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Immunity

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Perspective

Instructing durable humoral immunity for COVID-19 and other vaccinable diseases

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SUMMARY

Many aspects of SARS-CoV-2 have fully conformed with the principles established by decades of viral immunology research, ultimately leading to the crowning achievement of highly effective COVID-19 vaccines. Nonetheless, the pandemic has also exposed areas where our fundamental knowledge is thinner. Some key unknowns are the duration of humoral immunity post-primary infection or vaccination and how long booster shots confer protection. As a corollary, if protection does not last as long as desired, what are some ways it can be improved? Here, I discuss lessons from other infections and vaccines that point to several key features that influence durable antibody production and the perseverance of immunity. These include (1) the specific innate sensors that are initially triggered, (2) the kinetics of antigen delivery and persistence, (3) the starting B cell receptor (BCR) avidity and antigen valency, and (4) the memory B cell subsets that are recalled by boosters. I further highlight the fundamental B cell-intrinsic and B cell-extrinsic pathways that, if understood better, would provide a rational framework for vaccines to reliably provide durable immunity.

INTRODUCTION

In January of 2020, metagenomic sequencing identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as the etiological agent of pneumonia outbreaks in Wuhan (Wu et al., 2020; Zhou et al., 2020). This local epidemic rapidly turned into a global pandemic that, as of this writing, has led to over 400 million documented infections and 6 million deaths worldwide, both of which are almost certainly substantial underestimates of the true toll. In large part due to substantial presymptomatic transmission (Arons et al., 2020), non-pharmaceutical interventions proved less effective than they were against the first SARS-CoV in the early 2000s. The need was urgent for pharmaceutical interventions such as antiviral medications and vaccines. Remarkably, in less than a year since the identification of SARS-CoV-2, several different types of vaccines to protect against coronavirus disease 2019 (COVID-19) completed clinical trials and were authorized for use. Leading this class were the mRNA vaccines BNT162b2 and mRNA-1273, both of which reported efficacies of ~95% in preventing symptomatic illness (Baden et al., 2021; Polack et al., 2020). Other vaccines, including those that were based on replication-deficient adenoviral vectors, protein nanoparticles, or inactivated viruses also showed reasonable-to-high efficacies, especially against severe disease and hospitalization (Heath et al., 2021; Sadoff et al., 2021a; Tanriover et al., 2021; Voysey et al., 2021; Xia et al., 2021). It seemed that the pandemic would rapidly be put behind us. Unfortunately, this obviously has turned out not to be the case. For the purposes of this review, I will focus on the biological reasons for some of the dents in the armor of both vaccine- and infection-induced immunity.

As for many infections and almost all vaccines (Zinkernagel and Hengartner, 2006), neutralizing antibodies are the best immunological correlates and dominant mechanisms of protection against SARS-CoV-2 and COVID-19 (Gilbert et al., 2022; Khoury et al., 2021). As such, this perspective will primarily focus on perseverance of antibody responses, though as discussed later, neutralizing antibodies are unlikely to represent the sole mechanism of protection. Since the initial reports of high efficacies for vaccines and the relative infrequency of re-infections, these estimates of protection have progressively (and sometimes dramatically) declined. There are two main reasons for this. First, SARS-CoV-2 is evolving, with variants such as Omicron containing escape mutations in most known neutralizing antibody epitopes (Cele et al., 2022; Greaney et al., 2020, 2021a; Viana et al., 2022). Second, and in concert with the first point, despite relatively stable persistence of cellular memory (Dan et al., 2021; Goel et al., 2021; Rodda et al., 2021), neutralizing antibody production often declines to levels below what are needed for full protection. Frequent boosters every few months could conceivably maintain antibodies at high levels, but this does not seem like a realistic strategy going forward. In the U.S., roughly two-thirds of the population have received the primary vaccine series (which is an underwhelming number in and of itself), but only one-third have received a booster dose (CDC, 2020). Clearly, some more bang for the buck is needed for the vaccine doses that are administered. Whereas an initial decline in antibodies is fully expected in any immune response, a further decline in antibodies to background levels is very much not an inevitability (Amanna et al., 2007; Manz et al., 1997; Slifka et al., 1998). To begin to explain this point, a basic primer is needed on the cellular and molecular biology of antibody responses.

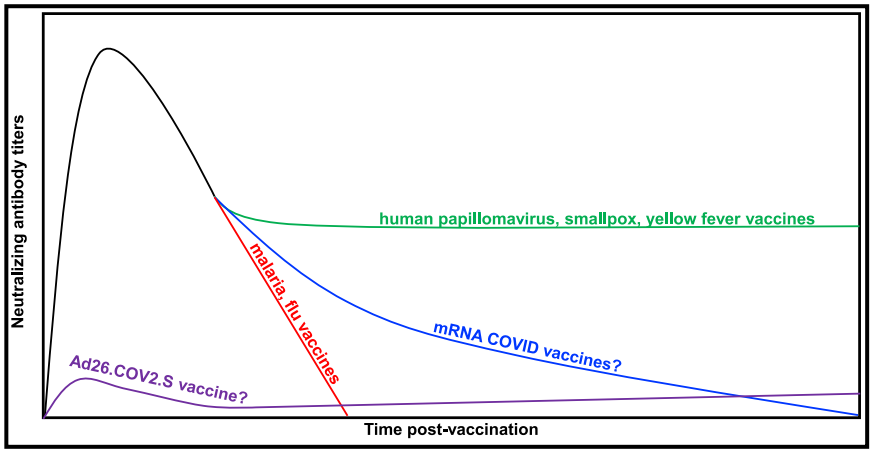

Figure 1. Duration of antibody production varies widely across vaccines

Most vaccines lead to a sharp rise and partial decline in antibody levels after the final dose of the primary series (black line). Afterwards, the rate of decline varies greatly. Human papillomavirus, yellow fever, and smallpox vaccines induce durable antibody production (green line), whereas the malaria and influenza vaccines lead to very transient antibody levels (red line). The kinetics of antibody production for the COVID-19 vaccines differ from each other. Whereas the BNT162b2 and mRNA-1273 vaccines induce a sharp rise in antibodies, this is followed by a prolonged decline phase (blue line). Ad26.CoV2.S yields lower initial titers, but more stable maintenance (purple line).

CELLULAR STEPS TO HUMORAL IMMUNITY

During a canonical T cell-dependent antibody response, recognition of cognate antigen by naive B cells leads to activation and differentiation to several possible fates: early memory B cells, antibody-secreting plasma cells, and germinal center B cells (Taylor et al., 2015). These early memory B cells are functionally and transcriptionally very similar to their naive precursors but are expanded in numbers and maintained stably (Pape et al., 2011; Taylor et al., 2012; Tomayko et al., 2008; Zuccarino-Catania et al., 2014). Presumably, these expanded frequencies increase the chances that antigen will be encountered quickly upon re-exposures, but it is not obvious that these early memory B cells are intrinsically more capable of rapid responses than are their naive counterparts. Early antibody-secreting cells, termed plasmablasts unless and until they exit cell cycle to become plasma cells (Kallies et al., 2004), are primarily localized to the extrafollicular regions of secondary lymphoid organs and collectively produce huge quantities of antibodies (Fagraeus, 1948; Sze et al., 2000). These early plasmablasts and plasma cells rapidly die by apoptosis such that their average lifespan is only a few days (Smith et al., 1994; Sze et al., 2000). Most of the antibodies they produce are encoded by germline sequences and are therefore of modest affinities (Eisen and Siskind, 1964; Jacob et al., 1991a), but by mass action, these early plasma cells can keep the infection under control until higher quality antibodies are refined in the germinal center reaction. Within germinal centers, B cells accumulate somatic mutations in their antibody receptor genes and are selected predominantly for clones that have accumulated affinity-enhancing changes (Jacob et al., 1991b, 1993; Weigert et al., 1970). Germinal center B cells that have acquired affinity-enhancing mutations can then differentiate into one of several lineages of memory B cells or into plasma cells (Victora and Nussenzweig, 2022). Importantly, as the affinity of the antibodies increases progressively, so too does the lifespan of the post-germinal center plasma cells (Han et al., 1995; Weisel et al., 2016). These two traits might or might not be directly linked (Gitlin et al., 2016; Wong et al., 2020), but the end result is the emergence of long-lived plasma cells that secrete highly avid antibodies. Numerically, these post-germinal center plasma cells, many of which migrate to the bone marrow, are far less abundant than the extrafollicular antibody-secreting cells formed early in the response (Benner et al., 1981; Manz et al., 1997; Slifka et al., 1998; Sze et al., 2000). Yet because of higher antibody avidity and a greater secretory rate than that of their short-lived counterparts (Lam et al., 2018), relatively fewer long-lived plasma cells are required to durably maintain humoral immunity (Purtha et al., 2011).

