and the geographical areas in that city's supply network. With this information in hand, the authors tested the idea that groups of cities with more-diverse supply chains are better able to buffer against food shocks than are groups whose supply chains are less diverse. Indeed, they found that cities importing food from suppliers that are more dissimilar from themselves are less likely to face shocks than are cities whose supply-chain partners are less diverse. Such supply-chain benefits would not be reaped from having solely local food systems.

Gomez *et al.* then considered design concepts from engineering, where infrastructure systems should be planned to withstand shocks — such as extreme flooding — of a given frequency and magnitude. The authors undertook some bold extrapolations, in which they estimated the size of food shocks that would be faced by different US cities given their current supply-chain diversity. They found that a rare shock, such as one occurring once in 100 years, would cause a food-supply loss of about 22–32% across different cities.

The other implicit finding from Gomez and colleagues' model is that even moderate supply-chain diversity is effective at reducing the probability of extremely large shocks. The authors also applied their analysis to shocks happening in multiple food sectors simultaneously. They obtained similar results to those for single-sector shocks — with supply-chain diversity also providing a buffering effect for these even rarer occurrences.

Gomez and colleagues' work has major implications for the way in which resilient food systems should be built, but it also has a few caveats. First, the authors used only four years of data for each city, posing problems for characterizing the distribution of shocks at each city. This limited time series makes it difficult to define the baseline variation in food supply — that is, what is considered normal — for consumers and retailers alike. It also makes it hard to see to what extent diversified supply chains buffer against food shortages under normal conditions compared with years marked by extreme events, and whether the net benefits are large enough to trigger a change in food-procurement policies.

Second, the food-flow data used by Gomez *et al.* do not represent actual flows for each year, but instead are simply annual production quantities proportionally distributed according to observed flows[5] in 2012. Therefore, the authors' analysis does not capture, or allow for, rerouting or other social responses at the onset of extreme events. Such social responses within and after shock years would result in changing food flows across the supply network.

Third, Gomez and colleagues did not validate the predictive worth of their model beyond the four years considered, or outside the United States. This lack of verification is perhaps most limiting for applying the findings in practice — partly because the stability of food supply is itself dynamic, and will change with increasing volumes and types of food consumed, as well as with production technology. Although the observed phenomenon and general patterns might hold in other years and geographical regions, no data or analyses exist to validate whether the authors' design suggestions will protect against future shocks to the degree claimed.

Designing urban food systems to specification is not as easy as engineering a bridge or dam that won't fail in 100 years. The major global concern with respect to urban food shortages and food security is for populations of middle- to low-income countries, particularly those that are dependent on imports[6]. Theoretically, supply-chain diversity will also have a buffering effect for these populations when the number of urban dwellers starts to drastically increase in the coming years, especially in Africa. However, such nations are probably not accurately described by the model presented. Moreover, they have different policy options and capacities for producing diverse supply chains compared with those possible in the United States. Nevertheless, Gomez and colleagues' work provides a timely and refreshing reminder that building diverse supply chains offers a crucial mechanism for protecting urban dwellers from food shortages.

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Immunology

Single-domain antibodies tackle COVID variants

James E. Voss

Camels and llamas make antibodies that bind to targets using small, 'nanobody' protein domains. Mice have now been engineered to make nanobodies that might be more effective than conventional antibodies in treating COVID-19. **See p.278**

How might the emergence of SARS-CoV-2 variants affect efforts to control the COVID-19 pandemic? The threat posed by such variants is focusing attention on vaccination and therapeutic options to grapple with the evolving coronavirus. On page 278, Xu *et al.*[1] describe the development of a genetically engineered mouse that can generate antibodies similar to those produced by camelids (an animal grouping that includes camels and llamas). These antibodies recognize targets using a single, small protein domain called a nanobody, also known as a VHH domain. Vaccination of these mice using proteins based on the SARS-CoV-2 spike protein resulted in the generation of antiviral nanobodies. These nanobodies could be produced in formats that were highly effective against COVID-19 variants that are impervious to many conventional antibodies being developed as therapies.

