Fighting Cancer with Viruses

By nature, viruses exist at the cost of other living organisms. They often target specific organs. The novel coronavirus, for instance, targets the lungs, rabies targets the brain and HIV targets the immune system. At the Klinikum rechts der Isar, researchers hope to harness the lethal power of viruses to combat malignant tumors. Dr. Jennifer E. Altomonte and her team are engineering viruses to optimize their therapeutic potential in cancer cells. In so doing, immune cells are also called onto the scene, which then contribute to controlling the cancer.

Link
www.med2.mri.tum.de/en/research/ag-altomonte.php

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Viren gegen Krebs

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Viren als Waffe gegen Krebs? Die Idee klingt bestechend – und ihre Realisierung rückt näher. Einen entscheidenden Beitrag leistet Privatdozentin Dr. Jennifer E. Altomonte am Klinikum rechts der Isar der TUM. Ihr Team hat zwei onkolytische Viren (onko = Geschwulst, lyse = Zerfall) gentechnisch verändert und zu einem hybriden Virus kombiniert, der sich in Tumorzellen – und nur dort! – rasant vermehrt und sie dabei zerstört. Die sterbenden Zellen entlassen nicht nur tausende Kopien der Viren, die weiteres Krebsgewebe zerstören. Überdies rufen sie körpereigene Immunzellen auf den Plan, die nun ebenfalls gegen die Tumorzellen vorgehen. Die hybriden Viren haben sich bereits in Zellkulturen und präklinischen Tiermodellen bewährt und erzeugen keine toxischen Nebenwirkungen. Damit sind die wichtigsten Hürden genommen, um die nächsten Schritte zu gehen: Die Forscherinnen planen die Aktivierung der Immunantwort weiter zu optimieren. Ebenfalls in Planung sind die kommerzielle Produktion der hybriden Viren und die Erprobung der neuen Virustherapie am Menschen. □

PD Dr. Jennifer E. Altomonte

Born in 1976, private lecturer Dr. Jennifer E. Altomonte studied microbiology, biochemistry and molecular biology at Pennsylvania State University. In 1999, she moved back to New York, her birthplace. After returning, she first worked at the Institute for Gene and Cell Medicine at the Mount Sinai School of Medicine, researching the development of viral vectors in gene therapy for metabolic disorders. Four years later, she moved to another laboratory within the same institution, where she began her research on oncolytic viruses. In parallel to this, she conducted research at John Jay College of Criminal Justice into molecular methods to clarify the causes of Sudden Infant Death Syndrome and received her Master of Science in Forensic Science in 2016. In 2006, she moved on to work at Dr. Oliver Ebert's laboratory at the Klinikum rechts der Isar and later obtained her doctorate at TUM before assuming management of the laboratory in 2016.

