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Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

COVID-19

Catching the breadth of broadly protective antibodies to SARS-CoV-2

Broadly protective antibodies to SARS-CoV-2 inform vaccine improvements and are directly used for treatment and prevention. New technologies are enabling the recovery of thousands of antibody examples, and workflows to rapidly identify the most potent examples are accelerating discovery.

Kevin R. McCarthy

Pandemics often emerge and spread in the absence of pre-existing population-level immunity. Immunity can be built through infection or vaccination and delivered as prophylactic or therapeutic monoclonal antibodies. Viruses can then evolve to evade immunity, which erodes protection conferred through these mechanisms. We have watched this process unfold in real time during the SARS-CoV-2 pandemic with the emergence of variants of concern (VOCs) and their descendants. Buoyed by recent technological advancements, rapid antibody discovery and characterization have delivered additional generations of monoclonal antibodies to the clinic and inform the design of vaccines that may confer more lasting immunity. In this issue of *Nature Immunology*, He et al.[1] describe and validate a preclinical workflow to rapidly recover and characterize large numbers of human antibodies that bind broadly to SARS-CoV-2, VOCs and divergent members of the Sarbecovirus subgenus and evaluate their efficacy in mouse models of infection.

The *Coronaviridae* are a diverse family of viruses distributed widely across geographies and across divergent avian and mammalian species. Many of these viruses seem to be adept at moving between species and adapting to new hosts. In the twenty-first century, at least three coronaviruses with likely ancestry in bat reservoirs have transmitted to humans: SARS-CoV (2002) via civets or other consumed wildlife, MERS (2012–present) via dromedary camels, and SARS-CoV-2 (2019) via an as-yet-unidentified source. Following its introduction into humans, SARS-CoV-2 has transmitted (and in some instances adapted) to an array of domestic, captive and wild animals. Persistence within new hosts also requires evading immunity built by prior infection. Within roughly a year of the emergence of the virus, SARS-CoV-2 VOCs had already acquired resistance to infection-elicited antibodies and spread across continents. Thus, the evolutionary plasticity of coronaviruses creates two distinct barriers to the realization of vaccines or monoclonal antibody therapies that protect against ongoing viral antigenic evolution and future pandemics from related viruses. First, a single virus (such as SARS-CoV-2) can quite rapidly amass resistance to dominant human immunity; and second, related viruses are continually changing as they move between species, adapt and diversify their antigenicity.

Many present-day SARS-CoV-2 vaccines deliver a spike glycoprotein, modified by mutating two key residues, which is stabilized in its pre-fusion conformation[2]. This immunogen was rationally designed, using structure and biochemistry, to appropriately present protective B cell epitopes to the immune system[3]. Antibodies elicited by these vaccines or through infection (or both) are now informing the design of improved immunogens. Already, while still in the pandemic phase of the pathogen, multiple rationally designed immunogens have been shown to elicit broadly protective antibody responses in animals. Although potentially rare, some antibodies engage conserved surfaces and as a result bind broadly across SARS-CoV-2 VOCs or even to other sarbecoviruses. These examples illustrate the potential of human antibody-mediated immunity. The discovery and characterization of such antibodies is the result of a confluence of technologies that permits the isolation of thousands of single B cells, cloning and sequencing their antibody genes and high-throughput structural determination brought about by cryogenic electron microscopy.

Isolating hundreds or thousands of B cells and profiling their antibodies is no longer the barrier to identifying antibodies that have potential clinical significance or that can inform the design of next-generation immunogens. The major challenge now lies in efficiently navigating this process to rapidly yield antibodies with demonstrably broad protective breadth. He et al.[1] demonstrate the utility of one discovery pipeline (Fig. 1). Humans with hybrid immunity, elicited by a primary SARS-CoV-2 infection followed by a standard series of vaccinations, mount more broadly binding antibody responses[4,5]. The authors selectively enrolled such donors and then used serological assays to identify individuals who mounted the most exceptional antibody responses. By combining this with an approach to

