Modulation of humoral immunity by γδ T cells: a potential adjuvant strategy for vaccination

Kirsty Emery [a b], Matthias Eberl [a b *]

[a] *Division of Infection and Immunity, School of Medicine, Cardiff University, Cardiff, United Kingdom*

[b] *Systems Immunity Research Institute, Cardiff University, Cardiff, United Kingdom*

[*] Corresponding author. e-mail address: eberlm@cf.ac.uk

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Contents

Abstract

Vaccination is arguably the most effective intervention in reducing the impact of infectious diseases. However, many vaccines provide only partial or transient protection, prompting the need for more effective solutions based on our growing understanding of the pivotal role of $CD4^+$ T follicular helper (Tfh) cells in humoral immunity and how they interact with B cells. Here we review how γδ T cells can boost antibody responses via crosstalk with both Tfh and B cells, which could lead to new adjuvant strategies to improve vaccination efficacy, achieve long-lasting protective immunity and prevent major infectious diseases of global importance.

Keywords

- γδ T cells
- T follicular helper cells
- B cells
- Broadly neutralising antibodies
- Humoral immunity
- Vaccines
- Adjuvant
- Tuberculosis
- Malaria
- HIV

Abbreviations

ADCC	Antibody-dependent cellular cytotoxicity
APC	Antigen presenting cell
Ascl2	Achaete-scute complex homolog 2
BCG	Bacille Calmette-Guérin
BCL6	B-cell lymphoma 6
BCR	B cell receptor
Blimp-1	B lymphocyte induced maturation protein 1
bnAbs	Broadly neutralising antibodies
BTN	Butyrophilin
CMV	Cytomegalovirus
COVID-19	Coronavirus disease 2019
cTfh	circulating follicular T helper
CXCL	CXC chemokine ligand
CXCR	CXC chemokine receptor
DC	Dendritic cell
FOXP3	Forkhead box P3
GC	Germinal centre
HIV	Human immunodeficiency virus
HMB-PP	(*E*)-4-Hydroxy-3-methyl-but-2-enyl pyrophosphate
ICOS	Inducible T cell costimulator (CD278)
ICOSL	Inducible T cell costimulator ligand (CD275)
MCMV	Murine cytomegalovirus
Mtb	*Mycobacterium tuberculosis*
PD-1	Programmed cell death protein 1 (CD279)
SAP	Signalling lymphocytic activation molecule-associated protein
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SHIV	Simian-human immunodeficiency virus
SIV	Simian immunodeficiency virus
TCR	T cell receptor
TB	Tuberculosis
Tfh	T follicular helper
Tfr	T follicular regulatory
Tox2	Thymocyte selection-associated high mobility group box protein 2
Treg	T regulatory

1. Introduction

Vaccination remains one of the most impactful medical interventions in history, significantly contributing to the reduction in mortality, morbidity and prevalence of some of the most detrimental human diseases (Li et al., 2021). Effective and safe vaccines have played a crucial role in combatting severe childhood infections such as measles, meningitis and diphtheria, have helped controlling the coronavirus disease 2019 (COVID-19) pandemic, and offer partial protection against seasonal influenza to the most vulnerable members of society (Emery et al., 2025). The global eradication of smallpox and the near-eradication of polio illustrate the remarkable success of worldwide immunisation efforts. In some cases, where no targeted treatment exists, such as polio and measles, vaccination and social distancing are in fact the only public health measures to prevent the spread of infection. However, despite impressive scientific and medical progress over the past decades, not all vaccines can completely prevent disease transmission, and for some priority pathogens there are still no effective vaccines available. Some of the major global health threats that fall foul of this issue include tuberculosis (TB), malaria and influenza, where existing vaccines at best provide only partial protection, and those which have no licensed vaccine at all, such as human immunodeficiency virus (HIV) (Boomgarden & Upadhyay, 2025).

Whilst many vaccines preferentially elicit either cytotoxic or antibody-mediated immune responses, innovative attempts at exploiting the complementary action of T cells and B cells and their mutual crosstalk are needed to optimise vaccine efficacy. In this chapter, we review the status of vaccines against major diseases of global relevance and explore how humoral immunity could be leveraged to provide better protection, above all through an improved understanding of the pivotal role of $CD4^+$ T

follicular helper (Tfh) cells. Although Tfh cells are now recognised as key players in supporting B cell responses and determining the production of effective antibodies in secondary lymphoid tissues, the molecular mechanisms driving the activation and differentiation of Tfh cells remain incompletely understood (Vinuesa et al., 2016; Crotty, 2019). This is especially true with regard to how Tfh cells are generated during acute infections *in vivo*, and how Tfh cells can be specifically targeted using new vaccination approaches. Of note, other types of T cells have also been found to possess Tfh-like qualities including $CD8^+$ T cells (Yu & Ye, 2018) and γδ T cells (Tyler et al., 2015), suggesting a potential synergy between *bona fide* Tfh cells and other follicular T cells in regulating antibody responses during infections.

γδ T cells are unconventional T cells which have been implicated in multiple infectious and non-infectious contexts, often straddling innate and adaptive immunity (Vantourout & Hayday, 2013; Vermijlen et al., 2018). This is particularly true for human γδ T cells carrying a Vγ9/Vδ2 T cell receptor (TCR) and harbouring a unique responsiveness towards the microbial metabolite (*E*)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMB-PP) (Eberl et al., 2003; Yuan et al., 2023). Being the most prominent γδ T cell population in human blood, Vγ9/Vδ2 T cells display pro-inflammatory and cytolytic activities but also the ability to assume functions associated with Tfh cells and professional antigen presenting cells (APCs), and are thereby capable of influencing the differentiation of B cells and $CD4^+$ T cells into antigen-specific effector cells (Tyler et al., 2015). The present review seeks to summarise our current understanding of the role of γδ T cells in infection, with a focus on their involvement in humoral responses. After providing a comprehensive overview of cutting-edge investigations in cell culture, human patients and animal models, we explore how specific targeting of γδ T cells and their downstream effect on Tfh cells

could be exploited for innovative adjuvant approaches aimed at improving vaccination outcomes across a number of infectious diseases.

2. The humoral immune response

2.1. B cells

B cells are lymphocytes which originate in the bone marrow and are key to the humoral arm of adaptive immunity, producing antibodies against pathogens, allergens and self-proteins. They are also part of a subset of cells known as professional APCs, such as dendritic cells (DCs) and macrophages, which specialise in presenting antigen to naïve T cells (Rastogi et al., 2022). B cells require the presence of their cognate antigen to become activated, predominantly in secondary lymphoid tissues (Batista & Harwood, 2009), and migrate to the follicles towards the B cell attracting chemokine CXCL13 (Legler et al., 1998). If a B cell does not encounter its cognate antigen it will leave the follicle, re-enter the blood stream and migrate to other lymphoid tissues to continue surveillance (Cyster & Allen, 2019). Upon recognition of antigen by the B cell receptor (BCR), B cells will internalise the BCR together with the bound antigen, leading to breakdown of the antigen and subsequent display of peptides on MHC II molecules on the surface of the B cell, ready for display to $CD4^+$ T cells (McShane & Malinova, 2022). B cells subsequently follow either an extrafollicular or GC differentiation pathway. The extrafollicular response involves differentiation into short-lived plasmablasts or short-lived memory B cells. GC B cells which receive 'help' from specialised $CD4^+$ T cells, known as Tfh cells, proliferate and differentiate into long-

lived plasmablasts or long-lived memory B cells through the GC reaction (Crotty, 2015).

Each B cell clone produces a single immunoglobulin isotype, specific for a given epitope, functions of which include direct neutralisation of pathogens, opsonisation of targets for destruction via the complement system, activation of antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent phagocytosis (Forthal, 2014). Naïve B cells will produce IgM and IgD antibodies and require antigenic stimulation as well as T cell help to undergo isotype switching to IgG, IgE and IgA isotypes, all of which display specific functions (Stavnezer et al., 2008). B cells also undergo somatic hypermutation leading to affinity maturation in response to T cell help, a process of acquiring random mutations in the genomic DNA encoding the antibodies. This process may either cause the loss of antigen recognition and eventually lead to apoptosis of the B cell, or improved recognition, thereby increasing survival and proliferation of the B cell and contributing to highly specific antibody production (Nothelfer et al., 2015).

In addition to the antibody-secreting function of B cells in response to an ongoing infection, an important mechanism of protection against infection is that of long-lasting B cell memory derived from differentiating GC B cells after additional antigen stimulation and T cell help (Akkaya et al., 2020). It is these cells that recall the initial infection (or vaccination), mounting an accelerated and antigen-specific immune response to rapidly clear infections by pathogens carrying the exact same epitopes as the original strain encountered. Memory B cells can persist for many years and, in some cases, provide life-long protection.

2.2. T follicular helper cells

The principle of T cell help to B cells is a crucial aspect of the development of immunological memory. Tfh cells were initially discovered in human tonsils, secondary lymphoid organs with an abundance of active germinal centres (GCs). The Tfh population was initially defined as $CD4^+$ αβ T cells expressing the chemokine receptor CXCR5, which binds CXCL13 (Breitfeld et al., 2000; Schaerli et al., 2000). B-cell lymphoma 6 (Bcl6) was later recognised to be the master transcription factor regulating the development of Tfh cells (Chtanova et al., 2004), which is counteracted by B lymphocyte induced maturation protein 1 (Blimp-1) (Johnston et al., 2009). More recently, a role for thymocyte selection-associated high mobility group box protein 2 (Tox2) in driving Bcl6 expression and in generating and maintaining Tfh cells was described (Xu et al., 2019; Horiuchi et al., 2019). Differentiation of Tfh cells is a multi-stage process dependent on a series of sequential interactions (Crotty, 2014). Tfh differentiation is initiated upon naïve $CD4^+$ T cell priming by APCs, most commonly dendritic cells (DCs) (Ballesteros-Tato & Randall, 2014). In mice, this interaction is regulated by APC expression of IL-6 (Nurieva et al., 2009), leading to the upregulation of the transcription factor achaete-scute complex homolog 2 (Ascl2), which in turn upregulates CXCR5 expression on $CD4^+$ T cells, thus enabling them to migrate to the CXCL13-rich B cell follicle where they undergo further differentiation (Liu et al., 2014). In humans, upregulation of CXCR5 and migration to the follicles is predominantly driven by IL-12 and IL-23 in combination with TGF-β (Schmitt et al., 2014). ICOS:ICOSL binding has also been shown to be an important factor in the early co-localisation of $CD4^+$ T cells and B cells (Xu et al., 2013), in most instances requiring the interaction with activated B cells displaying cognate antigen for Tfh differentiation (Crotty, 2011). The final stage of Tfh cell differentiation occurs within the B cell follicles,

where Tfh cells become GC Tfhs, characterised as CXCR5^{hi} PD-1^{hi} BCL6^{hi} Maf^{hi} SAP^{hi} cells which secrete IL-4, IL-21 and CXCL13. Signalling lymphocytic activation molecule-associated protein (SAP) is used to adhere to B cells allowing for sustained GC reactions, representing an essential mechanism in the generation of memory B cells and memory plasma cells (Crotty, 2014). GC Tfhs provide help to B cells through both secretion of cytokines and T:B cell interactions. Of note is the plasticity of Tfh cell differentiation, since Tfh cells may leave the GC to travel to other follicles, re-enter the same GC or become circulating memory Tfh cells (Crotty, 2014). Memory Tfh cells are long-lived and can rapidly become GC Tfh cells upon reactivation in response to B cell contact. This plasticity is also reflected in the production of cytokines, whereby Tfh cells can secrete IL-4 in the absence of other Th2-related markers, and may also secrete IFN-γ, thereby directing which antibody classes B cells switch to (Reinhardt et al., 2009). A specialised population of Tfh cells that expresses the FOXP3 master transcription factor for T regulatory (Treg) cells and can suppress Tfh cell-mediated antibody responses is referred to as T follicular regulatory (Tfr) cells (Sage & Sharpe, 2015; Fonseca et al., 2019).

2.3. Germinal centres

A large population of naïve B cells resides within the spleen and secondary lymphoid organs in structures called follicles, which also harbour follicular DCs and are surrounded by a T cell zone, containing Tfh cells as well as naïve CD4$^+$ and CD8$^+$ T cells. GCs are distinct secondary structures within the follicles, consisting of a light zone and a dark zone, where processes such as somatic hypermutation, affinity maturation, class-switch recombination, B cell proliferation, and differentiation of

plasma and memory B cells occur (Victora & Nussenzweig, 2012). Upon infection or vaccination, B cells that have encountered their cognate antigen differentiate into memory B cells, extrafollicular plasmablasts and GC B cells. These GC B cells seed the GC, migrating to the T cell border where they are selected for Tfh help on the basis of antigen affinity. High affinity clones migrate back to the dark zone where they undergo intense proliferation and somatic hypermutation, before repeating multiple rounds of selection, proliferation and affinity maturation (Young & Brink, 2021). From the GC reaction, memory B cells and long-lived plasma cells are produced, the latter of which consistently secrete high levels of antibodies into the circulation, thus conferring protection (Luo & Yin, 2021). B cells with lower affinity BCRs may not receive Tfh cell help and consequently undergo apoptosis. Tfh cell help consists of stimuli in the form of both cell contact-mediated ligation of receptors found on B cells through molecules such as ICOSL and CD40L, and soluble factors such as IL-4 and IL-21 (Crotty, 2015). It is worth noting that class-switch recombination is not limited to GC B cells and has been demonstrated to occur both before GC differentiation and in *in vitro* culture systems (Young & Brink, 2021).

2.4. Exploitation of the GC reaction for improved vaccine efficacy

Most vaccines aim to induce long-lasting protection through antibodies as opposed to cell-mediated responses, classical examples for which include the hepatitis B, yellow fever, smallpox and measles vaccines. However, the quality, quantity and longevity of antibody responses are often less than satisfactory, necessitating novel ways to induce, boost and maintain humoral immunity. In this respect, the induction of optimal Tfh responses to enhance vaccine efficacy is an active area of research (Linterman &

Hill, 2016; Law et al., 2020; Ritzau-Jost & Hutloff, 2021; Yu et al., 2022; Juno & Hill, 2022). Tfh cells are believed to possess at least four key functions that are relevant in the context of protective immunity. Firstly, supporting the production of protective antibodies; secondly, inducing the generation of memory B cells that can rapidly respond to re-infection; thirdly, sustaining $CD8^+$ T cell-mediated cytotoxicity; and lastly, regulating IgA quality and quantity in mucosal-associated lymphoid tissues (Yu et al., 2022). The generation of Tfh cells is associated with protective antibody responses across a wide variety of pathogens, including infections with Zika virus (Liang et al., 2019), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Charmetant et al., 2022) and chimeric simian-human immunodeficiency virus (SHIV) (Yamamoto et al., 2015), bacteria such as *Citrobacter rodentium* (Bai et al., 2020) and *Salmonella typhi* (Perez-Shibayama et al., 2014), and parasites such as *Plasmodium* spp. (Figueiredo et al., 2017; Chan et al., 2020). The presence of antigen-specific Tfh cell subsets circulating in the periphery is associated with protective antibody responses, for instance to influenza virus infection, and has been suggested as an early biomarker for predicting vaccine efficacy and potential for long-lasting antibody responses (Spensieri et al., 2016).

A range of adjuvants targeting Tfh cell differentiation have been shown to support the formation of GCs and increase the magnitude of antigen-specific B cell responses. For example, MF59 is an oil-in-water emulsion that induces high levels of functional antibodies and memory B cells by increasing APC recruitment to the draining lymph nodes. This in turn activates and promotes the differentiation of Tfh cells and amplifies the number of GC B cells, thereby affecting the magnitude of the GC response and the persistence of functional antibody production (Mastelic et al., 2015; Lofano et al., 2015). Incomplete Freund's adjuvant is another oil-in-water emulsion that similarly

drives Tfh cell differentiation and T cell-dependent antibody production (Riteau et al., 2016). Glucopyranosyl lipid adjuvant-stable emulsion (GLA-SE) promotes the expansion of circulating Tfh (cTfh) cells, leading to long-lasting IgG responses when used in experimental malaria vaccines in humans (Hill et al., 2019). Adjuvants for use with the Pfs25 vaccine against malaria are characterised by increased Tfh differentiation, a higher Tfh:Tfr ratio, and expansion of antigen-specific plasmablasts, corresponding with higher peak titres of antigen-specific IgG antibodies, both in the short and longer term (Radtke et al., 2017). Other strategies for vaccine development include the use of nanoparticles, which can drive Tfh differentiation and enhance B cell responses to malaria subunit vaccines (Moon et al., 2012), and elicit protective antibodies in mice in response to SARS-CoV-2 and influenza mRNA vaccines (Alameh et al., 2021). Whilst increased Tfh activity may also cause the expansion of autoreactive and low-affinity B cells (Roider et al., 2018), this can actually be of potential benefit for vaccine efficacy, as both autoreactive and broadly neutralising antibodies (bnAbs) typically derive from low-affinity B cell clones (Ronsard et al., 2023).

3. γδ T cells

3.1. γδ T cells in infection

Having been recognised as a novel and distinct T cell population set apart from classical $CD4^+$ and $CD8^+$ T cells (Brenner et al., 1986), γδ T cells were soon implicated in a wide range of infectious diseases including TB (Kabelitz et al., 1990). Patients with different bacterial infections were sometimes found to exhibit elevated levels of

Vγ9/Vδ2 T cells in their blood, suggesting their expansion in response to a common antigen shared by many microorganisms (Morita et al., 2007). This enigma was solved by the discovery of HMB-PP, a highly potent metabolite produced by most Gram-negative and many Gram-positive bacteria (Eberl et al., 2003). HMB-PP is also produced by apicomplexan protozoa such as malaria parasites and *Toxoplasma gondii*, consistent with their capacity to trigger Vγ9/Vδ2 T cell responses (Guenot et al., 2015; Junqueira et al., 2021; Ma et al., 2021). Vγ9/Vδ2 T cells actually do not recognise HMB-PP directly through their T cell receptors (TCRs) but instead sense this molecule via its binding to the intracellular domains of the butyrophilin (BTN) family members BTN2A1 and BTN3A1 (Yuan et al., 2023), leading to a conformational change of the BTN2A1/BTN3A1 complex on the cell surface (Fulford et al., 2024; Herrmann & Karunakaran, 2024). This mechanism contrasts starkly with the classical model of antigen presentation to $CD4^+$ and $CD8^+$ T cells in the context of MHC and MHC-related molecules.

