Coronavirus vaccine developers wary of errant antibodies

Concerns persist that COVID-19 vaccines could cause antibody-dependent enhancement, which can potentiate viral entry into host cells and worsen disease.

In late May, CanSino Biologics published the first data for its COVID-19 vaccine expressing spike protein. The vaccine generated neutralizing antibodies in many recipients and appeared safe, but the company, like others in this space, remains on alert for a dangerous phenomenon known as antibody-dependent enhancement (ADE). “It’s important to talk about it [ADE],” says Gregory Glenn, president of R&D at Novavax, which launched its COVID-19 vaccine trial in May. But “we can’t be overly cautious. People are dying. So we need to be aggressive here.”

There are mounting theoretical concerns that vaccines generating antibodies against SARS-CoV-2 may bind to the virus without neutralizing it. Should this happen, the non-neutralizing antibodies could enhance viral entry into cells and viral replication and end up worsening infection instead of offering protection, through the poorly understood phenomenon of ADE. ADE “is a genuine concern,” says virologist Kevin Gilligan, a senior consultant with Biologics Consulting, who advises thorough safety studies. “Because if the gun is jumped, and a vaccine is widely distributed that is disease enhancing, that would be worse than actually not doing any vaccination at all.”

The degree of ADE vaccine risk for SARS-CoV-2 is unknown.

“Most experts who look at it acknowledge the potential risk but don’t see compelling evidence for it in humans right now,” says

James Crowe, director of the Vanderbilt Vaccine Center. Some view coronavirus ADE as a laboratory phenomenon, at least so far. “The theoretical possibility [of ADE] is there,” says Rafi Ahmed, director of the Emory Vaccine Center. “The more difficult question becomes, how do you balance this concern with moving forward? There’s not an easy answer.”

ADE was first described in 1977 by virologist Scott Halstead, then at the University of Hawaii. Halstead studied dengue, caused by four related but antigenically distinct viruses known as ‘serotypes’. Halstead noted that animals previously infected with one serotype did worse if infected again with a different serotype than if never previously infected at all. He found antibodies to be responsible for this phenomenon. Instead of neutralizing the virus, the antibodies facilitated viral entry into host cells in vitro. In his publication, Halstead presciently wrote: “Non-neutralising antibody presumably provides a specific molecular ‘ride’ for an infectious dengue virion into the interior of a receptive phagocytic cell.”

Halstead’s speculation was later proven correct, not just for dengue, a flavivirus, but for other viruses, including coronaviruses, in cell culture experiments. The coronavirus uses its spike protein to bind host receptors and infect airway cells. But it also can infect immune cells, typically macrophages. Anti-spike antibodies ideally

Following vaccination, antibodies that bind the SARS-CoV-2 virus may still fail to neutralize it, and could even facilitate infection. Credit: Reprinted with permission from A. Iwasaki and Y. Yang, *Nat. Rev. Immunol.* **20**, 339–341 (2020)

A COVID-19 model

A mouse model of COVID-19 that mirrors several features of human disease has been developed using CRISPR–Cas9 knock-in technology. The model is the first to contain only the human version of the angiotensin-converting enzyme 2 (ACE2) — the receptor SARS-CoV-2 uses to enter cells. The new model could shed light on viral infection and transmission, as well as help investigators identify effective treatments and vaccines. Older models of coronavirus infection, developed in response to the 2002–2003 severe acute respiratory syndrome (SARS) epidemic, used transgene expression of human ACE2. Recently developed models use adenovirus-mediated delivery of human ACE2, but both types of model still express mouse ACE2, which doesn’t mediate viral entry, thus limiting their utility.

In the CRISPR–Cas9 version, You-Chun Wang from the National Institutes for Food and Drug Control, Beijing, and collaborators inserted cDNAs of human ACE2 into exon 2 of the mouse *Ace2* gene, located on the X chromosome, to abolish mouse *Ace2* expression. The human ACE2 gene is under control of mouse *Ace2* promoter. The authors note that the tissue distribution of ACE2 matches the clinical symptoms of COVID-19 in humans.

A key advantage of the humanized ACE2 mice over transgene models is that they achieve a much higher viral load (up to 10⁸ copies per gram of tissue) in lung following nasal infection with SARS-CoV-2. In the airway, club cells of the bronchiolar epithelium were the main cell type infected with SARS-CoV-2. The virus was also found in the brain, which is surprising given that few patients with COVID-19 develop neurological symptoms. The pulmonary pathology of the humanized ACE2 mice, characterized by inflammation in the alveolar walls, and an elevated inflammatory cytokine response were greater in aged animals than in younger ones, mirroring what is seen in humans. A drawback of the model, however, is that mice developed only mild infection; no clinical symptoms of COVID-19 or mortality were seen in this humanized ACE2 model.

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