What exactly does "durable" mean? Here, substantial complexity enters the equation. Each specific pathogen requires distinct thresholds and mechanisms of immunological protection. For some viruses, low levels of neutralizing antibodies may be enough to prevent infections outright (Purtha et al., 2011). In contrast, for parasites such as *Plasmodium falciparum*, a complete set of cellular and humoral components are almost certainly required to protect (Schofield et al., 1987). For some viruses, such as measles, viral evolution is not an especially important factor in subverting immunological protection (Greaney et al., 2021b), whereas for HIV, it clearly leads to antibody escape. Nonetheless, some general lessons can be drawn by comparing the host-intrinsic aspects of the immune response across different vaccines, irrespective of whether they are sufficient to confer protection against the pathogen in question. For example, after the initial decline as is seen in all responses (Figure 1), immunoglobulin (Ig) production can hit a stable nadir and antibody-mediated immunity maintained for life, as is seen after the human papillomavirus (HPV) vaccines (Olsson et al., 2007). Or it can last for only a few months, as is seen after the RTS,S malaria vaccine (Olotu et al., 2013; White et al., 2015). Or somewhere in between, as it is for most vaccines and as it seems likely to be for the COVID-19 vaccines (Amanna et al., 2007). At a basic level, these differences come down to the numbers and precise lifespans of the plasma cells that emerge post-immunization, which then begets the question, what controls plasma cell lifespan?

CELL-EXTRINSIC CONTROL OF PLASMA CELL LIFESPAN

A substantial fraction of long-lived plasma cells are exported from germinal centers to reside in the bone marrow, mainly through C-X-C Motif Chemokine Receptor 4 (CXCR4) and Sphingosine-1-Phosphate Receptor 1 (S1PR1)-dependent chemotaxis (Hargreaves et al., 2001; Kabashima et al., 2006). This has led to the

general thinking that specific niches in the bone marrow promote plasma cell survival. That extrinsic factors are required for plasma cell longevity is without question. Many extrinsic factors, such as interleukin-6 (IL-6), can promote plasma cell survival in culture (Cassese et al., 2003), although their requirements *in vivo* are less certain. As a stronger example, the cytokine A proliferation inducing ligand (APRIL) promotes plasma cell survival via its receptor B cell maturation antigen (BCMA) and subsequent expression of the anti-apoptotic protein myeloid cell leukemia-1 (MCL1) (Belnoue et al., 2008; O'Connor et al., 2004; Peperzak et al., 2013). These results have been shown in multiple independent studies, both *in vitro* using human plasma and myeloma cells and *in vivo* in mouse models. Thus, APRIL (and, in part, its family member B cell activating factor [BAFF]) represents the clearest example of a specific extrinsic factor that is required for plasma cell longevity. There is less consensus of how and whether APRIL and BAFF are organized and provided by physically discrete and specific niches. Many different cell types have been reported to express APRIL, including basophils, eosinophils, megakaryocytes, osteoclasts, and stromal cells of non-hematopoietic origin (Chu et al., 2011; Rodriguez Gomez et al., 2010; Winter et al., 2010; Zehentmeier et al., 2014). Most of these cells are much shorter-lived than the long-lived plasma cells they are reported to support. In this sense, it is a challenge to imagine how a continuous flux of short-lived cells would be able to provide a stable and organized niche (Bortnick et al., 2018; Cravedi et al., 2013; Wilmore and Allman, 2017). However, direct intravital imaging of plasma cells in the bone marrow revealed clustering and long periods without substantial movement, suggestive of a physical niche (Benet et al., 2021; Zehentmeier et al., 2014). Moreover, blockade of the adhesion molecule integrin $\alpha4\beta1$ causes the egress and loss of long-lived plasma cells (DiLillo et al., 2008). In addition, certain survival signals, such CD80/CD86-mediated engagement of CD28 on plasma cells and activation of aryl hydrocarbon receptor signaling, seem to occur uniquely in the bone marrow (Lightman et al., 2021; Rozanski et al., 2011). Together, there is little consensus on the details of how plasma cell survival is supported extrinsically. Defining additional essential extrinsic survival factors, development of sensitive reporters, and genetic tools to deplete factors from specific cell types would seem to be necessary to resolve some of these issues. Indeed, similar studies of the hematopoietic stem cell niche have led to at least some clarity of how they are maintained (Ding et al., 2012).

Irrespective of how extrinsic plasma cell survival factors are delivered spatially, these signals are unlikely to be sufficient to enforce longevity and rescue plasma cells otherwise destined for a short life. Although many long-lived plasma cells do localize to the bone marrow, shorter-lived cells can be found there as well (Halliley et al., 2015). For example, influenza vaccines lead to the development of bone marrow plasma cells, but these fail to persist for more than a few months (Davis et al., 2020). Reciprocally, not all plasma cells in the spleen are short-lived (Bohannon et al., 2016; Mahévas et al., 2013). Moreover, blood plasmablasts differ in their abilities to survive *in vitro* depending on the nature of the vaccine or infection (Nguyen et al., 2018). Given that the plasmablasts are exposed to identical concentrations of survival factors in these *in vitro* assays, these data suggest that extrinsic signals might be more permissive than instructive. Instead, the nature of the infection or vaccine seems to somehow intrinsically imprint the lifespan of plasma cells (Tarlinton, 2006).

CELL-INTRINSIC PATHWAYS THAT PROMOTE PLASMA CELL LONGEVITY

Mature plasma cells uniformly express high surface levels of CD138, thereby affording a convenient handle to purify these cells (Sanderson et al., 1989). However, efforts to molecularly distinguish short- and long-lived plasma cells have historically been hindered by the lack of methods and additional markers that would allow prospective separation and transcriptional comparisons. Theoretically, polyclonal plasma cells in the bone marrow could be compared with those in secondary lymphoid organs such as the spleen. Yet, as described above, this is not an entirely clean comparison. Thankfully, some markers have emerged both for human and mouse plasma cells that correlate with lifespan. For human plasma cells, a robust (but still imperfect) marker is CD19, with the longest-lived plasma cells tending to lack its expression (Brynjolfsson et al., 2017; Halliley et al., 2015; Mei et al., 2015). In mice, a more complex set of markers can be employed to separate plasma cell subsets of varying lifespans. These include B220, CD19, major histocompatibility complex II, CXCR3, CD93, and uptake of the fluorescent glucose analog 2-(N-(7-Nitrobenz-2-oxa-1,3-diazol-4-yl) Amino)-2-Deoxyglucose (Chernova et al., 2014; Chevrier et al., 2009; Lam et al., 2016, 2018; Pracht et al., 2017; Shi et al., 2015). Genetic reporters of B-lymphocyte-induced maturation protein 1 (BLIMP1), a key transcription factor for the plasma cell secretory program, can also distinguish between early cycling plasmablasts and mature plasma cells (Kallies et al., 2004). Yet despite direct evidence of differences between the longevity of these subsets, surprisingly few transcriptional differences are observed that can easily explain these properties (Halliley et al., 2015; Lam et al., 2018; Shi et al., 2015). For example, anti-apoptotic genes such as *Mcl1*, shown to be critical for plasma cell survival, are expressed at similar levels irrespective of longevity (Lam et al., 2018; Peperzak et al., 2013). Moreover, of the relatively few transcriptional differences at both population and single-cell resolution , the magnitude of the changes is quite modest and almost none are conserved between mice and humans (Lam et al., 2018). While subtle transcriptional changes could certainly impart large functional effects, it has been very difficult to experimentally leverage these findings into biological explanations of plasma cell longevity.

