Healthcare industry BW

Company profile

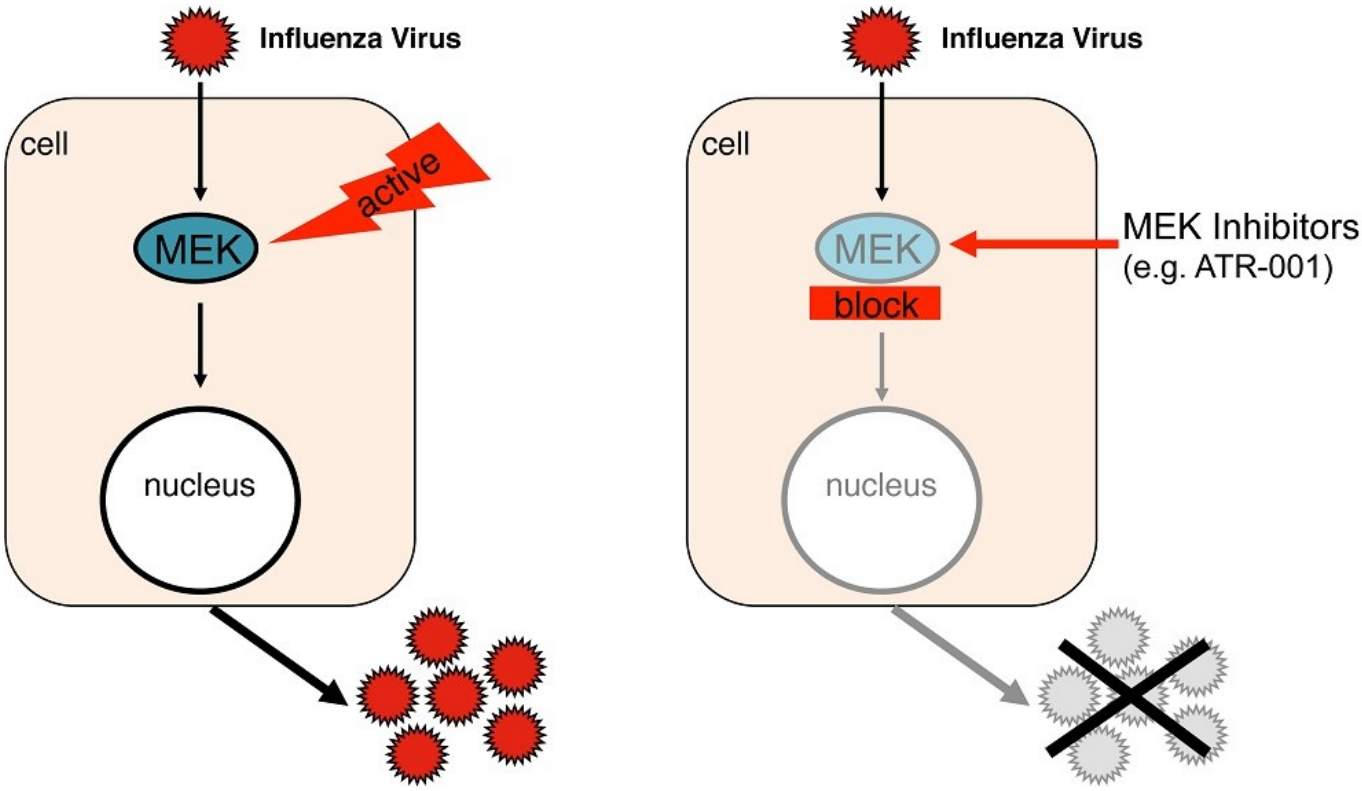
Atriva Therapeutics GmbH: new ways to treat influenza

Influenza viruses constantly change and mutate. This makes treatment difficult and vaccination rather touch and go. But what about targeting virus-manipulated cell events rather than using the virus itself as drug target? Atriva Therapeutics GmbH, a start-up company from Tübingen, shows how this works.

