News & Analysis

Biotech Innovations

New "Universal" Flu Vaccine Candidate Enters Clinical Trial
A phase 1 clinical trial for a "universal" influenza A vaccine candidate, BPL-1357, is now underway at the National Institutes of Health (NIH) Clinical Center, the agency announced. In an animal study not yet peer reviewed, mice and ferrets that received the vaccine survived lethal doses of 6 different flu strains, including subtypes not included in the 4 non-infectious, inactivated, avian flu virus strains that make up the experimental vaccine.

The trial will randomly assign up to 100 healthy adults aged 18 to 55 years to receive 2 doses, 28 days apart, of an active intramuscular vaccine and an intranasal placebo, an intranasal vaccine and intramuscular placebo, or 2 placebos.

Researchers at the National Institute of Allergy and Infectious Diseases (NIAID) developed the whole-virus vaccine candidate to induce a comprehensive cellular and mucosal immune response similar to natural infection. Blood and nasal mucosal samples taken monthly for 7 months will allow assessment of mucosal immunity's role, if any, in protecting against infection and whether inducing both cellular and mucosal immunity increases protection.

Worldwide, influenza causes about 3 million to 5 million severe illnesses and up to 650 000 deaths annually. Pandemics of new influenza strains to which populations have no immunity—such as the 1918 outbreak that caused at least 50 million deaths—are potentially exponentially more lethal than seasonal outbreaks.

If successful in humans, "vaccines that provide long-lasting protection against a wide range of seasonal influenza viruses as well as those with pandemic potential would be invaluable public health tools," NIAID Director Anthony S. Fauci, MD, said in the NIH announcement.

Evolving Omicron Subvariants Are More Resistant to Antibody Therapy
Most monoclonal antibody therapies that neutralized early variants of the SARS-CoV-2 virus are less effective or not effective against the BA.2.12.1, BA.4, and BA.5 Omicron subvariants that currently make up almost 99% of infections in the United States, according to a report in Nature.

Laboratory tests found that almost all of 21 monoclonal antibodies targeting SARS-CoV-2 spike proteins lost neutralizing activity completely or partially against BA.2.12.1 and BA.4/5. (BA.4 and BA.5 were grouped together in the tests because they share identical spike proteins.)

Monoclonal antibodies bind to the spike protein of SARS-CoV-2, prevent the virus from attaching to human cells, and tag it for destruction.

Among currently authorized therapeutic antibodies, only bebtelovimab retained full potency against BA.2.12.1 and BA.4/5. The combination of tixagivimab and cilgavimab (marketed as Evusheld) showed a modest loss of activity, the authors wrote. The findings are particularly concerning because the BA.2.12.1 and BA.4/5 variants are also more resistant to sera from vaccinated and boosted individuals than were earlier variants. Compared with the initial D614G strain of SARS-CoV-2, neutralizing titers were 8.1-fold lower for BA.2.12.1 and 19.2-fold lower for BA.4/5. These subvariants are also more resistant to sera neutralization than the earlier BA.2 subvariant.

In addition, BA.4/5 may have an even greater affinity than previous variants to the human angiotensin-converting enzyme 2 receptor, possibly making it more transmissible, the researchers noted. As a result, vaccine breakthrough infections may be more likely, making effective antibody treatment more important.

What's more, other variants are also likely to emerge. "[W]e must be mindful that each of the globally dominant variants of SARS-CoV-2 (Alpha, Delta, and Omicron) emerged stochastically and unexpectedly. Vigilance in our collective surveillance effort must be sustained," the authors wrote.

Finding Ways to Improve Patients’ Cancer Immunotherapy Response
An investigational tool using whole-exome sequencing (WES) more accurately identified genes and pathways that predict whether patients with cancer will respond to immune checkpoint blockade (ICB) than current tumor mutational burden (TMB) tests alone, researchers reported in Nature Communications.

TMB is often used to determine ICB eligibility and is generally calculated from a few hundred genes. The researchers sought to improve its performance by broadening analysis to the nearly 20 000 genes consistently captured by WES.

Their work generated nearly 130 000 high- and moderate-impact gene variants among the 319 patients analyzed, whose data were aggregated from 6 previous immunotherapy studies. Variants in the KRAS and BRAF genes were enriched among patients who responded to immunotherapy while variants in the TP53 and BCLAF1 genes were enriched among patients who did not respond. Similarly, 3 gene pathways were associated with ICB response.

A tool combining the WES-obtained data with other ICB response predictors, including age, tumor type, and TMB, was 10.5% more sensitive and 11% more specific in predicting ICB response than was TMB alone. The tool, called the Cancer Immunotherapy Response Classifier, or CIRCLE, also more accurately predicted cancer survival after immunotherapy. The approach was validated using WES data from 165 additional patients with cancer.

Although these results suggest that including more genomic data may improve prognostic accuracy, small sample size limits their significance. "[W]e hope that our study and other similar analyses will motivate more formal and prospective explorations into the routine clinical utility of these broader genomic assays," the authors wrote. – Howard D. Larkin

Note: Source references are available through embedded hyperlinks in the article text online.