In contrast to their similar transcriptional profiles, long- and short-lived plasma cells differ in metabolic pathway usage substantially and in functionally important ways (Ripperger and Bhattacharya, 2021). For example, while long-lived plasma cells predominantly use glucose for hexosamine biosynthesis and antibody glycosylation, they can divert glucose into glycolysis and use the resulting pyruvate for mitochondrial respiration when ATP stores are depleted (Lam et al., 2016). Short-lived plasma cells are less able to engage this backup ATP metabolism pathway. Long-lived plasma cells also express slightly higher surface levels of CD98, a common subunit to several amino acid transporters, than short-lived plasma cells, and their mitochondrial respiration more resistant to amino acid reduction *in vitro* (Lam et al., 2018; Tellier et al., 2016). Consistent with their

abilities to better utilize available nutrients, long-lived plasma cells possess more autophagic mass than do short-lived cells (Halliley et al., 2015; Lam et al., 2018). As another set of examples, CD28 and the enzyme ecto-nucleotide pyrophosphatase/phosphodiesterase-1 (ENPP1) cell-intrinsically promote pro-survival metabolic programs in long-lived plasma cells (Utley et al., 2020; Wang et al., 2017). Though long-lived plasma cells exit the cell cycle (whether this is irreversible remains debate [Landsverk et al., 2017; Tooze, 2013]), these metabolic differences seem to be unlinked from proliferative status (Lam et al., 2016, 2018). Together, these findings suggest that metabolic pathways and the ability to weather perturbations may be a defining characteristic of plasma-cell longevity. That these metabolic differences are seemingly unlinked from transcription is surprising on one hand. Yet on the other hand, many metabolic pathways are established and maintained through allostery and feedback loops that are regulated in microsecond timescales (Nelson and Cox, 2017). This is far too fast to be regulated by transcription of catalytic enzymes, especially those that are not rate limiting.

Some of the key traits of longevity seem to be defined within germinal center reactions from which long-lived plasma cells are derived (at least in T-dependent responses). In the absence of programmed cell death protein-1 (PD1)-PDL1/2-mediated interactions with T follicular helper (Tfh) cells, only the highest affinity plasma cells persist durably (Good-Jacobson et al., 2010). These data mirror deficiency of the transcription factor Aiolos, which primarily acts in germinal centers (Cortés and Georgopoulos, 2004). As another example, IL-21, a hallmark cytokine made by Tfh cells, is required for durable IgG responses (Avery et al., 2008; Linterman et al., 2010; Zotos et al., 2010). These data argue for a relatively early and intrinsic imprinting of plasma cell longevity derived from T cell help and B cell-intrinsic signals that is somehow tied to the nature of the vaccine or infection.

VACCINE- AND INFECTION-SPECIFIC INSTRUCTION OF PLASMA CELL LONGEVITY

A landmark study by Amanna and colleagues followed, over decades, antigen-specific antibody levels following a variety of infections and vaccines (Amanna et al., 2007). Importantly, these titers were tracked long after the initial decline phase of the response, allowing an accurate calculation of the half-lives of antibody production and, by extension, long-lived plasma cells. Striking differences were observed depending on the type of infection or vaccine. For instance, antibody production after diphtheria and tetanus toxoid vaccines showed half-lives of ~10–20 years, whereas antibodies following measles infections were maintained indefinitely. Other studies have also demonstrated wide variabilities in the duration of responses to different vaccines and infections. Smallpox and yellow fever virus vaccines elicit extremely durable antibody production, stable over the course of many decades (Crotty et al., 2003; Poland et al., 1981). In contrast, the RTS,S malaria and seasonal influenza vaccines promote antibody production for less than a year (Davis et al., 2020; White et al., 2015). Thus, the nature of the exposure seems to somehow instruct plasma cell lifespan.

One alternative interpretation to these data is that memory B cells are periodically and polyclonally stimulated, perhaps by toll-like receptor (TLR) ligands, to maintain serum antibodies (Bernasconi et al., 2002). If true, the studies above would not directly speak to plasma cell lifespans, but rather the activity of memory B cells. Yet the preponderance of data argues against this interpretation. Serum antibody responses correlate only modestly, if at all, with memory B cell numbers, which tend to be much more stable over time (Amanna et al., 2007; Crotty et al., 2003). Depletion of memory B cells with anti-CD20 antibodies, both in humans and in mice, had no impact on pre-existing vaccine-specific serum antibodies or plasma cells, which lack CD20 expression (Ahuja et al., 2008; Cambridge et al., 2003; DiLillo et al., 2008). *In vivo* mouse models showed no reactivation of memory B cells by TLR ligands alone (Richard et al., 2008), and vaccine-specific antibodies showed no periodic and coordinated rises and falls over time in humans as would be expected by polyclonal activation (Amanna et al., 2007). Both in humans and mice, the antibody repertoires of memory B cells and long-lived plasma cells are not fully congruent (Lavinder et al., 2014; Purtha et al., 2011; Smith et al., 1997). Finally, in a remarkable study, carbon-14 dating directly showed mean half-lives of over 20 years for $CD19^{-}$ plasma cells (Landsverk et al., 2017). None of this is to say that inflammatory or other non-specific stimuli play no role in the general maintenance of antibody production. For example, measles virus can directly infect plasma cells, leading to polyclonal loss of these cells (Mina et al., 2019). But these data do not speak to why certain types of responses are long-lived while others are not. Instead, the data strongly suggest that the duration of antibody production is directly linked to the lifespan of plasma cells, which in turn is somehow instructed by the specific vaccine or infection.

Unfortunately, the rules are not at all well-defined of how this instruction happens. Responses to SARS-CoV-2 infections and the different COVID-19 vaccines offer recent examples that further highlight this deficiency in our knowledge. Whereas early reports suggested an unusually rapid diminution of antibody responses following SARS-CoV-2 infections (Ibarrondo et al., 2020; Pollán et al., 2020; Seow et al., 2020), subsequent studies that followed the response for longer have shown a relatively stable nadir of antibody production (Dan et al., 2021; Isho et al., 2020; Iyer et al., 2020; Ripperger et al., 2020; Rodda et al., 2021; Wajnberg et al., 2020; Wang et al., 2021). Reciprocally, persistent germinal centers, very high initial antibody levels, and seeding of bone marrow plasma cells following mRNA-1273 or BNT162b2 vaccination suggested a high likelihood of durable antibody production (Kim et al., 2022; Lederer et al., 2022; Turner et al., 2021). Yet several side-by-side studies have suggested that unfortunately, serum antibody levels post-BNT162b2 vaccination decline more rapidly than those elicited by symptomatic infections (Israel et al., 2021; Wang et al., 2021). Relative to the two primary doses of the mRNA vaccines, the Ad26.CoV2.S vaccine induces lower initial levels of antibodies (Munro et al., 2021) (Figure 1). Yet afterwards, these antibodies are relatively stably maintained, perhaps even increasing with time (Sadoff et al., 2021b). These data demonstrate that early antibody response kinetics are not predictive of the duration of production, and that there are currently no shortcuts to longitudinal studies. Thus, a key goal is to define the molecular programs of plasma cell lifespan and the specific traits of vaccines and infections that influence these programs.

