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Perspective

Therapeutic Antibodies for Infectious Diseases: Recent Past, Present, and Future

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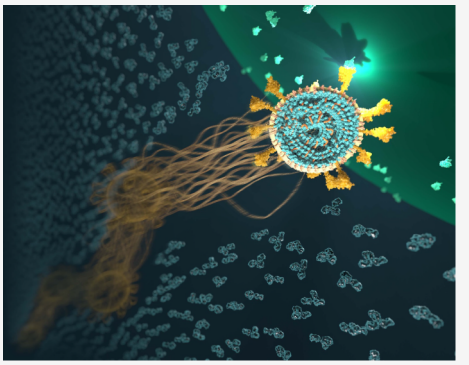
ABSTRACT: A central goal of modern infectious disease research is to discover safe prophylactic vaccines that can prevent infection. When this is not possible, or when preventive vaccines are still in development, it is critical to have interventions that can mitigate the spread of the disease both within infected individuals and in the population. In this short review, we explore the recent history of therapeutic antibody use, highlighting antibodies used over the last five years to treat COVID-19. We outline some of the challenges in developing antibodies rapidly in response to pandemic threats and suggest that emerging technologies for AI-driven design may offer exciting opportunities for the development of a broad class of protein therapies.



INTRODUCTION

Some of the major pandemics in the last two millennia have included the Justinian plague in 541 AD, thought to have killed about half of the world's population; the Black Death in 1340 AD, which killed about a quarter of the world's population; and the Spanish flu in 1918, which took the lives of ∼50 million people.[1,2] The death toll from the recent COVID-19 pandemic is thought to be at least 6 million, while HIV/AIDS has taken the lives of nearly 40 million people over the last four decades.[3−5] Vaccines, when safe and effective, are the best approach to preventing infection or severe disease. However, when vaccines are not an option due to the rapid emergence of diseases such as SARS-CoV-2 or HIV/AIDS, ready-to-deploy therapies can be used to prevent infection or treat disease in vulnerable populations. There are several examples of small molecules being successful in the treatment of infectious diseases, such as the HAART treatment for HIV/AIDS,[6] but in this review, we focus on antibody-based therapies.

Antibodies have several potential advantages over small molecules, including their high selectivity and the advancements in screening technology that allow for the rapid identification of high-affinity binders. Recent advances in computational tools, including AI, may enable the speedy development of early antibody leads, and highly effective antibodies can be identified quickly from convalescent plasma, as was the case with the antibody Bamlanivimab[7] for the treatment of COVID-19. Additionally, the Fc component of antibodies can provide a serum half-life of weeks, which allows for passive protection using antibodies. This may be necessary for immunocompromised individuals who do not respond to traditional vaccines. One example is the use of Palivizumab and Nirsevimab for the prevention or treatment of Respiratory Syncytial Virus (RSV) infection in children under 1 year.[8,9] As mentioned above, small-molecule antiviral drugs have been used extensively to control disease spread, especially for viral diseases such as HIV/AIDS and influenza.[10] Therapeutic antibodies have also been highly effective for the treatment of infectious diseases because they can target pathogens directly while minimizing the impact on the host's biological systems. In this article, we explore the journey of therapeutic antibodies from their inception to current applications and look ahead to their future potential in combating infectious diseases.

Therapeutic antibodies were first developed with the emergence of monoclonal antibody (mAb) technology in the 1970s.[11] Because these antibodies were generated in mice, they frequently triggered immune reactions in humans. In the early 1990s, this limitation was addressed by humanizing these antibodies with the development of Rituximab in 1993.[12] Rituximab, which targets the CD20 antigen, demonstrated efficacy in treatment of B-cell non-Hodgkin's lymphoma.[12] These advances were extended to infectious diseases with the development of Palivizumab that was approved in 1998 to prevent RSV infection and significantly reduced hospital

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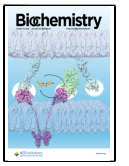

