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MINIREVIEW

# Antibody-Mediated Catalysis in Infection and Immunity

Anthony Bowen,[a] Maggie Wear,[b] Arturo Casadevall[b]

Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, New York, USA[a]; Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA[b]

**ABSTRACT** The existence of catalytic antibodies has been known for decades. Natural antibodies capable of cleaving nucleic acid, protein, and polysaccharide substrates have been described. Although the discovery of catalytic antibodies initially aroused great interest because of their promise for the development of new catalysts, their enzymatic performance has been disappointing due to low reaction rates. However, in the areas of infection and immunity, where processes often occur over much longer times and involve high antibody concentrations, even low catalytic rates have the potential to influence biological outcomes. In this regard, the presence of catalytic antibodies recognizing host antigens has been associated with several autoimmune diseases. Furthermore, naturally occurring catalytic antibodies to microbial determinants have been correlated with resistance to infection. Recently, there has been substantial interest in harnessing the power of antibody-mediated catalysis against microbial antigens for host defense. Additional work is needed, however, to better understand the prevalence, function, and structural basis of catalytic activity in antibodies. Here we review the available information and suggest that antibody-mediated catalysis is a fertile area for study with broad applications in infection and immunity.

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Address correspondence to Arturo Casadevall, acasade1@jhu.edu.

In 1969, as Kabat, Tonegawa, and many others were elucidating the mechanistic basis for the antibody (Ab) molecule's remarkable paratope diversity, the enzymologist William Jencks theorized that it should be possible to prepare antibodies capable of catalyzing chemical reactions (1). Jencks' rationale was based on the theory developed by Linus Pauling that enzymes functioned by stabilizing transition-state intermediates, thus lowering the activation energy and increasing the rate of chemical reactions (2). On the basis of the ability of antibodies to specifically recognize nearly any antigen, Jencks proposed that antibodies developed against a transition-state analogue (TSA) for a chemical reaction would theoretically function as enzymes by stabilizing the intermediate species, lowering the activation energy, and increasing the reaction rate. An experimental demonstration of this idea first appeared in 1975 with the production of antibodies to a haptenic TSA that catalyzed the transamination of L-tyrosine (3). Over the next 2 decades, the TSA-immunization approach was used to generate many antibodies capable of catalyzing a wide range of chemical reactions, including group transfers, additions, eliminations, oxidations, reductions, aldol condensations, pericyclic processes, and cofactor-dependent reactions (4). A related strategy was also developed by generating anti-idiotypic antibodies to enzymes as internal images of enzyme active sites (5, 6).

The early stages of the catalytic antibody field were permeated with excitement, as researchers envisioned the ability to generate selective, programmable catalysts for any chemical reaction compatible with a biological environment, as long as a suitable TSA could be designed. While this strategy allowed the generation of selective catalysts for reactions where traditional chemical methods have proved ineffective, its practicality

was frequently limited by low reaction rates. Catalytic antibodies are frequently described in terms of their Michaelis constant ($K_m$), turnover number ($k_{cat}$), and catalytic efficiency ($k_{cat}/K_m$). Much of the early catalytic antibody work focused on improving reaction velocity through TSA design, structural modification of the paratope, and improved screening of antibody candidates (4). However, these efforts were met with only modest success as even the best candidates have $k_{cat}/K_m$ values near $10^2$ to $10^4$ $s^{-1}$ $M^{-1}$ (4). By comparison, the fastest enzyme reactions have $k_{cat}/K_m$ values near the diffusion-controlled limit of $10^8$ $s^{-1}$ $M^{-1}$, although a recent review of the literature found that the average enzyme efficiency is much lower ($10^5$ $s^{-1}$ $M^{-1}$) (7). Comparing enzymes to antibodies by the use of the $k_{cat}/K_m$ value can also be somewhat misleading, as this value is related to the speed of catalysis under conditions of limiting substrate concentrations. Although antibodies typically have higher substrate affinities than enzymes, leading to $K_m$ values that are $10^1$-fold to $10^3$-fold lower, their $k_{cat}$ values are usually much ($10^3$-fold to $10^5$-fold) lower than those of enzymes. $k_{cat}$ represents the inherent reaction rate of an enzyme in the presence of excess substrate; thus, antibodies may have measures of catalytic efficiency similar to or slightly lower than those of enzymes but may still exhibit markedly lower rates of substrate conversion. The difficulty of generating sufficient amounts of antibody in a cost-effective manner has proven to be yet another barrier. Given the low catalysis rates of most catalytic antibodies, relatively high concentrations on the order of 10 $\mu$M (about 1.6 mg/ml for IgG) are needed for effective catalysis (4, 8). These challenges tempered the excitement surrounding the use of antibodies as a general-purpose tool for efficiently catalyzing chemical reactions.