Conventional antibodies such as those produced by humans and mice recognize antigens (protein fragments of disease-causing agents) by means of two variable domains (VH and VL), which are components of separate heavy- and light-chain proteins (Fig. 1). By contrast, camelids and cartilaginous fishes (such as sharks) can make heavy-chain-only antibodies that recognize antigens using single, variable VHH domains, or nanobodies. One advantage of nanobodies is their small size, which enables them to penetrate tissues and recognize epitopes (the region of an antigen to which an antibody binds) that are normally inaccessible to conventional antibodies.

Nanobodies are generally extremely stable and soluble, and their modular nature means they can be readily expressed alone or in a variety of formats: for example, fused to the human antibody Fc domain that boosts

defence responses[2]. These features make nanobody-based therapeutics a promising alternative to conventional monoclonal antibodies (antibodies with heavy and light chains that have a particular amino-acid sequence and antigen specificity). However, although 2021 saw regulatory approval of the 100th monoclonal-antibody treatment[3], only one nanobody-based therapy has been approved for clinical use by the US Food and Drug Administration (FDA)[4].

Currently, the only human monoclonal antibodies in advanced development as COVID-19 therapies (see go.nature.com/3xt9ku2) are a type called neutralizing antibodies (which block viral entry). Most of these were obtained from the antibody-producing cells of people who were infected during the first wave of the pandemic. Such antibodies target the receptor-binding domain (RBD) of the spike protein; the virus uses this domain to bind to the receptor that enables it to infect cells[5]. Human monoclonal antibodies are strongly preferred for clinical development because they are highly specific, are easily manufactured and work in concert with, and are well tolerated by, the human immune system[6]. However, there are strong arguments in favour of developing alternative, nanobody-based therapeutics in response to evolving human respiratory viruses such as SARS-CoV-2.

Since the virus began infecting people more than a year ago, the collective human neutralizing-antibody response generated against SARS-CoV-2 has applied a strong selection pressure on the spike-protein RBD. In fact, only two or three amino-acid-residue changes in versions of the virus that became dominant during the second and third waves of the pandemic were enough to render those versions substantially more resistant to neutralization by antibodies generated during the first wave — as assessed by tests on blood samples, known as convalescent serum, from individuals who have had COVID-19 (ref. 7).

It therefore follows that monoclonal-antibody therapies mined from antibody responses generated during the first wave of the pandemic might quickly become obsolete. RBD epitopes of the spike protein that are recognized by neutralizing nanobodies, and that are not under selection pressure as a consequence of epitope recognition by human antibodies, might provide COVID-19 antivirals that do not quickly become ineffective as viral variants emerge. Broadly neutralizing nanobodies — nanobodies that recognize evolutionarily conserved epitopes of the spike protein — might even be useful against other coronaviruses with the capacity to drive a future pandemic.

The small and soluble nature of nanobodies means that they should be inexpensive to produce and easy to administer directly by inhalation to target key initial sites of viral replication in the respiratory tract. A study[8] in hamsters, assessing the intranasal aerosol delivery of neutralizing nanobodies targeting SARS-CoV-2, reports that nanobodies were effectively deposited throughout the animals' respiratory tract, and that this treatment notably reduced the level of virus. As long as nanobody therapies are administered only once over a short period of time to people with an acute infection, then strong immune responses should not be directed towards the nanobody itself, rendering it ineffective. The issue of such immune responses is generally a concern in relation to monoclonal-antibody therapies being developed to treat diseases that require repeated antibody administration over longer periods of time.

Although there has been some hesitancy in moving nanobodies to the clinic, many studies have found that potently neutralizing nanobodies can be elicited in camelids using SARS-CoV-2 vaccines based on the spike protein[9–13]. Xu and colleagues now offer a way forward through their generation of heavy-chain-only antibody-producing 'nanomice'. The approach offers a system that should make nanobody discovery easier, faster and less expensive than was previously possible. Laboratory facilities to care for mice are inexpensive and ubiquitous, the mouse immune system is well understood, and high-quality tools such as those needed for cell sorting are readily available. Furthermore, immunizations in mice can occur on a much faster timescale than is possible for larger animal models — an important consideration when a rapid response to a newly emerging pandemic is required.