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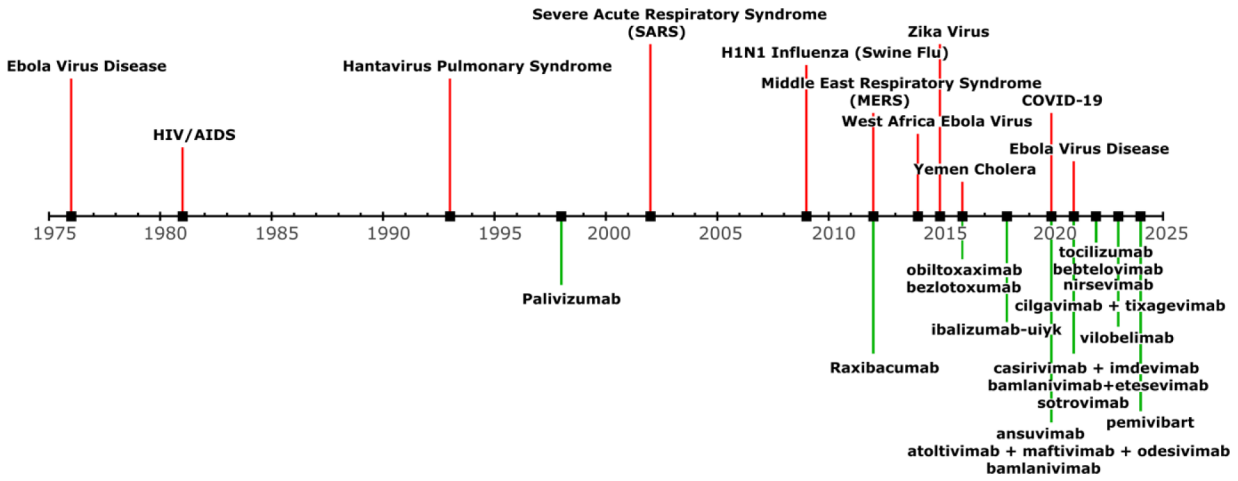

Figure 1. Timeline of the emergence of Pandemics (top, red)[2] and the initial FDA approval of therapeutic antibodies for infectious disease (bottom, green) over the past 50 years.[2] FDA Emergency Use Authorizations (EUAs) of therapeutics for infectious disease treatment are included in this timeline.[14] Nearly all antibodies for infectious disease have been approved within the last 10 years.