## NATURALLY OCCURRING CATALYTIC ANTIBODIES

In 1989, a study by Paul et al. described autoantibodies isolated from human sera that hydrolyzed vasoactive intestinal peptide (VIP) (9). That study provided the first indication that antibodies possessing catalytic activity can be produced *in vivo* without immunization with an artificial hapten. Earlier reports had already found that immunization with ground-state haptens could lead to the formation of rate-accelerating antibodies, suggesting that the use of artificial TSAs was not required in all cases (3, 10–12). That work was soon followed by the isolation of numerous catalytic antibodies from patients with various autoimmune pathologies (13–21). In contrast to the diversity of chemical reactions catalyzed by artificially generated antibodies, naturally occurring catalytic antibodies have predominately been found to carry out hydrolysis of peptide and phosphodiester bonds in protein or nucleic acid substrates. A recent report by our group also identified a natural antibody capable of hydrolyzing polysaccharide (22). Mechanistic studies have shown that at least some naturally occurring catalytic antibodies make use of hydrolytic mechanisms similar to those generated artificially with the TSA immunization approach (23, 24). Although natural catalytic antibodies appear to carry out a more limited repertoire of reactions, kinetic studies indicate that they often have measures of $K_m$, $k_{cat}$, and catalytic efficiency similar to those shown by their synthetic counterparts (Table 1). Early reports often linked the presence of catalytic antibodies to pathogenic roles, but recent studies have also suggested that some naturally occurring catalytic antibodies play positive roles in homeostasis, autoimmunity, and microbial defense (29, 30, 36–42).

Despite the number of studies identifying catalytic antibodies in patients, whether this catalytic activity is selected for during somatic diversification or resides within the germ line immunoglobulin genes remains an unresolved issue. Catalytic activity has been characterized in both constitutively produced antibodies and those that have undergone affinity maturation (43). The necessity for extended B cell receptor (BCR) occupancy in triggering an antibody response suggests that B cell selection is unlikely to be a successful mechanism for increasing catalytic rates to levels approaching those of enzymes, since rapid antigen catalysis would limit BCR occupancy. However, it is possible that selection for slow nucleophiles occurs

**TABLE 1** Kinetic efficiency of disease-related catalytic antibodies[a]

| Disease or microbe or molecule | Antibody | Moiety | Target | Reaction rate ($k_{cat}$) | Ab type | Reaction efficiency ($k_{cat}/K_m$) | Reference |
|---|---|---|---|---|---|---|---|
| HIV | 41S-2-L (IgG2b) | Light chain | gp41 (TP41-1) | 0.06 $min^{-1}$ | Ground-state antigen | $2.86 \times 10^5$ $M^{-1}$ $min^{-1}$ | 25 |
| *S. aureus* | Poly-IgG | Whole Abs | Efb | Not reported | Natural antibodies | $1.77 \times 10^5$ $M^{-1}$ $min^{-1}$ | 26 |
| Addiction | GNT Abs | Whole Abs | Cocaine | 0.1989 $min^{-1}$ | Transition-state analog antigen | $1.63 \times 10^7$ $M^{-1}$ $min^{-1}$ | 27 |
| Addiction | 15A10 (IgA) | Whole MAb | Cocaine | 2.3 $min^{-1}$ | Transition-state analog antigen | $1.0 \times 10^4$ $M^{-1}$ $min^{-1}$ | 28 |
| HIV | Yvo (IgM) | Whole Ab | gp120 | 0.04 $min^{-1}$ | Natural antibody | $2.8 \times 10^4$ $M^{-1}$ $min^{-1}$ | 29 |
| HIV | Poly-sIgA | Whole Abs | gp120 | Not reported | Natural antibody | $1.1 \times 10^4$ $M^{-1}$ $min^{-1}$ | 30 |
| Alzheimer's disease | 2E6 (nat. IgV) | Variable domain construct | A$\beta$-40 | 8.2 $min^{-1}$ | Natural antibody | $3.3 \times 10^6$ $M^{-1}$ $min^{-1}$ | 31 |
| Asthma | Poly-IgG | Whole Ab | VIP | 15.6 $min^{-1}$ | Natural antibody | $4.1 \times 10^7$ $M^{-1}$ $min^{-1}$ | 9[b] |
| Breast cancer | 3D8 $V_L$ variant | Light chain | Her2/neu mRNA | 0.102 $min^{-1}$ | Variant of natural antibody | $1.81 \times 10^5$ $M^{-1}$ $min^{-1}$ | 32 |
| Hashimoto's thyroiditis | Tg-Ab (IgG) | Whole Ab | Thyroglobulin | 0.0039 $min^{-1}$ | Natural antibody | $1.0 \times 10^5$ $M^{-1}$ $min^{-1}$ | 14 |
| *H. pylori* | UA15-L | Light chain | UreB (TP41-1) | 0.24 $min^{-1}$ | Ground-state antigen | $3.87 \times 10^3$ $M^{-1}$ $min^{-1}$ | 33 |
| *Cryptococcus neoformans* | 18B7 (IgG1) | Whole Ab | GXM | 0.6 $min^{-1}$ | Ground-state antigen | $3.67 \times 10^4$ $M^{-1}$ $min^{-1}$ | 22 |
| Influenza virus | 22F6-L | Light chain | pBR322 | 0.0101 $min^{-1}$ | Ground-state antigen | $2.31 \times 10^4$ $M^{-1}$ $min^{-1}$ | 34 |
| Enzyme[c] | Trypsin | NA | ZLNPE | $3.0–8.4 \times 10^3$ $min^{-1}$ | NA | $1.2 \times 10^1–9.42 \times 10^4$ $M^{-1}$ $min^{-1}$ | 35 |

