

## Developing a Rabies Antibody Combination

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We are developing a human monoclonal antibody combination for the post-exposure treatment of rabies. The use of Crucell's MAbstract® technology resulted in a combination of two human anti-rabies antibodies. The monoclonal antibodies are produced on Crucell's PER.C6® technology.

### Discovery

Crucell scientists collaborated with scientists from Thomas Jefferson University (TJU) in Philadelphia and the US Centers for Disease Control and Prevention in Atlanta, USA to discover a combination of human monoclonal antibodies (mAbs) for the post-exposure treatment of rabies. Crucell's innovative MAbstract® and PER.C6® technologies played a crucial role in this discovery. The candidate mAb product is designed to be used together with rabies vaccine. Preclinical studies conducted during 2004 indicated that the mAb combination could neutralize (inactivate) rabies virus at least as effectively as human rabies immune globulin (HRIG), the current gold standard for providing immediate protection against rabies virus.

### Research and development

Since then, the rabies mAb combination has successfully progressed through phase I clinical trials in the USA and India (in 2006-7) and phase II trials in the USA and the Philippines.

- In Phase I studies, the primary goal was to demonstrate the safety and tolerability of the rabies mAb combination in small groups of healthy human volunteers. However, while testing for safety, the researchers also measured the neutralizing activity of the mAb mixture, in order to get an indication of efficacy in humans. Results of these studies were very encouraging.
- The results of the phase II US study, presented at the Rabies in the Americas (RITA) conference in October 2008, provided the solid efficacy data rabies experts had been waiting for. As well as confirming that the mAb combination is very safe and well tolerated in adults, the study showed that it gives them the same level of protection against rabies as HRIG.
- The same findings were announced in June 2009 for the second phase II trial, which involved children and adolescents living in a part of the Philippines with high rabies endemicity, and therefore high risk of infection. Children are even more likely than adults to be bitten by a rabid animal.
- The Indian authorities released the material for an additional Phase II study in India. This start of this trial is now imminent. This study is designed to collect safety and neutralizing activity data of the CL184 antibody in combination with the vaccine in a simulated rabies post-exposure prophylaxis setting. For regulatory reasons, developing countries use a different rabies vaccine than the USA and Europe.

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## **Accelerating innovation**

Since January 2008, the route toward global availability of this next-generation, life-saving rabies biological has been facilitated by a strategic partnership between Crucell and sanofi pasteur, a world leader in rabies immunization. Under the terms of this agreement, Crucell will be responsible for manufacturing the commercial product and has retained exclusive distribution rights in Europe, co-exclusive distribution rights in China and the rights to sell to supranational organizations such as UNICEF, while sanofi pasteur will have exclusive distribution rights for all other territories and co-exclusive distribution rights in China. Completion of the phase II studies in the USA and the Philippines triggered milestone payments from sanofi pasteur as part of the eligible amount of €66.5 million.

The US Food and Drug Administration (FDA) has granted the rabies mAb combination Fast Track status, paving the way for priority handling of the regulatory dossier.



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## About Rabies

Rabies is a viral disease of mammals and is most often transmitted through the bite of a rabid animal. The virus infects the central nervous system, causing encephalitis (inflammation of the brain) and ultimately death if appropriate medical intervention is not given promptly.

### Morbidity and Mortality

Globally, around 10 million people a year are treated after exposure to rabies virus, but around 55,000 people die of rabies each year, mainly in Africa, China and India. Most of those who die receive rabies vaccine only, rather than the proper post-exposure treatment consisting of anti-rabies antibodies as well as vaccine. Concerns about the availability and safety of the current, blood-derived antibody treatment have prompted the search for a safe, effective and affordable alternative.

### Geographical Distribution

Rabies is prevalent in all the continental regions of Asia, America and Africa. Stray dogs are the main global reservoir for the virus, but bats have emerged as an important epidemiological reservoir in many parts of the world. Although wildlife vaccination campaigns have eliminated rabies from animals in western European countries, rabies, persists in terrestrial wildlife and bats in Northern America. Greenland and eastern European countries also have wildlife rabies and still have a small number of human rabies cases each year.

### Transmission

Transmission of rabies usually occurs when infected saliva is passed to an uninfected animal or person, most commonly through the bite of a rabid animal. The rabies virus spreads from the site of infection through the nerves—where it multiplies rapidly—to the spinal cord, brain and salivary glands. The incubation period after infection is usually 1-3 months, but may be shorter or up to 1 year. The behavioral changes associated with rabies develop when the virus reaches the brain, after which death usually occurs within weeks.

### Symptoms

The first signs of rabies are usually nonspecific symptoms involving the respiratory, gastrointestinal and/or central nervous system. They may progress to hyperactivity (furious rabies) or paralysis (dumb rabies), both of which progress to complete paralysis followed by coma and death in all cases.



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## **Treatment and Prevention**

There is no treatment for rabies once disease symptoms have appeared. However, people who have been exposed to rabies virus can be protected from developing symptomatic disease if immediate action is taken. They need to receive immediate protection in the form of a single shot of antibodies directed against the rabies virus (passive immunization) as well as rabies vaccine (five doses over 4 weeks) to stimulate the body's own immune defenses (active immunization). The current gold standard for passive immunization is human rabies immunoglobulin's (RIG), a blood-derived product that is in short supply worldwide and not affordable for most countries where rabies is a common threat. RIG derived from equine (horse) blood is a cheaper alternative, but associated with serious side-effects.

Crucell and strategic partner sanofi pasteur are co-developing a rabies antibody product that is not derived from blood and would be affordable for everyone. Other important potential advantages of this monoclonal antibody (mAb) product compared to RIG include more consistent production volumes and less painful administration due to smaller injections.



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