The link between bacterial HMB-PP production and Vγ9/Vδ2 T cell responses *in vivo* was elegantly shown in individuals with acute peritonitis where infections caused by HMB-PP producing species lead to a local increase in Vγ9/Vδ2 T cell in the abdomen compared to pre-infection levels and to levels in blood (Liuzzi et al., 2024). Recruitment from blood to sites of infection may indeed explain why levels of circulating Vγ9/Vδ2 T cell often drop in severe conditions such as sepsis (Eberl, 2025). However, not all bacteria associated with elevated blood levels of Vγ9/Vδ2 T cells produce HMB-PP, such as *Legionella* spp. (Kroca et al., 2001). More recently, the HMB-PP deficient bacterium *Staphylococcus aureus* was associated with a potential to skew Vγ9/Vδ2 TCR repertoires in neonatal sepsis (Giannoni et al., 2024), indicating

that microbial factors other than HMB-PP may also be able to trigger Vγ9/Vδ2 T cells either directly or indirectly (Kistowska et al., 2008; Cooper et al., 2020).

In addition to their responsiveness to bacterial infections, human γδ T cells also possess a remarkable potential to respond in viral diseases, most prominently in infections caused by cytomegalovirus (CMV). Patients developing CMV infections in the context of therapeutic immunosuppression after receiving transplants of kidney (Dechanet et al., 1999), lung (Stankovic et al., 2020) or stem cells (Knight et al., 2010) present with elevated levels of γδ T cells in their blood. This long-lasting expansion is restricted to γδ T cells expressing Vδ1, Vδ3 or Vδ5 TCR chains (often referred to collectively as Vδ2^{neg} γδ T cells), and directly correlated with the successful clearance of infection (Kaminski et al., 2020). A difference in the Vδ2^{neg} γδ T cell compartment is also apparent when comparing CMV seropositive and seronegative immunocompetent donors (Pitard et al., 2008). Unexpectedly, these CMV-driven γδ T cell responses do not appear to involve recognition of viral epitopes themselves (Vermijlen et al., 2018). In fact, all ligands for Vδ2^{neg} γδ T cell clones isolated from CMV patients so far have turned out to represent stress-related self-proteins such as endothelial cell protein C receptor (Willcox et al., 2012) and ephrin type-A receptor 2 (Harly et al., 2021), suggesting a role for Vδ2^{neg} γδ T cell in stress surveillance rather than a direct response to viral antigens (Prinz & Koenecke, 2023). Despite this bias towards conserved self-proteins, analysis of virus-reactive γδ TCR repertoires in stem cell transplant recipients with CMV reactivation (Ravens et al., 2017) and in CMV seropositive donors (Davey et al., 2017) provided clonotypic evidence for adaptive γδ T cell responses. It is interesting to note that controlled malaria infection in human volunteers induced not only expansion of Vδ2^{+} T cells but also activation of Vδ1^{+} and other Vδ2^{neg} γδ T cells, resembling the CMV infection response. This may point toward

a recognition of both HMB-PP and stress-related self-molecules in malaria (Rutishauser et al., 2020), a finding that was subsequently corroborated in children and adults with naturally occurring disease (von Borstel et al., 2021).

Besides HMB-PP producing microorganisms and CMV, human γδ T cells have also been implicated in the immune response to other infectious agents including HCV (Agrati et al., 2001), influenza (Sant et al., 2019), SARS-CoV-2 (Lei et al., 2020; Fears et al., 2022; von Borstel et al., 2023) and emerging viruses (Cimini & Agrati, 2022), as well as the measles, mumps, and rubella attenuated virus vaccine (Röring et al., 2024). The role of γδ T cells in mouse models of bacterial, viral, fungal and parasitic infection has been reviewed expertly by others (Andrew & Carding, 2005; Lalor & McLoughlin, 2016; Comeau et al., 2020; Fischer et al., 2020). However, the unclear antigen specificity of the vast majority of murine γδ TCRs combined with differences in pathogen tropism and the fact that mouse γδ T cells comprise anatomically distinct and clonotypically restricted populations, often without immediate human homologues, makes it difficult to reconcile data on γδ T cells during infections in mice with the function of their human counterparts in patients (Eberl, 2025).

3.2. Functional plasticity of γδ T cells

Human γδ T cells are typically regarded as pro-inflammatory and cytotoxic effector cells, combining functions of $CD8^+$ T cells and NK cells, in particular the expression of IFN-γ, TNF-α, perforin and granzymes, rendering them potent effectors against intracellular bacteria and parasites (Huang et al., 2008; Costa et al., 2011). However, investigations of how the prevailing cytokine milieu influences these cells during stimulation *in vitro* revealed that not all activated and proliferating Vγ9/Vδ2 T cells

possess a pro-inflammatory phenotype. As such, human Vγ9/Vδ2 T cells can be skewed into either IFN-γ producing or IL-4 producing effector cells, akin to the classical dichotomy of Th1 and Th2 cells in the $CD4^+$ T cell compartment (Wesch et al., 2001; Dagna et al., 2002), as confirmed in comprehensive microarray studies (Vermijlen et al., 2007). In the presence of IL-21, a cytokine closely related to IL-2 and IL-15, Vγ9/Vδ2 T cells do not produce pro-inflammatory cytokines (Eberl et al., 2002) and instead express molecules related to B cell help, most notably CXCL13 (Vermijlen et al., 2007; Bansal et al., 2012). Of note, Vγ9/Vδ2 T cells expanded in the presence of IL-2 appear to respond differently to cytokines like IL-21 compared to freshly isolated Vγ9/Vδ2 T cells, with reports showing that stimulation with IL-21 can increase the cytotoxicity of Vγ9/Vδ2 T cell lines (Joalland et al., 2018) but also give rise to a regulatory population expressing the ectonucleotidase CD73 as well as IL-10 and CXCL8 (Barjon et al., 2017). Culture in the presence of TGF-β and IL-15 gives rise to a population of Treg-like $FOXP3^+$ Vγ9/Vδ2 T cells (Casetti et al., 2009) that also produce IL-9 (Peters et al., 2016). Finally, and in contrast to the ease of inducing the above effector states in Vγ9/Vδ2 T cells, the *in vitro* generation of IL-17 and IL-22 producing Vγ9/Vδ2 T cells is possible but conspicuously inefficient and requires extended culture periods (Ness-Schwickerath et al., 2010). In this respect neonatal Vγ9/Vδ2 T cells appear to be more prone to producing IL-17 than those from adults (Moens et al., 2011).

Analysis of human tissue samples demonstrated that such phenotypes can also be found under physiological conditions, namely IL-4 producing Vγ9/Vδ2 T cells in the blood of healthy controls and HIV patients (Dobmeyer et al., 2002), GATA3 expressing Vγ9/Vδ2 T cells in the blood of patients with IgG4-related disease (Li et al., 2025) and low but detectable levels of IL-4 production by Vγ9/Vδ2 T cells in human spleen (Wang

et al., 2024). Coulter et al. (2017) found a very low proportion of IL-17 producing Vγ9/Vδ2 T cells in TB patients, whereas marginally elevated levels of IL-17$^+$ Vγ9/Vδ2 T cells are present in autoimmune regulator gene (AIRE) deficient patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (Fujikado et al., 2016). Together, these findings suggest that Vγ9/Vδ2 T cells are in fact highly pleiotropic cells that may assume a range of different regulatory and effector functions depending on the anatomical location and microenvironmental conditions, similarly to the well-established plasticity of CD4$^+$ T cells (Figure 1). The lack of suitable antigens to specifically stimulate non-Vγ9/Vδ2 T cells *in vitro* and *in vivo* has largely prevented similar studies on the potential plasticity of other γδ T cell subsets in humans and animal models.

3.3. γδ T cell crosstalk with B cells

Shortly after their first detection in tonsils, lymph nodes and spleen (Groh et al., 1989), a direct role for γδ T cells in modulating antibody production and humoral immunity was demonstrated. Rajagopalan et al. (1990) described the isolation of anti-DNA autoantibody-inducing γδ T cells from the blood of lupus patients; four selected γδ T cell clones were later sequenced and found to possess unusual Vδ2^{neg} TCRs (Rajagopalan et al., 1992). In similar experiments, γδ T cells isolated from patients with Sjögren's syndrome (Gerli et al., 1993), IgA nephropathy (Toyabe et al., 2001) and IgG4-related disease (Li et al., 2025) were able to provide B cell help *in vitro*, and supernatants from *Paracoccidioides brasiliensis*-stimulated human γδ T cells supported proliferation and antibody production by B cells (Munk et al., 1995).

These findings were corroborated in mouse models where γδ T cells restricted by the MHC class Ib molecule Qa-1 help B cells to produce antigen-specific antibodies (Vidovic & Dembic, 1991). In fact, TCRα$^{-/-}$ mice deficient in αβ T cells are still able to produce class-switched IgG and IgE antibodies (Wen et al., 1994), and γδ T cells on their own are capable of GC formation in TCRα$^{-/-}$ (Dianda et al., 1996) and TCRβ$^{-/-}$ mice (Pao et al., 1996) and upon transfer of γδ T cells into SCID mice (Wen et al., 1996). However, many γδ T cell-driven antibodies appear to be autoreactive (Wen et al., 1994), suggesting a qualitative difference between the help provided by αβ T cells and γδ T cells. In support, infection of TCRβ$^{-/-}$ mice with the parasite *Eimeria vermiformis* gave rise to antibodies that were frequently directed against self rather than against the parasite (Pao et al., 1996), contributing to a failure of TCRβ$^{-/-}$ mice to mount protective immunity upon infectious challenge (Roberts et al., 1996). Similarly, γδ T cells in the murine skin that are involved in stress surveillance drive class switching in B cells and accumulation of autoreactive IgE after topical challenge with carcinogen (Crawford et al., 2018). With regard to the underlying molecular mechanisms, expression of CD40L by activated γδ T cells was shown to be key to inducing isotype switching to IgE in mice (Horner et al., 1995). Other investigations identified a prominent role for cytokines, in particular IL-4, in providing B cell help (Felices et al., 2009; Qi et al., 2009; Huang et al., 2015). IL-4 producing γδ T cells sustain GC reactions in murine secondary lymphoid tissues and drive class-switching towards IgA (Ullrich et al., 2021), with evidence for a direct interaction between γδ T cells and B cells in the spleen (Huang et al., 2016; Rampoldi et al., 2022). In other physiological contexts and models, γδ T cells can also modulate antibody production via secretion of IFN-γ (McMenamin et al., 1995; Maloy et al., 1998).

In humans, the observation that Vγ9/Vδ2 T cells upregulate CCR7 upon activation suggested a potential to migrate to draining lymph nodes and modulate adaptive immune responses, supported by the detection of γδ T cells in GCs and direct evidence for B cell help *in vitro* (Brandes et al., 2003). More recent studies detected γδ T cells both within the T cell zone of human tonsils and spleen but also adjacent to it and within the B cell zone (Hagel et al., 2021; Charmetant et al., 2025). While circulating Vγ9/Vδ2 T cells do not express CXCR5 or BCL6 (Bansal et al., 2012; Barber-Axthelm et al., 2023), tonsillar Vγ9/Vδ2 T cells readily upregulate CXCR5 in response to HMB-PP (Bansal et al., 2012). Microarray analyses identified a particular role for the Tfh signature cytokine IL-21 in inducing CXCL13 in human Vγ9/Vδ2 T cells (Vermijlen et al., 2007). IL-21 also enhances the potential of Vγ9/Vδ2 T cells to provide B cell help, as shown by induction of APC marker expression by B cells and their secretion of IgG and IgA (Bansal et al., 2012). Of note, the positive effect on B cell maturation and antibody production is not an intrinsic feature of human Vγ9/Vδ2 T cells (Petrasca & Doherty, 2014) but is also seen in other γδ T cells (Petrasca et al., 2018), and even extends to other unconventional T cell populations including natural killer T cells (Galli et al., 2003) and mucosal-associated invariant T cells (Bennet et al., 2017; Jensen et al., 2022).

These experimental insights evoke a role for γδ T cells in supporting and modulating humoral immune responses in different physiological scenarios, be it in an infectious or autoimmune context (Figure 1). The fact that most γδ T cell ligands identified so far are stress-related proteins or BTN family members (Vermijlen et al., 2018) may explain in part why γδ T cell-induced antibody responses on their own often appear to be directed against self, with the actual antigen specificity of the immune response against microbial or viral epitopes rather provided by individual Tfh cells with fitting

clonotypes. However, γδ T cells have another trick up their sleeves that may compensate for their missing selectiveness for foreign antigens during an ongoing immune response – their potential to act as APCs themselves.

3.4. Antigen presentation by γδ T cells

Activated Vγ9/Vδ2 T cells express CCR7 and thus are likely to gain access to draining lymph nodes (Brandes et al., 2003) but unexpectedly also acquire markers typically associated with antigen presenting cells such as HLA-DR, CD80 and CD86, as well as elevated levels of HLA-ABC (Brandes et al., 2005). While HLA-DR is expressed by many activated T cells and may allow antigen presentation to neighbouring $CD4^+$ T cells, only Vγ9/Vδ2 T cells appear to be able to act as truly professional APCs by priming naïve $CD4^+$ and $CD8^+$ T cells (Brandes et al., 2005). In fact, this striking capacity is comparable to the potency of other professional APCs such as monocyte-derived DCs. Activated Vγ9/Vδ2 T cells are particularly effective in taking up exogenous proteins and larger aggregates including virions, and cross-presenting these to naïve $CD8^+$ T cells (Brandes et al., 2009; Meuter et al., 2010), thus inducing antigen-specific cytotoxic $CD8^+$ T cell responses with promise for novel immunotherapies (Landmeier et al., 2009; Himoudi et al., 2012; Holmen Olofsson et al., 2021; Wu et al., 2025). One report even suggested that Vγ9/Vδ2 T cells are capable of taking up whole bacteria (Barisa et al., 2017). Anatomical evidence shows that human γδ T cells co-localise with other T cells in lymphoid tissues such as tonsils (Hagel et al., 2021) but also in the gut (Oliver et al., 2024), suggesting their functional interaction during ongoing immune responses. Duringmixed lymphocyte reactions in co-culture with naïve $CD4^+$ T cells from allogeneic donors, activated Vγ9/Vδ2 T cells

readily induce proliferation and differentiation of naïve CD4⁺ T cells towards distinct effector populations, including Th1 and Th22 but not Th17 cells, depending on the prevalent cytokine milieu during such experiments (Tyler et al., 2017); more recently, induction of IL-10 expression in naïve CD4⁺ T cells by IL-21 activated Vγ9/Vδ2 T cells was described (Tyler et al., 2024). It at present is unclear whether antigen presenting Vγ9/Vδ2 T cells can also polarise naïve human CD4⁺ T cells towards other effector functions under the right conditions, perhaps including a Tfh cell profile.

In mice, activated γδ T cells can express MHC II molecules and present peptides to antigen-experienced αβ T cells (Cheng et al., 2008) and regulate IgE antibody production (Huang et al., 2013). A peculiar population of regulatory γδ T cells that express latency-associated peptide (LAP) was identified in murine Peyer's patches and lamina propria of the small intestine. These cells co-express MHC II, CD40 and CD86, and are able to induce CD4⁺ Foxp3⁺ Treg cells (Rezende et al., 2015). In addition to mice and humans, activated γδ T cells in cattle (Collins et al.,1998), pigs (Takamatsu et al., 2002) and even zebrafish (Wan et al., 2017) can also express MHC II and induce recall responses by antigen-specific T cells, demonstrating an evolutionarily conserved role of APC-like γδ T cells in driving adaptive immune responses. Depletion and adoptive transfer studies confirmed that zebrafish γδ T cells actively boost the proliferation of antigen-primed CD4⁺ T cells and B cells, as well as supporting antigen-specific antibody production *in vivo* (Wan et al., 2017). However, a professional APC function for γδ T cells in non-human species has thus far only been demonstrated in a limited number of studies, using naïve CD4⁺ T cells as responder cells (Rezende et al., 2015). The wider physiological relevance of antigen presenting γδ T cells in animal models therefore requires closer attention.

In humans, Vγ9/Vδ2 T cells with APC characteristics have been described in patients with malaria (Howard et al., 2017; Dooley et al., 2023), HIV (Griffith et al., 2025), sepsis (Yang et al., 2022; León-Lara et al., 2024), rheumatoid arthritis (Hu et al., 2011) and cervical cancer (Wu et al., 2025), and may well play a key part in driving protective but also autoreactive immune responses and in affecting the development of immunological memory. As such, it is conceivable that γδ T cells may be able to modulate humoral immune responses not only by directly interacting with B cells but also indirectly by giving rise to antigen-specific Tfh cells, thereby affording an important role to all three cell types in the generation of high affinity, class-switched antibodies (Figure 1). As reviewed in the next section, this may well be the case.

