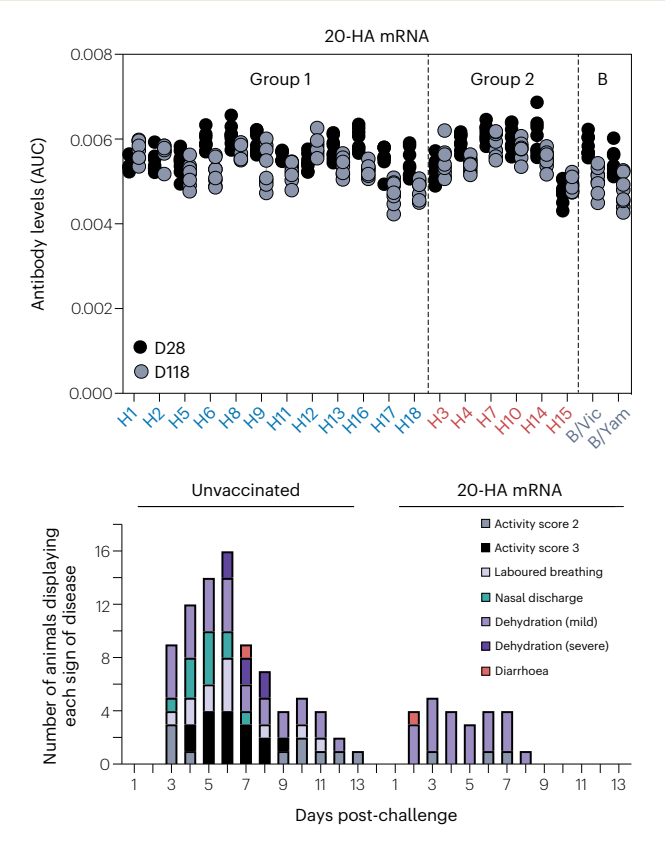
https://doi.org/10.1038/s41563-022-01452-6

mRNA vaccines

Towards a universal flu vaccine



Licensed influenza vaccines contain three or four strains of either inactivated or live attenuated influenza viruses and need to be reformulated annually for the Northern and Southern Hemispheres due to the continuous virus evolution that enables escape from natural immunity. Annually, global monitoring of the genetic drift of circulating strains guides the vaccine formulation. The approach has proved useful in preserving public health, but it is not ideal since the vaccine efficacy varies yearly and typically lies below 60%.

Now, Arevalo et al. report on a multivalent mRNA lipid nanoparticle vaccine that elicits antibodies against all known influenza virus subtypes (*Science* **378**, 899–904; 2022). There are currently at least 18 influenza A and 2 influenza B subtypes in nature, all containing the viral protein hemagglutinin (HA) (top panel). Most attempts at generating universal influenza vaccines focus on generating cross-reactive antibodies against HA epitopes that are conserved across several virus subtypes. A variety of such formulations is currently undergoing clinical trials. However, none of the reported ones are effective against all 20 subtypes. Arevalo et al. took a radically different yet conceptually simple approach based on incorporating 20 different antigens derived from every known influenza virus subtype into a single vaccine formulation so that a variety of distinct antibodies could be generated after a single injection. Notably, this is only practically achievable thanks to mRNA vaccine technology.

The researchers had previously observed that substituting the nucleoside uridine with a modified pseudouridine led to mRNA with a higher translational capacity, and used this approach to develop an mRNA lipid nanoparticle vaccine capable of eliciting antibodies against both HA head and stalk of a single influenza virus subtype. Now, by first optimizing 20 HA-encoding mRNA lipid nanoparticle vaccines for each influenza A and B subtype individually and subsequently combining them in a single cocktail formulation, the researchers were able to generate a nucleoside-modified mRNA lipid nanoparticle vaccine protecting against all the subtypes, with antibody levels remaining stable up to 118 days after the first injection in mice (top panel). The vaccine offers different levels of protection to matched and mismatched viral challenges in mice and ferrets, ranging from effective virus neutralization for matched viruses to largely reduced infection severity and duration via non-neutralizing mechanisms for mismatched viruses (bottom panel). While the approach is still in its infancy, it is broad-spectrum, potentially increasing vaccine efficacy and eliminating the need for annual vaccine reformulation. Moreover, its principles can be easily translated to other viruses, including coronaviruses, offering new directions for vaccine development via mRNA lipid nanoparticle technology.

Cristina Lo Giudice

Published online: 20 December 2022