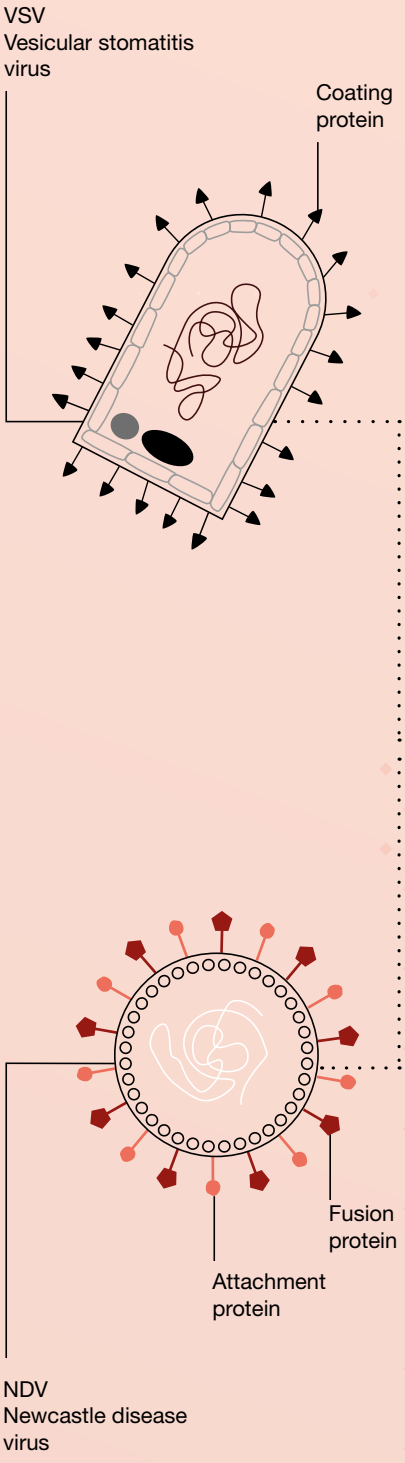
Picture credit: Juli Eberle

Using viruses as a weapon against cancer? A fascinating idea – and by no means a new one. Back in 1904, American Professor of Medicine George Dock described the case of a leukemia patient whose symptoms diminished following a bout of cowpox. Soon after, reports circulated of a young woman with cervical cancer whose condition had temporarily improved following contact with the rabies virus. “Even back then, some had speculated on the therapeutic potential of viruses. Yet it is only in the last 30 years or so that we have had the knowledge and scientific tools needed to develop viable therapies,” says private lecturer Dr. Jennifer Altomonte, who researches virus-based cancer therapies at the Klinikum rechts der Isar.

Research groups around the world are working to improve virus therapies

Since then, biologists have identified more than two dozen viruses that can multiply in tumor cells and kill them. These oncolytic viruses (onco = tumor, lysis = degradation) include well-known infectious agents like the pathogens that cause polio, herpes and chickenpox, as well as species that would not normally affect humans. In China, a modified adenovirus has been approved as a treatment for carcinomas in the head and neck region since 2003. In Europe and the USA, a modified herpes virus has been marketed as a therapy for specific forms of skin cancer since 2015. Numerous research groups around the world are working to improve the efficacy and safety of virus therapies.

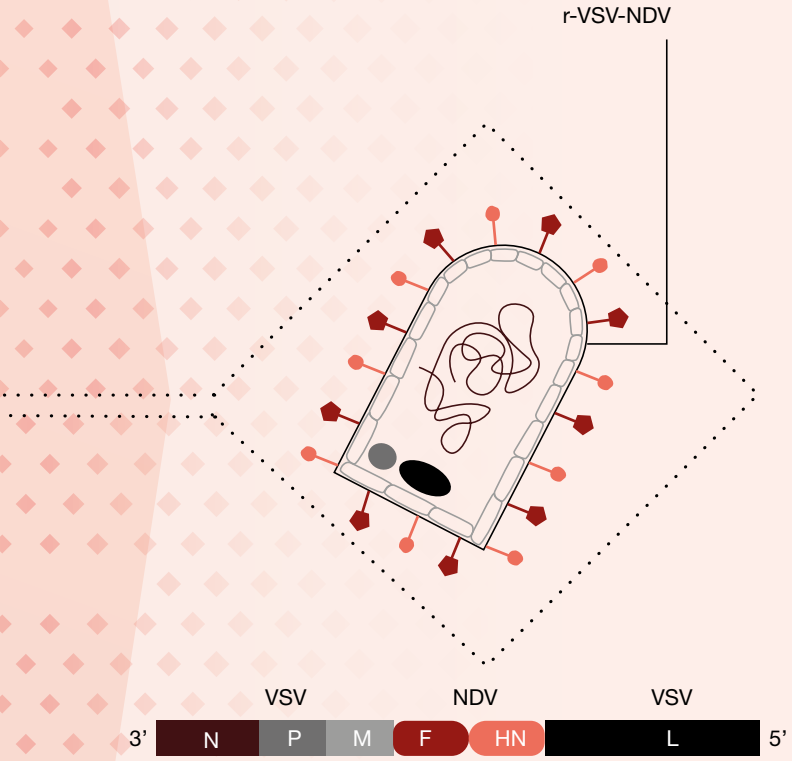
In the 16 years she has devoted to this novel biotherapy to date, Jennifer Altomonte has made decisive advances. Born in the USA, Altomonte focuses her research on the vesicular stomatitis virus (VSV) and the Newcastle disease virus (NDV), both of which are known for their oncolytic effects. VSV usually afflicts hoofed animals such as goats and cattle, while NDV infects birds. These pathogens do not cause illnesses in humans, which presents enormous benefits for their medical application. “Under normal circumstances, the human immune system does not come into contact with VSV or NDV,” explains Altomonte, who holds a doctorate in microbiology. “This means it has no experience handling these viruses. It therefore takes a while for our immune system to detect them in the body and eradicate them. During this time, the viruses can make their way to the tumor cells and destroy them.”



