour immune response, thus promoting the healing process. At present, virotherapy involves the local injection of viruses; administration through the bloodstream is not yet possible. However, the viruses have to enter the blood circulation to be able to reach all tumours and metastases in the body. Kreppel has found a solution to the problem that enables him to exploit the full potential of virotherapies. This involves equipping the viruses with a "molecular swim cap" that protects them against host immune attacks so they can reach tumour cells.

The new approach uses human type 5 adenoviruses. There are good reasons for this. Adenoviral structure, genome and multiplication mechanisms have been studied in great detail, the viruses are highly effective in infecting tumour cells and have been thoroughly clinically tested. Moreover, the start-up's approach can be used to genetically modify the surface of the viral capsule to create a docking site for a polymer without interfering with the viruses' infectious potential and replication, and thus their oncolytic properties. Polymer molecules are chemically coupled to the docking site and protect the virus against undesired immune attacks in the blood.

Knowledge of the virus' vulnerable spots is important for systemic administration

Without such protection, the oncoloytic viruses would be eliminated within seconds of being administered into the blood, rendering them unable to reach the tumour. If the "vulnerable spots" of the virus were protected against host immune system attacks, it would be relatively easy to produce virus particles that could be administered into the blood circulation without the risk of being destroyed. This discovery marked the start of the development of the new technology that originated in the company's vaccine project. Kreppel explains that identifying the viruses' vulnerable spots was of pivotal importance for the current project. Back in 1999, other researchers had already managed to package the entire virus into proteins, but this venture was rather unsuccessful as the packaging resulted in the loss of the viruses' oncolytic properties.

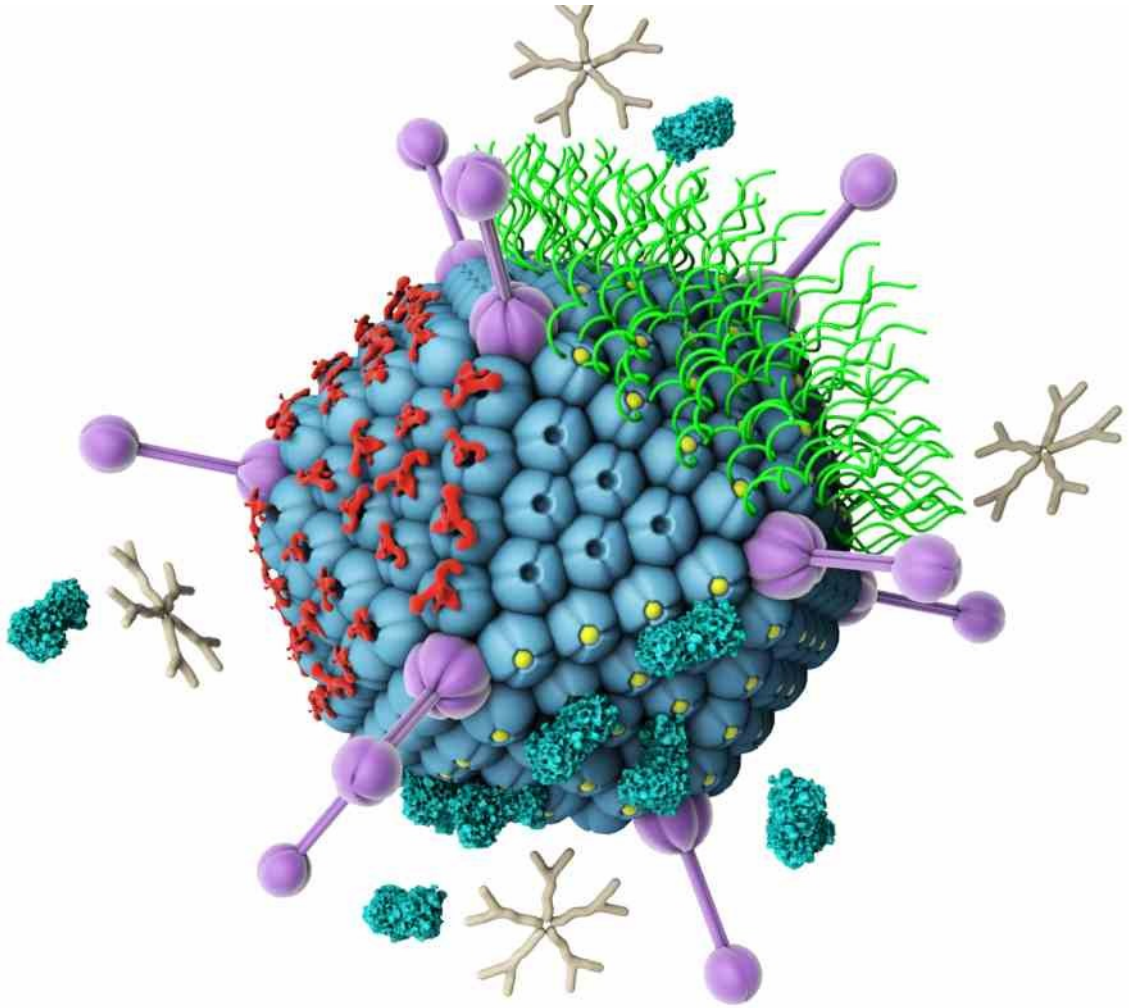
The vulnerabilities of the virus gradually became known over the last ten years. In 2008, a group of English researchers found out why adenoviruses always ended up in the liver rather than tumour cells. The answer stunned the scientists: human adenoviruses bind to coagulation factor X that circulates in the blood, and this interaction targets the virus to specific receptors on human hepatocytes. Nobody had expected this host factor to play a role in the biology of the virus in the host organism. As Ad-O-Lytics' technology only protects the sites on the virus that interact with blood constituents, the virus retains its oncolytic properties, explains Kreppel.