3.5. γδ T cell modulation of Tfh cells

In addition to the well-documented interaction between γδ T cells and B cells, there is growing evidence for direct modulation of Tfh responses by γδ T cells. For instance, Mou et al. (2017) identified CXCR5$^+$ Tfh-like γδ cells in neuroblastoma patients and showed that their levels positively correlate with total serum IgG and CD19$^+$ CD27^{hi} plasma cells, potentially via an enhanced production of IL-4 and IL-10 by γδ T cells. Chen et al. (2018) activated human CD4$^+$ T cells with influenza-pulsed DCs, before co-culturing them with autologous B cells and human Vδ2$^+$ T cells. This experimental system led to the adoption of a Tfh-like phenotype by Vδ2$^+$ T cells, characterised by expression of CXCR5, PD-1, CD40 and ICOS, as well as expression of the APC markers HLA-DR, CD80 and CD86. In turn, these γδ T cells generated CXCR5$^+$ BCL6$^+$ Tfh cells through cell-cell contact with CD4$^+$ T cells (Chen et al., 2018). By helping virus-specific antibody responses in a CD4$^+$ T cell dependent manner, this co-culture

system confirmed that the premise of Tfh differentiation by antigen presenting γδ T cells is not only possible but functional (Chen et al., 2018). In a similar set-up using co-culture of BCR-primed B cells, allogeneic $CD4^+$ T cells and syngeneic γδ T cells, Charmetant et al. (2025) failed to demonstrate a Tfh or APC-like function for human γδ T cells, most likely due to the absence of an appropriate stimulus to activate γδ T cells.

In a mouse model of *Plasmodium berghei* infection, $TCR\delta^{-/-}$ mice displayed reduced levels of antigen-specific antibodies and fewer Tfh and GC B cells during late-phase infection compared to wild-type mice, suggesting a role for γδ T cell-derived IL-21 and IFN-γ in the development and maintenance of Tfh and GC B cells (Inoue et al., 2018). When immunising mice with Mtb-containing complete Freund's adjuvant, increased expression of CXCR5 was seen on $V\gamma1^+$ T cells (but not other γδ T cells) in the draining lymph nodes, in a TCR-dependent manner (Rezende et al., 2018). These $CXCR5^+$ γδ T cells did not express CD40L or IL-21 and were not able to provide direct B cell help themselves. However, they co-expressed MHC II, CD40, CD86 and Wnt8b, a member of the Wnt agonist family, which was previously shown to initiate the Tfh differentiation pathway in mice through upregulation of Ascl2 (Liu et al., 2014). Since Ascl2 in turn induces CXCR5 expression and proliferation of naïve $CD4^+$ T cells (Liu et al., 2014), these findings are the first demonstration in any species of γδ T cells polarising $CD4^+$ T cells towards a Tfh phenotype (Rezende et al., 2018). $CXCR5^+$ γδ T cells were also seen in mice with lupus induced by injection of pristane, a natural saturated terpenoid alkane from shark liver oil, where they are likely to contribute to autoantibody production and the development of glomerulonephritis (Rezende et al., 2018; Kaminski et al., 2021).

In humans, the molecular signals by which γδ T cells might trigger generation of Tfh cells remain to be identified. Earlier work on the regulation of $CD4^+$ T cell differentiation by antigen presenting Vγ9/Vδ2 T cells already identified a role for IFN-γ and CD70 in Th1 polarisation, and for TNF-α and ICOSL in generating Th22 cells (Tyler et al., 2017). Vγ9/Vδ2 T cells can also give rise to IL-10 producing, Tr1-like $CD4^+$ T cells via an unknown mechanism potentially involving CD30 (Tyler et al., 2024), which is preferentially expressed on Th2-like Vγ9/Vδ2 T cells (Spinozzi et al., 1995; Dagna et al., 2002). It is noteworthy that Vγ9/Vδ2 T cells not only act as professional APCs themselves but also readily induce the maturation of DCs and the differentiation of monocytes and neutrophils into APCs, which likely boosts antigen presentation to $CD4^+$ T cells and activation and polarisation of $CD4^+$ T cells both at local sites of inflammation and in secondary lymphoid tissues (Ismaili et al., 2002; Tyler et al., 2015).

4. γδ T cells and vaccines against infections of global priority

While the mechanisms underlying initiation and modulation of humoral immune responses by Tfh cells are slowly being understood better, this knowledge has yet to be translated into the clinic for improved vaccine efficacy. Here we focus on some of the most pressing global health threats, including TB, HIV, CMV and malaria, which together claim millions of lives each year, and where γδ T cells may not only mediate direct cytotoxicity against infected cells but also modulate and boost pathogen-specific humoral immune responses to promote generation of protective antibodies.

4.1. Tuberculosis

With 1.25 million deaths in 2023, TB remains the leading cause of death from a singular infectious agent and was only briefly knocked off top spot during the recent COVID-19 pandemic (WHO, 2024a). To date, the single preventative measure against TB is the Bacille Calmette-Guérin (BCG) vaccine, a live attenuated strain of *Mycobacterium bovis* that was introduced a century ago and has not been modified since (Chen et al., 2023). Although it provides protection against primary childhood disease when given early in life, this approach has proven ineffective at an older age, and sparked controversy surrounding whether BCG can indeed prevent pulmonary disease (Hatherill & Cobelens, 2022; Martinez et al., 2022). These inadequacies underly the dire need for an improved and effective vaccine that works in all demographics.

The mechanism of protection afforded by the BCG vaccine is widely believed to constitute a cell-mediated process, and the involvement of humoral immunity to an intracellular pathogen that is not exposed to antibodies is largely neglected. Yet, there is growing evidence to support the involvement of B cells in protection against TB (Achkar & Casadevall, 2013; Kozakiewicz et al., 2013; Tanner et al., 2019). Mechanisms of antibody-mediated protection include neutralisation of bacteria, enhanced phagocytosis and phagolysosome formation, and formation of antibody-bacteria complexes, which increase T cell activation and cytotoxicity through improved antigen presentation (Tanner et al., 2019). Consideration of humoral immunity in TB thus offers a new facet of protection in the race to develop a vaccine that is both efficacious in all ages and effective against pulmonary disease.

Swanson et al. (2023) found a protective role for Tfh-like cells in mediating immunity against TB, through localisation of Tfh-like cells in granuloma-associated lymphoid tissues both in mice and macaques. In rhesus macaques, $CXCR5^+$ $CD4^+$ T cell localisation within granulomas is associated with better outcomes, and secretion of multiple pro-inflammatory cytokines is a correlate of protection (Slight et al., 2013). Activated $CXCR5^+$ $CXCR3^+$ Tfh cells can be found in the draining lymph nodes in TB (Prota et al., 2015), and accumulation of $CXCR5^+$ $CD4^+$ T cells appears to be needed for optimal macrophage activation (Gopal et al., 2013). Tfh cells produce large amounts of IL-21, which is necessary for maintaining pulmonary $CD8^+$ T cell responses in mouse models of TB, and promoting NK cell activation in humans, further cementing the role of Tfh cells in TB (Burkert & Schumann, 2020).

While antibodies may not have a direct protective function in TB, they may instead prevent Mtb dissemination (Swanson et al., 2023). Antibody signatures differ between active and latent TB, and correlate with increased FcγRIII binding. This in turn can upregulate NK cell activation and ADCC, as well as macrophage killing of Mtb, and contribute to infection outcomes (Lu et al., 2016). The importance of B cells and antibodies as key contributors to protective immune response in TB has been addressed in several vaccine trials, which identified a correlation between the induction of antigen-specific antibodies and vaccine efficacy (Rijnink et al., 2021). Tfh-like cells and antibodies thus have significance when considering vaccine design, as they are clearly implicated in the response to TB. Whilst the humoral response alone may not mediate total protection against the disease, engagement of this axis of defence may provide the tipping point for effective vaccines, especially in pulmonary TB.

It has long been understood that γδ T cells play a role in adaptive immunity to BCG and Mtb infections (Shen et al., 2002). Human Vγ9/Vδ2 T cells have a directly protective non-redundant role in volunteers with either latent TB or after BCG vaccination (Abate et al., 2015). Elevated γδ T cell frequencies are associated with host protection after intravenous administration of BCG in macaques (Darrah et al., 2020; Morrison et al., 2023). In humans, γδ T cells do not appear to change in frequency after BCG primary or booster vaccination in adults (Gela et al., 2022; James et al., 2022) but change their transcriptional programme towards a more pro-inflammatory phenotype likely to confer both protection against TB and cross-protection against heterologous infections (Suen et al., 2024). γδ T cells were found to be expanded in BCG vaccinated newborns (Gela et al., 2022), and specific TCR-Vδ2 clonotypes are enriched after BCG re-vaccination (James et al., 2022). This is in line with findings that potentially protective and antigen-specific clonotypes of γδ T cells are shared across individuals in diverse populations (Xia et al., 2023). However, such a BCG driven expansion of γδ T cells was not seen in another study and may be confounded by environmental phosphoantigen exposure early after birth (Papadopoulou et al., 2020). The protective role of γδ T cells is mediated through direct killing of intracellular Mtb as well as contact-dependent boosting of APC functions through CD40-CD40L interactions, thus enhancing the expansion of Mtb-reactive $CD4^+$ and $CD8^+$ T cells (Abate et al., 2015). In response to BCG, a tripartite immune cell co-operation mechanism occurs, wherein cytokines produced by DCs and $CD4^+$ T cells contribute to the activation of Vγ9/Vδ2 T cells (Fowler et al., 2013). However, with most investigations on γδ T cells in response to BCG and TB vaccination focussing on their cytotoxic potential, there is a missed opportunity to address and exploit the humoral role of γδ T cells in TB.

4.2. Malaria

In 2023, there were over 250 million malaria cases and almost 600 000 malaria deaths worldwide (WHO, 2024b). Malaria is caused by the parasite *Plasmodium falciparum* and four other closely related species with complex life cycle, which makes vaccine design challenging and has led to the development of separate strategies to protect against liver-stage and blood-stage infections. Recent breakthroughs include the successful licensing of vaccines RTS,S and R21, which both target the circumsporozoite protein and prevent liver infection via antibody-mediated protection. Whilst these vaccines will undoubtedly save countless lives, they only provide protection for a limited duration and require annual boosters. Moreover, they are only indicated for children and in the case of RTS,S require specialist components of which there is a finite amount (Duffy et al., 2024). Other vaccines are only in preclinical development to exploit other mechanisms of protection, including $CD4^+$ T cell, $CD8^+$ T cell, γδ T cell and antibody-mediated approaches (Cockburn & Seder, 2018; Kurup et al., 2019; Duffy et al., 2024).

A fully functioning Tfh response is deemed necessary for elimination of blood stage infection in mouse models of malaria (Pérez-Mazliah et al., 2017). In humans, *Plasmodium* infection is typically characterised by IFN-γ and TNF-α production, with a tendency to induce the differentiation of $CXCR5^+$ $CXCR3^-$ Th1-type cTfh cells. These cells are associated with impaired B cell function and a reduction in antibody quality and quantity, as well as poor differentiation of pre-Tfh cells into GC Tfhs (Obeng-Adjei et al., 2015; Hansen et al., 2017; Bowyer et al., 2018). Other cTfh subsets including a $CXCR3^-$ cTfh subset (Obeng-Adjei et al., 2015) and a Th2-type cTfh subset (Chan et al., 2020) have been associated with functional antibody responses to malaria

infection, prompting suggestions to target the differentiation of these populations during vaccination. Whilst Th1-type cTfh cells have been implicated in the induction of atypical memory B cell responses, which have been suggested to act as nutrient sinks affecting GC formation, evidence has emerged that such memory responses have fast recall abilities and the best capacity to give rise to complement-fixing protective IgG3 antibodies (Soon et al., 2021). Breadth of specificity and antibody response magnitude have been associated with protection in natural malaria infection, especially with specific antigen combinations (Osier et al., 2008). Tfh cells have an exhausted phenotype in malaria infections, with studies in mice demonstrating that blockade of IFN-γ and TNF-α can restore functionality to Tfh cells (Ryg-Cornejo et al., 2016). In addition, therapeutic ligation of OX40 can enhance T cell dependent humoral immunity to malaria in mice (Zander et al., 2016), and blockade of PD-L1 and Lag3 can enhance pathogen clearance by rescuing $CD4^+$ T cell exhaustion (Butler et al., 2011).

γδ T cells become activated early in malaria patients, with greater Vγ9/Vδ2 T cell numbers associated with protection (Mwakingwe-Omari et al., 2021), potentially as a result of enhanced $CD8^+$ T cell responses in the liver. Vγ9/Vδ2 T cell levels were also elevated in individuals protected from *P. falciparum* infection after receiving the irradiated sporozoite vaccine that confers sterile immunity (Zaidi et al., 2017). However, $Vδ1^+$ and $Vδ1^-Vδ2^-$ γδ T cells have also been demonstrated to respond in malaria infection (Rutishauser et al., 2020). Repeated malarial exposure results in a loss of $Vδ2^+$ T cells, correlating with improved clinical tolerance, a state that may contribute to ineffective pathogen clearance and enhanced transmissibility (Jagannathan et al., 2014; Jagannathan et al., 2017). As age increases so does control of blood stage infection, which could be attributed to development of humoral immunity but may also be due to the gain of effector functions by $Vδ2^+$ T cells, such

as phagocytosis or increased CD16 expression and ADCC activity (Jagannathan et al., 2017). de Jong et al. (2017) found that Vδ2$^+$ T cell levels increased in asymptomatic infected children and decreased after parasite clearance, a finding also corroborated in adults.

In mice immunised with circumsporozoite protein, γδ T cells provide help to B cells in the early response, leading to isotype switching from IgM to IgG (McNamara et al., 2022). γδ T cell deficiency in mice is associated with decreased Tfh and GC B cell numbers, and reduced antigen-specific antibody levels, presumably due to a lack of γδ T cell-derived IL-21 and IFN-γ (Inoue et al., 2018), suggesting a key role for γδ T cells in the humoral response to malaria infection (Bayarsaikhan et al., 2023). However, it is it unclear how this would translate into clinical settings, since Tfh cell differentiation in humans is controlled by different mechanisms (Crotty, 2014). There is also evidence that murine γδ T cells accumulate in the splenic white pulp during infection and provide support for maturation and activation of DCs, leading to optimal Th1 priming by the DCs (Ibraheem et al., 2024).

Supporting the capacity of γδ T cells to modulate humoral responses, human Vδ2$^+$ T cells can be distantly activated by schizont rupture of *P. falciparum*-infected red blood cells, demonstrating that blood stage culture supernatants are potent activators of Vδ2$^+$ T cells (Guenot et al., 2015), in agreement with the potential of malaria parasites to produce HMB-PP (Wiesner et al., 2003). These malaria parasite-activated Vδ2$^+$ T cells upregulate APC markers and can induce proliferation of CD4$^+$ and CD8$^+$ T cells (Howard et al., 2017). However, more work is needed to understand the targeting of γδ T cells in vaccination to optimise malaria-specific antibody production and T cell responses (Dantzler & Jagannathan, 2018).

4.3. Human immunodeficiency virus

HIV remains a major global health challenge for which there is no vaccine available despite four decades of research. The HIV pandemic has claimed more than 40 million lives to date, with a further 40 million people estimated to be living with HIV currently, and over 600,000 people succumbing to HIV-related causes in 2023 alone (WHO, 2024c). Antiretroviral therapy reduces viral load and shedding to ameliorate symptoms, prevent disease progression and reduce transmission of HIV, but it cannot protect against acquiring the disease, and patients remain on daily medication for life. The ultimate goal of a HIV vaccine is sterilising immunity. However, this has proven elusive, and efforts have moved towards taking control of viral load and transmission through vaccination. While T cell-mediated immunity is critical for resistance to HIV, the enormous genetic diversity of the virus, high rate of viral recombination and lack of effective antibody responses to the virus make the achievement of viral clearance though vaccination a Herculean task (Boomgarden & Upadhyay, 2025). The current focus of most HIV vaccine research surrounds the attempt to induce broadly neutralising antibodies (bnAbs), which have been shown in multiple clinical trials to be safe and efficacious in their antiretroviral activity (Boomgarden & Upadhyay, 2025). bnAbs are a result of extensive somatic hypermutation driving affinity maturation, a process controlled by the crosstalk between Tfh cells and B cells, indicating that Tfh cell responses to vaccination are crucial in the development of bnAbs against HIV (Moysi et al., 2018; Niessl & Kaufmann, 2018). Strategies to improve the quality and quantity of the Tfh cell response include the enhancement of APC recruitment and function, as well as the induction of Tfh cell promoting signals (Niessl & Kaufmann, 2018).

Of particular note for the design of HIV vaccines was the discovery of a circulating memory population of PD-1^{+} CXCR5^{+} CXCR3^{-} CD4^{+} T cells, which resemble the GC Tfh population and are highly functional in providing B cell help (Locci et al., 2013). These cells are over-represented in HIV-infected individuals who produce bnAbs against HIV. This is supported by the observation that an abundance of circulating memory Tfh cells correlates with the potential to develop bnAbs to HIV, along with a rise in autoantibodies, which may be due to increased Tfh cell frequencies (Moody et al., 2016). Higher PD-1 expression was also observed on Treg cells and Tfr cells, which may indicate a higher degree of immune activation leading to inhibition of regulatory processes (Moody et al., 2016). An expansion of blood CXCR5^{+} CXCR3^{+} PD-1^{lo} Tfh cells may indicate proliferation of precursors to the PD-1^{hi} Tfh-like population that supports development of bnAbs, and has been associated with the ability of individuals to control HIV infection (Martin-Gayo et al., 2017). Of note, children with HIV have a significantly higher number of Tfh cells than adults, both in blood and lymphoid tissues, and a larger proportion of HIV-specific Tfh cells capable of secreting IL-21 (Roider et al., 2018). Children with HIV are also characterised by a higher abundance of Tfr cells and HIV-specific CXCR5^{+} CD8^{+} T cells, all possibly contributing to a greater propensity to develop bnAbs compared to adults (Roider et al., 2018). Mathematical modelling by De Boer & Perelson (2017) indicated that increasing the breadth and magnitude of the Tfh cell response might facilitate the evolution of bnAbs, by allowing broadly reactive B cells to interact with a larger proportion of the Tfh cell population. Barouch et al. (2010) demonstrated the use of mosaic antigens in rhesus monkeys to widen the breadth and depth of the T cell response to HIV infection, which may overcome issues with virus diversity and viral escape mechanisms.