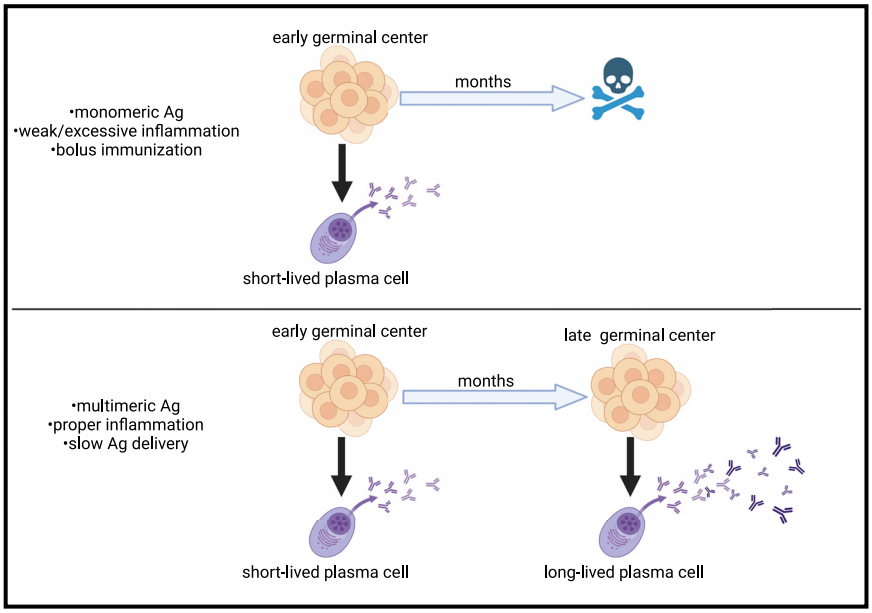

Figure 2. Germinal center persistence depends on the nature of the antigen, innate signals, and kinetics of delivery

Bolus immunizations with suboptimal inflammatory signals lead to transient germinal centers that export predominantly short-lived plasma cells (top). In contrast, slow antigen delivery or multimerized innate signals lead to persistent germinal centers (bottom). In the early phases of the response, plasma cells are predominantly short-lived, yet those exported from later germinal centers tend to be much longer lived and possess elevated secretory capacity.

As an aside, these types of comparisons have been used by some to argue that SARS-CoV-2 infections are a preferred way to generate immunity. This is a peculiar argument. The purpose of these vaccines is to generate immunity without having to suffer the consequences of COVID-19. Whether the resulting vaccine-induced immunity is subtly shorter-lived than that caused by an infection seems beside the point.

INNATE INSTRUCTION OF DURABLE IMMUNITY

The leading candidates of variables that influence durable immunity are (1) the specific innate sensors that are triggered, (2) the kinetics of antigen delivery and persistence, and (3) starting antigen valency and B cell receptor avidity. There are several lines of evidence suggesting the importance of the initial innate signals in imprinting the durability of immunity. Most clinically used vaccines contain an adjuvant to induce transient inflammation. These can include extrinsically added components, such as aluminum salts, or in the case of live-attenuated vaccines, genetically encoded pathogen-associated molecular patterns (McKee et al., 2007). While most studies on adjuvants have focused on the initial magnitude of antibody production, there are intriguing hints that the presence and nature of the adjuvant also influence the durability of the humoral response. The seasonal inactivated influenza vaccine, which is unadjuvanted, provides only transient immunity and very poorly induces CD4 T cells, which are presumably required for the formation of post-germinal center long-lived plasma cells (Hoft et al., 2011). This stands in contrast to live-attenuated influenza vaccines, which, at least in children, induce strong T cell responses (Hoft et al., 2011), and primary infections, which can induce lifelong antibody production (Yu et al., 2008). Studies in mice have also shown that the nature of the adjuvant strongly influences the duration of antibody production. A cholera-toxin based adjuvant induces much more stable antibody production than do alum or Ribi, an oil-in-water emulsion adjuvant that contains TLR ligands (Bemark et al., 2011). Yet when TLR ligands are assembled into multimeric nanoparticles as adjuvants, germinal center and antibody responses are exceptionally long-lived (Kasturi et al., 2011) (Figure 2). This seems likely to be driven by differential activation of antigen presenting cells and as a result, qualitatively different Tfh cells (Malherbe et al., 2008). Adjuvants also seem to work at least in part by directly or indirectly imprinting distinct survival programs (Hou et al., 2011; Pasare and Medzhitov, 2005; Tian et al., 2018). An example in support of this concept comes from the adjuvant-specific and B cell-intrinsic requirement for the transcription factor Zinc Finger And BTB Domain Containing 20 (ZBTB20) in promoting durable antibody responses (Wang and Bhattacharya, 2014).

Studies of patients who either succumbed or recovered from COVID-19 also support the argument that innate signals and inflammation influence the kinetics of extrafollicular plasma cell production. Lymph node biopsies or autopsy samples from patients with severe COVID-19 showed few well-organized germinal centers, likely because of an absence of Tfh cells (Kaneko et al., 2020; Röltgen et al., 2022). These data suggest that the excessive inflammation seen in severe COVID-19 might inhibit germinal centers, thereby prolonging the extrafollicular short-lived antibody response (Figure 2). Similar observations have been documented in studies of influenza, *Plasmodium*, and bacterial infections, in which excessive tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ) inhibits Tfh cells and germinal centers (Keitany et al., 2016; Popescu et al., 2019; Rothaeusler and Baumgarth, 2010; Ryg-Cornejo et al., 2016). When this inflammation is resolved in those who recovered from severe COVID-19 or had only mild infections to begin with, germinal centers seem to eventually come back online to mediate prolonged affinity maturation (Sokal et al., 2021; Wang et al., 2021). Together, these data suggest that, in Goldilocks fashion, just the right amount of inflammation is needed to drive an optimal antibody response.

Despite these studies, the dearth of mechanistic details of how these adjuvants and innate signals function has hindered the construction of a general playbook of how best to induce durable antibody responses. For example, the most commonly used clinical adjuvant is alum, but its mechanism of action remains unresolved well over a century after its first description (Behring, 1913). The NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome was considered to be an essential

sensor for antibody responses downstream of alum, but the results on this point have not been consistent across studies (Eisenbarth et al., 2008; McKee et al., 2009). Oil-in-water emulsion adjuvants seem to function in part by inducing cell death (Kim et al., 2020), but how this promotes antibody responses is not resolved.

The innate signals triggered by the COVID-19 mRNA vaccines pose an additional mystery on this front. Work by Karikó and Weissman showed that transfected RNA oligonucleotides triggered massive type I IFN responses, thereby leading to cell death and no detectable translation of the RNA into protein (Karikó et al., 2005). Yet modifying the RNA to contain a 5′ methyl cap and replacing uridines with pseudouridines led to the evasion of viral RNA sensors such as TLR3, TLR7, retinoic acid-inducible gene I (RIG-I), and melanoma differentiation-associated protein 5 (MDA-5). For these reasons, the major adjuvanting activity within the mRNA vaccines seems to come from the lipid nanoparticles that encompass the mRNA and allow cellular entry (Alameh et al., 2021). Empty lipid nanoparticles were sufficient to trigger antibody responses to protein antigens independently of myeloid differentiation primary response 88 (MYD88) and MAVS but dependent on IL-6, which presumably promotes Tfh cell differentiation along with IL-21 (Eto et al., 2011). MYD88-independence would seem to rule out TLRs as sensors for the ionizable lipid nanoparticles (although TIR domain-containing adaptor-inducing IFN-β [TRIF]-mediated TLR4 signaling remains a possibility [Zhang et al., 2021]), but also the inflammasome, which initiates a MYD88-dependent IL-1 family-member-driven signaling cascade (Adachi et al., 1998; Li et al., 2022). The remaining sensor(s) that trigger this inflammation are thus not known. Despite its modifications, the mRNA itself does still induce some type I IFN and MYD88-dependent innate signals that help the antibody response as well (Alameh et al., 2021; Warren et al., 2010). Adenovirus-based vaccines presumably trigger innate DNA sensors for pathogen-associated molecular patterns, but which of these sensors are critical for promoting adaptive responses also remains understudied. Adenoviral infections activate the cyclic GMP–AMP synthase-stimulator of IFN genes (cGAS-STING) pathway, but this seems dispensable for adaptive responses (Anghelina et al., 2016). TLR signaling also seems dispensable (Nociari et al., 2007), suggesting that perhaps activation of the AIM2 and NLRP3 inflammasomes might be important innate signals (Barlan et al., 2011; Liu et al., 2017). Even less is known about more novel saponin-like adjuvants such as Matrix M, used in Novavax's nanoparticle COVID-19 vaccine (Magnusson et al., 2018). Thus, many vaccines and adjuvants seem to defy the logical predictions of specific innate sensors required for antibody responses.