Previously inaccessible sites of action can be reached

The systemic administration of oncoloytic viruses into the bloodstream has many advantages as it enables the metastases and the primary tumour to be targeted through the oxygen and nutrient supply route. This is all the more important if the tumour has already formed so many metastases that surgery is no longer possible and in cases where the tumour and/or the metastases are located in places that are difficult to reach surgically.

If the adenovirus, equipped with its immunological invisibility cap, is able to enter the bloodstream, a few built-in safety switches prevent it from proliferating in normal tissues. Through the chemical coupling of these surface molecules, which cannot be passed on from one virus generation to another, the newly formed viruses inside the tumour tissue are no longer protected against immune system attacks and will be devoured by macrophages. Moreover, the tumour cells break up, the release of new viruses boosts the immune response and indirectly supports the virus in its fight against the tumour. These protective molecules have already been clinically tested.

Molecular swim cap with a tip



After injection into the bloodstream, oncolytic adenoviruses are rapidly covered and neutralised by various blood components (red: factor X; turquoise: complement system; grey: antibodies), so that they are unable to reach the cancer cells. Ad-O-Lytics has developed a technology that protects the vulnerable areas of the viruses against blood components. This is achieved by attaching polymer molecules (green chains), carbohydrates or proteins to the viral surface. These molecules act like small swim caps, and protect the virus against neutralising blood components. The viruses can thus reach and destroy tumours and metastases.

Since the protected viral particles circulate in the blood for quite a long time, they are able to enter solid tumours whose blood vessels are still full of holes during growth. Virus particles that reach the tumour are able to dock because they have a key to the lock on the surface of the tumour cells. Their molecular swim cap has a "tip", in other words, the polymers are equipped with ligands that are specific for the receptors on the tumour cells. Therefore, Ad-O-Lytics' technology not only makes it easier for the viruses to reach the tumour cells, but also facilitates their entry into these cells. The objective is to ensure that the first dose of oncolytic viruses reaches as many tumour cells as possible. If more tumour cells are lysed, more tumour fragments are created and the stronger the immune response will be.

The development of the platform technology is complete, and efficiency tests will be carried out in a mouse tumour model up until spring 2017. The researchers from Ulm are convinced that the approach will work quite well, as they have already shown that it works in the blood of humans and mice. The oncolytic ability of viruses is beyond dispute, so it is highly likely that the approach will also work in living organisms.

Ad-O-Lytics' technology specifically targets solid tumours, including well-vascularised tumours such as ovarian, prostate or liver cancer. The researchers are currently working on identifying the indication where the technology will be the most successful. They have a great deal of data available from many patients who have undergone intravenous injection of adenoviruses, meaning that the dose range for avoiding adverse effects is already known.

Another weapon in the fight against cancer

Virotherapy does not exclude traditional cancer therapy; instead it is "another weapon in the fight against this disease". The researchers hope to achieve maximum effect by combining virotherapy with other therapies as is the case with advanced chemotherapeutic drugs or monoclonal antibodies.

Good combination of science and business

Barbara Eberbach, Prof. Dr. Stefan Kochanek, PD Dr. Florian Kreppel and Dr. Andrea Hoffmeister (from left to right) want to establish their own business.

Ad-O-Lytics GmbH will have four key members: Andrea Hoffmeister, Barbara Eberbach, Florian Kreppel and Stefan Kochanek. Besides scientific experience, the team of four also brings business skills to the new company: Hoffmeister has a PhD in immunology and is an expert in producing, purifying and modifying viruses as well as animal experiments. Eberbach is an economist with long-standing industry experience and has quit her job in industry to set up the company. Biochemist Florian Kreppel is the inventor of the technology. He has been working on the development of viruses for use in gene transfer for nearly 20 years. Physician Stefan Kochanek specialises in vector development and gene therapy. He is also the head of the Department of Gene Therapy at the University Hospital in Ulm and has already founded another company (Cevec Pharmaceuticals). He therefore brings both scientific expertise and entrepreneurial experience to the new company.

The start-up project has been funded by the German Ministry of Economics' EXIST funding programme since 2015, and according to the funding guidelines, the planned company will have to be established within two years of funding. The researchers were awarded the German Bioregions' Innovation Award in spring 2016, which put them into the limelight for the first time. The company founders now have to knuckle down and concentrate on taking the idea from academia to the commercial biotech industry.