The role of γδ T cells in HIV has been studied extensively, yet predominantly with a view for use in the cure of HIV, not the prevention (Pauza et al., 2015; Biradar et al., 2020; Juno & Kent, 2020; Mann et al., 2020). Vδ2$^+$ T cells are generally found to be depleted in chronic HIV infection but increased in those who are natural viral suppressors (Riedel et al., 2009). Li et al. (2008) identified a positive correlation between γδ T cell numbers and the ability to control HIV, indicating the importance of this cell subset in the context of infection. It is thought that they contribute to protection through their cytotoxic potential, including ADCC *ex vivo* (Poonia & Pauza, 2012) and in HIV patients (He et al., 2013). A protective ability to inhibit replication and clear autologous CD4$^+$ HIV reservoirs *ex vivo* has been demonstrated for both Vδ1$^+$ T cells (Yonekawa et al., 2019) and Vδ2$^+$ T cells (Garrido et al., 2018). In support, higher levels of CD16 and CD57 expression on Vδ2$^+$ T cells are associated with the development of neutralisation breadth, that is, the ability of antibodies to bind epitopes that differ minorly from their target immunogen (Griffith et al., 2025). This benefit may be mediated by the ability of Vδ2$^+$ T cells to become APCs when in contact with opsonised target cells via CD16 (Himoudi et al., 2012). However, there has been some concern regarding evidence that Vδ2$^+$ T cells can be productively infected by HIV and represent a latent reservoir for the virus (Juno & Kent, 2020). Activation of γδ T cells as an adjuvant in a preventative vaccine should mitigate this risk.

4.4. Cytomegalovirus

CMV is a widespread virus carried by two in three adults in industrialised countries, with even higher prevalence in low and middle income countries (Fulkerson et al., 2021). Although usually only causing mild or no symptoms at all, CMV can lead to

severe disease in immunocompromised individuals, including neurodevelopmental disorders in congenital infections and complications in transplant recipients (Fulkerson et al., 2021). The immune system mounts both innate and adaptive responses to control CMV infection through the action of $CD8^+$ T cells, NK cells, γδ T cells and neutralising antibodies. However, the sophisticated ability of CMV to establish latency by evading immune detection and subverting antiviral mechanisms remains a challenge for the establishment of long-lasting protection, and no licenced vaccine against CMV is available (Plotkin & Boppana, 2019; Chiavarini et al., 2025).

A strong Tfh response to CMV and the generation of neutralising antibodies are believed to be key for effective viral control in immunocompetent individuals, which is weakened upon immunosuppressive treatment in transplant patients (Bruno et al., 2016). In support, Suàrez-Fernández et al. (2021) identified a correlation between pre-transplant cTfh levels and a lower incidence of CMV infection in kidney transplant recipients, presumably achieved by driving the production of CMV-specific neutralising antibodies and through IL-21-mediated enhancement of antiviral $CD8^+$ T cells. This is mirrored by findings in mice where deficiency in the NK receptor NCR1 (NKp46) led to a limited Tfh cell maturation and diminished generation of protective antibodies after infection with murine CMV (MCMV), a virus closely related to human CMV (Miletic et al., 2017). It is thus conceivable that a vaccine-mediated boost of cTfh levels and activities may contribute to increasing the resistance to CMV recurrence. Given the importance of humoral responses in protection against CMV, current efforts with regard to CMV vaccine research focus on the identification of neutralising antibodies (Gardner et al., 2016) and on exploiting ADCC as an effector mechanism (Vlahava et al., 2021; Semmes et al., 2023). As a case in point, a CMV mRNA-1647 vaccine that contains the coding sequences for components of the viral pentamer complex and the

full-length glycoprotein B (gB) elicits both broad neutralisation and potent ADCC responses (Hu et al., 2024).

γδ T cells play a key role in controlling CMV, to a large extent via direct cytotoxicity towards infected cells. This anti-CMV response by γδ T cells is driven by both $V\delta2^{neg}$ γδ T cells and a recently identified subset of $V\gamma9^{-}$ $V\delta2^{+}$ T cells (Kaminski et al., 2020). In experimental models using MCMV, γδ T cells participate in early antiviral responses (Ninomiya et al., 2000) and provide long-term protection in the absence of other T cells, B cells and NK cells (Sell et al., 2015; Khairallah et al., 2015; Yared et al., 2024). In addition to their recognition of stress-related proteins expressed by CMV-infected cells (Vermijlen et al., 2018), human γδ T cells can also become activated via antibodies triggering the low-affinity IgG receptor CD16 (FcγRIIIa). This allows γδ T cells not only to mount antiviral responses to antibody-opsonised virions (Couzi et al., 2012) and protect the foetus against congenital transmission by binding maternal antibodies (Vermijlen et al., 2010; Semmes et al., 2024) but may also contribute to the development of donor-specific antibody-mediated allograft lesions in transplant recipients (Bachelet et al., 2014; Kaminski et al., 2021). Therefore, the combination of TCR and CD16-mediated cytotoxicity as well as the ability to boost antiviral Tfh and B cell responses make γδ T cells a promising target for novel CMV vaccines, especially against congenital infections. However, the potential risk of enhancing allograft rejection and autoantibody generation needs to be considered.

4.5. Other priority areas for global health

An adjuvant strategy targeting γδ T cells could potentially help with the development of vaccines in countless other disease models, given the widespread benefit of

antibodies across many infections. For instance, seasonal influenza vaccines do not provide optimal protection against circulating influenza strains and only provide little protection against the threat of zoonotic or pandemic potential strains, necessitating the need for broadly effective, long-lasting protective vaccines (Fox et al., 2018). cTfh cells that express ICOS, CXCR3 and CXCR5 correlate with protective responses against influenza through interaction with memory B cells, inducing the production of high-titre specific antibodies, a key mediator of antigen specific immunity (Bentebibel et al., 2013; Hill et al., 2021). Thus, the above rationale applied to strategies using γδ T cells for vaccine design against HIV may also hold for influenza and other diseases for which bnAbs are required and where γδ T cells have been implicated in post-vaccination responses, such as COVID-19 (Terzoli et al., 2024; Andreu-Ballester et al., 2024). It is noteworthy that aging appears to result in alterations of the γδ T cell response that might have negative implications for conventional influenza vaccination efficacy (Stervbo et al., 2017).

Visceral leishmaniasis is an example of a neglected tropical disease for which there is no effective vaccine. It is a potentially lethal chronic infection associated with the development of hypergammaglobulinaemia of hyper-mutated, class-switched, low-affinity antibodies that contribute to disease progression in mice (Silva-Barrios & Stäger, 2019). These defective immune responses are thought to be caused by the loss of both fDCs and Tfh cells during chronic infection in mice and rhesus macaques (Stanley & Engwerda, 2006; Rodrigues et al., 2014), leading to alterations in the architecture of lymphoid structures and causing loss of GCs and the ability to produce parasite-specific antibodies (Rodrigues et al., 2016). In addition, suppression of cell-mediated immunity via IL-10 production is a major component of the immunopathology observed in visceral leishmaniasis (Rodrigues et al., 2016). γδ T cells respond to

Leishmania donovani amastigotes *in vitro* (Saha et al., 1999) and are elevated in the blood of patients with visceral leishmaniasis (Raziuddin et al., 1992; Russo et al., 1993), with a high proportion expressing HLA-DR (Raziuddin et al., 1992). Besides expressing IFN-γ, patient-derived γδ T cells have also been found to produce a B cell growth factor (most likely IL-4) (Raziuddin et al., 1992) and IL-10 (Lagler et al., 2003), and may thus affect humoral immune responses. It is currently unknown whether priming of antigen-specific γδ T cells during vaccination could provide long-term antigen reservoirs to sustain the Tfh response and production of parasite-specific antibodies, thereby replacing the fDCs lost in chronic infection, and whether abrogation of this deleterious effect on Tfh cells could lead to protection from disease.

5. Targeting γδ T cells for novel vaccine strategies

The potent contribution of γδ T cells to humoral immune responses as outlined in this review may be important for the design of novel vaccine regimes, by exploiting a potential adjuvant effect on B cells and Tfh cells and enhancing antibody titres, improving antibody affinities and breadth, and/or ensuring the generation of appropriate isotypes (Figure 1). However, while there is considerable clinical interest in utilising the cytotoxic potential of γδ T cells for immunotherapeutic purposes, especially with regard to the treatment of solid and haematological malignancies (Saura-Esteller et al., 2022; Hayday et al., 2024; Arias-Badia et al., 2024), the application of our expanding knowledge of γδ T cell influence on B cells and Tfh cells into the clinic for the design of novel vaccines is still in its infancy (Box 1).

In the most direct way, targeting human γδ T cells could be achieved by administration of HMB-PP or related compounds to boost the B cell helper capacity of γδ T cells. In fact, treatment with HMB-PP or synthetic derivatives readily leads to a systemic activation of Vγ9/Vδ2 T cells in cynomolgus macaques (Ali et al., 2007), pigtail macaques (Barber-Axthelm et al., 2023) and marmosets (Rowland et al., 2012). Similarly, the humanised antibody ICT01 that targets BTN3A specifically activates Vγ9/Vδ2 T cells in cynomolgus macaques (de Gassart et al., 2021). These studies successfully established non-human primates as suitable model to study Vγ9/Vδ2 T cell responses *in vivo* and demonstrated the safety of Vγ9/Vδ2 T cell activating compounds. The efficacy of Vγ9/Vδ2 T cells against microbial infections has been investigated in a number of contexts, with mixed outcomes. While treatment of marmosets with an HMB-PP analogue had no effect against respiratory *Burkholderia pseudomallei* infection (Laws et al., 2013), treatment of cynomolgus macaques conferred protection against pneumonic plague lesions after *Yersinia pestis* inhalation (Huang et al., 2009) and reduced bacterial burdens in a TB model (Chen et al., 2013).

There are no clinically approved HMB-PP derivatives available as yet that could be used directly in humans. However, the aminobisphosphonate drug zoledronate, which is used to treat bone resorption disorders associated with osteoporosis, multiple myeloma and bone metastasis, readily activates Vγ9/Vδ2 T cells via causing intracellular accumulation of the low affinity BTN2A1/BTN3A1 ligand isopentenyl pyrophosphate in target cells (Roelofs et al., 2009; Welton et al., 2013; Yuan et al., 2023). In cynomolgus macaques infected with multidrug-resistant Mtb, adjunctive administration of zoledronate and IL-2 alongside antimicrobial therapy led to the expansion of Vγ9/Vδ2 T cells and a sustained increase of Th1-like $CD4^+$ and $CD8^+$ T cells, resulting in a decreased bacterial burden and milder pathology compared to drug

treatment alone (Shen et al., 2022). In contrast to these promising findings, treatment of experimental TB in SIV co-infected macaques with zoledronate and IL-2 had no beneficial effect on host resistance (Larson et al., 2024), perhaps in part due to the suppression of Mtb-reactive Vγ9/Vδ2 T cells upon co-infection with SIV (Zhou et al., 2003).

Together, these studies demonstrate that Vγ9/Vδ2 T cells can be targeted *in vivo* with encouraging results with respect to protection and infection control in some settings (Table 1). While the mechanisms involved are typically associated with cytotoxic responses by Vγ9/Vδ2 T cells themselves and other T cell subsets, little attention has been paid to boosting antigen-specific adaptive immune responses in those models, and only a few studies have looked at the effect of Vγ9/Vδ2 T cell stimulation on B cells *in vivo*. When administering the anti-BTN3A antibody ICT01, de Gassart et al. (2021) observed no significant activation of immune cells other than Vγ9/Vδ2 T cells, both in macaques and in patients with advanced stage solid cancers. However, in support of an adjuvant effect of γδ T cells, administration of HMB-PP and IL-2 to rhesus macaques infected with SHIV led to Vγ9/Vδ2 T cell expansion and transient increases in circulating $CD4^+$ and $CD8^+$ αβ T cells when given during early infection, and boosted HIV envelope glycoprotein-specific antibody titres when given during the chronic infection (Ali et al., 2009). To directly examine the adjuvant properties of Vγ9/Vδ2 T cells as a novel TB vaccine, Cendron et al. (2007) tested a combination of a mycobacterial ESAT-6-Ag85B fusion protein with a synthetic HMB-PP analogue, which induced distinct waves of αβ and γδ T cell responses in cynomolgus macaques, yet with no apparent boost in antigen-specific immunity (Cendron et al., 2007). Unfortunately, no data on antibody responses are available from that study. Gertner-Dardenne et al. (2009) tested a synthetic analogue of HMB-PP in conjunction with the

anti-CD20 monoclonal antibody rituximab in cynomolgus macaques and showed enhanced B cell depletion from blood and lymph nodes via ADCC, demonstrating a positive effect of Vγ9/Vδ2 T cells with potential for novel immunotherapies.

It is striking that the vast majority of clinical and preclinical studies so far have included co-administration of IL-2, based on the early observation that IL-2 supports Vγ9/Vδ2 T cell proliferation *in vitro* and *in vivo* (Casetti et al., 2005). However, IL-2 also drives expression of cytokines like IFN-γ and TNF-α and polarises Vγ9/Vδ2 T cells towards a pro-inflammatory and cytotoxic phenotype (Vermijlen et al., 2007). The fact that Vγ9/Vδ2 T cells display a striking functional plasticity and readily assume different roles *in vitro* in the presence of cytokines other than IL-2 (Tyler et al., 2017; Tyler et al., 2024) has yet to be exploited *in vivo*, for instance by replacing the standard IL-2 regime with cytokines such as IL-4 or IL-21. Indeed, here is considerable interest in testing IL-21 in clinical trials, albeit predominantly in the context of cancer immunotherapy (Li et al., 2024). In support of its potential as an adjuvant in boosting humoral immune responses, co-delivery of IL-21 enhanced flu vaccine-induced antibody responses and modulated GC activity in aged SIV-positive rhesus macaques (Kvistad et al., 2021). Targeting γδ T cells *in vivo* in the context of IL-21 may thus deserve closer attention (Box 1).

6. Conclusion and future perspectives

As summarised in this review, γδ T cells are important effector populations in many infections and in vaccine-mediated protection against bacterial, viral and parasitic diseases. While this was classically believed to be achieved predominantly via the

capacity of γδ T cells to trigger inflammatory responses and/or directly kill infected cells, the contribution of γδ T cells to humoral immunity upon natural infection and vaccination has been a sorely under-researched area and is only now beginning to be understood better (Born et al., 2017; Rampoldi et al., 2020; Qiu et al., 2023). In this respect, it is conceivable that the activation of antigen presenting γδ T cells may contribute to the priming of Tfh cells *in vivo*, and provide an additional facet to enhance the breadth and depth of Tfh responses, with the potential to boost the development of protective antibodies including bnAbs (Wan et al., 2017; Chen et al., 2018; Inoue et al., 2018; Rezende et al., 2018). This mechanism could be of potential adjuvant use in many infections that pose a global threat. By targeting γδ T cells during vaccination to boost Tfh cells, it may be possible to harness the synergistic effects of both antibody-mediated and cell-mediated protection against pathogens. Future studies should thus seek to characterise the influence of γδ T cells on humoral responses, representing an exciting new avenue of research into how γδ T cells can contribute to the development of efficacious vaccines (Box 1). As a flip side, given the interdependence of Tfh cells, γδ T cells and B cells in modulating antibody responses, dampening overactive γδ T cell functions may offer new opportunities for therapeutic intervention in conditions marked by excessive production of autoantibodies. γδ T cells have clearly come of age as all-rounders not only through their capacity to bridge innate and adaptive immunity but also by linking cellular and humoral immunity, with more discoveries and their ultimate translation into the clinic awaiting.

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References

Abate G, Spencer CT, Hamzabegovic F, Blazevic A, Xia M, Hoft DF. Mycobacterium-Specific γ9δ2 T Cells Mediate Both Pathogen-Inhibitory and CD40 Ligand-Dependent Antigen Presentation Effects Important for Tuberculosis Immunity. Infect Immun. 2015 Dec 7;84(2):580-9.

Achkar JM, Casadevall A. Antibody-mediated immunity against tuberculosis: implications for vaccine development. Cell Host Microbe. 2013 Mar 13;13(3):250-62.

Agrati C, D'Offizi G, Narciso P, Abrignani S, Ippolito G, Colizzi V, Poccia F. Vdelta1 T lymphocytes expressing a Th1 phenotype are the major gammadelta T cell subset infiltrating the liver of HCV-infected persons. Mol Med. 2001 Jan;7(1):11-9.

Akkaya M, Kwak K, Pierce SK. B cell memory: building two walls of protection against pathogens. Nat Rev Immunol. 2020 Apr;20(4):229-238.

Alameh MG, Tombácz I, Bettini E, Lederer K, Sittplangkoon C, Wilmore JR, Gaudette BT, Soliman OY, Pine M, Hicks P, Manzoni TB, Knox JJ, Johnson JL, Laczkó D, Muramatsu H, Davis B, Meng W, Rosenfeld AM, Strohmeier S, Lin PJC, Mui BL, Tam YK, Karikó K, Jacquet A, Krammer F, Bates P, Cancro MP, Weissman D, Luning Prak ET, Allman D, Locci M, Pardi N. Lipid nanoparticles enhance the efficacy of mRNA and protein subunit vaccines by inducing robust T follicular helper cell and humoral responses. Immunity. 2021 Dec 14;54(12):2877-2892.e7.