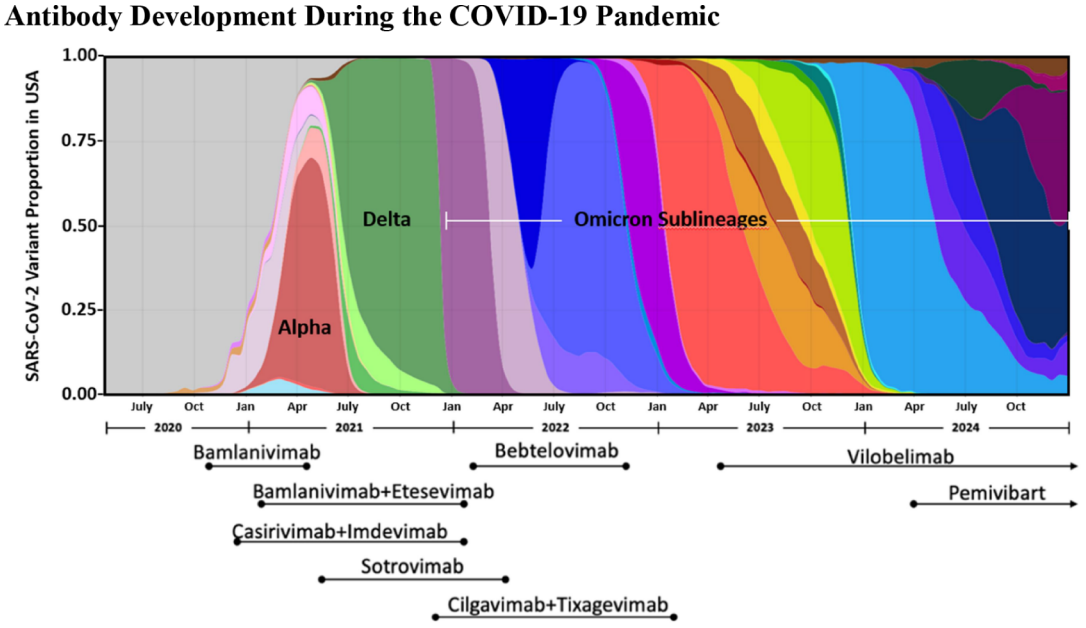

Figure 2. Relative prevalence of SARS-CoV-2 variant evolution (top) and the time frame for approved use for therapeutic antibodies (bottom) throughout the COVID-19 pandemic.[14] Variant proportion data from the United States were generated using data available at http://covariants.org. Major variants, achieving greater than 50% prevalence (Alpha, Delta, and Omicron sublineages), are specifically labeled.

admissions.[8] More recently, FDA approved Inmazeb in 2020, which reduced mortality in patients infected by Ebola in the Democratic Republic of the Congo.[13]

In the last few decades, we have seen an increased incidence of viral outbreaks, with the growing prevalence of air travel and greater interactions between humans, animals, and the environment as contributing factors. Viral outbreaks that might have been contained to a local area a century ago can now spread globally within a few hours; therefore, containment becomes far more challenging. Additionally, improvements in diagnostics and reporting allow for the identification of outbreaks that may have gone undetected previously. While there are still only a handful of antibodies approved for use in the treatment of infectious diseases, the number of approved antibodies continues to increase, with approvals in the last 7 years almost matching the combined number of approvals in all previous years.[14] Recent approvals also include antibodies targeting bacterial infections—for example, Bezlotoxumab, approved to prevent recurrence of *Clostridium difficile* infections, targets toxin B and significantly reduces recurrence rates when used in combination with standard antibiotic therapies.[15] A timeline of the major viral outbreaks over the last 50 years, as well as the steady increase in approved antibody treatments, is presented graphically in Figure 1.

ANTIBODY DEVELOPMENT DURING THE COVID-19 PANDEMIC

The COVID-19 pandemic provides a compelling example of the potential for expedited therapeutic antibody development against an emerging virus. Early in the COVID-19 pandemic, the rapid development and emergency use approval of the monoclonal antibody Bamlanivimab and the Casirivimab−Imdevimab cocktail became effective avenues for treatment.[16]

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Table 1. Therapeutic Antibodies Approved during the COVID-19 Pandemic

Therapeutic Antibody	Months with EUA	Development and Efficacy Details
Bamlanivimab	5	Developed by AbCellera and Eli Lilly, this antibody was initially effective against prevalent SARS-CoV-2 lineages but was later found to be less effective against later variants like Beta (B.1.351) and Gamma (P.1).[7,17]
Etesevimab	11	Used in combination with Bamlanivimab, this combination was effective against the original strain and some early variants but began to lose effectiveness against later variants such as Delta.[7,17,18]
Casirivimab and Imdevimab (REGEN-COV)	14	This combination by Regeneron was effective against many of the earlier variants, including Alpha and Beta. However, its effectiveness diminished with the emergence of the Omicron sublineages, which have multiple mutations in their spike glycoprotein.[7,17,18]
Sotrovimab	13	Initially, Sotrovimab was one of the few antibody therapies to retain activity against the Delta variant. Its efficacy against Omicron was limited, and it was less effective against later sublineages of Omicron.[18]
Tixagevimab and Cilgavimab (EVUSHELD)	5	Developed by AstraZeneca, this combination was designed for pre-exposure prophylaxis and showed effectiveness against several early variants but lost efficacy against Omicron sublineages—a broad theme across the efficacy of COVID-19 antibody therapeutics.[18]
Bebtelovimab	9	This antibody was developed by Eli Lilly as a follow up to Bamlanivimab to treat the emergence of the initial Omicron sublineage. Bebtelovimab's Emergency Use Authorization (EUA) was revoked due to the expectation of lack of efficacy against BQ.1 and BQ.1.1 sublineages.[19]
Vilobelimab	Currently approved	Developed by InflaRx, Vilobelimab blocks the activity of complement factor C5a and subsequently tampers the immune reaction to SARS-CoV-2. Vilobelimab stands in contrast to all other EUA antibodies which target the SARS-CoV-2 spike protein.[20]
Pemivibart	Currently approved	Developed by Invivyd, Pemivibart is approved for prophylactic use in immunocompromised patients who are unlikely to mount an adequate immune response to COVID-19 vaccination.[21]