[a]nat. IgV, natural Ig variable domain construct; GNT, a transition-state hapten cocaine analogue; NA, not applicable.

[b]In this reference, $k_{cat}$ was computed based on a VIP-specific IgG subset, while for other studies of polyclonal antibodies, it was computed based on the total isotype concentration.

[c]Kinetic data for trypsin hydrolysis of $\alpha$-benzyloxycarbonyl–L-lysine-*p*-nitrophenyl ester (ZLNPE) are shown for a range of pH values from 2.55 to 7.80 with the highest rates at the highest pH (35).

during somatic diversification based on the observation that immunization with artificial electrophiles can induce proteolytic antibodies (43–45). This is presumed to occur through covalent attachment to BCR nucleophilic residues. Along these lines, the standard proteolytic mechanism proceeds through a covalent intermediate that may exist long enough in the presence of a slow catalyst to influence B cell selection. Another possibility proposed in the literature involves BCR signal transduction operating through an unknown mechanism making use of the free energy released from antigen hydrolysis (43).

## STRUCTURAL BASIS FOR CATALYTIC ACTIVITY IN ANTIBODIES

While many naturally occurring catalytic antibodies have been identified, the mechanism of their activity remains poorly understood. Only a small number of studies have successfully identified antibody residues that specifically confer catalytic activity. Two examples of antibodies with peptidase activity were shown to use a serine protease-like triad in the light-chain variable region ($V_L$) with D1, S27a, and H93, using Kabat numbering (24, 46, 47). Another was described using a distinct mechanism involving the generation of $H_2O_2$ from the oxidation of water (48, 49). Other antibodies have been characterized with thiol-, acid-like, and metal-dependent proteolytic activity, but the exact mechanism has not been elucidated (50, 51). Naturally occurring catalytic antibodies with the D1-S27a-H93 serine protease-like triad represent perhaps the best-understood group, with several studies illustrating a $V_L$ germ line origin for these catalytic residues in several kappa V region gene families based on sequence alignments of proteolytic antibodies (25, 52, 53). In the catalytic split-site model, catalysis occurs via a two-step process involving noncovalent binding followed by catalytic cleavage at two coordinated but distinct sites of activity within the catalyst (43). The hypothesis that some antibodies use this model is supported by the observation that certain mutations in the V region of a VIP-hydrolyzing antibody reduced affinity for the substrate but did not affect catalytic efficiency as measured by $k_{cat}/K_m$ (24, 54). The reduced substrate affinity was offset by an increase in $k_{cat}$, which was attributed to a reduction in ground-state stabilization. This result suggests that the mutated residues important in binding the ground-state substrate are distinct from those involved in stabilizing the transition-state intermediate and catalyzing hydrolysis.