These viruses do not represent a danger to any other organs. Although they also penetrate healthy cells in the human body, these cells are able to identify them as hostile and eliminate them within hours. This defense mechanism is lost during the transformation of healthy cells into tumor cells, which explains why the viruses have an easy job killing these malignant cells – and only these malignant cells.

A virus that kills tumor cells but does not harm humans nor the environment

In principle, this applies to all types of tumor, though Altomonte and her team are currently concentrating their efforts on liver cancer. VSV can amplify itself extremely rapidly in host cells and subsequently spread to surrounding tumor cells to kill them, too. NDV has special attachment and fusion proteins that cause infected tumor cells to fuse with neighboring cells. When employed as oncolytic viruses, the two pathogens work in different ways, but both are effective in the destruction of tumor tissue. Nevertheless, these beneficial qualities are associated with the risk of serious side effects. “We know that VSV can lead to toxic side effects in the brains and livers of mice and rats – and potentially also in humans – when administered at elevated doses,” says Altomonte. “While NDV is not dangerous to humans, it is deadly to birds and can pose a serious threat to the environment and the poultry industry. We have engineered a hybrid of the two viruses, in which the positive qualities of both species were retained, while the unacceptable safety risks were eliminated.” ▷



Graphics: ediundsepp (source: TUM)

Best of both: Researchers have combined the features of two oncological viruses to create a hybrid virus. The basic structure of this chimeric virus is taken from vesicular stomatitis virus (VSV). The coating protein of VSV (arrows) contributes to its safety risks; it has been replaced with two beneficial proteins from Newcastle disease virus (NDV). The HN protein allows the virus to attach to cancer cells, while the F protein causes infected tumor cells to fuse with neighboring cells. The newly created construct, rVSV-NDV, possesses enhanced oncolytic characteristics compared to the parental viruses, while eliminating the risks of undesirable side effects for humans and the environment.

The result is a viral construct called rVSV-NDV (see Fig. 1). This hybrid virus has already demonstrated its proof of concept in cell culture systems and animal models for tumor diseases. The TUM researchers have achieved impressive results in preclinical animal models of liver cancer: In mice treated with the novel virus, the malignant tumors showed a reduction in size, which led, on average, to a doubling of survival time compared to the placebo-treated control animals. Altomonte has now been able to demonstrate an exciting additional aspect of the therapy for the first time in mice with skin cancer. “In most of the animals, even tumors that had not been directly infected with viruses underwent a reduction in size or delayed tumor growth,” she explains. “We can also rule out the possibility that the viruses reached the distant tumors through the bloodstream. The tumor remission must therefore be the result of the body’s own immune system fighting against the cancer.” ▷