To generate these nanomice, Xu *et al.* replaced a large region of genomic DNA, containing all of the mouse heavy-chain variable (*V*) genes, with a region of DNA comprising 30 heavy-chain *V* genes derived from alpaca, dromedary and Bactrian camels. Each gene was fused to a DNA sequence that enabled the gene to form the usual connection (through a process termed recombination) to mouse heavy-chain *D* and *J* genes to make complete *VHH* genes. The *V* genes were also fused to promoter DNA sequences so that the *VHH* genes could be expressed in mouse antibody-producing B cells. Each developing B cell could indeed recombine a single camelid *V*, mouse *D* and mouse *J* gene to generate B-cell populations expressing different *VHH*-gene sequences as heavy-chain-only antibodies. The authors demonstrated that these cells could respond normally to immunization, undergoing a process (termed affinity maturation) that boosts the potency and specificity of antibodies for the antigen that they respond to.

Xu and colleagues then immunized three nanomice and one llama with the SARS-CoV-2 spike protein and RBD. They identified neutralizing nanobodies in both animal models. These nanobodies could be formatted to be expressed as three tandem nanobody copies fused to a human antibody Fc domain (Fig. 1). This domain is a key feature of conventional antibodies: it enables an antibody to transit around the body, improves the antibody's lifespan and boosts interactions with other

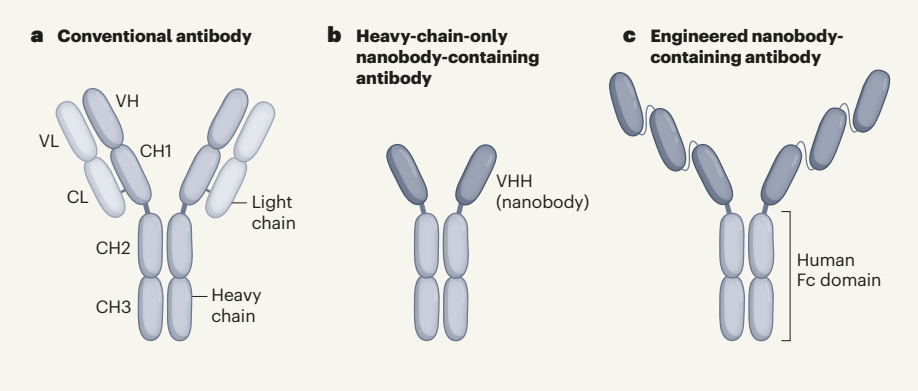

Figure 1 | Different types of antibody can target SARS-CoV-2. a, Human and mouse antibodies bind to their targets using two variable domains (VH and VL) on separate light- and heavy-chain proteins. These light and heavy chains pair through a connection between the light-chain CL domain and the heavy-chain CH1 domain. The paired domains are part of the constant regions of the heavy and light chains. The heavy-chain constant region consists of two other domains (CH2 and CH3, which form what is called the Fc domain) that help antibodies to travel around the body and interact with other components of the immune system. **b**, Camelid animals, such as camels and llamas, can produce heavy-chain-only antibodies because some of their genes encode heavy-chain proteins that lack CH1 domains. These antibodies recognize their targets using only a single variable domain (VHH) region, which is also known as a nanobody. Xu *et al.*[1] have developed mice that make a similar type of antibody. **c**, The authors genetically engineered mice to produce antibodies consisting of heavy chains containing three tandem copies of camelid nanobodies and a human Fc domain. They report that these antibodies could prevent SARS-CoV-2 from infecting human cells when tested *in vitro*, and that such 'neutralizing' antibodies were effective against SARS-CoV-2 variants of concern that emerged during the second and third waves of the pandemic.

components of the immune system. This format using tandem nanobodies should help to boost antigen binding by the antibodies. The authors' evidence indicates that these engineered antibodies could potently neutralize all of the tested SARS-CoV-2 variants of concern (viruses with RBD mutations and which were associated with the second and third waves of the pandemic). Moreover, the proteins from nanomice recognized evolutionarily conserved epitopes on the RBD that do not overlap with regions commonly recognized by human antibodies.

The COVID-19 pandemic presents a unique opportunity for nanobodies to shine in the clinic, and the nanomouse platform is poised to help bring higher-quality therapeutic-nanobody options to the table, pushing the odds of success even higher. Just as the development of mice with antibodies containing human variable domains (such as Regeneron's VelocImmune mouse) has helped to deliver the 100th FDA-approved monoclonal antibody, perhaps the nanomouse will give nanobody-based therapeutics a push in the same direction.