For these reasons, frustratingly few specific conclusions can be drawn as to the optimal levels and combinations of innate signals, adjuvants, and inflammatory mediators that promote durable humoral immunity. If one knew the molecular signatures of durable antibody responses, then rapid iterative improvements could be employed to optimize the duration of immunity without necessarily waiting for years to see how each change fared. Moreover, vaccine adjuvants could be designed logically to promote durable immunity. To get to this point, much more work is needed to define innate pathways that are necessary and sufficient for durable immunity, the identities and optimal levels of downstream inflammatory mediators, the cell types that are triggered and induce this inflammation, and the corresponding molecular signatures they impart on B cells as they differentiate into long-lived plasma cells.

KINETICS OF ANTIGEN DELIVERY INFLUENCE GERMINAL CENTER AND PLASMA CELL PERSISTENCE

A second aspect of durable humoral immunity is the kinetics and persistence of antigen and germinal center reactions. Though persistent and spontaneous germinal centers have long been observed in the context of autoimmunity (Domeier et al., 2017; Mietzner et al., 2008), the perseverance of these structures in responses to foreign antigens and continuous export of memory B cells and plasma cells has been underappreciated. This is largely because much of the prior work on this topic has come from single bolus hapten-protein immunizations in mice. In these settings, germinal centers rarely persist for more than several weeks (Kaji et al., 2012). This makes perfect sense, as 1 or 2 somatic changes in the B cell receptor can yield enormous improvements in anti-hapten affinity (Cumano and Rajewsky, 1986; Furukawa et al., 1999). Thus, there is no particular reason why germinal centers would or should persist. Yet for protein antigens, the affinity maturation process is far more complex, requiring the gradual accumulation of many somatic mutations to reach maximal affinity (Kuraoka et al., 2016; Tas et al., 2016). For some broadly neutralizing HIV antibodies, this process can take years (Liao et al., 2013). Even for acute infections where the pathogen is presumably cleared, such as influenza virus, germinal centers can persist for long periods of time (Bannard et al., 2013; Rothaeusler and Baumgarth, 2010; Yewdell et al., 2021). For vaccines to engage this lengthy process, the kinetics of antigen delivery and persistence are critical. A large bolus injection of antigen leads to relatively short-lived germinal centers in non-human primates, but a slower delivery or repeated injections of small doses of protein antigen lead to markedly prolonged germinal centers and continuous improvements in antibody affinity (Cirelli et al., 2019; Lee et al., 2021). Because these experiments used recombinant proteins, there is no possibility of "hidden" replication of viruses or other pathogens that maintain antigen. Instead, antigen might be retained for very long periods of time on follicular dendritic cells via Fc and complement receptors to drive persistent germinal centers (Hanna and Szakal, 1968; Heesters et al., 2013; Nossal et al., 1968).

Persistent germinal centers could drive durable humoral immunity in several ways. First, continuous production of plasma cells, even if relatively short-lived, would be expected to prolong antibody production and humoral immunity. Second, the nature of the germinal center changes over time to promote plasma cell longevity (Weisel et al., 2016) (Figure 2). This is correlated with changes in the cytokine profiles of Tfh cells. For example, in helminth infections, IL-21-producing Tfh cells dominate the early response, but this progressively shifts to cells producing IL-4 (Weinstein et al., 2016). Moreover, as the germinal center continues, the levels of interleukin-2 and frequencies of forkhead box P3 (Foxp3)-expressing Tfh cells change (Botta et al., 2017), which in turn influence the persistence of germinal centers (Jacobsen et al., 2021). How and whether these specific cytokine and cellular changes influence plasma cell longevity is not

known, but these studies highlight the dynamic nature of the germinal center and its potential to deliver distinct signals in early versus late stages of the response.

Indirect evidence suggests that germinal centers after SARS-CoV-2 infections persist for many months, evidenced by the continuous emergence of memory B cell clones carrying new somatic mutations (Wang et al., 2021). Direct sampling of lymph nodes showed that mRNA vaccines can also induce germinal centers that can be detected for months (Lederer et al., 2022; Turner et al., 2021), perhaps because of the persistence of antigen (Röltgen et al., 2022). However, the absolute numbers of these germinal center cells might decline over time (Lederer et al., 2022), as the extent and duration of clonal evolution and affinity maturation seem to be less than that of infections (Wang et al., 2021).

ANTIGEN VALENCY AND BCR AVIDITY IN PROGRAMMING PLASMA CELL LIFESPAN

For some infections and vaccines, heterogeneity is observed in the perseverance of Ig production depending on the antibody specificity. For example, in SARS-CoV-2 infections, antibodies against the nucleocapsid protein seem to wane more quickly than those against the spike receptor-binding domain (Ripperger et al., 2020). Similarly, based on rapidly declining vaccine effectiveness against the Omicron variant after a third mRNA dose, it may be that cross-neutralizing antibodies are lost preferentially over time relative to other variant-specific antibodies (Chatterjee et al., 2022). Given that this happens within the same infection or vaccine response, these observations cannot be easily explained by differences in innate signals or the kinetics of antigen delivery. Instead, a third variable that correlates with the perseverance of antibody responses is precursor BCR avidity and, relatedly, antigen valency (Slifka and Amanna, 2019). B cells with high starting avidity for their antigens are preferentially recruited into the response, are clonally expanded in germinal centers, and are more resistant to apoptosis than are lower affinity counterparts (Anderson et al., 2009; Chan et al., 2009; Fischer et al., 1998; Gitlin et al., 2014; Schwickert et al., 2011; Shih et al., 2002; Taylor et al., 2015) (Figure 2). Perhaps as a result, B cells with high germline avidities are more likely to become long-lived plasma cells than those of lower avidity (Wong et al., 2020). Reciprocally, engineering immunogens into nanoparticles to enhance valency leads to qualitatively improved germinal center and antibody responses (Abbott et al., 2018; Kato et al., 2020; Marcandalli et al., 2019). IgD likely mediates these responses through the preferential engagement of multivalent antigens (Übelhart et al., 2015).

The spike protein valency of SARS-CoV-2 has been defined through cryoelectron microscopy studies. Each virus has on average ~25 spike trimers distributed across ~100 nm diameter particles (Ke et al., 2020). How closely the mRNA and adenovirus vaccines mimic this valency is not known. For both platforms, the specific cells that are transduced have not been fully defined (though lymph node macrophages and dendritic cells are the likeliest candidates), nor have the copies of spike protein per cell surface area been calculated. For these reasons, many immunologists were highly enthusiastic about the more defined spike-multimerized nanoparticle platform of Novavax's COVID-19 vaccine (Bangaru et al., 2020) but have been highly disappointed by the manufacturing problems and slow pace of regulatory approvals. Other nanoparticle platforms, both for SARS-CoV-2 and other viruses such as respiratory syncytial virus, have shown promising preclinical results in non-human primates (King et al., 2021; Marcandalli et al., 2019; Walls et al., 2020). The hope going forward is that these alternatives will be less encumbered by manufacturing issues and will provide some viable competition to mRNA- and adenovirus-based COVID-19 vaccines.

Real-world examples of vaccines seem to reinforce the importance of antigen valency (Slifka and Amanna, 2019). Some of the best vaccines at inducing durable antibody production are live attenuated, thereby generating virions with the proper structure and high antigen valency. Examples include yellow fever and smallpox vaccines (Crotty et al., 2003; Poland et al., 1981). As an example of an outstanding non-replicating vaccine, the remarkably effective and durable HPV vaccine uses the L1 protein, which self-assembles into virus-like particles with high antigen valency (Einstein et al., 2014; Garland et al., 2007). Reciprocally, monovalent vaccines such as those against diphtheria and tetanus tend to induce more transient antibody production (Amanna et al., 2007).