## CATALYTIC AUTOANTIBODIES AND DISEASE

Naturally occurring catalytic antibodies have been implicated in both pathogenic and beneficial roles in a variety of autoimmune diseases. The extent and importance of catalytic activity in the antibody repertoire, however, remain matters of debate. While the reaction rates of catalytic antibodies are typically several orders of magnitude lower than those of typical enzymes, catalytic antibodies are found in the serum at much higher concentrations (1 to 10 mg/ml) and can persist with very long half-lives (1 to 3 weeks) (55–57). This raises the possibility that the combination of increased antibody concentration and longer duration of action compensates for low catalysis rates, especially in the case of chronic illness or latent infection, and that the catalytic activity of naturally occurring antibodies may play an important role in illness and immunity. Antibody-mediated DNA and RNA hydrolysis was associated with patients suffering from autoimmune diseases. The DNA-cleaving activity of antibodies is correlated with both disease severity in systemic lupus erythematosus (SLE) and cytotoxicity to tumor cell lines (13, 58, 59). Proteolytic antibodies that hydrolyze thyroglobulin with a nanomolar Michaelis constant ($K_m$) have been implicated in autoimmune thyroiditis (14). The first identified natural catalytic antibody hydrolyzed host VIP, a peptide neurotransmitter involved in smooth muscle relaxation. It was hypothesized that catalytic degradation of VIP could contribute to airway hyperresponsiveness in asthma (9). Several other studies have found catalytic activity in human Bence Jones proteins (BJPs), which are aggregates of monoclonal light chains produced by neoplastic plasma cells and commonly found in the urine of patients with multiple myeloma or Walden-

ström's macroglobulinemia (15, 16). Renal damage is a common complication of these cancers and is thought to be due to the cytotoxicity of BJP aggregates. Studies have correlated the catalytic activity of BJPs with renal damage in multiple myeloma patients and have also shown that inhibition of catalysis results in decreased *in vitro* cytotoxicity (17). These results suggest that BJP catalytic activity has a direct role in renal damage. The catalytic activity of antibodies with respect to myelin basic protein was previously correlated with disease severity in multiple sclerosis (60). Hemophilia A patients have also been found to have high levels of proteolytic autoantibodies to procoagulant factor VIII, potentially worsening their coagulopathy (20, 61). On the other hand, some patients with acquired hemophilia were shown to possess catalytic antibodies capable of activating procoagulant factor IX, which could lead to improved hemostasis (37). Amyloid $\beta$-hydrolyzing antibodies have also been characterized in human sera, with results suggesting that some catalytic antibodies may play a homeostatic role and offer protection from Alzheimer's disease (AD) (38).

## CATALYTIC ANTIBODIES TO MICROBES

Numerous studies have suggested that catalytic antibodies function in microbial defense. The presence of serine protease-like IgG activity is correlated with positive outcomes in sepsis, possibly by limiting inflammation (62). Catalytic antibodies to DNA, RNA, and protease-activated receptor-2 (PAR-2) are found in the breast milk of healthy human mothers, possibly affording protection against infection (36, 39, 40). Polyclonal IgG preparations cause cleavage of the *Staphylococcus aureus*-secreted virulence factor extracellular fibrinogen-binding protein (Efb) (26). Secretion of urease by *Helicobacter pylori* is essential for colonization of the gut and results in neutralization of stomach acidity. Catalytic monoclonal antibody (MAb) UA15 was shown to cleave *H. pylori* urease and to decrease CFU levels per gram of stomach tissue in infected mice (33). One of the virulence factors of the pathogenic fungus *Cryptococcus neoformans*, the polysaccharide capsule, is targeted by several antibodies that have been found to possess catalytic activity. Results from our laboratory have shown that MAb 3E5 and several isotype-switch variants hydrolyze a peptide antigen mimetic of capsular polysaccharide (63, 64). The similar 18B7 MAb, which was considered a therapeutic candidate for *C. neoformans* infection, also possesses peptidase activity (22, 65). Of greater biological relevance, 18B7 was found to possess glycosidic activity against an oligosaccharide antigen mimetic and was found to alter the structure of the polysaccharide capsule consistent with capsule hydrolysis after prolonged incubation (22). A number of studies have also characterized naturally occurring catalytic antibodies to specific viral proteins, including HIV gp120 and integrase (29, 30, 39, 41, 42, 44, 50, 66). The results from those studies, performed with antibodies to *S. aureus*, *H. pylori*, *C. neoformans*, and HIV antigens, suggest that antibody-mediated catalysis may play a role in the natural humoral response to infection.