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Earth science

Buried extinct volcanoes cause small earthquakes

Catherine A. Rychert & Nicholas Harmon

Imaging of a region where an oceanic tectonic plate descends below another plate reveals evidence that fluid-rich extinct volcanoes can help to lubricate the interface between plates — reducing the potential for large earthquakes. **See p.255**

At subduction zones, the force of gravity drags dense tectonic plates beneath other, more buoyant plates. As the plates slide past one another, stress builds and is eventually released in the largest and most destructive types of earthquake on Earth. Various factors are thought to have a role in determining the location, type and magnitude of these earthquakes. Working out when and where each of these factors is at play is central to understanding earthquake processes and mitigating the associated hazards. The characteristics of the down-going plate are thought to be a crucial contributor.

However, finding direct links between the features of a down-going plate and the associated earthquake characteristics has proved challenging. Chesley *et al.*[1] report on page 255 their use of a technique called electromagnetic imaging to investigate extinct underwater volcanoes, known as seamounts, on the Pacific plate as it descends beneath New Zealand. The authors show that the seamounts bring fluid into Earth's interior that is later released into the overlying plate, effectively lubricating the system and potentially lowering the likelihood of large earthquakes.This use of electromagnetic imaging has produced one of the first high-resolution images of a feature on the down-going slab that directly links the release of fluids to the type and size of earthquakes.

A range of factors dictate the probable location and magnitude of earthquakes[2]. One such factor is the frictional properties of the interface between the plates. Fluids that are carried into Earth by the down-going plate can reduce the force of friction if they increase the fluid pressure in the fault zone. This, in turn, could decrease the likelihood of large earthquakes[3]. Alternatively, if the sea floor of the down-going plate is rough, because of features such as seamounts, this might produce areas of higher friction at a fault interface, increasing the likelihood of large earthquakes[4].

To investigate this issue, Chesley *et al.* carried out electromagnetic imaging of the subduction zone in New Zealand. The technology uses either artificial or naturally occurring electric and magnetic fields to determine the degree to which geological features in Earth's interior are electrically conductive or resistive. The method is particularly sensitive to the presence of interconnected fluids.

The authors produced high-resolution images of a seamount on a section of the Pacific plate that is about to be subducted. They observed that the interior of the seamount is highly conductive, but is overlain by a thin, electrically resistive layer of material (Fig. 1). The authors propose that the conductive interior is fluid-rich, and that the resistive layer is fluid-poor, with low porosity. The resistive layer therefore acts as a cap, limiting the release of fluids from the deeper conductive region until the plate reaches greater depths.

Chesley *et al.* also imaged an anomalously resistive feature deeper in the subduction zone, on top of the down-going plate. This corresponds to another seamount that had previously been imaged using seismic waves[5,6]. The anomaly resides beneath a conductive, fluid-rich region of the over-riding plate and is associated with a swarm of overlying small earthquakes (Fig. 1). The authors conclude that the previously observed seamount was the origin of the fluid in the conductive region now observed over the anomaly, and infer that the small earthquakes occur as the fluid moves through the system. So, although the rough topography of seamounts might be expected to increase friction at faults, seamounts can also decrease friction — and the potential for large 'mega-thrust' earthquakes — if they damage the upper plate and release fluids.

Some questions remain. How much fluid is left in the subducted seamount, and how much, if any, is carried deeper into the subduction zone? Deeply transported fluids are also important in subduction-zone settings, because they decrease the melting temperature of the mantle, resulting in hazardous volcanism at the surface[7].

More work is required to determine the global role of seamounts in influencing subduction dynamics and earthquake hazard. In some locations, seamounts have been associated with aseismic slip[8] (movement on faults that does not cause big earthquakes), whereas in other locations they have been linked to large earthquakes[4]. One explanation for these divergent effects is that seamounts have different hydration levels and are variably fractured around the world; those that are strong, dry and less fractured produce large earthquakes. If this is correct, then what processes cause seamounts to become hydrated or weak? And what is the relative contribution of factors such as sea-floor characteristics, the age of the plate beneath the volcano and the time elapsed since the seamount was an active volcano?