Despite the highly successful template provided by the HPV vaccine, unfortunately, it still is not always sufficient to try and simply replicate this formula. Infections with HPV, presumably with high L1 valency, induce quite weak antibody responses (Carter et al., 2000), perhaps because of genetically encoded mechanisms to subvert innate recognition. The RTS,S/AS01E malaria vaccine, at least superficially, seems similar to HPV in terms of adjuvants and assembly into virus-like particles (Stoute et al., 1997). Yet antibody responses to RTS,S/AS01E persist for only a few months (White et al., 2015). At least some of this problem is linked to the nature of prior exposures in the target populations. In malaria-endemic countries, individuals are repeatedly infected by *Plasmodium* parasites each wet season when mosquito vectors are abundant. Thus, much of the target population for the vaccine is not truly immunologically naive. Rather, responses to the vaccine are likely driven by pre-existing memory B and Tfh cells, a large proportion of which shows signs of dysfunction (Obeng-Adjei et al., 2017; Weiss et al., 2009, 2010). This might be due to the same types of inflammation that prevent germinal centers in *Plasmodium* infections (Keitany et al., 2016; Ryg-Cornejo et al., 2016). In further support of this point, responses to RTS,S/AS01E in immunologically naive Western populations are reported to be better than those in the target Sub-Saharan Africa populations (Stoute et al., 1997). More broadly, these data raise an important point: most primary vaccine series involve multiple doses. Thus, although much of the discussion above has focused on primary responses, in actuality, most of the vaccine antibody response is driven by memory B cells, which are entirely different and more complicated beasts than are naive B cells.

MEMORY B CELL RECALL RESPONSES

The heterogeneity of memory B cell subsets underlies the complexity in secondary responses. Whereas primary T cell-dependent responses are presumably dominated by follicular

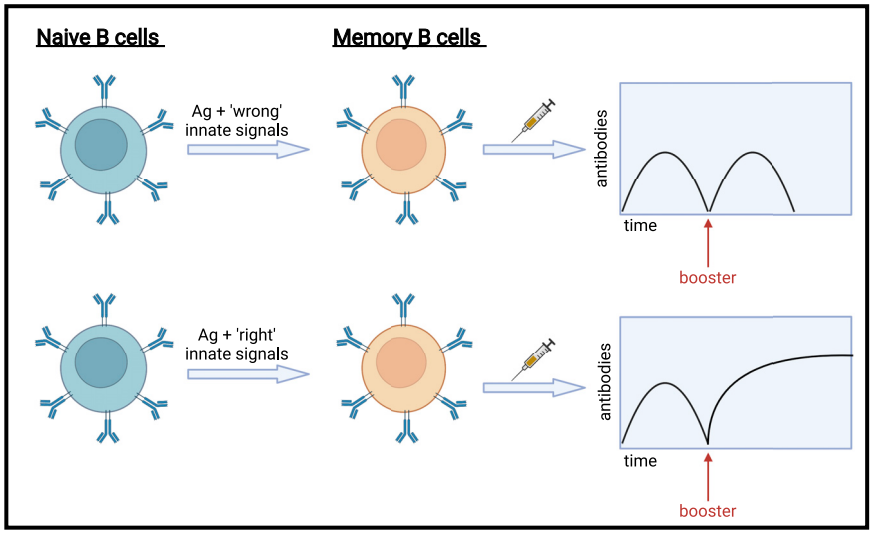

Figure 3. Early imprinting of memory B cells

Primary immunizations with suboptimal innate signals may lead to qualitatively distinct memory B cells than those generated with more optimal inflammatory mediators. Upon booster immunization with the same immunogen, these two types of memory B cells mediate markedly distinct responses. Those that were generated under suboptimal responses may produce shorter-lived plasma cells than those generated under more optimal conditions.

B2 cells, a wide range of memory B cell subsets can respond to subsequent exposure in ways that are not easily predictable. In both mice and humans, the antibody isotype of memory B cells correlates somewhat with their differentiation potentials. Those that remain IgM^+ tend to be capable of re-initiating germinal center reactions, whereas those that have isotype-switched to IgG generally re-initiate plasma cell differentiation upon antigenic exposures (Dogan et al., 2009; Pape et al., 2011; Seifert et al., 2015). IgG isotypes can mediate stronger signals than IgM (Casola et al., 2006; Engels et al., 2009; Horikawa et al., 2007), perhaps biasing fates toward the plasma cell lineage. Yet this is not axiomatically true and the correlation between antibody isotype and the lineage potential of memory B cells is imperfect (Kometani et al., 2013; Krishnamurty et al., 2016; Mcheyzer-Williams et al., 2015; Zuccarino-Catania et al., 2014). In mice, additional markers such as CD80, PDL2, CD73, and CCR6 can help refine these populations in ways that are more predictive of their lineage potentials than antibody isotype alone (Bhattacharya et al., 2007; Tomayko et al., 2008; Zuccarino-Catania et al., 2014). In humans, definitively assigning functions of the subsets is more difficult, but based on *in vitro* differentiation and transcriptional similarities to mouse subsets, functions can be putatively inferred. Aside from the general human memory B cell marker CD27 (alongside B cell markers such as CD19 or CD20), expression of CD21 versus CD11c can help distinguish classical memory B cells from those that appear to be either recently activated or biased toward the plasma cell fate (Ellebedy et al., 2016; Knox et al., 2019; Lau et al., 2017). In addition, other subsets of antigen-experienced B cells can lack CD27. Their function is not fully understood, but these cells often appear in settings of autoimmunity, chronic infections, and inflammation, such as after severe COVID-19 (Ehrhardt et al., 2005; Jenks et al., 2018; Woodruff et al., 2020). There remains substantial uncertainty as to whether these cells are anergic and dysfunctional or capable of contributing to the antibody response productively (Muellenbeck et al., 2013; Pérez-Mazliah et al., 2018; Portugal et al., 2015). Even if the functional potentials of these subsets could be assigned definitively, they do not seem to necessarily contribute to recall responses in proportion to their relative abundance. Despite the presence of memory subsets with germinal center potential, under several different conditions, recall responses in mice seem to be heavily skewed to plasma cells rather than secondary germinal centers (Mesin et al., 2020; Pape et al., 2011; Wong et al., 2020). In humans, recall responses are equally unpredictable. Some individuals re-initiate germinal centers after influenza vaccination, whereas others do not (Turner et al., 2020). The subsets that respond and whether they transit through secondary germinal centers might influence the subsequent duration of antibody production.

The duration of antibody production in recall responses is thus not straightforward to predict. *In vitro* experiments have found that memory B cells more readily give rise to long-lived plasma cells than naive B cells do (Cocco et al., 2012; Jourdan et al., 2014), justifying strategies to improve both the magnitude and durability of antibody production with multiple doses and boosters. Indeed, after the third dose of a Japanese encephalitis vaccine, antibody production becomes quite durable (Paulke-Korinek et al., 2015). However, for influenza vaccinations in which memory responses dominate, antibody production and plasma cell persistence are relatively short-lived (Davis et al., 2020). These differences likely relate to the nature of both the primary and secondary exposures (Figure 3). As an example, the transcription factor ZBTB32, which is highly expressed in plasma cell-biased memory B cells (Lau et al., 2017; Zuccarino-Catania et al., 2014), limits the duration of antibody production in recall responses to unadjuvanted hapten-protein conjugates in mice (Jash et al., 2016). Yet this requirement depends on the adjuvant used in the *primary* immunization (Jash et al., 2016, 2019). When alum is used as the adjuvant in the prime, subsequent recall responses to soluble antigens are short-lived and restricted by ZBTB32 (Jash et al., 2016). Yet when Ribi is used as the primary adjuvant, recall responses are long-lived already and ablation of ZBTB32 has no effect (Jash et al., 2019). Similarly, ZBTB32 restricts antibody responses to chronic infections like murine cytomegalovirus but not recall responses to intestinal microbiota or unadjuvanted influenza vaccines after a primary infection (Jash et al., 2019). Thus, just as with plasma cells in a primary response, there seems to be an early imprinting of memory B cells that defines the duration of antibody production in recall responses (Figure 3). Whether and how this program is influenced

by the nature of the secondary challenge is unknown, as are the specific transcriptional, epigenetic, and other molecular features that distinguish memory B cells arising from different primary challenges. It is also unknown how these features influence recall responses to heterologous infections or vaccines, where it would seem beneficial for cross-reactive memory B cells to eventually stand down so that primary variant-specific responses can take over later in the response (Amanat et al., 2021; Sokal et al., 2021).