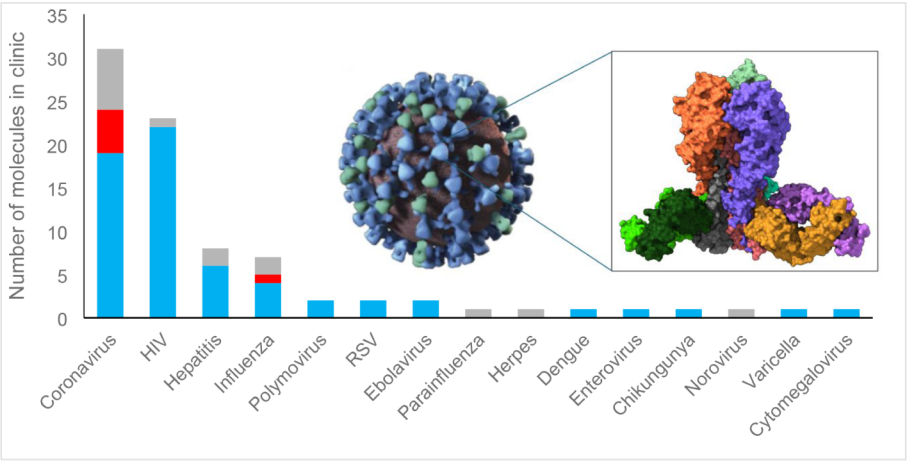

Figure 3. Number of biologics in development in Phase I, II, or III clinical trials based on targeted disease indication. mAbs are shown in blue, blood-derived polyclonal antibodies are shown in red, and recombinant proteins are shown in gray. The left inset shows a representation of the three-dimensional structure of the H1N1 influenza virion derived from cryo-electron tomography illustrating the distribution of unliganded (green) HA spikes and those bound to the C179 neutralizing antibody (blue) on the viral membrane (brick red).[54] The right inset shows an atomic model depicting the structure (PDB ID: 5JW4) of one HA spike bound to another broadly neutralizing antibody MEDI8852, with each protomer of the HA trimer shown in different colors (dark purple, orange and green).[55] The light and heavy chains of the MEDI8852 neutralizing antibody that bind the highly conserved stem region are shown at the base of the spike in separate colors. Left inset reproduced with permission from ref. 54.

These antibodies target the spike glycoprotein of the SARS-CoV-2 virus and block viral entry. Bamlanivimab, in combination with Etesevimab, was shown to reduce COVID-19 hospitalizations and deaths by up to 70% in high-risk patients when administered early.[7] Unfortunately, with the continuous emergence of mutations in the viral spike glycoprotein, nearly all approved antibody therapies for COVID-19 eventually became ineffective.[17] Furthermore, many newly discovered antibodies became ineffective before they could be approved or shortly after their approval, as summarized in Figure 2 and Table 1.

