Atriva Therapeutics GmbH
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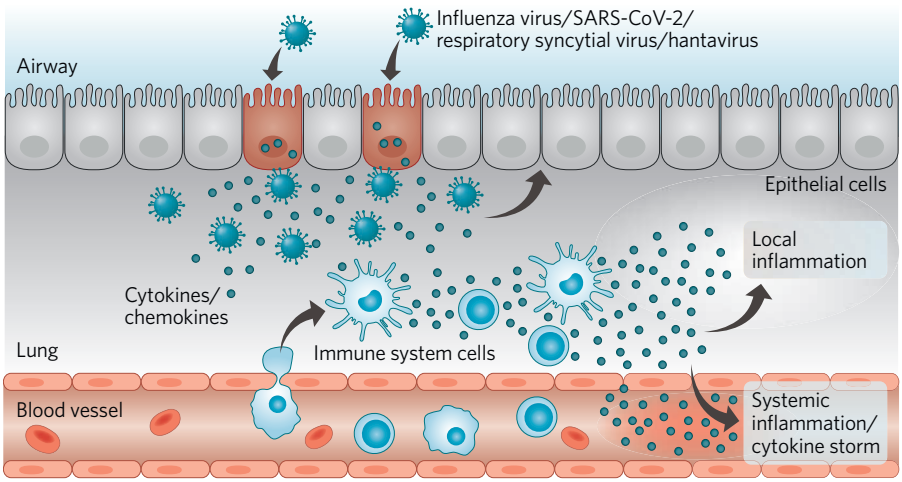
Atriva Therapeutics: transforming antiviral therapies

By acting directly on human cell machinery, Atriva Therapeutics' lead candidate antiviral ATR-002 combines several advantages over existing therapies and could combat respiratory diseases such as influenza and COVID-19.

With the world in the grip of a rapidly spreading pandemic caused by a lethal respiratory virus, the need for an effective antiviral treatment has never been greater. Coronavirus disease (COVID-19) is wreaking havoc around the world, devastating lives and economies. At the same time, the next influenza outbreak is a matter of when—not if, and will add to the healthcare and financial burden.

Unfortunately, no vaccines are available for COVID-19, and treatment options are very limited. Influenza vaccines can be only partially effective or not effective at all in some seasons. Moreover, currently approved antiviral therapies for influenza virus must be administered soon after the onset of symptoms (typically within 48 hours) and rapidly become ineffective as the virus mutates. "There is a dire need for a safe and efficacious therapy that avoids resistance, has a broader treatment window, and is suitable for high-risk groups," said Rainer Lichtenberger, co-founder and CEO of Atriva Therapeutics.



Viral multiplication and cytokine storm. ATR-002 addresses these effects, which often lead to severe progression of respiratory viral infections.

A novel approach

Atriva Therapeutics, a biopharmaceutical company based in Tübingen, Germany, is set to revolutionize the treatment of influenza, COVID-19 and other potentially life-threatening respiratory diseases. Conventional treatments are limited by a narrow window of therapeutic efficacy and, because they target viral proteins, show reduced efficacy once specific mutations appear in the virus. In contrast, Atriva's antiviral acts on the intracellular mechanism that is essential for viral propagation—an elegant approach that avoids resistance and broadens the time frame for application.

Influenza and some other RNA viruses rely on the Raf/MEK/ERK signaling pathway inside human cells to replicate. Atriva's lead candidate, ATR-002, is a small-molecule inhibitor of MEK, one of the key enzymes in the pathway, thereby preventing export of the viral genome protein complexes from the nucleus to the cytoplasm, in the case of influenza virus. Without these crucial building blocks, viral particles cannot be assembled and the virus can no longer propagate. This considerably controls the infection, ultimately reducing viral load in the body and allowing the adaptive immune system to clear the initial infection. Because the virus is not the target of the drug, it cannot escape the drug by mutation and thus, the risk of resistance developing is considerably lower.

In preclinical studies, the drug candidate rapidly blocked the Raf/MEK/ERK signaling pathway, significantly reducing influenza virus particle production in the body. Phase 1 data show that ATR-002 is safe and well tolerated and has a longer effective treatment window compared with standard-of-care therapies—a further notable benefit.

Calming the storm

Fatalities from COVID-19 and influenza are correlated with an overreaction of the body's immune system called a "cytokine storm". Although production of cytokines and chemokines is a normal part of the body's response to infections, certain cytokines can lead to inflammation. In some people, production of these pro-inflammatory cytokines can be excessive and damaging: cytokines and chemokines flood the body, attracting further immune cells to the site of infection, which in turn triggers production of more cytokines and chemokines—a vicious cycle of inflammation. In COVID-19 in particular, the site of infection is typically the lungs, with a cytokine storm leading to pneumonia and respiratory distress that in many cases is followed by organ failure and death.

This is where ATR-002 provides another significant advantage over standard treatments: the Raf/MEK/ERK pathway also regulates the gene expression of various cytokines and chemokines; blocking MEK, therefore, also prevents excessive cytokine/chemokine production. The MEK inhibitor ATR-002 reduces the overwhelming cytokine/chemokine response that is the cause of many fatalities. Thus, preventing hyper-inflammation is particularly important in the course of COVID-19.

ATR-002 has already shown promise to work in COVID-19 in preclinical studies, demonstrating both antiviral efficacy and immunomodulatory effects against SARS-CoV-2 in vitro. Given the great and urgent need for a safe and effective treatment for COVID-19, Atriva is prioritizing this indication for development; a phase 2 study in hospitalized patients with moderate COVID-19 is scheduled to begin in Q3 2020.

Potential in pandemics and beyond

ATR-002 has broad efficacy against RNA viruses that require the Raf/MEK/ERK signaling pathway for replication, including hantavirus and respiratory syncytial virus (RSV), which are also targets in the company's pipeline. Atriva welcomes new development partnerships with industry and academia for its proprietary candidate. "In COVID-19, influenza and other serious respiratory diseases, the death toll is driven by a combination of the viral infection and an overwhelming cytokine response," said Lichtenberger. "ATR-002, with its antiviral and immunomodulatory effects, has a double advantage over existing therapies and is uniquely positioned to benefit patients most at risk. This should help ease the burden on healthcare systems, particularly in pandemic environments."

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