These concepts are becoming important in the context of the COVID-19 pandemic, as a large percentage of the population has now been exposed multiple times to either the virus or vaccines. When individuals are first infected and then vaccinated or suffer post-vaccination infections, a marked initial increase in neutralizing antibodies is observed in what is known as hybrid immunity (Crotty, 2021). Does the order of exposures influence the duration of antibody production, and how does this compare with individuals who received 3 (or more) doses of vaccine? How do heterologous vaccine platforms influence the duration of immunity? For now, it is too soon to be able to address these questions definitively, but the answers have major implications for the expected duration of humoral immunity and the frequency of needed boosters.

The magnitude of the increase in antibodies and breadth of the response in hybrid immunity seems greater than can be easily explained by just any additional exposure to the virus or vaccine. This can be explained in part by the elevated frequency of memory B cells induced by infection relative to mRNA vaccination, which in turn correlates well with the magnitude of subsequent anamnestic responses (Goel et al., 2021, 2022; Rodda et al., 2022). Infection also seems to induce more IFN-γ^+ IL-10$^+$ CD4 memory T cells and CD21$^-$ CD11c$^+$ memory B cells than vaccination, both of which may also influence recall responses (Pape et al., 2021; Rodda et al., 2022). Part of hybrid immunity may also relate to differences in the anatomical sites of vaccination versus infection that then draws non-overlapping cells into the response. Relatedly, pre-existing mucosal antibodies from an infection might not substantially mask spike epitopes and impede systemic recall responses to an intramuscular vaccine (which is discussed in more detail below). Another important aspect is the timing between infections and vaccines. For both infections and mRNA vaccines, germinal centers persist for months, continuously exporting memory B cells of progressively increasing affinity and breadth (Lederer et al., 2022; Turner et al., 2021; Wang et al., 2021). Although the current schedules of several COVID-19 vaccines recommend only a 3-to-4 week spacing between doses in the primary series, an increasing body of antibody and real-world effectiveness studies demonstrates that this is far from the optimal immunological timing. Increasing the spacing to >8 weeks improves the magnitude and breadth of the recall response (Chatterjee et al., 2022; Payne et al., 2021; Skowronski et al., 2021; Tauzin et al., 2022; Voysey et al., 2021). Moreover, a 3rd vaccine dose, delivered long after the primary series, markedly increases effectiveness against variants of concern such as Delta and Omicron (Barda et al., 2021; Collie et al., 2022; Muik et al., 2022; Thompson, 2022). Presumably, this is because of recalling a greater breadth of more affinity-matured memory B cells (Muecksch et al., 2022a; Pape et al., 2021). Intriguingly, preliminary studies hint that lengthening the spacing between doses might also improve the durability of antibody production (Flaxman et al., 2021), an observation that has been seen in other vaccines as well (Paulke-Korinek et al., 2015). This is consistent with the idea that memory B cells have an intrinsic program that instructs the duration of downstream plasma cell longevity. In this case, perhaps memory B cells that emerge from later germinal centers are better than early emigrants at promoting durable responses. The data are far from resolved on this front, but the preponderance of evidence thus far supports a longer spacing interval between doses in the primary vaccine series.

NON-NEUTRALIZING ANTIBODIES AND CELLULAR MEMORY IN PROTECTION AGAINST COVID-19

The discussion has thus far focused on neutralizing antibodies as the major determinant of protection and memory B cells simply as a vector to promote such antibodies before an exposure to SARS-CoV-2. While pre-existing neutralizing antibodies are the best correlate of protection, they are unlikely to be the only mechanism. Neutralizing antibody levels correlate reasonably well with measured efficacies across different vaccines (Gilbert et al., 2022; Khoury et al., 2021). However, variants with substantial escape mutations have not dropped efficacies *within* a given vaccine response to the levels expected if neutralizing antibodies were the only mechanism of protection. For example, the Ad26.CoV2.S vaccine maintained similar efficacies against ancestral SARS-CoV-2 as it did against the Beta and Gamma variants (Sadoff et al., 2021a), which substantially escape neutralizing antibodies (Edara et al., 2021; Garcia-Beltran et al., 2021; Geers et al., 2021). While a complete loss of pre-existing neutralizing antibodies is unlikely to be fully compensated by other mechanisms, partial losses likely can be mitigated by non-neutralizing antibodies, memory B cell responses, and memory T cells, all of which resist viral mutations and persist for far longer than neutralizing antibodies (Dan et al., 2021; Geers et al., 2021; GeurtsvanKessel et al., 2022; Goel et al., 2021; Jergovic et al., 2022; Muecksch et al., 2022b; Purtha et al., 2011; Tarke et al., 2021, 2022; Wang et al., 2021).

Many of the recurrent and key mutations that have been observed in variants of concern ablate neutralizing, rather than non-neutralizing antibody epitopes. This in and of itself suggests that the major immunological selective pressures on viral evolution and transmission are neutralizing antibodies. Yet the majority of viral shedding of SARS-CoV-2 occurs within a few days before and after symptom onset (Kang et al., 2021). Thus, any impact by non-neutralizing antibodies to slow subsequent viral spread and limit severe disease would not be expected to have a large impact on viral transmission or selection. This being the case, one should not conclude that pre-existing non-neutralizing antibodies are uninvolved or unimportant for protection against COVID-19. Indeed, antibody-dependent cellular cytotoxic activity has been observed in the plasma of SARS-CoV-2-immune individuals that is largely preserved against variants of concern (Geers et al., 2021; Tso et al., 2021). Such Fc-dependent effector functions are important for limiting disease when monoclonal antibodies are used therapeutically (Winkler et al., 2021). Reciprocally, afucosylated Fc regions of antibodies, as seen in severe COVID-19, can exacerbate disease while

fucosylated antibodies elicited by vaccination attenuate inflammation (Chakraborty et al., 2021). Together, these observations suggest an important, if sub-dominant role of non-neutralizing antibodies in protection against COVID-19.

Memory B cells and anamnestic responses represent a second layer of immune defense aside from the pre-existing antibodies produced by long-lived plasma cells. When pre-existing neutralizing antibody titers are high and stoichiometrically exceed the infectious or vaccine dose, antigenic epitopes are blocked and memory B cells do not robustly participate in the response (Andrews et al., 2015; Goel et al., 2022). Yet when neutralizing antibody concentrations drop below those needed to confer sterilizing immunity, either due to waning or because of viral escape mutations, memory B cells can be engaged. As discussed above, germinal centers continue to produce memory B cells of enhanced breadth over the course of months after SARS-CoV-2 infections or vaccines (Lederer et al., 2022; Muecksch et al., 2022b; Turner et al., 2021; Wang et al., 2021). Moreover, prior studies in other systems have shown that memory B cells have improved breadth and diversity relative to serum antibodies contemporaneously produced by long-lived plasma cells, increasing the chances that they can recognize viruses despite escape mutations (Purtha et al., 2011). Upon recognition, antibody recall responses to SARS-CoV-2 tend to begin at least several days before primary responses (Koutsakos et al., 2021), thereby at least theoretically increasing the chances that infections can be terminated even before symptom onset. Yet as SARS-CoV-2 has evolved, the incubation period, which is the time between infection and symptom onset, has shortened (Kang et al., 2021). Thus, the window within which memory B cells can shut down an infection prior to illness has shrunken substantially relative to the beginning days of the pandemic and vaccine rollout. Nonetheless, it is likely that the rapid viral clearance observed in post-vaccination infections relative to primary infections is mediated at least in part by anamnestic memory responses (Chia et al., 2022). This in turn likely reduces the chances of both onward transmission and severe disease.