## THERAPEUTIC DEVELOPMENT OF CATALYTIC ANTIBODIES

Several catalytic antibodies have been characterized and studied with the intention of producing therapeutic applications. The 18B7 MAb was studied in a phase I clinical trial for the treatment of *C. neoformans* infection, although its catalytic activity was not known at the time (65). Catalytic antibodies targeting influenza virus (34, 67), rabies virus (53), and HIV (68) are currently in early development but show potential for future applications. Another catalytic antibody generated using a synthetic randomized peptide library was found to hydrolyze Her2 mRNA in breast cancer cells, indicating a potential therapeutic role in gene silencing (32).

Outside the realm of infectious disease, efforts are under way to develop catalytic antibody therapies for cocaine addiction and Alzheimer's disease (AD). The psychoactive and addictive properties of cocaine have led researchers to develop inhibitory therapies, including the use of cocaine-hydrolyzing antibodies (69–72). A recent therapeutic strategy that has met moderate success in mice is based on eliciting a catalytic antibody response to cocaine with a haptenic vaccine (27). Aggregation-associated

neurodegenerative diseases such as AD are characterized by protein or peptide aggregates that are thought to contribute to neuron death. Recent work by numerous groups has led to the identification of monoclonal (31, 38, 73) and polyclonal (74) antibodies with peptidase activity against the amyloid $\beta$-40 (A$\beta$-40) and A$\beta$-42 peptides, which are prevalent in AD protein aggregates. Some of those studies showed that hydrolysis of A$\beta$-40 and A$\beta$-42 by antibodies occurs within alpha-helix regions (amino acids 15 to 24 and 28 to 36) (38) and reduces A$\beta$ plaque burden in brain tissue (31). A$\beta$ aggregates are cleaved by a serine protease-like mechanism, with at least one antibody construct possessing metal dependence with the requirement of $Zn^{2+}$ or $Co^{2+}$ cofactors (73, 75). A$\beta$ hydrolytic activity can be found in the innate antibody repertoire and is being investigated for therapeutic applications (31).

HIV infection of CD4 cells requires the binding of HIV surface glycoprotein gp120 to the CD4 receptor. Both IgG and IgM MAbs have been shown to possess peptidase activity against gp120 (30, 44, 68). Prolonged HIV infection in patients who do not progress to AIDS is associated with a modest increase in catalytic secretory IgA (sIgA) to gp120 (68). This activity has also been found in sIgA from individuals without prior HIV infection, suggesting a role in resistance to infection (30). HIV envelope glycoprotein gp41, which mediates viral membrane fusion to host cells, is another target for catalytic antibody development (25). Purified light chains from the IgG2b MAb 41S-2-L are able to cleave the TP41-1 peptide, which mimics a highly conserved region of gp41 (76). When the reaction was monitored over 120 h, a slow-step or induction phase was observed between 0 and 50 h (77). Interestingly, when additional TP41-1 substrate was added at 135 h, this slow step did not occur (25). The presence of an induction phase is thought to be due to a necessary structural conformation change such as induced fitting.

The reaction rates of several characterized catalytic antibodies seem quite low in comparison to those seen with classic enzymes (Table 1). However, considering the high concentrations of antibody in serum, antibody-mediated catalysis can be viewed as therapeutically applicable. For example, Planque and colleagues estimated that a catalytic sIgA to HIV gp120 used at a physiologic concentration of 0.3 mg/ml could cleave 90% of the viral protein in 5 min in the presence of $10^6$ HIV/ml with an estimated 100 gp120 molecules per virion (30). Viewing catalytic antibodies in this light, their potential therapeutic applications are much more favorable. Irrespective of their ultimate applicability in passive immunotherapy, the capacity of natural antibodies to hydrolyze antigens is an important consideration in evaluating their potential role in infection and immunity. While it has been documented that circulating antibodies occur at concentrations between 1 and 10 mg/ml, the typical levels of circulating catalytic antibodies are not known. It has also been found that rare catalytic antibodies present in polyclonal preparations may be responsible for most of the sample's catalytic activity. Thus, purifying and concentrating these rare antibodies should lead to the availability of antibody preparations with increased catalytic rates.