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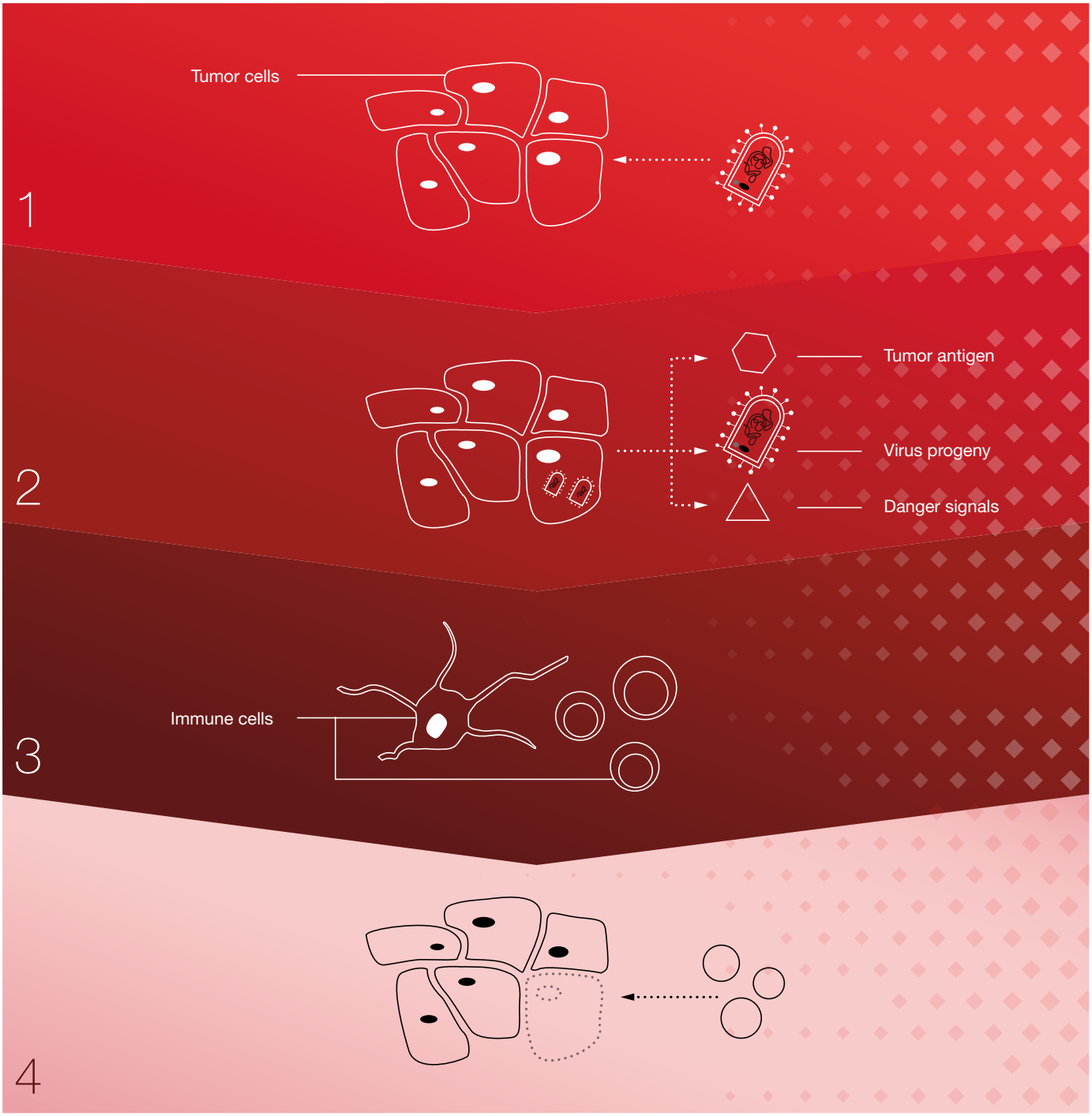
Jennifer Altomonte

◁ **Jennifer Altomonte and her doctoral student Teresa Krabbe** hope to start a biotech company and eventually develop and market the novel hybrid oncolytic viruses. In 2019, they received the m4 Award from the Bavarian Ministry of Economic Affairs and the EXIST Transfer of Research from the Federal Ministry for Economic Affairs and Energy.

