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Review Article

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Camelid Antibodies May well be effective Against SARS-CoV-2 variants

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Editorial

Are camels at the origin of a new treatment against Covid-19? What is certain is that these animals have small antibodies, absent in humans, which neutralize SARS-CoV-2 and some of its variants, according to Australian scientists.

To put an end to the Covid-19 pandemic, scientists are not short of ideas. The most unexpected involves llamas. Indeed, camels produce very small antibodies, nano-antibodies, absent in humans. Several studies have highlighted the ability of nano-antibodies to neutralize SARS-CoV-2, but it has not yet been exploited to make it a therapeutic or prophylactic treatment against Covid-19. Indeed, in vivo experiments with nano-antibodies are delicate because they are quickly filtered by the kidneys after their injection. This does not prevent scientists from continuing their research efforts [1].

An Australian team has identified four nano-antibodies that inhibit the interaction between S protein, even mutated, and the ACE2 cell receptor. Injected into mice before infection, the nano-antibodies protect them from disease. They publish their results in PNAS [2].

Camelid nano-antibodies attacking the coronavirus

The WNb2, 15, 7 and 36 nano-antibodies were purified from the serum of two Australian camelids immunized with the S protein and its fraction which interacts with ACE2, the receptor binding domain (RBD). Among the fifty different nano-antibodies produced following this immunization, only the four previously named bind firmly to the S protein of SARS-CoV-2. They can be separated into two groups: WNb2 and 36 form cluster 1 and WNb7 and 15 form cluster 2.

They all attach themselves to RBD but not in the same place, they act non-competitively. Using them in a cocktail would therefore increase their neutralizing power. In addition, the N501Y mutation, located in RBD and present in several variants of concern, does not interfere with their binding [3].

Tested As a Preventive Treatment in Mice

Scientists also performed in vivo experiments on mice. In their protocol, the nano-antibodies are not used for therapeutic purposes, but prophylactic. That is, they are administered before infection to limit the development of Covid-19. The nano-antibodies are injected into the peritoneum of rodents, and 24 hours later they are infected with a human strain of SARS-CoV-2 possessing the N501Y mutation [4, 5].

After three days, the scientists studied the condition of their lungs. Preventive treatment with one of the four nano-antibodies saved the lungs of virtually all rodents. Only one, immunized with WNb2, showed tissue damage in the lungs. The treatment also had an effect on the level of viral RNA, which was reduced by a factor of 10,000 in the treated animals [6].

Preventive treatment with nano-antibodies, alone or in a cocktail, could be considered in people who respond poorly to vaccination, according to scientists. Nano-antibodies could also be interesting for controlling the spread of more contagious variants of the coronavirus [7].

A few months ago, winter the llama identified nano-antibodies (VHH), very small single-chain antibodies produced by camels that neutralize SARS-CoV-2.

A publication in Science, published on November 5, describes a similar story, except that researchers at the University of Pittsburgh chose another lama, Wally. They also used a different approach which made it possible to isolate nano-antibodies whose neutralizing power is, according to them, 100 to 1,000 times greater than those of Winter [8].

Wally was immunized with the part of S protein that recognizes the cellular receptor, the receptor binding domain (RBD). About two months later, scientists extracted the famous nano-antibodies from his plasma [9].

In the experiment carried out on Winter, the nano-antibodies most affine for the S protein of SARS-CoV-2 were identified by the phage display technique. Here, a technique based on mass spectroscopy

has been favored, allowing the identification of several thousand high affinity nano-antibodies [10, 11].

Three nano-antibodies stand out: Nbs 89, 20 and 21. The neutralizing capacity of this trio was therefore tested during an experiment making it possible to determine the quantity necessary to neutralize 50% (IC50) of the cellular damage induced by the virus in vitro. It turns out that a very small amount of these nano-antibodies is needed to reach the IC50, of the order of nanomolar (0.045 nM for the most effective) [12].

A Specific Binding to the Receptor Binding Domain

Nbs 21 is the most neutralizing nano-antibody among those identified in Wally's plasma. The peculiar way it attaches to RBD seems to be the cause. Thanks to the analysis of the crystallographic structure of the Nbs21-RBD complex, it appears in fact that this nano-antibody binds firmly to the RBD by numerous hydrophobic and polar interactions which entirely cover the RBD, when the other nano-antibodies do not. Attach that to an outer loop of the protein [13].

These nano-antibodies are more stable than human immunoglobulins, they can be stored for up to six weeks at room temperature. As with other treatments, researchers at the University of Pittsburgh imagine diffusing their nano-antibody through a spray to protect the airways from potential infection [14].

Llama Antibodies Could Help Beat Coronavirus

The plasma of a young Belgian llama contains specific small antibodies. The latter are able to neutralize the infection of coronaviruses, responsible for SARS, the Seas but also for Covid-19 [12, 14].

Winter is a four-year-old llama who peacefully grazes the grass of the meadows near the city of Ghent in Belgium. The young camelid could also play a key role in the search for treatments against Covid-19 [15].

Indeed, Winter was immunized with an infusion containing the surface proteins (S protein) of two coronaviruses: Mers-CoV and Sars-CoV-1. Scientists identified small neutralizing antibodies in llama's plasma that were effective against two pseudo-typed viral particles (a lentivirus modified to express the surface proteins of coronaviruses) mimicking the two strains of coronavirus that Winter was immunized against. , as well as Sars-CoV-2. The results of this study will appear in the Cell journal [16].

Small Neutralizing Antibodies

These particular antibodies are a subclass of IgG specific to camels called VHH. They only have one heavy chain while conventional IgGs have a light chain and a heavy chain. The VHH therefore have only one variable domain, located on the heavy chain.

A crystallographic analysis made it possible to determine on which part of the reconstituted virus the VHH from Winter's plasma bind: the receptor binding domain (RBD) of protein S. Several have demonstrated their neutralizing action against Sars-CoV-1 and Mers-CoV on in vitro cell cultures. One of them, VHH-72, is able to neutralize the infection of the viral pseudo-particle mimicking Sars-CoV-1 but also that mimicking Sars-CoV-2 [16].

Smaller than conventional IgGs, VHHs are stable and could be administered via an inhalation spray, especially to treat respiratory infections. Scientists hope that llama VHH's neutralizing ability makes them serious candidates for treating Covid-19.

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