The majority of early monoclonal antibodies retained effectiveness against the Alpha variant (B.1.1.7), but the Beta (B.1.351) and Gamma (P.1) variants exhibited escape from certain monoclonal treatments, such as Bamlanivimab, leading to its discontinuation as a single therapeutic agent. Reduced antibody efficiency against the Delta variant (B.1.617.2) prompted a shift toward using antibody combinations. When the Omicron variant and its sublineages emerged, the significantly higher number of mutations in these variant spike glycoproteins led to the complete loss of efficacy for most single-agent and combination antibodies.[17,18]

■ ANTIBODY THERAPIES CURRENTLY IN THE CLINIC

Against the backdrop of antibody therapies for the treatment of COVID-19, it is interesting to examine the antibodies currently in clinical development at the preapproval stage for treating various infectious diseases. Antibody drugs have represented a growing fraction of FDA-approved drugs in the past decade and account for about a third of the FDA-approved drugs in the last five years.[22] Nevertheless, there are still only a limited number of Phase I, II, and III trials underway in the clinic targeting infectious diseases (Figure 3). Clinical trials targeting coronaviruses (including SARS-CoV-2) and HIV make up the majority, with significantly fewer trials underway, even for persistent viral threats such as influenza.

Most clinical trials underway utilize monoclonal antibodies that were derived by immunization, and typically require

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expensive and time-consuming processes and advanced manufacturing facilities. The median development time from discovery to approval for antibody therapies in general has been over 10 years,[5] with some notable recent exceptions in the context of COVID-19 therapeutics. The high cost of producing antibodies during outbreaks can be especially challenging in low- and middle-income countries.[23] Further, the rapid emergence of escape variants in major infectious disease outbreaks is another major challenge for the development and delivery of antibody treatments in a timely manner.

Solutions are already being explored to address some of these challenges. One approach is the development of bispecific and multispecific antibodies that bind to two or more epitopes, which can be on different pathogens or also different parts of the same pathogen. This can allow the antibody to inhibit multiple pathways or engage distinct cellular mechanism to treat diseases such as HIV-1[24] or tuberculosis.[25] Blocking multiple targets typically could slow mutational escape, as a variant would need multiple escape mutations to evolve resistance to more than one of the targeting arms.[26] Another promising approach is the design and development of "universal" antibodies that target conserved regions of viruses or bacteria, making them much less susceptible to mutational escape during an infectious disease outbreak. This strategy requires the identification of highly conserved epitopes but can be difficult because highly conserved epitopes are often buried within pathogenic proteins, making them difficult to access.[27,28] An excellent example of this approach is the work to develop broadly neutralizing antibodies that target the conserved stem region in the influenza HA spike protein[29] (Figure 3 inset). Accelerating the identification of antibodies from survivors of infectious diseases, in combination with the use of next-generation sequencing (NGS) technologies, is yet another rapid path to antibody discovery since these antibodies are potentially already derisked from a safety perspective.[30,31]

Even with the emergency approval of antibody therapeutics during the COVID-19 pandemic, over a year after discovery was still required to obtain emergency approval. Because of the rapid mutation rate of SARS-CoV-2, by the time these therapies were approved, they were no longer effective against the strains circulating at that time. One potential idea would be to anticipate the future mutations through monitoring global viral strain patterns, experimental evolution, and deep mutation scanning to identify the potential strains with the greatest likelihood of developing into a global threat.[32] This approach has been applied to vaccines to anticipate future strains and could be extended to create a library of antibodies ready to deploy when a new variant of concern is identified.[33]

Although not the focus of this review, it is important to note that technologies for antibody discovery from patient samples and immunization have seen dramatic advances over the past decade.[30,34] Rapid single-cell screening of both patient samples and immunized animals has become routine. Cells producing functional antibodies can be rapidly isolated and subsequently sequenced. NGS approaches and advancements in display technologies (phage, yeast, and mammalian display) have combined to both accelerate and broaden therapeutic antibody development.[35,36]