Ali Z, Shao L, Halliday L, Reichenberg A, Hintz M, Jomaa H, Chen ZW. Prolonged (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate-driven antimicrobial and cytotoxic

responses of pulmonary and systemic Vγ2Vδ2 T cells in macaques. J Immunol. 2007 Dec 15;179(12):8287-96.

Ali Z, Yan L, Plagman N, Reichenberg A, Hintz M, Jomaa H, Villinger F, Chen ZW. γδ T cell immune manipulation during chronic phase of simian-human immunodeficiency virus infection [corrected] confers immunological benefits. J Immunol. 2009 Oct 15;183(8):5407-17.

Andreu-Ballester JC, Galindo-Regal L, Cuéllar C, López-Chuliá F, García-Ballesteros C, Fernández-Murga L, Llombart-Cussac A, Domínguez-Márquez MV. A Low Number of Baselines γδ T Cells Increases the Risk of SARS-CoV-2 Post-Vaccination Infection. Vaccines (Basel). 2024 May 18;12(5):553.

Andrew EM, Carding SR. Murine gammadelta T cells in infections: beneficial or deleterious? Microbes Infect. 2005 Mar;7(3):529-36.

Arias-Badia M, Chang R, Fong L. γδ T cells as critical anti-tumor immune effectors. Nat Cancer. 2024 Aug;5(8):1145-1157.

Bachelet T, Couzi L, Pitard V, Sicard X, Rigothier C, Lepreux S, Moreau JF, Taupin JL, Merville P, Déchanet-Merville J. Cytomegalovirus-responsive γδ T cells: novel effector cells in antibody-mediated kidney allograft microcirculation lesions. J Am Soc Nephrol. 2014 Nov;25(11):2471-82.

Bai X, Chi X, Qiao Q, Xie S, Wan S, Ni L, Wang P, Jin W, Dong C. T Follicular Helper Cells Regulate Humoral Response for Host Protection against Intestinal Citrobacter rodentium Infection. J Immunol. 2020 May 15;204(10):2754-2761.

Baldwin CL, Yirsaw A, Gillespie A, Le Page L, Zhang F, Damani-Yokota P, Telfer JC. γδ T cells in livestock: Responses to pathogens and vaccine potential. Transbound Emerg Dis. 2020 Jul;67 Suppl 2:119-128.

Ballesteros-Tato A, Randall TD. Priming of T follicular helper cells by dendritic cells. Immunol Cell Biol. 2014 Jan;92(1):22-7.

Bansal RR, Mackay CR, Moser B, Eberl M. IL-21 enhances the potential of human γδ T cells to provide B-cell help. Eur J Immunol. 2012 Jan;42(1):110-9.

Barber-Axthelm IM, Wragg KM, Esterbauer R, Amarasena TH, Barber-Axthelm VRB, Wheatley AK, Gibbon AM, Kent SJ, Juno JA. Phenotypic and functional characterization of pharmacologically expanded Vγ9Vδ2 T cells in pigtail macaques. iScience. 2023 Feb 25;26(3):106269.

Barisa M, Kramer AM, Majani Y, Moulding D, Saraiva L, Bajaj-Elliott M, Anderson J, Gustafsson K. E. coli promotes human Vγ9Vδ2 T cell transition from cytokine-producing bactericidal effectors to professional phagocytic killers in a TCR-dependent manner. Sci Rep. 2017 Jun 5;7(1):2805.

Barjon C, Michaud HA, Fages A, Dejou C, Zampieri A, They L, Gennetier A, Sanchez F, Gros L, Eliaou JF, Bonnefoy N, Lafont V. IL-21 promotes the development of a CD73-positive Vγ9Vδ2 T cell regulatory population. Oncoimmunology. 2017 Oct 4;7(1):e1379642.

Barouch DH, O'Brien KL, Simmons NL, King SL, Abbink P, Maxfield LF, Sun YH, La Porte A, Riggs AM, Lynch DM, Clark SL, Backus K, Perry JR, Seaman MS, Carville A, Mansfield KG, Szinger JJ, Fischer W, Muldoon M, Korber B. Mosaic HIV-1

vaccines expand the breadth and depth of cellular immune responses in rhesus monkeys. Nat Med. 2010 Mar;16(3):319-23.

Batista FD, Harwood NE. The who, how and where of antigen presentation to B cells. Nat Rev Immunol. 2009 Jan;9(1):15-27.

Bayarsaikhan G, Ibraheem Y, Inoue SI. γδ T-cell-mediated immune responses to malaria. Microbiol Immunol. 2023 May;67(5):239-247.

Bennett MS, Trivedi S, Iyer AS, Hale JS, Leung DT. Human mucosal-associated invariant T (MAIT) cells possess capacity for B cell help. J Leukoc Biol. 2017 Nov;102(5):1261-1269.

Bentebibel SE, Lopez S, Obermoser G, Schmitt N, Mueller C, Harrod C, Flano E, Mejias A, Albrecht RA, Blankenship D, Xu H, Pascual V, Banchereau J, Garcia-Sastre A, Palucka AK, Ramilo O, Ueno H. Induction of ICOS+CXCR3+CXCR5+ TH cells correlates with antibody responses to influenza vaccination. Sci Transl Med. 2013 Mar 13;5(176):176ra32.

Biradar S, Lotze MT, Mailliard RB. The Unknown Unknowns: Recovering Gamma-Delta T Cells for Control of Human Immunodeficiency Virus (HIV). Viruses. 2020 Dec 17;12(12):1455.

Boomgarden AC, Upadhyay C. Progress and Challenges in HIV-1 Vaccine Research: A Comprehensive Overview. Vaccines (Basel). 2025 Jan 31;13(2):148.

Born WK, Huang Y, Reinhardt RL, Huang H, Sun D, O'Brien RL. γδ T Cells and B Cells. Adv Immunol. 2017;134:1-45.

Bowyer G, Grobbelaar A, Rampling T, Venkatraman N, Morelle D, Ballou RW, Hill AVS, Ewer KJ. CXCR3+ T Follicular Helper Cells Induced by Co-Administration of RTS,S/AS01B and Viral-Vectored Vaccines Are Associated With Reduced Immunogenicity and Efficacy Against Malaria. Front Immunol. 2018 Jul 25;9:1660.

Brandes M, Willimann K, Lang AB, Nam KH, Jin C, Brenner MB, Morita CT, Moser B. Flexible migration program regulates γδ T-cell involvement in humoral immunity. Blood. 2003 Nov 15;102(10):3693-701.

Brandes M, Willimann K, Moser B. Professional antigen-presentation function by human γδ T Cells. Science. 2005 Jul 8;309(5732):264-8.

Brandes M, Willimann K, Bioley G, Lévy N, Eberl M, Luo M, Tampé R, Lévy F, Romero P, Moser B. Cross-presenting human γδ T cells induce robust CD8+ alphabeta T cell responses. Proc Natl Acad Sci U S A. 2009 Feb 17;106(7):2307-12.

Breitfeld D, Ohl L, Kremmer E, Ellwart J, Sallusto F, Lipp M, Förster R. Follicular B helper T cells express CXC chemokine receptor 5, localize to B cell follicles, and support immunoglobulin production. J Exp Med. 2000 Dec 4;192(11):1545-52.

Brenner MB, McLean J, Dialynas DP, Strominger JL, Smith JA, Owen FL, Seidman JG, Ip S, Rosen F, Krangel MS. Identification of a putative second T-cell receptor. Nature. 1986 Jul 10-16;322(6075):145-9.

Bruno F, Fornara C, Zelini P, Furione M, Carrara E, Scaramuzzi L, Cane I, Mele F, Sallusto F, Lilleri D, Gerna G. Follicular helper T-cells and virus-specific antibody response in primary and reactivated human cytomegalovirus infections of the immunocompetent and immunocompromised transplant patients. J Gen Virol. 2016 Aug;97(8):1928-1941.

Burkert S, Schumann RR. RNA Sensing of Mycobacterium tuberculosis and Its Impact on TB Vaccination Strategies. Vaccines (Basel). 2020 Feb 4;8(1):67.

Butler NS, Moebius J, Pewe LL, Traore B, Doumbo OK, Tygrett LT, Waldschmidt TJ, Crompton PD, Harty JT. Therapeutic blockade of PD-L1 and LAG-3 rapidly clears established blood-stage Plasmodium infection. Nat Immunol. 2011 Dec 11;13(2):188-95.

Casetti R, Perretta G, Taglioni A, Mattei M, Colizzi V, Dieli F, D'Offizi G, Malkovsky M, Poccia F. Drug-induced expansion and differentiation of V gamma 9V delta 2 T cells in vivo: the role of exogenous IL-2. J Immunol. 2005 Aug 1;175(3):1593-8.

Casetti R, Agrati C, Wallace M, Sacchi A, Martini F, Martino A, Rinaldi A, Malkovsky M. Cutting edge: TGF-beta1 and IL-15 Induce FOXP3+ gammadelta regulatory T cells in the presence of antigen stimulation. J Immunol. 2009 Sep 15;183(6):3574-7.

Cendron D, Ingoure S, Martino A, Casetti R, Horand F, Romagné F, Sicard H, Fournié JJ, Poccia F. A tuberculosis vaccine based on phosphoantigens and fusion proteins induces distinct gammadelta and alphabeta T cell responses in primates. Eur J Immunol. 2007 Feb;37(2):549-65.

Chan JA, Loughland JR, de Labastida Rivera F, SheelaNair A, Andrew DW, Dooley NL, Wines BD, Amante FH, Webb L, Hogarth PM, McCarthy JS, Beeson JG, Engwerda CR, Boyle MJ. Th2-like T Follicular Helper Cells Promote Functional Antibody Production during Plasmodium falciparum Infection. Cell Rep Med. 2020 Dec 22;1(9):100157.

Charmetant X, Rigault G, Chen CC, Kaminski H, Visentin J, Taton B, Marseres G, Mathias V, Koenig A, Barba T, Merville P, Graff-Dubois S, Morelon E, Déchanet-Merville J, Dubois V, Duong van Huyen JP, Couzi L, Thaunat O. γδ T Cells' Role in Donor-Specific Antibody Generation: Insights From Transplant Recipients and Experimental Models. Transpl Int. 2025 Jan 29;38:12859.

Charmetant X, Espi M, Benotmane I, Barateau V, Heibel F, Buron F, Gautier-Vargas G, Delafosse M, Perrin P, Koenig A, Cognard N, Levi C, Gallais F, Manière L, Rossolillo P, Soulier E, Pierre F, Ovize A, Morelon E, Defrance T, Fafi-Kremer S, Caillard S, Thaunat O. Infection or a third dose of mRNA vaccine elicits neutralizing antibody responses against SARS-CoV-2 in kidney transplant recipients. Sci Transl Med. 2022 Mar 16;14(636):eabl6141.

Chen CY, Yao S, Huang D, Wei H, Sicard H, Zeng G, Jomaa H, Larsen MH, Jacobs WR Jr, Wang R, Letvin N, Shen Y, Qiu L, Shen L, Chen ZW. Phosphoantigen/IL2 expansion and differentiation of Vγ2Vδ2 T cells increase resistance to tuberculosis in nonhuman primates. PLoS Pathog. 2013 Aug;9(8):e1003501.

Chen Q, Wen K, Lv A, Liu M, Ni K, Xiang Z, Liu Y, Tu W. Human Vγ9Vδ2-T Cells Synergize CD4+ T Follicular Helper Cells to Produce Influenza Virus-Specific Antibody. Front Immunol. 2018 Apr 4;9:599.

Chen J, Gao L, Wu X, Fan Y, Liu M, Peng L, Song J, Li B, Liu A, Bao F. BCG-induced trained immunity: history, mechanisms and potential applications. J Transl Med. 2023 Feb 10;21(1):106.

Cheng L, Cui Y, Shao H, Han G, Zhu L, Huang Y, O'Brien RL, Born WK, Kaplan HJ, Sun D. Mouse γδ T cells are capable of expressing MHC class II molecules, and of functioning as antigen-presenting cells. J Neuroimmunol. 2008 Oct 15;203(1):3-11.

Chiavarini M, Genga A, Ricciotti GM, D'Errico MM, Barbadoro P. Safety, Immunogenicity, and Efficacy of Cytomegalovirus Vaccines: A Systematic Review of Randomized Controlled Trials. Vaccines (Basel). 2025 Jan 17;13(1):85.

Chtanova T, Tangye SG, Newton R, Frank N, Hodge MR, Rolph MS, Mackay CR. T follicular helper cells express a distinctive transcriptional profile, reflecting their role as non-Th1/Th2 effector cells that provide help for B cells. J Immunol. 2004 Jul 1;173(1):68-78.

Cimini E, Agrati C. γδ T Cells in Emerging Viral Infection: An Overview. Viruses. 2022 May 27;14(6):1166.

Cockburn IA, Seder RA. Malaria prevention: from immunological concepts to effective vaccines and protective antibodies. Nat Immunol. 2018 Nov;19(11):1199-1211.

Collins RA, Werling D, Duggan SE, Bland AP, Parsons KR, Howard CJ. Gammadelta T cells present antigen to CD4+ alphabeta T cells. J Leukoc Biol. 1998 Jun;63(6):707-14.

Comeau K, Paradis P, Schiffrin EL. Human and murine memory γδ T cells: Evidence for acquired immune memory in bacterial and viral infections and autoimmunity. Cell Immunol. 2020 Nov;357:104217.

Cooper AJR, Lalor SJ, McLoughlin RM. Activation of Human Vδ2^{+} γδ T Cells by *Staphylococcus aureus* Promotes Enhanced Anti-Staphylococcal Adaptive Immunity. J Immunol. 2020 Aug 15;205(4):1039-1049.

Costa G, Loizon S, Guenot M, Mocan I, Halary F, de Saint-Basile G, Pitard V, Déchanet-Merville J, Moreau JF, Troye-Blomberg M, Mercereau-Puijalon O, Behr C. Control of Plasmodium falciparum erythrocytic cycle: γδ T cells target the red blood cell-invasive merozoites. Blood. 2011 Dec 22;118(26):6952-62.

Coulter F, Parrish A, Manning D, Kampmann B, Mendy J, Garand M, Lewinsohn DM, Riley EM, Sutherland JS. IL-17 Production from T Helper 17, Mucosal-Associated Invariant T, and γδ Cells in Tuberculosis Infection and Disease. Front Immunol. 2017 Oct 11;8:1252.

Couzi L, Pitard V, Sicard X, Garrigue I, Hawchar O, Merville P, Moreau JF, Déchanet-Merville J. Antibody-dependent anti-cytomegalovirus activity of human γδ T cells expressing CD16 (FcγRIIIa). Blood. 2012 Feb 9;119(6):1418-27.

Crawford G, Hayes MD, Seoane RC, Ward S, Dalessandri T, Lai C, Healy E, Kipling D, Proby C, Moyes C, Green K, Best K, Haniffa M, Botto M, Dunn-Walters D, Strid J. Epithelial damage and tissue γδ T cells promote a unique tumor-protective IgE response. Nat Immunol. 2018 Aug;19(8):859-870.

Crotty S. Follicular helper CD4 T cells (TFH). Annu Rev Immunol. 2011;29:621-63.

Crotty S. T follicular helper cell differentiation, function, and roles in disease. Immunity. 2014 Oct 16;41(4):529-42.

Crotty S. A brief history of T cell help to B cells. Nat Rev Immunol. 2015 Mar;15(3):185-9.

Crotty S. T Follicular Helper Cell Biology: A Decade of Discovery and Diseases. Immunity. 2019 May 21;50(5):1132-1148.

Cyster JG, Allen CDC. B Cell Responses: Cell Interaction Dynamics and Decisions. Cell. 2019 Apr 18;177(3):524-540.

Dagna L, Iellem A, Biswas P, Resta D, Tantardini F, Fortis C, Sabbadini MG, D'Ambrosio D, Manfredi AA, Ferrarini M. Skewing of cytotoxic activity and chemokine production, but not of chemokine receptor expression, in human type-1/-2 gamma delta T lymphocytes. Eur J Immunol. 2002 Oct;32(10):2934-43.

Dantzler KW, de la Parte L, Jagannathan P. Emerging role of γδ T cells in vaccine-mediated protection from infectious diseases. Clin Transl Immunology. 2019 Aug 28;8(8):e1072.

Darrah PA, Zeppa JJ, Maiello P, Hackney JA, Wadsworth MH 2nd, Hughes TK, Pokkali S, Swanson PA 2nd, Grant NL, Rodgers MA, Kamath M, Causgrove CM, Laddy DJ, Bonavia A, Casimiro D, Lin PL, Klein E, White AG, Scanga CA, Shalek AK, Roederer M, Flynn JL, Seder RA. Prevention of tuberculosis in macaques after intravenous BCG immunization. Nature. 2020 Jan;577(7788):95-102.

Davey MS, Lin CY, Roberts GW, Heuston S, Brown AC, Chess JA, Toleman MA, Gahan CG, Hill C, Parish T, Williams JD, Davies SJ, Johnson DW, Topley N, Moser B, Eberl M. Human neutrophil clearance of bacterial pathogens triggers anti-microbial γδ T cell responses in early infection. PLoS Pathog. 2011 May;7(5):e1002040.

Davey MS, Willcox CR, Joyce SP, Ladell K, Kasatskaya SA, McLaren JE, Hunter S, Salim M, Mohammed F, Price DA, Chudakov DM, Willcox BE. Clonal selection in the human Vδ1 T cell repertoire indicates γδ TCR-dependent adaptive immune surveillance. Nat Commun. 2017 Mar 1;8:14760.

De Boer RJ, Perelson AS. How Germinal Centers Evolve Broadly Neutralizing Antibodies: the Breadth of the Follicular Helper T Cell Response. J Virol. 2017 Oct 27;91(22):e00983-17.

