

Towards a universal antibody treatment for influenza

March 2011

Imagine a single product that could solve all the problems currently limiting influenza control. It would have to reliably protect all subgroups of the population—especially the elderly—against serious illness and death, regardless of the causal viral strain. Ideally, it would both prevent and cure influenza. Crucell researchers have discovered a new class of monoclonal antibodies (mAbs) with this unprecedented potential.

In December 2008, Crucell announced this discovery and reported the results of preclinical studies involving a representative of this new mAb class, CR6261. The antibody was shown to neutralize a broad range of influenza viruses, including the currently circulating H1N1 seasonal flu strains (genetic descendants of the virus responsible for 40 million deaths during the pandemic of 1918–1919) and the highly pathogenic H5N1 ('bird flu') virus. More recent tests have shown that CR6261 also combats the novel H1N1 virus that caused the 2009 pandemic.

In a preclinical study comparing CR6261 with the leading antiviral drug, oseltamivir, Crucell's mAb strongly outperformed oseltamivir for influenza prevention and treatment. The study showed that CR6261 provides immediate protection against influenza viruses, suggesting that it will be able to prevent disease spread and therefore ward off a threatening pandemic. In contrast, oseltamivir was less effective and in some cases, not effective at all.

How does it work?

In February 2009, the prestigious journal *Science* published the results of a study designed to understand how Crucell's CR6261 antibody can neutralize different influenza viruses. X-ray crystallography was used to create three-dimensional molecular snapshots of CR6261 attached to the hemagglutinin (H) protein on the surface of different influenza viruses. The images revealed that Crucell's mAb binds to a part of the H surface protein that does not change when the virus mutates—which it does with great ease.

The researchers went on to show that the invariable site on the H surface protein that is recognized by CR6261 is crucial for replication of the influenza virus. Once this site is bound by an antibody, the virus cannot fuse with membranes inside the host's cells and therefore cannot reproduce. The finding confirmed the feasibility of developing a universal mAb product for treating and preventing seasonal and pandemic influenza.

Partners in innovation

In August 2009, Crucell received an award from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), for the development of its influenza mAbs. The agreement provides funding of up to US\$ 40.7 million, with additional options worth a further US\$ 28.4 million, for a potential total of US\$ 69.1 million.

In September 2009, Johnson & Johnson (JNJ), through its subsidiary Ortho-McNeil-Janssen Pharmaceuticals, Inc., and Crucell entered into a strategic collaboration for the development and commercialize a universal monoclonal antibody product (flu-mAb) for the treatment and prevention of influenza. An important activity in the development of this flu-mAb has been the first production of this antibody product in a mobile a fully disposable FlexFactory®. In addition the strategic collaboration involves four innovative discovery programs focusing on the development and commercialization of a universal influenza vaccine as well as vaccines directed against three other infectious and non-infectious disease targets - one of which is RSV (see below). Activities for the universal influenza vaccine, which started in January, are ongoing. The universal influenza vaccine will be designed based on specific epitopes of our broadly cross-neutralizing influenza antibodies. The selection of the other innovation targets is ongoing.

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About influenza

Influenza, commonly called the flu, is an acute viral infection of the respiratory tract. It spreads easily from person to person via infectious droplets produced by coughing or sneezing. Influenza viruses circulate worldwide, infecting people of all ages. Epidemics of influenza occur annually, peaking during the winter months in temperate regions. In tropical regions, influenza may occur at any time of the year.

Influenza is an especially elusive infectious disease. The genetic composition of an influenza virus is especially geared to change, so that each year the prevailing flu strains differ in subtle but important ways from the ones circulating the previous year. This gradual and continuous process of genetic variation—known as antigenic drift—underlies the ability of seasonal influenza viruses to stay one step ahead of our bodies' immune defenses.

Every so often, an influenza virus undergoes a major genetic mutation, giving rise to a radically new type of influenza virus. Influenza viruses wear a spiky 'coat' made of hemagglutinin (H) and neuraminidase (N) proteins. These are the viral components (antigens) that the immune system can learn to recognize. An abrupt genetic change affecting the H or N proteins is known as antigenic shift and feared for its potential to unleash a deadly pandemic.