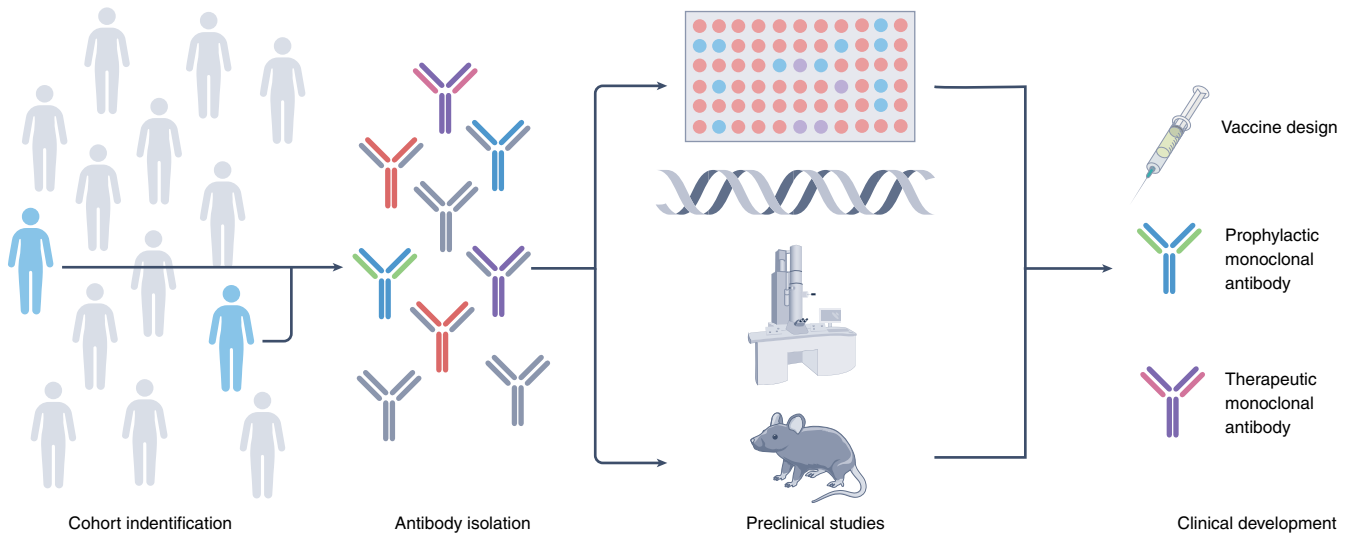

Fig. 1 | Rapidly isolating and characterizing broadly protective antibodies. A representation of the workflow used by He et al.[1] to isolate and characterize antibodies that protect against SARS-CoV-2 VOCs and divergent sarbecoviruses. It begins with identifying donors most likely to harbor these antibodies and characterizing their antibodies to identify the most potent examples. This workflow can inform future clinical developments.

recover B cells that produce antibodies with expansive breadth of binding, they isolated an impressive >100 monoclonal antibodies that engage both SARS-CoV-2 and SARS-CoV. To identify the most potent examples, they first characterized these antibodies with binding assays and pseudotype virus neutralization assays. These higher-throughput assays yielded a select few antibodies to be characterized in detail using structural approaches followed by protection studies conducted in an ABSL-3 environment. When administered prophylactically, three antibodies protected mice against severe disease when they were challenged by three divergent sarbecoviruses (SARS-CoV-2, SARS-CoV and SCH014).

Given the scale of this study, we have not only learned about the very best antibodies, but also discovered those that are likely to be generated in most humans. He et al.[1] demonstrate that broadly binding monoclonal antibodies can be genetically diverse, while subsets are enriched for common gene usages. Thus, the capacity to produce these antibodies is unrestricted, but elements that are 'hard-wired' into the human genome might bias an antibody toward a broadly protective outcome. Genetic diversity of these antibodies produces a collection of examples, all directed to a common conserved surface on the spike receptor binding domain, but that engage it in different ways. Diversity in how broadly protective epitopes are engaged might minimize the likelihood of a virus gaining full resistance to this panel of antibodies.

As the SARS-CoV-2 pandemic and the virus itself continue to evolve, so has our expectation of protective immunity. The unprecedented surge of cases in previously immune populations due to the Omicron variant (B.1.1.529) demonstrated that prior immunity imparted by infection, vaccination or both might be insufficient to confer sterilizing immunity but does limit disease severity, hospitalization and death. As we move to the next phases of the pandemic, we must consider the next phases of immunity. We will probably need to maintain and update an arsenal of therapeutic antibodies to save lives when an individual's immunity fails. Many people cannot mount sufficient immune responses, despite additional vaccinations, and will require prophylactic antibodies and cocktails thereof. Protecting those who cannot protect themselves can limit deaths, hospital burden and possibly further viral evolution. At present, only one of the therapeutic antibodies authorized by the US Food and Drug Administration under an Emergency Use Authorization is likely to remain efficacious against the dominant Omicron sublineage BA.2[6]. So far, a single antibody has been given an Emergency Use Authorization as a prophylactic therapy, and the emergence of the Omicron variant required its dosage to be doubled to retain efficacy[7]. Approaches such as the one described by He et al.[1] and many others have the potential to continually replenish our ever-depleted antibody pool to bring protection to the most vulnerable patient populations. ❐

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Competing interests

The author declares no competing interests