Déchanet J, Merville P, Lim A, Retière C, Pitard V, Lafarge X, Michelson S, Méric C, Hallet MM, Kourilsky P, Potaux L, Bonneville M, Moreau JF. Implication of gammadelta T cells in the human immune response to cytomegalovirus. J Clin Invest. 1999 May 15;103(10):1437-49.

De Gassart A, Le KS, Brune P, Agaugué S, Sims J, Goubard A, Castellano R, Joalland N, Scotet E, Collette Y, Valentin E, Ghigo C, Pasero C, Colazet M, Guillén J, Cano CE, Marabelle A, De Bonno J, Hoet R, Truneh A, Olive D, Frohna P. Development of ICT01, a first-in-class, anti-BTN3A antibody for activating Vγ9Vδ2 T cell-mediated antitumor immune response. Sci Transl Med. 2021 Oct 20;13(616):eabj0835.

de Jong SE, Asscher VER, Wammes LJ, Wiria AE, Hamid F, Sartono E, Supali T, Smits HH, Luty AJF, Yazdanbakhsh M. Longitudinal study of changes in γδ T cells and CD4+ T cells upon asymptomatic malaria infection in Indonesian children. Sci Rep. 2017 Aug 18;7(1):8844.

Dianda L, Gulbranson-Judge A, Pao W, Hayday AC, MacLennan IC, Owen MJ. Germinal center formation in mice lacking alpha beta T cells. Eur J Immunol. 1996 Jul;26(7):1603-7.

Dobmeyer TS, Dobmeyer R, Wesch D, Helm EB, Hoelzer D, Kabelitz D. Reciprocal alterations of Th1/Th2 function in gammadelta T-cell subsets of human immunodeficiency virus-1-infected patients. Br J Haematol. 2002 Jul;118(1):282-8.

Dooley NL, Chabikwa TG, Pava Z, Loughland JR, Hamelink J, Berry K, Andrew D, Soon MSF, SheelaNair A, Piera KA, William T, Barber BE, Grigg MJ, Engwerda CR, Lopez JA, Anstey NM, Boyle MJ. Single cell transcriptomics shows that malaria promotes unique regulatory responses across multiple immune cell subsets. Nat Commun. 2023 Nov 15;14(1):7387.

Duffy PE, Gorres JP, Healy SA, Fried M. Malaria vaccines: a new era of prevention and control. Nat Rev Microbiol. 2024 Dec;22(12):756-772.

Eberl M, Engel R, Beck E, Jomaa H. Differentiation of human γδ T cells towards distinct memory phenotypes. Cell Immunol. 2002 Jul-Aug;218(1-2):1-6.

Eberl M, Hintz M, Reichenberg A, Kollas AK, Wiesner J, Jomaa H. Microbial isoprenoid biosynthesis and human gammadelta T cell activation. FEBS Lett. 2003 Jun 5;544(1-3):4-10.

Eberl M. Highlights of 2024: γδ T cells and bad blood. Immunol Cell Biol. 2025 Mar 9.

Emery K, Dhaliwal J, Light R, Eberl M, Cruickshank SM. Enabling Vaccine Uptake: Strategies for the Public Health Sector. Br J Hosp Med (Lond). 2025 in press

Fears AC, Walker EM, Chirichella N, Slisarenko N, Merino KM, Golden N, Picou B, Spencer S, Russell-Lodrigue KE, Doyle-Meyers LA, Blair RV, Beddingfield BJ, Maness NJ, Roy CJ, Rout N. The dynamics of γδ T cell responses in nonhuman primates during SARS-CoV-2 infection. Commun Biol. 2022 Dec 16;5(1):1380.

Felices M, Yin CC, Kosaka Y, Kang J, Berg LJ. Tec kinase Itk in gammadeltaT cells is pivotal for controlling IgE production in vivo. Proc Natl Acad Sci U S A. 2009 May 19;106(20):8308-13.

Figueiredo MM, Costa PAC, Diniz SQ, Henriques PM, Kano FS, Tada MS, Pereira DB, Soares IS, Martins-Filho OA, Jankovic D, Gazzinelli RT, Antonelli LRDV. T follicular helper cells regulate the activation of B lymphocytes and antibody production during Plasmodium vivax infection. PLoS Pathog. 2017 Jul 10;13(7):e1006484.

Fonseca VR, Ribeiro F, Graca L. T follicular regulatory (Tfr) cells: Dissecting the complexity of Tfr-cell compartments. Immunol Rev. 2019 Mar;288(1):112-127.

Fowler DW, Copier J, Dalgleish AG, Bodman-Smith MD. Tripartite immune cell co-operation in the Bacillus Calmette Guérin-induced activation of γδ T cells. Immunol Cell Biol. 2013 Aug;91(7):461-8.

Fox A, Quinn KM, Subbarao K. Extending the Breadth of Influenza Vaccines: Status and Prospects for a Universal Vaccine. Drugs. 2018 Sep;78(13):1297-1308.

Frencher JT, Shen H, Yan L, Wilson JO, Freitag NE, Rizzo AN, Chen CY, Chen ZW. HMBPP-deficient Listeria mutant immunization alters pulmonary/systemic responses, effector functions, and memory polarization of Vγ2Vδ2 T cells. J Leukoc Biol. 2014 Dec;96(6):957-67.

Fujikado N, Mann AO, Bansal K, Romito KR, Ferre EMN, Rosenzweig SD, Lionakis MS, Benoist C, Mathis D. Aire Inhibits the Generation of a Perinatal Population of Interleukin-17A-Producing γδ T Cells to Promote Immunologic Tolerance. Immunity. 2016 Nov 15;45(5):999-1012.

Fulford TS, Soliman C, Castle RG, Rigau M, Ruan Z, Dolezal O, Seneviratna R, Brown HG, Hanssen E, Hammet A, Li S, Redmond SJ, Chung A, Gorman MA, Parker MW, Patel O, Peat TS, Newman J, Behren A, Gherardin NA, Godfrey DI, Uldrich AP. Vγ9Vδ2 T cells recognize butyrophilin 2A1 and 3A1 heteromers. Nat Immunol. 2024 Aug;25(8):1355-1366.

Fulkerson HL, Nogalski MT, Collins-McMillen D, Yurochko AD. Overview of Human Cytomegalovirus Pathogenesis. Methods Mol Biol. 2021;2244:1-18.

Galli G, Nuti S, Tavarini S, Galli-Stampino L, De Lalla C, Casorati G, Dellabona P, Abrignani S. CD1d-restricted help to B cells by human invariant natural killer T lymphocytes. J Exp Med. 2003 Apr 21;197(8):1051-7.

Gardner TJ, Stein KR, Duty JA, Schwarz TM, Noriega VM, Kraus T, Moran TM, Tortorella D. Functional screening for anti-CMV biologics identifies a broadly neutralizing epitope of an essential envelope protein. Nat Commun. 2016 Dec 14;7:13627.

Garrido C, Clohosey ML, Whitworth CP, Hudgens M, Margolis DM, Soriano-Sarabia N. γδ T cells: an immunotherapeutic approach for HIV cure strategies. JCI Insight. 2018 Jun 21;3(12):e120121.

Gela A, Murphy M, Rodo M, Hadley K, Hanekom WA, Boom WH, Johnson JL, Hoft DF, Joosten SA, Ottenhoff THM, Suliman S, Moody DB, Lewinsohn DM, Hatherill

M, Seshadri C, Nemes E, Scriba TJ, Briel L, Veldtsman H, Khomba N, Pienaar B, Africa H, Steyn M; Delayed BCG Study Team. Effects of BCG vaccination on donor unrestricted T cells in two prospective cohort studies. EBioMedicine. 2022 Feb;76:103839.

Gerli R, Agea E, Muscat C, Bertotto A, Ercolani R, Bistoni O, Bini P, Spinozzi F, Venanzi F. Functional characterization of T cells bearing the gamma/delta T-cell receptor in patients with primary Sjögren's syndrome. Clin Exp Rheumatol. 1993 May-Jun;11(3):295-9.

Gertner-Dardenne J, Bonnafous C, Bezombes C, Capietto AH, Scaglione V, Ingoure S, Cendron D, Gross E, Lepage JF, Quillet-Mary A, Ysebaert L, Laurent G, Sicard H, Fournié JJ. Bromohydrin pyrophosphate enhances antibody-dependent cell-mediated cytotoxicity induced by therapeutic antibodies. Blood. 2009 May 14;113(20):4875-84.

Giannoni E, Sanchez Sanchez G, Verdebout I, Papadopoulou M, Rezwani M, Ahmed R, Ladell K, Miners KL, McLaren JE, Fraser DJ, Price DA, Eberl M; Swiss Pediatric Sepsis Study; Agyeman PKA, Schlapbach LJ, Vermijlen D. Sepsis shapes the human γδ TCR repertoire in an age- and pathogen-dependent manner. Eur J Immunol. 2024 Oct;54(10):e2451190.

Gopal R, Rangel-Moreno J, Slight S, Lin Y, Nawar HF, Fallert Junecko BA, Reinhart TA, Kolls J, Randall TD, Connell TD, Khader SA. Interleukin-17-dependent CXCL13 mediates mucosal vaccine-induced immunity against tuberculosis. Mucosal Immunol. 2013 Sep;6(5):972-84.

Griffith GL, Machmach K, Jian N, Kim D, Costanzo MC, Creegan M, Swafford I, Kundu G, Yum L, Bolton JS, Smith L, Slike BM, Bergmann-Leitner ES, Thomas R, Michael NL, Ake JA, Eller LA, Robb ML, Townsley SM, Krebs SJ, Paquin-Proulx D; RV217 Study Group. CD16 and CD57 expressing gamma delta T cells in acute HIV-1 infection are associated with the development of neutralization breadth. PLoS Pathog. 2025 Jan 31;21(1):e1012916.

Groh V, Porcelli S, Fabbi M, Lanier LL, Picker LJ, Anderson T, Warnke RA, Bhan AK, Strominger JL, Brenner MB. Human lymphocytes bearing T cell receptor gamma/delta are phenotypically diverse and evenly distributed throughout the lymphoid system. J Exp Med. 1989 Apr 1;169(4):1277-94.

Guenot M, Loizon S, Howard J, Costa G, Baker DA, Mohabeer SY, Troye-Blomberg M, Moreau JF, Déchanet-Merville J, Mercereau-Puijalon O, Mamani-Matsuda M, Behr C. Phosphoantigen Burst upon Plasmodium falciparum Schizont Rupture Can Distantly Activate Vγ9Vδ2 T Cells. Infect Immun. 2015 Oct;83(10):3816-24.

Hagel JP, Bennett K, Buffa F, Klenerman P, Willberg CB, Powell K. Defining T Cell Subsets in Human Tonsils Using ChipCytometry. J Immunol. 2021 Jun 15;206(12):3073-3082.

Hansen DS, Obeng-Adjei N, Ly A, Ioannidis LJ, Crompton PD. Emerging concepts in T follicular helper cell responses to malaria. Int J Parasitol. 2017 Feb;47(2-3):105-110.

Harly C, Guillaume Y, Nedellec S, Peigné CM, Mönkkönen H, Mönkkönen J, Li J, Kuball J, Adams EJ, Netzer S, Déchanet-Merville J, Léger A, Herrmann T, Breathnach R, Olive D, Bonneville M, Scotet E. Key implication of

CD277/butyrophilin-3 (BTN3A) in cellular stress sensing by a major human γδ T-cell subset. Blood. 2012 Sep 13;120(11):2269-79.

Harly C, Joyce SP, Domblides C, Bachelet T, Pitard V, Mannat C, Pappalardo A, Couzi L, Netzer S, Massara L, Obre E, Hawchar O, Lartigue L, Claverol S, Cano C, Moreau JF, Mahouche I, Soubeyran I, Rossignol R, Viollet B, Willcox CR, Mohammed F, Willcox BE, Faustin B, Déchanet-Merville J. Human γδ T cell sensing of AMPK-dependent metabolic tumor reprogramming through TCR recognition of EphA2. Sci Immunol. 2021 Jul 30;6(61):eaba9010.

Hatherill M, Cobelens F. Infant BCG vaccination is beneficial, but not sufficient. Lancet Glob Health. 2022 Sep;10(9):e1220-e1221.

Hayday A, Dechanet-Merville J, Rossjohn J, Silva-Santos B. Cancer immunotherapy by γδ T cells. Science. 2024 Oct 4;386(6717):eabq7248.

He X, Liang H, Hong K, Li H, Peng H, Zhao Y, Jia M, Ruan Y, Shao Y. The potential role of CD16+ Vγ2Vδ2 T cell-mediated antibody-dependent cell-mediated cytotoxicity in control of HIV type 1 disease. AIDS Res Hum Retroviruses. 2013 Dec;29(12):1562-70.

Hill DL, Pierson W, Bolland DJ, Mkindi C, Carr EJ, Wang J, Houard S, Wingett SW, Audran R, Wallin EF, Jongo SA, Kamaka K, Zand M, Spertini F, Daubenberger C, Corcoran AE, Linterman MA. The adjuvant GLA-SE promotes human Tfh cell expansion and emergence of public TCRβ clonotypes. J Exp Med. 2019 Aug 5;216(8):1857-1873.

Hill DL, Whyte CE, Innocentin S, Lee JL, Dooley J, Wang J, James EA, Lee JC, Kwok WW, Zand MS, Liston A, Carr EJ, Linterman MA. Impaired HA-specific T follicular

helper cell and antibody responses to influenza vaccination are linked to inflammation in humans. Elife. 2021 Nov 2;10:e70554.

Himoudi N, Morgenstern DA, Yan M, Vernay B, Saraiva L, Wu Y, Cohen CJ, Gustafsson K, Anderson J. Human γδ T lymphocytes are licensed for professional antigen presentation by interaction with opsonized target cells. J Immunol. 2012 Feb 15;188(4):1708-16.

Holmen Olofsson G, Idorn M, Carnaz Simões AM, Aehnlich P, Skadborg SK, Noessner E, Debets R, Moser B, Met Ö, Thor Straten P. Vγ9Vδ2 T Cells Concurrently Kill Cancer Cells and Cross-Present Tumor Antigens. Front Immunol. 2021 Jun 2;12:645131.

Horiuchi S, Wu H, Liu WC, Schmitt N, Provot J, Liu Y, Bentebibel SE, Albrecht RA, Schotsaert M, Forst CV, Zhang B, Ueno H. Tox2 is required for the maintenance of GC TFH cells and the generation of memory TFH cells. Sci Adv. 2021 Oct 8;7(41):eabj1249.

Horner AA, Jabara H, Ramesh N, Geha RS. gamma/delta T lymphocytes express CD40 ligand and induce isotype switching in B lymphocytes. J Exp Med. 1995 Mar 1;181(3):1239-44.

Howard J, Loizon S, Tyler CJ, Duluc D, Moser B, Mechain M, Duvignaud A, Malvy D, Troye-Blomberg M, Moreau JF, Eberl M, Mercereau-Puijalon O, Déchanet-Merville J, Behr C, Mamani-Matsuda M. The Antigen-Presenting Potential of Vγ9Vδ2 T Cells During Plasmodium falciparum Blood-Stage Infection. J Infect Dis. 2017 May 15;215(10):1569-1579.

Hu C, Qian L, Miao Y, Huang Q, Miao P, Wang P, Yu Q, Nie H, Zhang J, He D, Xu R, Chen X, Liu B, Zhang D. Antigen-presenting effects of effector memory Vγ9Vδ2 T cells in rheumatoid arthritis. Cell Mol Immunol. 2012 May;9(3):245-54.

Hu X, Karthigeyan KP, Herbek S, Valencia SM, Jenks JA, Webster H, Miller IG, Connors M, Pollara J, Andy C, Gerber LM, Walter EB, Edwards KM, Bernstein DI, Hou J, Koch M, Panther L, Carfi A, Wu K, Permar SR. Human Cytomegalovirus mRNA-1647 Vaccine Candidate Elicits Potent and Broad Neutralization and Higher Antibody-Dependent Cellular Cytotoxicity Responses Than the gB/MF59 Vaccine. J Infect Dis. 2024 Aug 16;230(2):455-466.

Huang D, Shen Y, Qiu L, Chen CY, Shen L, Estep J, Hunt R, Vasconcelos D, Du G, Aye P, Lackner AA, Larsen MH, Jacobs WR Jr, Haynes BF, Letvin NL, Chen ZW. Immune distribution and localization of phosphoantigen-specific Vgamma2Vdelta2 T cells in lymphoid and nonlymphoid tissues in Mycobacterium tuberculosis infection. Infect Immun. 2008 Jan;76(1):426-36.

Huang D, Chen CY, Ali Z, Shao L, Shen L, Lockman HA, Barnewall RE, Sabourin C, Eestep J, Reichenberg A, Hintz M, Jomaa H, Wang R, Chen ZW. Antigen-specific Vgamma2Vdelta2 T effector cells confer homeostatic protection against pneumonic plaque lesions. Proc Natl Acad Sci U S A. 2009 May 5;106(18):7553-8.

Huang Y, Aydintug MK, Loomis J, Macleod MK, McKee AS, Kirchenbaum G, Jakubzick CV, Kedl RM, Sun D, Jacobelli J, O'Brien RL, Born WK. Antigen-specific regulation of IgE antibodies by non-antigen-specific γδ T cells. J Immunol. 2013 Feb 1;190(3):913-21.

Huang Y, Heiser RA, Detanico TO, Getahun A, Kirchenbaum GA, Casper TL, Aydintug MK, Carding SR, Ikuta K, Huang H, Cambier JC, Wysocki LJ, O'Brien RL, Born WK. γδ T cells affect IL-4 production and B-cell tolerance. Proc Natl Acad Sci U S A. 2015 Jan 6;112(1):E39-48.