AI AND ANTIBODY DISCOVERY

Recent developments in artificial intelligence (AI) and its application to biochemistry bring a whole new set of opportunities that could further revolutionize the antibody discovery process.[37] Once approved therapies are deployed widely, AI-based methods can integrate data from clinical trials and real-world patient data to predict the outcomes of antibody therapies across different populations.[38] Additionally, AI may help identify which combinations of antibodies and other treatments (such as antivirals or antibiotics) are likely to be most effective, make real-time adjustments to therapeutic dosages, and suggest more effective therapeutic combinations. But can AI be used to dramatically accelerate the speed of the earliest stages of infectious disease therapeutic discovery? What if it were possible to bypass the lengthy process of antibody discovery that we currently have and rapidly design antibodies on-the-fly, *in silico*, ready for large-scale manufacturing as new antigens and new variants are identified? Is the collective knowledge gained about antigen−antibody interactions and the effects of various antibody therapies over the past 50 years sufficient to apply emerging AI-based tools to discover and deploy antibodies? If this can be done successfully and quickly, it may be an effective way to manage the challenge of viral escape.

Here, we explore this question in the context of the revolution in protein structure prediction and design catalyzed by the advent of tools such as AlphaFold and RFdiffusion.[39,40] Numerous recent publications suggest that some degree of *de novo* antibody design may be possible.[40,41] A recent publication reported generating antibody structures *de novo* using a fine-tuned version of RFdiffusion trained on additional antibody−antigen structure complexes; however, this method has a low success rate, and the resulting low-affinity antibodies required wet-lab-based affinity maturation to produce high-affinity antibodies. Related publications and preprints suggest that AI-driven design approaches may be more reliable if one could start with the known structures of an existing antigen−antibody pair, which lowers the degree of difficulty in improving the binding strength of a given antibody.[42−44] For example, Desautels et al. recently demonstrated the recovery of binding of an antibody against multiple SARS-CoV-2 Omicron variants with the use of previously generated structures to guide the antibody design.[43] Another approach has employed computational design principles[45,46] to introduce mutations into the known structure of proteins/antibodies and score them subsequently, combined with AI methods to select specific combinations of mutations from an exhaustive list of single-point mutations.[44]

To compare the predictive accuracy of AlphaFold3—the current state-of-the-art tool in structure prediction—we tested its performance on various reported protein complexes. These included 100 structures each for Fab, VHH, and scFv antibodies targeting the SARS-CoV-2 receptor-binding domain (RBD), influenza (HA1 or HA2), and HIV glycoproteins. For the Fab complexes, we focused exclusively on Fab-SARS-CoV-2 RBD complexes. Additionally, we assessed prediction accuracy for two other classes of complexes: those bound to designed ankyrin repeat proteins (DARPins) (limited to a sample size of 48 due to the availability of this class of structures in the Protein Data Bank) and 100 natural peptide complexes targeting a variety of proteins.[47] DARPins and natural peptides were chosen to test the ability of AlphaFold3 to predict non-antibody protein−protein complexes. We measured prediction accuracy using DockQ scores, which evaluate the ligand root-mean-square deviation (LRMSD), interface RMSD (iRMSD), and the fraction of native interfacial