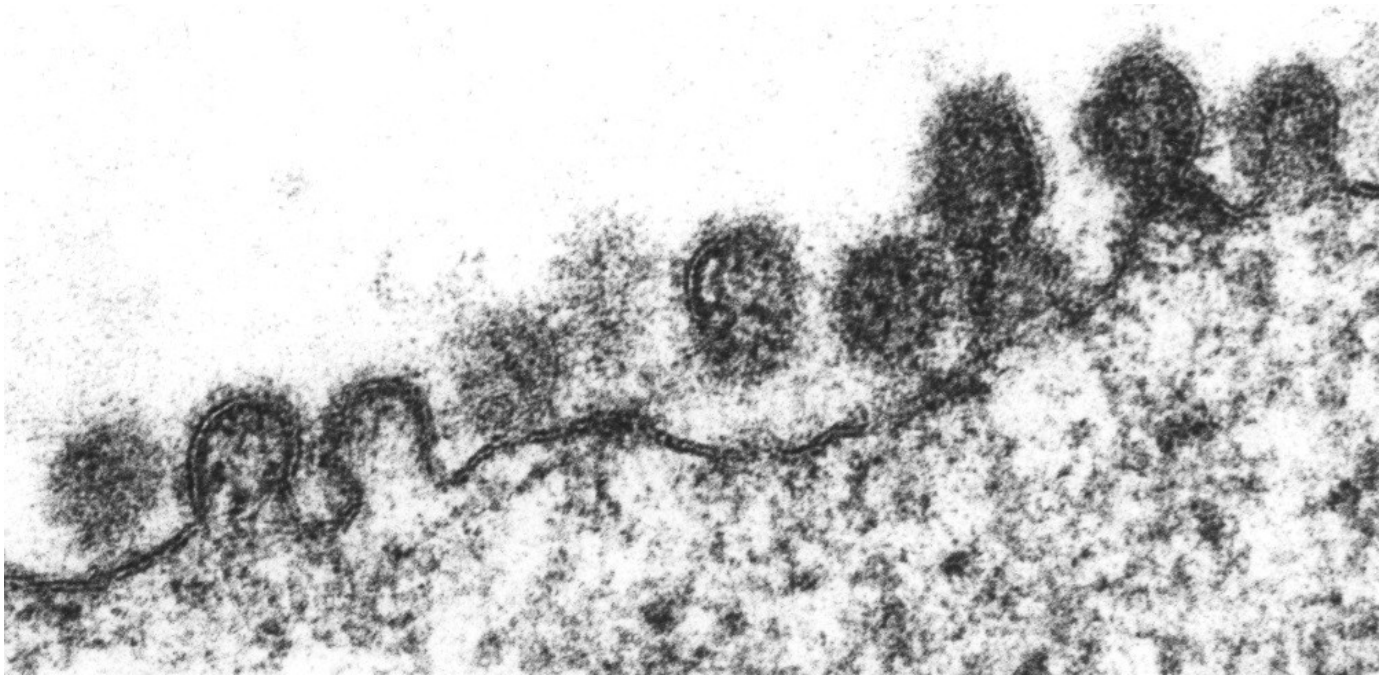
The 1918/19 flu pandemic, generally known as Spanish flu, infected millions of people around the globe and resulted in between 25 and 50 million deaths (different sources provide different figures). Such high numbers of deaths are hard to imagine nowadays due to better health standards and treatment options as well as relatively effective vaccines. Yet many people still die every year from flu, even in highly developed countries, including Germany. So-called neuraminidase inhibitors are currently the most successful antiviral agents; they fight both symptoms and pathogens. These compounds block the enzyme neuraminidase that enables the virus to be released from the host cell after replication. However, this strategy is only successful if the neuraminidase inhibitor is administered within 48 hours after onset of the disease. This is not always easy to do. In addition, virus strains that are resistant against neuraminidase inhibitors have been discovered, so that alternative strategies to combat the virus are most welcome, and this is exactly what a company called Atriva Therapeutics GmbH from Tübingen is working on.

The start-up company from Tübingen is pursuing a completely new approach to flu treatment. The approach targets the human host cell rather than the virus itself, and is based on the use of MEK (mitogen-activated protein kinase (MAPK) kinase) inhibitors which block enzymatic signal factors in the human host cell that the virus requires for replication. Some MEK inhibitors have already been approved for cancer treatment. The compound that is now used by Atriva Therapeutics was originally developed as anti-tumour medicine by the well-known pharma company, Pfizer, but did not live up to the company's expectations and was discontinued. "The compound was found to be unsuitable as anti-tumour medicine due to its low absorption rate and bioavailability, which is why Pfizer has discontinued further development. The situation is completely different with influenza, and this is why the compound works," says virologist Prof. Dr. Oliver Planz, who is recognised as an important source of ideas. Planz works in the Department of Immunology at the Interfaculty Institute for Cell Biology (IFIZ) at the University of Tübingen and is one of the company's founding members.