Huang Y, Getahun A, Heiser RA, Detanico TO, Aviszus K, Kirchenbaum GA, Casper TL, Huang C, Aydintug MK, Carding SR, Ikuta K, Huang H, Wysocki LJ, Cambier JC, O'Brien RL, Born WK. γδ T Cells Shape Preimmune Peripheral B Cell Populations. J Immunol. 2016 Jan 1;196(1):217-31.

Ibraheem Y, Bayarsaikhan G, Macalinao ML, Kimura K, Yui K, Aoshi T, Inoue SI. γδ T cell-mediated activation of cDC1 orchestrates CD4+ Th1 cell priming in malaria. Front Immunol. 2024 Aug 15;15:1426316.

Inoue SI, Niikura M, Asahi H, Kawakami Y, Kobayashi F. γδ T cells modulate humoral immunity against Plasmodium berghei infection. Immunology. 2018 Dec;155(4):519-532.

Ismaili J, Olislagers V, Poupot R, Fournié JJ, Goldman M. Human gamma delta T cells induce dendritic cell maturation. Clin Immunol. 2002 Jun;103(3 Pt 1):296-302.

Jagannathan P, Kim CC, Greenhouse B, Nankya F, Bowen K, Eccles-James I, Muhindo MK, Arinaitwe E, Tappero JW, Kamya MR, Dorsey G, Feeney ME. Loss and dysfunction of Vδ2^{+} γδ T cells are associated with clinical tolerance to malaria. Sci Transl Med. 2014 Aug 27;6(251):251ra117.

Jagannathan P, Lutwama F, Boyle MJ, Nankya F, Farrington LA, McIntyre TI, Bowen K, Naluwu K, Nalubega M, Musinguzi K, Sikyomu E, Budker R, Katureebe A, Rek

J, Greenhouse B, Dorsey G, Kamya MR, Feeney ME. Vδ2+ T cell response to malaria correlates with protection from infection but is attenuated with repeated exposure. Sci Rep. 2017 Sep 13;7(1):11487.

James CA, Yu KKQ, Mayer-Blackwell K, Fiore-Gartland A, Smith MT, Layton ED, Johnson JL, Hanekom WA, Scriba TJ, Seshadri C. Durable Expansion of TCR-δ Meta-Clonotypes After BCG Revaccination in Humans. Front Immunol. 2022 Mar 30;13:834757.

Jensen O, Trivedi S, Meier JD, Fairfax KC, Hale JS, Leung DT. A subset of follicular helper-like MAIT cells can provide B cell help and support antibody production in the mucosa. Sci Immunol. 2022 Jan 14;7(67):eabe8931.

Joalland N, Chauvin C, Oliver L, Vallette FM, Pecqueur C, Jarry U, Scotet E. IL-21 Increases the Reactivity of Allogeneic Human Vγ9Vδ2 T Cells Against Primary Glioblastoma Tumors. J Immunother. 2018 Jun;41(5):224-231.

Johnston RJ, Poholek AC, DiToro D, Yusuf I, Eto D, Barnett B, Dent AL, Craft J, Crotty S. Bcl6 and Blimp-1 are reciprocal and antagonistic regulators of T follicular helper cell differentiation. Science. 2009 Aug 21;325(5943):1006-10.

Juno JA, Kent SJ. What Can Gamma Delta T Cells Contribute to an HIV Cure? Front Cell Infect Microbiol. 2020 May 19;10:233.

Juno JA, Hill DL. T follicular helper cells and their impact on humoral responses during pathogen and vaccine challenge. Curr Opin Immunol. 2022 Feb;74:112-117.

Junqueira C, Polidoro RB, Castro G, Absalon S, Liang Z, Sen Santara S, Crespo Â, Pereira DB, Gazzinelli RT, Dvorin JD, Lieberman J. γδ T cells suppress

Plasmodium falciparum blood-stage infection by direct killing and phagocytosis. Nat Immunol. 2021 Mar;22(3):347-357.

Kabelitz D, Bender A, Schondelmaier S, Schoel B, Kaufmann SH. A large fraction of human peripheral blood gamma/delta + T cells is activated by Mycobacterium tuberculosis but not by its 65-kD heat shock protein. J Exp Med. 1990 Mar 1;171(3):667-79.

Kaminski H, Marsères G, Cosentino A, Guerville F, Pitard V, Fournié JJ, Merville P, Déchanet-Merville J, Couzi L. Understanding human γδ T cell biology toward a better management of cytomegalovirus infection. Immunol Rev. 2020 Nov;298(1):264-288.

Kaminski H, Couzi L, Eberl M. Unconventional T cells and kidney disease. Nat Rev Nephrol. 2021 Dec;17(12):795-813.

Khairallah C, Netzer S, Villacreces A, Juzan M, Rousseau B, Dulanto S, Giese A, Costet P, Praloran V, Moreau JF, Dubus P, Vermijlen D, Déchanet-Merville J, Capone M. γδ T cells confer protection against murine cytomegalovirus (MCMV). PLoS Pathog. 2015 Mar 6;11(3):e1004702.

Kistowska M, Rossy E, Sansano S, Gober HJ, Landmann R, Mori L, De Libero G. Dysregulation of the host mevalonate pathway during early bacterial infection activates human TCR gamma delta cells. Eur J Immunol. 2008 Aug;38(8):2200-9.

Knight A, Madrigal AJ, Grace S, Sivakumaran J, Kottaridis P, Mackinnon S, Travers PJ, Lowdell MW. The role of Vδ2-negative γδ T cells during cytomegalovirus reactivation in recipients of allogeneic stem cell transplantation. Blood. 2010 Sep 23;116(12):2164-72.

Kozakiewicz L, Phuah J, Flynn J, Chan J. The role of B cells and humoral immunity in Mycobacterium tuberculosis infection. Adv Exp Med Biol. 2013;783:225-50.

Kroca M, Johansson A, Sjöstedt A, Tärnvik A. V gamma 9V delta 2 T cells in human legionellosis. Clin Diagn Lab Immunol. 2001 Sep;8(5):949-54.

Kurup SP, Butler NS, Harty JT. T cell-mediated immunity to malaria. Nat Rev Immunol. 2019 Jul;19(7):457-471.

Kvistad D, Pallikkuth S, Sirupangi T, Pahwa R, Kizhner A, Petrovas C, Villinger F, Pahwa S. IL-21 enhances influenza vaccine responses in aged macaques with suppressed SIV infection. JCI Insight. 2021 Oct 22;6(20):e150888.

Lagler H, Willheim M, Traunmüller F, Wahl K, Winkler H, Ramharter M, Graninger W, Winkler S. Cellular profile of cytokine production in a patient with visceral leishmaniasis: gammadelta+ T cells express both type 1 cytokines and interleukin-10. Scand J Immunol. 2003 Mar;57(3):291-5.

Lalor SJ, McLoughlin RM. Memory γδ T Cells-Newly Appreciated Protagonists in Infection and Immunity. Trends Immunol. 2016 Oct;37(10):690-702.

Landmeier S, Altvater B, Pscherer S, Juergens H, Varnholt L, Hansmeier A, Bollard CM, Moosmann A, Bisping G, Rossig C. Activated human gammadelta T cells as stimulators of specific CD8+ T-cell responses to subdominant Epstein Barr virus epitopes: potential for immunotherapy of cancer. J Immunother. 2009 Apr;32(3):310-21.

Larson EC, Ellis AL, Rodgers MA, Gubernat AK, Gleim JL, Moriarty RV, Balgeman AJ, de Menezes YT, Ameel CL, Fillmore DJ, Pergalske SM, Juno JA, Maiello P, Chishti

HB, Lin PL, Godfrey DI, Kent SJ, Pellicci DG, Ndhlovu LC, O'Connor SL, Scanga CA. Transiently boosting Vγ9+Vδ2+ γδ T cells early in Mtb coinfection of SIV-infected juvenile macaques does not improve Mtb host resistance. Infect Immun. 2024 Dec 10;92(12):e0031324.

Law H, Venturi V, Kelleher A, Munier CML. Tfh Cells in Health and Immunity: Potential Targets for Systems Biology Approaches to Vaccination. Int J Mol Sci. 2020 Nov 12;21(22):8524.

Laws TR, Nelson M, Bonnafous C, Sicard H, Taylor C, Salguero FJ, Atkins TP, Oyston PC, Rowland CA. In vivo manipulation of γ9(+) T cells in the common marmoset (Callithrix Jacchus) with phosphoantigen and effect on the progression of respiratory melioidosis. PLoS One. 2013 Sep 30;8(9):e74789.

Le Floch AC, Imbert C, Boucherit N, Gorvel L, Fattori S, Orlanducci F, Le Roy A, Archetti L, Crescence L, Panicot-Dubois L, Dubois C, Vey N, Briantais A, Anastasio A, Cano C, Guittard G, Frechin M, Olive D. Targeting BTN2A1 Enhances Vγ9Vδ2 T-Cell Effector Functions and Triggers Tumor Cell Pyroptosis. Cancer Immunol Res. 2024 Dec 3;12(12):1677-1690.

Legler DF, Loetscher M, Roos RS, Clark-Lewis I, Baggiolini M, Moser B. B cell-attracting chemokine 1, a human CXC chemokine expressed in lymphoid tissues, selectively attracts B lymphocytes via BLR1/CXCR5. J Exp Med. 1998 Feb 16;187(4):655-60.

Lei L, Qian H, Yang X, Zhang X, Zhang D, Dai T, Guo R, Shi L, Cheng Y, Zhang B, Zhou X, Hu J, Guo Y. The phenotypic changes of γδ T cells in COVID-19 patients. J Cell Mol Med. 2020 Oct;24(19):11603-11606.

León-Lara X, Fichtner AS, Willers M, Yang T, Schaper K, Riemann L, Schöning J, Harms A, Almeida V, Schimrock A, Janssen A, Ospina-Quintero L, von Kaisenberg C, Förster R, Eberl M, Richter MF, Pirr S, Viemann D, Ravens S. γδ T cell profiling in a cohort of preterm infants reveals elevated frequencies of CD83+ γδ T cells in sepsis. J Exp Med. 2024 Jul 1;221(7):e20231987.

Li H, Peng H, Ma P, Ruan Y, Su B, Ding X, Xu C, Pauza CD, Shao Y. Association between Vgamma2Vdelta2 T cells and disease progression after infection with closely related strains of HIV in China. Clin Infect Dis. 2008 May 1;46(9):1466-72.

Li J, Wang M, Zhou J, Fei Y, Li M, Zhao Y, Zeng X, Peng L, Zhang W. Polarization of Vδ2 T cells to a Th2-like phenotype promotes plasmablast differentiation and possesses pro-fibrotic properties in IgG4-related disease. Front Immunol. 2025 Mar 27;16:1550405.

Li X, Mukandavire C, Cucunubá ZM, Echeverria Londono S, Abbas K, Clapham HE, Jit M, Johnson HL, Papadopoulos T, Vynnycky E, Brisson M, Carter ED, Clark A, de Villiers MJ, Eilertson K, Ferrari MJ, Gamkrelidze I, Gaythorpe KAM, Grassly NC, Hallett TB, Hinsley W, Jackson ML, Jean K, Karachaliou A, Klepac P, Lessler J, Li X, Moore SM, Nayagam S, Nguyen DM, Razavi H, Razavi-Shearer D, Resch S, Sanderson C, Sweet S, Sy S, Tam Y, Tanvir H, Tran QM, Trotter CL, Truelove S, van Zandvoort K, Verguet S, Walker N, Winter A, Woodruff K, Ferguson NM, Garske T; Vaccine Impact Modelling Consortium. Estimating the health impact of vaccination against ten pathogens in 98 low-income and middle-income countries from 2000 to 2030: a modelling study. Lancet. 2021 Jan 30;397(10272):398-408.

Li X, Wu M, Lu J, Yu J, Chen D. Interleukin-21 as an adjuvant in cancer immunotherapy: Current advances and future directions. Biochim Biophys Acta Rev Cancer. 2024 Mar;1879(2):189084.

Liang H, Tang J, Liu Z, Liu Y, Huang Y, Xu Y, Hao P, Yin Z, Zhong J, Ye L, Jin X, Wang H. ZIKV infection induces robust Th1-like Tfh cell and long-term protective antibody responses in immunocompetent mice. Nat Commun. 2019 Aug 27;10(1):3859.

Linterman MA, Hill DL. Can follicular helper T cells be targeted to improve vaccine efficacy? F1000Res. 2016 Jan 20;5:F1000 Faculty Rev-88.

Liu X, Chen X, Zhong B, Wang A, Wang X, Chu F, Nurieva RI, Yan X, Chen P, van der Flier LG, Nakatsukasa H, Neelapu SS, Chen W, Clevers H, Tian Q, Qi H, Wei L, Dong C. Transcription factor achaete-scute homologue 2 initiates follicular T-helper-cell development. Nature. 2014 Mar 27;507(7493):513-8.

Liuzzi AR, Kift-Morgan A, Lopez-Anton M, Friberg IM, Zhang J, Brook AC, Roberts GW, Donovan KL, Colmont CS, Toleman MA, Bowen T, Johnson DW, Topley N, Moser B, Fraser DJ, Eberl M. Unconventional Human T Cells Accumulate at the Site of Infection in Response to Microbial Ligands and Induce Local Tissue Remodeling. J Immunol. 2016 Sep 15;197(6):2195-207.

Locci M, Havenar-Daughton C, Landais E, Wu J, Kroenke MA, Arlehamn CL, Su LF, Cubas R, Davis MM, Sette A, Haddad EK; International AIDS Vaccine Initiative Protocol C Principal Investigators; Poignard P, Crotty S. Human circulating PD-1+CXCR3-CXCR5+ memory Tfh cells are highly functional and correlate with broadly neutralizing HIV antibody responses. Immunity. 2013 Oct 17;39(4):758-69.

Lofano G, Mancini F, Salvatore G, Cantisani R, Monaci E, Carrisi C, Tavarini S, Sammicheli C, Rossi Paccani S, Soldaini E, Laera D, Finco O, Nuti S, Rappuoli R, De Gregorio E, Bagnoli F, Bertholet S. Oil-in-Water Emulsion MF59 Increases Germinal Center B Cell Differentiation and Persistence in Response to Vaccination. J Immunol. 2015 Aug 15;195(4):1617-27.

Lu LL, Chung AW, Rosebrock TR, Ghebremichael M, Yu WH, Grace PS, Schoen MK, Tafesse F, Martin C, Leung V, Mahan AE, Sips M, Kumar MP, Tedesco J, Robinson H, Tkachenko E, Draghi M, Freedberg KJ, Streeck H, Suscovich TJ, Lauffenburger DA, Restrepo BI, Day C, Fortune SM, Alter G. A Functional Role for Antibodies in Tuberculosis. Cell. 2016 Oct 6;167(2):433-443.e14.

Luo W, Yin Q. B Cell Response to Vaccination. Immunol Invest. 2021 Oct;50(7):780-801.

Ma L, Papadopoulou M, Taton M, Genco F, Marchant A, Meroni V, Vermijlen D. Effector Vγ9Vδ2 T cell response to congenital Toxoplasma gondii infection. JCI Insight. 2021 Aug 23;6(16):e138066.

Maloy KJ, Odermatt B, Hengartner H, Zinkernagel RM. Interferon gamma-producing gammadelta T cell-dependent antibody isotype switching in the absence of germinal center formation during virus infection. Proc Natl Acad Sci U S A. 1998 Feb 3;95(3):1160-5.

Mann BT, Sambrano E 3rd, Maggirwar SB, Soriano-Sarabia N. Boosting the Immune System for HIV Cure: A γδ T Cell Perspective. Front Cell Infect Microbiol. 2020 May 19;10:221.

Martin-Gayo E, Cronin J, Hickman T, Ouyang Z, Lindqvist M, Kolb KE, Schulze Zur Wiesch J, Cubas R, Porichis F, Shalek AK, van Lunzen J, Haddad EK, Walker BD, Kaufmann DE, Lichterfeld M, Yu XG. Circulating CXCR5+CXCR3+PD-1lo Tfh-like cells in HIV-1 controllers with neutralizing antibody breadth. JCI Insight. 2017 Jan 26;2(2):e89574.

Martinez L, Cords O, Liu Q, Acuna-Villaorduna C, Bonnet M, Fox GJ, Carvalho ACC, Chan PC, Croda J, Hill PC, Lopez-Varela E, Donkor S, Fielding K, Graham SM, Espinal MA, Kampmann B, Reingold A, Huerga H, Villalba JA, Grandjean L, Sotgiu G, Egere U, Singh S, Zhu L, Lienhardt C, Denholm JT, Seddon JA, Whalen CC, García-Basteiro AL, Triasih R, Chen C, Singh J, Huang LM, Sharma S, Hannoun D, Del Corral H, Mandalakas AM, Malone LL, Ling DL, Kritski A, Stein CM, Vashishtha R, Boulahbal F, Fang CT, Boom WH, Netto EM, Lemos AC, Hesseling AC, Kay A, Jones-López EC, Horsburgh CR, Lange C, Andrews JR. Infant BCG vaccination and risk of pulmonary and extrapulmonary tuberculosis throughout the life course: a systematic review and individual participant data meta-analysis. Lancet Glob Health. 2022 Sep;10(9):e1307-e1316.

Mastelic Gavillet B, Eberhardt CS, Auderset F, Castellino F, Seubert A, Tregoning JS, Lambert PH, de Gregorio E, Del Giudice G, Siegrist CA. MF59 Mediates Its B Cell Adjuvanticity by Promoting T Follicular Helper Cells and Thus Germinal Center Responses in Adult and Early Life. J Immunol. 2015 May 15;194(10):4836-45.

McMenamin C, McKersey M, Kühnlein P, Hünig T, Holt PG. Gamma delta T cells down-regulate primary IgE responses in rats to inhaled soluble protein antigens. J Immunol. 1995 May 1;154(9):4390-4.