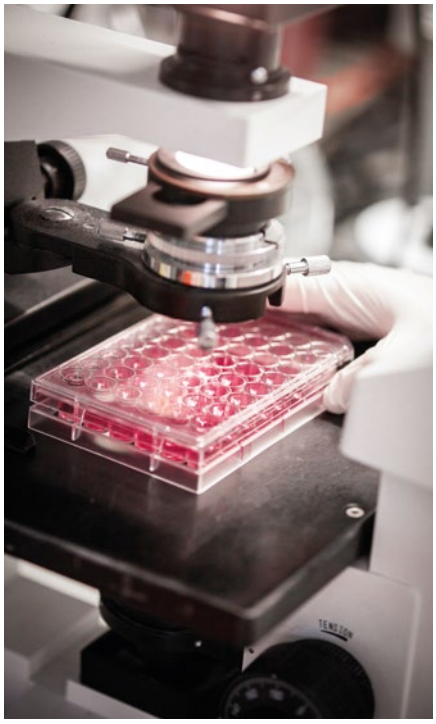


Fusing together with the tumor: Oncolytic viruses specifically infect tumor cells (1) and multiply within them. The dying cancer cells (2) not only release thousands of copies of the virus – which infect further cancer cells – but also tumor antigens and chemical signals, which bring the body's immune system to the scene. This process activates specific immune cells (3) that also identify uninfected cancer cells and destroy them with the help of cytotoxins (4). This immune response targets both the primary tumor and its metastases – and remains even long after the viral infection has receded.

Graphics: ediundsepp (source: TUM); Picture credit: Juli Eberle

"We hope to gain approval for our first clinical study in the next two years."

Jennifer Altomonte



A researcher prepares a dilution of oncolytic virus in saline solution for infection of tumor cells grown in multi-well dishes. The cells are examined under the microscope to assess for changes in cell morphology in response to virus infection.

A biotech company is planned

Part of this therapy concept involves mobilizing specific immune cells. This makes use of a phenomenon that goes hand in hand with viral infection, namely that when pathogens multiply in tumor tissue and destroy it, the dying cells send out warning signals. At the same time, the virus infection modulates certain mechanisms that cancer cells normally use to evade detection and clearance by the immune system. These two effects essentially remove the tumor's cloak of invisibility and make it detectable by the body's immune defenses. Specific immune cells are promptly activated and attack tumor cells – even those that are distant from the viral infection. This side effect of viral infection, which is exceptionally welcome from a therapeutic perspective, has emphatically manifested itself in Altomonte's studies. "We have some long-term survivors who no longer display any sign of tumor cells," says Altomonte. "Furthermore, when we re-inject cancer cells into these animals, no new tumors develop. The immune-mediated protection therefore remains even long after the oncolytic virus has been cleared from the body," she emphasizes.

Altomonte, who now lives in Munich, is also pleased with the results of the studies from a safety perspective. Even very high doses of the engineered virus have not caused any detectable toxic effects in healthy mice. This removes the largest hurdles to the clinical translation of the therapeutic approach. Ongoing and planned projects include the development of new strategies to further activate the immune response, as well as the large-scale commercial production of the hybrid viruses, and testing the new virus therapy on human subjects. These projects all entail significant costs. In light of their highly promising nature and intelligent planning, however, around €3 million of funding has been obtained from various sources. In the fall of 2019, Jennifer Altomonte and her doctoral student Teresa Krabbe received the m4 Award from the Bavarian Ministry of Economic Affairs and the EXIST Transfer of Research from the Federal Ministry for Economic Affairs and Energy. It is hoped that the two prizes, endowed with a combined €1.5 million budget, will enable the founding of a planned biotech company called FUSIX, which aims to develop and eventually market the novel hybrid oncolytic

viruses. “We hope to reach the next major milestone – gaining approval for our first clinical study – in the next two years,” says Altomonte.

Particularly high expectations rest on a project by the name of ONCO-VAX, which the European Research Council is supporting in the form of a Starting Grant from 2020 for a five-year term. The aim is to develop a vaccine that amplifies the immune response triggered by a viral infection in order to secure long-term protection against tumor cells. This gives rise to the following conceivable scenario: First, researchers would take a biopsy from a patient to obtain cancer cells and cultivate in a petri dish. They would then infect these tumor cells with rVSV-NDV – which would kill the cells and reveal the cells’ tumor antigens. Specific immune cells from the blood of the same patient would be exposed to these antigens, thereby activating them and enabling them to precisely identify the specific antigens of these tumor cells. Immune cells activated in this way would then be injected into the patient as a vaccine, offering an efficient and long-lasting immune protection against the tumor and its metastases.

A bold vision. But will it come to fruition – and, if so, when? Jennifer Altomonte remains realistic. “Even if we are only able to help a few patients with this therapy and manage to slow the progress of their cancer, this would extend their life,” she says. “What’s more, it would do so without the distressing side effects of therapies available today.” ■

Monika Offenberger

Picture credit: Juli Eberle