One of the most important implications from the findings in antibody-mediated catalysis is the possibility that many therapeutic or nontherapeutic antibodies might have the capacity to cleave antigen. A structural template-matching algorithm developed by our group was used to identify antibody structures in the Protein Data Bank (PDB) that contained a putative hydrolytic motif present in the catalytic 3E5 MAb to *C. neoformans* (22). Antibody structures were compared to a mean template motif generated from a serine protease-like triad identified in the 3E5 $V_L$ at positions D1-S26-H93 (using Kabat numbering) (63). We found that this motif was enriched in known catalytic antibody structures (14 of 63, 22.2%) and present in a substantial proportion of antibodies with no prior annotation of catalytic activity (119 of 1,602, 7.4%), 30 of which bind microbial antigens or are involved in microbial neutralization (Table 2). Although such predictions must be confirmed experimentally, distinct catalytic motifs are likely present in many other antibody lineages. If even a subset of antibodies with putative hydrolytic motifs possess catalytic activity, their existence would introduce new dimen-

**TABLE 2** Antibodies to infectious disease-related antigens predicted to have catalytic activity by a structural template algorithm[a]

| PDB ID | Description | Isotype | Natural antigen | Triad motif[b] | RMSD (Å)[c] | Structure resolution (Å) | Disease association | Reference |
|---|---|---|---|---|---|---|---|---|
| 4HXB | 6B9 group B meningococcal anticapsular polysaccharide | IgG2a | N-Propionylated polysialic acid | D1L-H93L-S26L | 0.386 | 2.45 | *Niesseria meningitidis* infection | 78 |
| 4HDI | 3E5 anti-GXM *Cryptococcus neoformans* | IgG3 kappa | GXM | D1L-H98L-S26L | 0.489 | 2.45 | *Cryptococcus neoformans* infection | 79 |
| 3JAU | D5 against enterovirus 71 | IgG | Surface-exposed VP1 | D1L-H98L-S26L | 0.634 | 4.8 | EV 71 (HFMD) | 80 |
| 4HZL | MAb #8 HCV neutralizing anti-epitope II | IgG | Envelope glycoprotein E2 | D1L-H98L-S26L | 0.691 | 2.85 | Hepatitis C | 81 |
| 4WHT | MAb 3/11 HCV neutralizing anti-epitope II | Unknown | Envelope glycoprotein E2 | D1L-H98L-S26L | 0.432 | 2.22 | Hepatitis C | 82 |
| 2EH8 | Humanized kr127 anti-HBV | Unknown | Pre-S1 HBV surface protein | D1L-H93L-S26L | 0.532 | 2.6 | Hepatitis B | 83 |
| 1CL7 | 1696 anti-HIV protease | IgG1 | HIV-1 and HIV-2 protease | D1L-H93L-S26L | 0.574 | 3 | HIV infection | 84 |
| 1NAK | 83.1 anti-HIV-1 gp120 | IgG1 | HIV gp41 | D1L-H93L-S26L | 0.392 | 2.57 | HIV infection | 85 |
| 1NLD | 1583 anti-HIV gp41 | Unknown | HIV gp41 | D1L-H93L-S26L | 0.515 | 2.9 | HIV infection | 86 |
| 3LEX | 11F10 anti-HIV gp41 epitope scaffold | IgG2a kappa | HIV gp41 | D1L-H98L-S26L | 0.346 | 1.97 | HIV infection | 87 |
| 3LEY | 6a7 anti-HIV gp41 epitope scaffold | IgG2a kappa | HIV gp41 | D1L-H98L-S26L | 0.396 | 1.99 | HIV infection | 87 |
| 3NZ8 | 7C8 HIV-2 neutralizing anti-gp125 | IgG1 | HIV-2 gp125 | D1L-H93L-S26L | 0.47 | 2.7 | HIV infection | 88 |
| 3TCL | PG9 HIV neutralizing anti-gp120 | IgG | V1/V2 region of gp120 | D1L-H93L-S26L | 0.983 | 1.91 | HIV infection | 89 |