Morbidity and mortality

Influenza is a serious public health problem. The World Health Organization (WHO) estimates that seasonal influenza viruses infect 5–15% of the population annually, causing severe illness in 3 to 5 million people worldwide. Each year, an estimated 250,000 to 500,000 people die from influenza-related complications. The elderly are especially vulnerable: 90% of the deaths due to seasonal influenza in industrialized countries occurs in the over-65 age group. People with chronic illness and young children are also at higher risk of influenza complications. In addition to these health risks, seasonal flu epidemics can burden healthcare services and cause significant economic and logistical problems due to lost work productivity.

The impact of influenza pandemics is potentially much greater. There were three pandemics during the 20th century, when viruses of the influenza A subtype underwent major genetic changes, mainly affecting their H component. Each of these antigenic shifts resulted in a global pandemic with a terrible toll in terms of illness and death. The worst was the 'Spanish Flu' pandemic of 1918–1919, caused by the emergence of H1N1, which killed an estimated 40 million people around the world.

A virus thought to have pandemic potential is H5N1, the highly pathogenic 'bird flu' virus. So far, this virus has only been transmitted directly from birds to humans, so its impact has been relatively confined. However, many infectious diseases experts believe it could mutate into a form that spreads rapidly from human to human, with devastating consequences.

The pandemic (H1N1) 2009 virus

The history of influenza pandemics explains the alarm surrounding the emergence of a new human H1N1 influenza virus in April 2009. The novel virus first infected people in Mexico and spread rapidly around the globe. Genetic analysis revealed that the virus was not related to the seasonal H1N1 viruses that have been circulating among humans since 1977, but arose when a novel mix of genes from bird, pig and human influenza viruses recombined inside infected pig cells. The WHO declared the novel H1N1 influenza a pandemic on June 11, 2009.

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The global impact of the pandemic (H1N1) 2009 virus, popularly called the Mexican flu or Swine flu, has not yet been assessed using statistical models. The latest WHO update, on 24 February 2010, reported more than 16,000 deaths known to have been caused by the pandemic virus, but as this figure reflects individually tested and confirmed cases, the real death toll must be significantly higher.

Unlike the 'ordinary' seasonal flu, which causes most deaths among the elderly, the pandemic (H1N1) 2009 virus has mostly infected and killed younger people, including fit young adults.

Overall, the novel virus has proven to be highly contagious among humans, but significantly less deadly than initially was feared. However, no one can predict how the virus will evolve. It might disappear, or return as a seasonal influenza strain, picking up genetic characteristics from other influenza viruses over the years. In a very bad possible scenario, this easily transmissible virus might take on the virulence (disease-causing power) of the H5N1 bird flu.

Symptoms

Influenza symptoms can range from mild to severe. Typical symptoms of seasonal influenza include the sudden onset of high fever, cough, headache, muscle and joint pain, extreme fatigue, sore throat and runny nose. Most people recover within a week without needing medical care, but seasonal influenza can cause severe illness or death in people at high risk: infants, the elderly, chronically ill patients and individuals with weak immune systems.

Influenza prevention and treatment

The recipe for flu vaccine is rewritten each year by the WHO's Global Influenza Surveillance Network, which monitors the influenza viruses circulating among humans and annually recommends a vaccine that targets the three most virulent strains in circulation. Influenza vaccines typically induce a potent antibody response only to the particular viral strains they contain, and closely related viruses. According to the WHO, a seasonal flu vaccine is generally very effective (70–90%) in terms of reducing influenza morbidity in healthy adults. But the annual reformulations are an economic burden for health systems and the experts do not always get the recipe right.

A more important limitation of preventive vaccination as a strategy for influenza control is that flu vaccines are least effective in the people who most need protection: infants, immunocompromised individuals and the elderly. These are the groups at greatest risk of becoming seriously ill or dying from influenza, and their immune systems are often unable to mount a sufficient response after vaccination.

To compound the problem, the chances of successfully treating flu victims are limited. Widespread resistance to the leading antiviral drug, oseltamivir, has emerged swiftly among the influenza strains now in circulation. Resistance is less likely to arise to zanamivir, an inhaled drug with a different mode of action, but its use is restricted to people who can actively use an inhaler. This excludes young children, frail elderly or patients with underlying airway disease—once again, the groups most likely to suffer serious flu complications.

Innovative strategies for influenza control

Crucell is working in collaboration with Johnson & Johnson to develop and commercialize a universal monoclonal antibody product for the treatment and prevention of all strains of influenza. The promising results already achieved in this program form a springboard for designing a universal influenza vaccine. Crucell is also pushing forward with a program to manufacture seasonal influenza vaccines on PER.C6® human cells, a technology that has major efficiency and safety advantages over the traditional vaccine production method.



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