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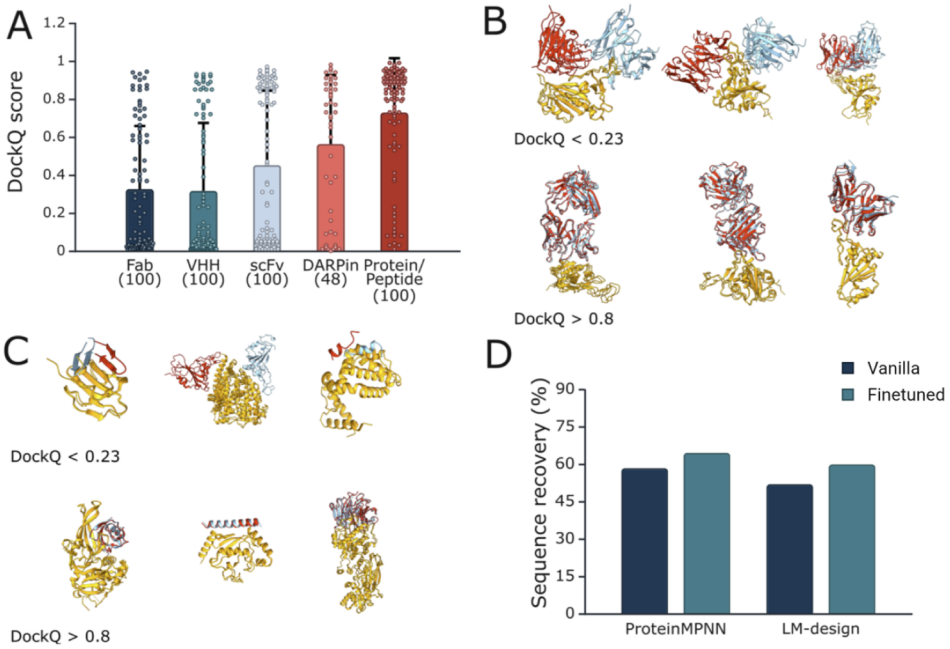

Figure 4. (A) Comparison of the prediction accuracy of AlphaFold3 for different binder types assessed using DockQ scores. The column heights and error bars for each group represents the mean and standard deviations, respectively. Each point in the graph represents the score for a single complex. The number of samples (N) is shown at the bottom for each group. (B, C) Representative predicted structures, with the antigen shown in gold, the predicted binder in red and the experimentally determined structure in cyan. Panel (B) structures are for VHH, scFv, and Fab binders and Panel (C) structures are for protein/peptide binders. The top row of structures in panels (B, C) show selected examples with DockQ scores <0.23 where there are large deviations between the predicted and experimentally observed structures, while the bottom row of structures show selected examples with DockQ scores >0.80 where there is a close match between the predicted and experimentally observed structures. (D) Sequence recovery (percent of correct amino acids in the prediction as compared to ground truth structures) from 1000 CDR H3 predictions of a SARS-CoV2 RBD binding antibody using vanilla (blue) or fine-tuned (teal) ProteinMPNN and LM-Design.

contacts (FNAT) that is maintained in the predicted complex relative to the experimentally determined structures. The DockQ score quantitatively measures the match between the predicted and experimentally determined structures, with values ranging from 0 (lowest accuracy) to 1 (highest accuracy).[42]

A summary of the trends in prediction accuracy is presented in Figure 4A. For the prediction of complexes with antibody-based moieties (Fabs, scFvs, and VHHs), the resulting DockQ scores show a wide range of variability in prediction success, with many that are far from the experimentally observed structures of the complexes. These results demonstrate the known challenges that even the state-of-the-art prediction tool, AlphaFold3, faces in predicting antibody−antigen complexes.[48,49] Among the antibody types, scFv predictions slightly outperformed VHHs and Fabs, though not in a statistically significant manner, suggesting comparable performance across all three binder types. AlphaFold3 performs better with DARPin complexes, but we observed the best performance with the prediction of natural protein and peptide complexes. In this latter class, binding typically is mediated via regular structural elements such as α-helices and β-strands, in contrast to the flexible complementarity-determining region (CDR) loops involved in the binding of antibodies, providing a plausible structural explanation for the differences in prediction accuracy.

Another way to assess the feasibility of the *de novo* design of antibodies is to evaluate the likelihood of generating the correct amino acid sequence in the CDR to induce binding to the target. The computational tool that has demonstrated the greatest success so far in addressing this "inverse folding" problem (i.e., the problem of *de novo* generation of a successful binder) is ProteinMPNN.[50] Used by the Baker group in their RFdiffusion workflow, ProteinMPNN has successfully generated small protein binders against numerous targets. The performance of tools such as ProteinMPNN can be quantified by the relative success with which the correct sequence of a known binder can be recovered. The sequence recovery score for ProteinMPNN was originally reported to be 52.4%.[50] However, this value was obtained after training the model on the entire PDB database, where the majority of structures of complexes are unrelated to typical antigen−antibody complex interfaces.