Targeting viral manipulation of the host cell



Influenza viruses use the MEK signalling pathway in the host cells to propagate (left). Atriva Therapeutics' MEK inhibitors block the signalling pathway (right), thus preventing replication, release and further spread of the virus.



The replication of flu viruses depends on the incorporation of the viral DNA into the host cell's genetic material. New flu viruses are released from the host cell when they bud off from the cell membrane, and are then ready to infect other cells. Atriva's drugs interfere with the viral replication cycle.

Planz developed the new flu treatment strategy with his colleagues, Prof. Dr. Stephan Ludwig from the University of Münster and Prof. Dr. Stephan Pleschka from the University of Gießen, after many years of research. Once the researchers had the concept in place, they went on to plan the setting up of Atriva, and won BioRegio Management GmbH's Science2Start idea competition in 2014. "The first

place in the Science2Start competition was really the main reason that we were able to spin out Atriva Therapeutics GmbH. As the three of us had the scientific skills required for company foundation, but limited knowledge of business development and corporate governance, we decided to take appropriate experts on board," says Planz. Atriva Therapeutics is now managed by a five-member management team with CEO Dr. Rainer Lichtenberg at the helm.

The reason why a drug that was originally planned for treating cancer can be used for treating flu is down to huge differences in disease processes, specifically molecular signalling processes. In cancer, mutations generate abnormal proteins that lead to the uninterrupted, uncontrolled transmission of signals, and hence to the growth of tumour cells. MEK inhibitors would have to be administered over a relatively long time in high doses in order to impede signal transmission and tumour growth. However, the infection of cells with viruses does not damage the signalling mechanisms, which is why the cells must "only" be blocked for a short time, so that the virus cannot exploit them for its own purposes. After a few hours, once the virus has been killed and removed by the cellular waste disposal machinery, the signalling pathway can be re-activated and will work normally. The researchers assume that due to the short treatment time, the MEK inhibitor will not lead to any adverse drug effects.

Planz explains the principle as follows: "Envisage the body cell as a windowless room in which people work with artificial light and where the virus wants to use the light for carrying out vital processes. We then use the drug to switch off the light for a period of two hours, and the virus will disappear. In cancer, we have no such switch, the light is on continuously and you would have to destroy the lamp to make the room dark." Transferred to a disease scenario, this would mean administering large amounts of drug over a relatively long time. And this might lead to adverse effects, including skin redness, diarrhoea and fatigue. As usual, the dose is also the poison. "To treat cancer, you would have to administer drug concentrations that were five times higher over a period of three months. To treat influenza, we plan to administer low doses of the drug for a few days only," says Planz.

Well-filled company pipeline: a lot of potential for other drugs for treating viral infections

The scientists are currently working on the optimal treatment regimen and the final drug formulation. In addition, the effect and tolerability of the drug will have to be verified in clinical trials. This will take some time, but is to the company's advantage as Pfizer still owns the patent for the MEK inhibitor. However, patent protection ends in 2018. "By the time we are ready to place our drug on the market, patent protection will no longer be an issue. That said, we have of course consulted with Pfizer," says Planz. By the time the MEK inhibitor is ready for application in humans, the Atriva team will have several other MEK inhibitors in the starting blocks. We have already collected valid data on the use of MEK inhibitors against hantaviruses and preliminary data on their use for treating SARS and MERS infections," says Planz. The pipeline is very full and Atriva Therapeutics is very likely to come up with new antiviral therapies.

Press release 05-Jun-2016 (excerpt)

Atriva Therapeutics GmbH announces the acquisition of the co-infection patent (Application Nr: PCT/IB2015/053644) from the University of Muenster, Germany. This patent covers the beneficial and potentially lifesaving use of MEK inhibitors against co-infections of bacteria, including multi-resistant bacterial strains such as MRSA, which often occurs following a severe influenza viral infection and can be fatal to high-risk influenza patients.

Article

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Further information

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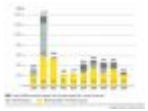

The different phases of company foundation

virus | basic research | influenza | active pharmaceutical ingredient | drug approval | defence mechanisms | pathogen