The importance of memory T cells in protection against COVID-19 and SARS-CoV-2 transmission represents an unusually polarizing topic. Because many individuals possess memory T cells from prior common coronavirus infections that cross-react with SARS-CoV-2 (Grifoni et al., 2020; Mateus et al., 2020; Sekine et al., 2020), T cell memory was proposed as a major contributor to herd immunity. Yet because T cells respond to infections only after they have already occurred, their impact on transmission in the absence of any other immune mechanisms is expected to be modest (Lipsitch et al., 2020). That said, it should not be concluded that T cells play no role whatsoever in limiting infections or disease. For example, patients with X-linked agammaglobulinemia were able to clear the infection (Soresina et al., 2020), albeit with the assistance of antiviral medications. In another set of examples, household contacts and healthcare workers who were likely exposed to SARS-CoV-2 showed elevated T cell frequencies, perhaps indicative of a recall response, despite never having tested positive for the virus, not reporting any symptomatic infections, and failing to generate a detectable antibody response (Sekine et al., 2020; da Silva Antunes et al., 2021; Swadling et al., 2022). The absence of a positive SARS-CoV-2 test makes these studies difficult to fully interpret, but the results do provide some circumstantial evidence that in some cases, memory T cells can abort infections prior to symptom onset even when antibodies are not detectably induced. Additionally, pre-existing SARS-CoV-2-reactive memory CD4 T cells correlate well with the magnitude of antibody responses after infection or vaccination (Loyal et al., 2021). In other cases, T cell responses correlate with reduced severity of symptoms (Liao et al., 2020; Sagar et al., 2021). Finally, non-human primate models confirm that CD8 T cells can help clear infections when neutralizing antibody levels are suboptimal (McMahan et al., 2021), though when antibodies are completely absent in genetic mouse models, their contribution is more modest (Israelow et al., 2021). Together, these data suggest that T cells do contribute to protection against COVID-19. Though it is unwise to rely on T cells alone, their contributions may become clearer as variants continue to emerge with escape mutations that ablate neutralizing antibody epitopes, but not antigenic peptides presented to T cells.

PAN-SARBECOVIRUS AND MUCOSAL VACCINES

This perspective has focused on mechanisms and variables that maintain antibody production. As mentioned at the beginning, this is only one part of the equation for durable humoral immunity. Viral evolution and immune escape can substantially reduce the effectiveness of prior immunity even if antibodies are maintained stably. Whereas periodic infections with common coronaviruses are often considered to be because of the waning of antibodies (Callow et al., 1990; Edridge et al., 2020), these ''re-infections'' are likely heterologous and might be driven more by antigenic drift than by waning (Eguia et al., 2021; Reed, 1984). As a second example, crossover trials of the mRNA COVID-19 vaccines revealed only a partial contribution of immunological waning to the overall decline in efficacy against the Delta variant (El Sahly et al., 2021). For this reason, efforts to develop variant-proof vaccines are underway. In general, these strategies involve the inclusion of multiple versions of the spike protein such that a wide breadth of possibilities are covered by antibody responses (Cohen et al., 2021; Martinez et al., 2021; Walls et al., 2020). Hopes that this strategy might work in humans were strengthened by data showing that survivors of SARS-CoV who were vaccinated against COVID-19 demonstrated exceptionally high neutralization against a wide variety of sarbecoviruses, including SARS-CoV-2 variants of concern (Tan et al., 2021). Yet how this smorgasbord of spike proteins is delivered may make a big difference for the subsequent durability of the antibody response. For the purposes of achieving high antigen valency and durable antibody production, mosaic nanoparticle-based strategies may be ideal (Cohen et al., 2021; Walls et al., 2020).

An additional strategy to prolonging the duration of immunity is to reduce the quantity of antibodies required to protect against infection. Serum IgG, as generated by intramuscular vaccines, inefficiently crosses the mucosal epithelial barrier in the upper respiratory tract, with an estimated 200-to-1,000-fold loss in titers along the way (Wagner et al., 1987). In contrast, dimeric IgA is transcytosed relatively efficiently via the polyIg receptor (Mostov, 1994). While some IgA is induced by the COVID-19 vaccines, which in turn correlates with protection against infections, these levels are far less than those induced by SARS-CoV-2

infections (Nahass et al., 2021; Sheikh-Mohamed et al., 2022; Turner et al., 2021). Thus, one way to lower the immunological bar needed to protect against SARS-CoV-2 infections is through mucosal vaccines that elicit potent IgA responses at the site of exposure. Moreover, intranasal vaccines might be leveraged to establish local tissue-resident memory B and T cells, thereby shortening the response time of cellular memory (Allie et al., 2019; Masopust et al., 2001). All of this is much easier said than done, as FluMist, the only intranasal vaccine in routine clinical use, has a mixed record of success relative to intramuscular immunizations (Belshe et al., 2007; Ohmit et al., 2006). Nonetheless, several efforts to develop mucosal vaccines are underway and their success would be a landmark achievement (Alu et al., 2022; Hassan et al., 2020; Johnson et al., 2022; Mao et al., 2022).

IgA responses following SARS-CoV-2 infections are short-lived relative to IgG (Isho et al., 2020). Moreover, IgA responses in the intestine are restricted in part by competition with other plasma cells (Hapfelmeier et al., 2010). Given that new plasma cells are continuously generated through exposure to microbes and environmental antigens, mucosal antibody production may be inherently short-lived (Yewdell, 2021). This is not necessarily the case. Carbon dating of $CD19^{-}$ plasma cells isolated from human small intestines demonstrated half-lives of several decades (Landsverk et al., 2017). Moreover, following respiratory infections with common coronaviruses, nasal IgA levels are actually maintained quite stably (Callow et al., 1990). Thus, a mucosal vaccine that elicits durable immunity, while perhaps not easily achievable with our current knowledge, is certainly biologically possible, especially if paired with pan-sarbecovirus vaccine strategies.

CONCLUDING REMARKS

Over two years into the pandemic, one can be forgiven for becoming discouraged that the vaccines will not be able to keep up with the virus and that waning immunity will doom us to booster shots every few months. Yet I firmly believe that this is not our fate. There are enough biological counterexamples to support my view. Many of these prior successes have perhaps occurred as much by luck as by plan, but these examples have provided footholds to vary, measure, and define the key vaccine features. By focusing on the basics and defining specific rules of durable humoral immunity, there is every reason to think that vaccines can be designed to confer broad and lasting immunity.

As we define these rules, what am I most optimistic about in the short-term given the general knowledge and vaccine platforms before us? There are a few items, organized in order of what is immediately available now to what I expect will be coming in the next few years. First, early evidence seems to suggest that the Ad26.Cov2.S vaccine, which yields modest antibody levels as a single primary shot, may maintain antibody production more stably than another mRNA dose when given as a booster (Liu et al., 2022). Second, this "best of both worlds" strategy will be further supported once the Ad26.Cov2.S (and mRNA) vaccines are updated to match at least the Omicron variant but ideally contain a few different circulating spike variants to broaden antigenic coverage as much as possible. Third, intranasal adenovirus-based vaccine trials are currently ongoing (Bharat Biotech International Limited, 2021), potentially allowing for local mucosal immunity through a "prime and pull" strategy akin to animal models of vaccination against herpes simplex virus (Shin and Iwasaki, 2012). Fourth, variant-proof pan-sarbecovirus nanoparticle vaccines are coming (Dolgin, 2022). Which of these specific platforms wins out remains to be seen and may be driven as much by logistical and manufacturing considerations as by effectiveness. Yet, given all of the pre-clinical data thus far, it seems very likely that such vaccines will at the minimum lengthen the amount of time it takes for the virus to escape neutralizing antibodies. If one is allowed to hope a bit, combining these strategies could leave one protected against SARS-CoV-2 for life.

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DECLARATION OF INTERESTS

Sana Biotechnology has licensed intellectual property of D.B. and Washington University in St. Louis. Gilead Sciences has licensed intellectual property of D.B. and Stanford University. D.B. is a co-founder of Clade Therapeutics. D.B. serves on an advisory panel for GlaxoSmithKline. D.B. and The University of Arizona hold a patent on SARS-CoV-2 serological assays.

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