| 4YWG | 830A HIV neutralizing anti-gp120 | IgG3 | V1/V2 region of gp120 | D1L-H93L-S26L | 0.561 | 3 | HIV infection | 90 |
| 1QFU | Influenza virus neutralizing anti-hemagglutinin | IgG1 kappa | Influenza A virus hemagglutinin | D1L-H93L-S26L | 0.472 | 2.8 | Influenza A | 91 |
| 2AEP | Mem5 anti-neuraminidase (cryo) | IgG2b kappa | Neuraminidase | D1L-H93L-S26L | 0.502 | 2.1 | Influenza A (H3N2) | 92 |
| 2AEQ | Mem5 anti-neuraminidase (room temp) | IgG2b kappa | Neuraminidase | D1L-H93L-S26L | 0.698 | 3 | Influenza A (H3N2) | 92 |
| 5DLM | 148 Influenza virus neutralizing anti-M2e | IgG1 | M2 ectodomain | D1L-H98L-S26L | 0.464 | 2.2 | Influenza A (H3N2) | 93 |
| 4Q0X | MAb #12 HCV nonneutralizing anti-epitope II | IgG | Envelope glycoprotein E2 | D1L-H98L-S26L | 0.446 | 2.9 | Hepatitis C | 94 |
| 1FPT | C3 anti-poliovirus type 1 neutralizing | IgG2a kappa | Poliovirus 1 | D1L-H93L-S26L | 0.882 | 3 | Poliovirus infection | 95 |
| 1CR9 | 3F4 anti-prion | IgG2a | Syrian hamster PrP | D1L-H93L-S26L | 0.291 | 2 | Prion disease | 96 |
| 1TPX | Recombinant ovine variant VRQ | IgG2a kappa | Sheep PrP variant | D1L-H93L-S26L | 0.476 | 2.56 | Prion disease | 97 |
| 1RMF | Anti-ICAM-1 R6.5 blocking human rhinovirus | IgG2a kappa | ICAM-1 | D1L-H98L-S26L | 0.642 | 2.8 | Rhinovirus infection | 98 |
| 3QG6 | 24H11 anti-*Staphylococcus aureus* AIP | IgG | AIP-4 | D1L-H93L-S26L | 0.187 | 2.5 | *Staphylococcus aureus* (MRSA) infection | 99 |
| 3QG7 | 24H11 anti-*Staphylococcus aureus* AIP | IgG | AIP-4 | D1L-H93L-S26L | 0.281 | 2.78 | *Staphylococcus aureus* (MRSA) infection | 99 |
| 1M71 | SYA/J6 anti-O-polysaccharide, *Shigella flexneri* Y | IgG3 kappa | Capsular polysaccharide | D1L-H93L-S26L | 0.623 | 2.8 | *Shigella flexneri* Y infection (shigellosis) | 100 |
| 4PB0 | Ab53 anti-FtGroEL | IgG2a kappa | GroEL (HSP60) | D1L-H93L-S26L | 0.559 | 2.5 | *Francisella tularensis* infection (tularemia) | 101 |
| 4LU5 | A20G2 EEV anti-A33 | IgG2a | A33 glycoprotein | D1L-H98L-S26L | 0.513 | 2.9 | Vaccinia (orthopoxvirus) | 102 |
| 4U6H | M12B9 neutralizing EEV anti-L1 protein | IgG2a | Mature virus subunit L1 | D1L-H98L-S26L | 0.9 | 3.1 | Vaccinia (orthopoxvirus) | 103 |
| 5EOQ | 1G6 VACV neutralizing anti-A27 | IgG2a | A27 glycosaminoglycan | D1L-H98L-S26L | 0.682 | 1.95 | Vaccinia (orthopoxvirus) | 104 |

[a]The structural template algorithm used was developed by Bowen et al. (22). AIP, autoinducing peptide; cryo, cryoelectron microscopy; EEV, equine encephalosis virus; EV 71, enterovirus 71; FtGroEL, *Francisella tularensis* GroEL; HBV, hepatitis B virus; HCV, hepatitis C virus; HFMD, hand, foot, and mouth disease; HIV-1, human immunodeficiency type 1; ID, identifier; MRSA, methicillin-resistant *Staphylococcus aureus*; VACV, vaccinia virus.
[b]The first part of each triad motif designation indicates the residue on the corresponding chain. For example, notation D1L refers to residue D1 on the L chain.
[c]Data indicate root mean square deviation (RMSD) values determined from the mean catalytic motif template based on the proposed catalytic triad (D1L-H98L-S26L) (PDB ID 4HDI).

sions with respect to how antibodies mediate immunity and how these molecules can be exploited for therapeutic development.

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