Restricting the foundation model to using a database containing only the known structures of antigen−antibody complexes can provide a more specific assessment of the accuracy of sequence recovery for antigen−antibody complexes. This strategy can improve outcomes and has recently been applied to some inverse folding models, such as AbMPNN for ProteinMPNN[51] or Antifold for ESM-IF1.[52] The improvements in these instances were modest, but the significant diversity in the nature and folded structure of the antigens may have limited the general applicability of this approach. To assess whether an even finer tuning of the data set could improve sequence predictions, we tested whether we could enhance the success of sequence recovery by restricting the training to a subset of similar antigen−antibody complexes where there is minimal structural variation in the antigen. Using a reference data set of 200 published RBD-antibody complexes at reported resolutions higher than 3.2 Å, we fine-tuned ProteinMPNN[50] and LM-Design, a combined protein language model that uses ProteinMPNN to inform structure.[53]

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Both of these models were used to predict residues in CDR H3 of an RBD-binding antibody that was not included in the training set. We observed a slight improvement in the accuracy with which the correct sequence can be recovered by using this more restrictive data set for training (Figure 4B).

These computational experiments, as well as the published literature to date, suggest that the successful *de novo* prediction of antibody binders is a field still in its infancy. However, the pace of progress is rapid, as evidenced by increasingly sophisticated models being reported. The slight increase we observe in the success of sequence recovery (Figure 4B) using a relatively small set of closely related structures leads to the intriguing hypothesis that there is room for further improvement in the prediction of sequences that bind if the training data set could be expanded, as the model can learn more from the additional data to better capture the relationship between sequence and structure. The data set of publicly available RBD structures contains various mutations in the SARS-CoV-2 spike protein that have emerged during the COVID-19 pandemic. It is thus conceivable that doubling or tripling the number of RBD-antibody complexes in the structural database may result in meaningful improvements in the prediction of antibody sequences that bind to future SARS-CoV-2 variants.

FUTURE PERSPECTIVE

Treatment of infectious diseases with therapeutic antibodies, especially in the absence of a vaccine, could be an important tool in our arsenal to treat infectious diseases. Integration of next-generation sequencing, display technologies, and AI-based methods could reduce the time required for development of the antibodies and enhance the efficacy. The generation of bispecific antibodies, which can engage more than one target and/or influence multiple immune pathways also presents new therapeutic possibilities. However, traditional antibody discovery workflows and timelines are inherently reactive and not conducive to proactively developing therapies in response to a pandemic. To prepare for future pandemics, it will be essential to develop effective proactive approaches that enable a rapid response. In all likelihood, the next pandemic will likely arise from a known virus family; therefore, the generation of a large libraries of neutralizing antibodies against each family could be a good strategy to roll out therapeutics rapidly. However, one of the greatest challenges during the COVID-19 pandemic was the rapid rate at which escape mutations emerged, resulting in a quick loss of efficacy of vaccines and antibody therapies over the course of months. As the success of AI-driven predictive strategies improves, in a few years, it may be possible to generate antibodies "on-the-fly" by effectively leveraging existing databases of structures of related antigens. An even more ambitious goal would be to extend this further and use AI-based methods to anticipate viral evolution and preemptively design an arsenal of potential therapeutic antibody- or protein-based therapeutics to enable health care providers to switch to a proactive response for viral outbreaks. We do not know when the next pandemic will strike, but our success in managing future pandemics will depend on having a multiplicity of both prophylactic and therapeutic strategies readily available.

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Notes

The authors declare the following competing financial interest(s): S.S. is the founder and CEO of Gandeeva Therapeutics, a drug discovery company based in Vancouver, Canada. L.F. was previously an employee of Gandeeva Therapeutics. J.S. is an employee of Meso Scale Diagnostics, a biotechnology company in Rockville.

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