McNamara HA, Lahoud MH, Cai Y, Durrant-Whyte J, O'Connor JH, Caminschi I, Cockburn IA. Splenic Dendritic Cells and Macrophages Drive B Cells to Adopt a Plasmablast Cell Fate. Front Immunol. 2022 Apr 12;13:825207.

McShane AN, Malinova D. The Ins and Outs of Antigen Uptake in B cells. Front Immunol. 2022 Apr 26;13:892169.

Meuter S, Eberl M, Moser B. Prolonged antigen survival and cytosolic export in cross-presenting human γδ T cells. Proc Natl Acad Sci U S A. 2010 May 11;107(19):8730-5.

Miletic A, Lenartic M, Popovic B, Brizic I, Trsan T, Miklic K, Mandelboim O, Krmpotic A, Jonjic S. NCR1-deficiency diminishes the generation of protective murine cytomegalovirus antibodies by limiting follicular helper T-cell maturation. Eur J Immunol. 2017 Sep;47(9):1443-1456.

Moens E, Brouwer M, Dimova T, Goldman M, Willems F, Vermijlen D. IL-23R and TCR signaling drives the generation of neonatal Vgamma9Vdelta2 T cells expressing high levels of cytotoxic mediators and producing IFN-gamma and IL-17. J Leukoc Biol. 2011 May;89(5):743-52.

Moody MA, Pedroza-Pacheco I, Vandergrift NA, Chui C, Lloyd KE, Parks R, Soderberg KA, Ogbe AT, Cohen MS, Liao HX, Gao F, McMichael AJ, Montefiori DC, Verkoczy L, Kelsoe G, Huang J, Shea PR, Connors M, Borrow P, Haynes BF. Immune perturbations in HIV-1-infected individuals who make broadly neutralizing antibodies. Sci Immunol. 2016 Jul 29;1(1):aag0851.

Moon JJ, Suh H, Li AV, Ockenhouse CF, Yadava A, Irvine DJ. Enhancing humoral responses to a malaria antigen with nanoparticle vaccines that expand Tfh cells and

promote germinal center induction. Proc Natl Acad Sci U S A. 2012 Jan 24;109(4):1080-5.

Morita CT, Jin C, Sarikonda G, Wang H. Nonpeptide antigens, presentation mechanisms, and immunological memory of human Vgamma2Vdelta2 T cells: discriminating friend from foe through the recognition of prenyl pyrophosphate antigens. Immunol Rev. 2007 Feb;215:59-76.

Morrison AL, Sarfas C, Sibley L, Williams J, Mabbutt A, Dennis MJ, Lawrence S, White AD, Bodman-Smith M, Sharpe SA. IV BCG Vaccination and Aerosol BCG Revaccination Induce Mycobacteria-Responsive γδ T Cells Associated with Protective Efficacy against *M. tb* Challenge. Vaccines (Basel). 2023 Oct 17;11(10):1604.

Mou W, Han W, Ma X, Wang X, Qin H, Zhao W, Ren X, Chen X, Yang W, Cheng H, Wang X, Zhang H, Ni X, Wang H, Gui J. γδTFH cells promote B cell maturation and antibody production in neuroblastoma. BMC Immunol. 2017 Jul 7;18(1):36.

Moysi E, Petrovas C, Koup RA. The role of follicular helper CD4 T cells in the development of HIV-1 specific broadly neutralizing antibody responses. Retrovirology. 2018 Aug 6;15(1):54.

Munk ME, Fazioli RA, Calich VL, Kaufmann SH. Paracoccidioides brasiliensis-stimulated human gamma/delta T cells support antibody production by B cells. Infect Immun. 1995 Apr;63(4):1608-10.

Mwakingwe-Omari A, Healy SA, Lane J, Cook DM, Kalhori S, Wyatt C, Kolluri A, Marte-Salcedo O, Imeru A, Nason M, Ding LK, Decederfelt H, Duan J, Neal J, Raiten J, Lee G, Hume JCC, Jeon JE, Ikpeama I, Kc N, Chakravarty S, Murshedkar

T, Church LWP, Manoj A, Gunasekera A, Anderson C, Murphy SC, March S, Bhatia SN, James ER, Billingsley PF, Sim BKL, Richie TL, Zaidi I, Hoffman SL, Duffy PE. Two chemoattenuated PfSPZ malaria vaccines induce sterile hepatic immunity. Nature. 2021 Jul;595(7866):289-294.

Ness-Schwickerath KJ, Jin C, Morita CT. Cytokine requirements for the differentiation and expansion of IL-17A- and IL-22-producing human Vgamma2Vdelta2 T cells. J Immunol. 2010 Jun 15;184(12):7268-80.

Niessl J, Kaufmann DE. Harnessing T Follicular Helper Cell Responses for HIV Vaccine Development. Viruses. 2018 Jun 19;10(6):336.

Ninomiya T, Takimoto H, Matsuzaki G, Hamano S, Yoshida H, Yoshikai Y, Kimura G, Nomoto K. Vgamma1+ gammadelta T cells play protective roles at an early phase of murine cytomegalovirus infection through production of interferon-gamma. Immunology. 2000 Feb;99(2):187-94.

Nothelfer K, Sansonetti PJ, Phalipon A. Pathogen manipulation of B cells: the best defence is a good offence. Nat Rev Microbiol. 2015 Mar;13(3):173-84.

Nurieva RI, Chung Y, Martinez GJ, Yang XO, Tanaka S, Matskevitch TD, Wang YH, Dong C. Bcl6 mediates the development of T follicular helper cells. Science. 2009 Aug 21;325(5943):1001-5.

Obeng-Adjei N, Portugal S, Tran TM, Yazew TB, Skinner J, Li S, Jain A, Felgner PL, Doumbo OK, Kayentao K, Ongoiba A, Traore B, Crompton PD. Circulating Th1-Cell-type Tfh Cells that Exhibit Impaired B Cell Help Are Preferentially Activated during Acute Malaria in Children. Cell Rep. 2015 Oct 13;13(2):425-39.

Oliver AJ, Huang N, Bartolome-Casado R, Li R, Koplev S, Nilsen HR, Moy M, Cakir B, Polanski K, Gudiño V, Melón-Ardanaz E, Sumanaweera D, Dimitrov D, Milchsack LM, FitzPatrick MEB, Provine NM, Boccacino JM, Dann E, Predeus AV, To K, Prete M, Chapman JA, Masi AC, Stephenson E, Engelbert J, Lobentanzer S, Perera S, Richardson L, Kapuge R, Wilbrey-Clark A, Semprich CI, Ellams S, Tudor C, Joseph P, Garrido-Trigo A, Corraliza AM, Oliver TRW, Hook CE, James KR, Mahbubani KT, Saeb-Parsy K, Zilbauer M, Saez-Rodriguez J, Høivik ML, Bækkevold ES, Stewart CJ, Berrington JE, Meyer KB, Klenerman P, Salas A, Haniffa M, Jahnsen FL, Elmentaite R, Teichmann SA. Single-cell integration reveals metaplasia in inflammatory gut diseases. Nature. 2024 Nov;635(8039):699-707.

Osier FH, Fegan G, Polley SD, Murungi L, Verra F, Tetteh KK, Lowe B, Mwangi T, Bull PC, Thomas AW, Cavanagh DR, McBride JS, Lanar DE, Mackinnon MJ, Conway DJ, Marsh K. Breadth and magnitude of antibody responses to multiple Plasmodium falciparum merozoite antigens are associated with protection from clinical malaria. Infect Immun. 2008 May;76(5):2240-8.

Pao W, Wen L, Smith AL, Gulbranson-Judge A, Zheng B, Kelsoe G, MacLennan IC, Owen MJ, Hayday AC. Gamma delta T cell help of B cells is induced by repeated parasitic infection, in the absence of other T cells. Curr Biol. 1996 Oct 1;6(10):1317-25.

Papadopoulou M, Dimova T, Shey M, Briel L, Veldtsman H, Khomba N, Africa H, Steyn M, Hanekom WA, Scriba TJ, Nemes E, Vermijlen D. Fetal public Vγ9Vδ2 T cells expand and gain potent cytotoxic functions early after birth. Proc Natl Acad Sci U S A. 2020 Aug 4;117(31):18638-18648.

Pauza CD, Poonia B, Li H, Cairo C, Chaudhry S. γδ T Cells in HIV Disease: Past, Present, and Future. Front Immunol. 2015 Jan 30;5:687.

Pérez-Mazliah D, Nguyen MP, Hosking C, McLaughlin S, Lewis MD, Tumwine I, Levy P, Langhorne J. Follicular Helper T Cells are Essential for the Elimination of Plasmodium Infection. EBioMedicine. 2017 Oct;24:216-230.

Perez-Shibayama C, Gil-Cruz C, Pastelin-Palacios R, Cervantes-Barragan L, Hisaki E, Chai Q, Onder L, Scandella E, Regen T, Waisman A, Isibasi A, Lopez-Macias C, Ludewig B. IFN-γ-producing CD4+ T cells promote generation of protective germinal center-derived IgM+ B cell memory against Salmonella Typhi. J Immunol. 2014 Jun 1;192(11):5192-200.

Peters C, Häsler R, Wesch D, Kabelitz D. Human Vδ2 T cells are a major source of interleukin-9. Proc Natl Acad Sci U S A. 2016 Nov 1;113(44):12520-12525.

Petrasca A, Doherty DG. Human Vδ2(+) γδ T Cells Differentially Induce Maturation, Cytokine Production, and Alloreactive T Cell Stimulation by Dendritic Cells and B Cells. Front Immunol. 2014 Dec 19;5:650.

Petrasca A, Melo AM, Breen EP, Doherty DG. Human Vδ3^{+} γδ T cells induce maturation and IgM secretion by B cells. Immunol Lett. 2018 Apr;196:126-134.

Pitard V, Roumanes D, Lafarge X, Couzi L, Garrigue I, Lafon ME, Merville P, Moreau JF, Déchanet-Merville J. Long-term expansion of effector/memory Vdelta2-gammadelta T cells is a specific blood signature of CMV infection. Blood. 2008 Aug 15;112(4):1317-24.

Plotkin SA, Boppana SB. Vaccination against the human cytomegalovirus. Vaccine. 2019 Nov 28;37(50):7437-7442.

Poonia B, Pauza CD. Gamma delta T cells from HIV+ donors can be expanded in vitro by zoledronate/interleukin-2 to become cytotoxic effectors for antibody-dependent cellular cytotoxicity. Cytotherapy. 2012 Feb;14(2):173-81.

Prinz I, Koenecke C. Antigen-specific γδ T cells contribute to cytomegalovirus control after stem cell transplantation. Curr Opin Immunol. 2023 Jun;82:102303.

Prota G, Christensen D, Andersen P, Medaglini D, Ciabattini A. Peptide-specific T helper cells identified by MHC class II tetramers differentiate into several subtypes upon immunization with CAF01 adjuvanted H56 tuberculosis vaccine formulation. Vaccine. 2015 Nov 27;33(48):6823-30.

Qi Q, Xia M, Hu J, Hicks E, Iyer A, Xiong N, August A. Enhanced development of CD4+ gammadelta T cells in the absence of Itk results in elevated IgE production. Blood. 2009 Jul 16;114(3):564-71.

Qiu L, Zhang Y, Zeng X. The function of γδ T cells in humoral immune responses. Inflamm Res. 2023 Apr;72(4):747-755.

Radtke AJ, Anderson CF, Riteau N, Rausch K, Scaria P, Kelnhofer ER, Howard RF, Sher A, Germain RN, Duffy P. Adjuvant and carrier protein-dependent T-cell priming promotes a robust antibody response against the Plasmodium falciparum Pfs25 vaccine candidate. Sci Rep. 2017 Jan 16;7:40312.

Rajagopalan S, Zordan T, Tsokos GC, Datta SK. Pathogenic anti-DNA autoantibody-inducing T helper cell lines from patients with active lupus nephritis: isolation of

CD4-8- T helper cell lines that express the gamma delta T-cell antigen receptor. Proc Natl Acad Sci U S A. 1990 Sep;87(18):7020-4.

Rajagopalan S, Mao C, Datta SK. Pathogenic autoantibody-inducing gamma/delta T helper cells from patients with lupus nephritis express unusual T cell receptors. Clin Immunol Immunopathol. 1992 Mar;62(3):344-50.

Rampoldi F, Ullrich L, Prinz I. Revisiting the Interaction of γδ T-Cells and B-Cells. Cells. 2020 Mar 18;9(3):743.

Rampoldi F, Donato E, Ullrich L, Deseke M, Janssen A, Demera A, Sandrock I, Bubke A, Juergens AL, Swallow M, Sparwasser T, Falk C, Tan L, Trumpp A, Prinz I. γδ T cells license immature B cells to produce a broad range of polyreactive antibodies. Cell Rep. 2022 May 24;39(8):110854.

Rastogi I, Jeon D, Moseman JE, Muralidhar A, Potluri HK, McNeel DG. Role of B cells as antigen presenting cells. Front Immunol. 2022 Sep 8;13:954936.

Ravens S, Schultze-Florey C, Raha S, Sandrock I, Drenker M, Oberdörfer L, Reinhardt A, Ravens I, Beck M, Geffers R, von Kaisenberg C, Heuser M, Thol F, Ganser A, Förster R, Koenecke C, Prinz I. Human γδ T cells are quickly reconstituted after stem-cell transplantation and show adaptive clonal expansion in response to viral infection. Nat Immunol. 2017 Apr;18(4):393-401.

Raziuddin S, Telmasani AW, el-Hag el-Awad M, al-Amari O, al-Janadi M. Gamma delta T cells and the immune response in visceral leishmaniasis. Eur J Immunol. 1992 May;22(5):1143-8.

Reinhardt RL, Liang HE, Locksley RM. Cytokine-secreting follicular T cells shape the antibody repertoire. Nat Immunol. 2009 Apr;10(4):385-93.

Rezende RM, da Cunha AP, Kuhn C, Rubino S, M'Hamdi H, Gabriely G, Vandeventer T, Liu S, Cialic R, Pinheiro-Rosa N, Oliveira RP, Gaublomme JT, Obholzer N, Kozubek J, Pochet N, Faria AMC, Weiner HL. Identification and characterization of latency-associated peptide-expressing γδ T cells. Nat Commun. 2015 Dec 8;6:8726.

Rezende RM, Lanser AJ, Rubino S, Kuhn C, Skillin N, Moreira TG, Liu S, Gabriely G, David BA, Menezes GB, Weiner HL. γδ T cells control humoral immune response by inducing T follicular helper cell differentiation. Nat Commun. 2018 Aug 8;9(1):3151.

Riedel DJ, Sajadi MM, Armstrong CL, Cummings JS, Cairo C, Redfield RR, Pauza CD. Natural viral suppressors of HIV-1 have a unique capacity to maintain gammadelta T cells. AIDS. 2009 Sep 24;23(15):1955-64.

Rijnink WF, Ottenhoff THM, Joosten SA. B-Cells and Antibodies as Contributors to Effector Immune Responses in Tuberculosis. Front Immunol. 2021 Feb 18;12:640168.

Riteau N, Radtke AJ, Shenderov K, Mittereder L, Oland SD, Hieny S, Jankovic D, Sher A. Water-in-Oil-Only Adjuvants Selectively Promote T Follicular Helper Cell Polarization through a Type I IFN and IL-6-Dependent Pathway. J Immunol. 2016 Nov 15;197(10):3884-3893.

Ritzau-Jost J, Hutloff A. T Cell/B Cell Interactions in the Establishment of Protective Immunity. Vaccines (Basel). 2021 Sep 24;9(10):1074.

Roberts SJ, Smith AL, West AB, Wen L, Findly RC, Owen MJ, Hayday AC. T-cell alpha beta + and gamma delta + deficient mice display abnormal but distinct phenotypes toward a natural, widespread infection of the intestinal epithelium. Proc Natl Acad Sci U S A. 1996 Oct 15;93(21):11774-9.

Rodrigues V, Laforge M, Campillo-Gimenez L, Soundaramourty C, Correia-de-Oliveira A, Dinis-Oliveira RJ, Ouaissi A, Cordeiro-da-Silva A, Silvestre R, Estaquier J. Abortive T follicular helper development is associated with a defective humoral response in Leishmania infantum-infected macaques. PLoS Pathog. 2014 Apr 24;10(4):e1004096.

Rodrigues V, Cordeiro-da-Silva A, Laforge M, Silvestre R, Estaquier J. Regulation of immunity during visceral Leishmania infection. Parasit Vectors. 2016 Mar 1;9:118.

Roelofs AJ, Jauhiainen M, Mönkkönen H, Rogers MJ, Mönkkönen J, Thompson K. Peripheral blood monocytes are responsible for gammadelta T cell activation induced by zoledronic acid through accumulation of IPP/DMAPP. Br J Haematol. 2009 Jan;144(2):245-50.

Roider J, Maehara T, Ngoepe A, Ramsuran D, Muenchhoff M, Adland E, Aicher T, Kazer SW, Jooste P, Karim F, Kuhn W, Shalek AK, Ndung'u T, Morris L, Moore PL, Pillai S, Kløverpris H, Goulder P, Leslie A. High-Frequency, Functional HIV-Specific T-Follicular Helper and Regulatory Cells Are Present Within Germinal Centers in Children but Not Adults. Front Immunol. 2018 Sep 12;9:1975.

Ronsard L, Yousif AS, Nait Mohamed FA, Feldman J, Okonkwo V, McCarthy C, Schnabel J, Caradonna T, Barnes RM, Rohrer D, Lonberg N, Schmidt A, Lingwood

D. Engaging an HIV vaccine target through the acquisition of low B cell affinity. Nat Commun. 2023 Aug 28;14(1):5249.

Rowland CA, Laws TR, Oyston PC. An assessment of common marmoset (Callithrix jacchus) γ9(+) T cells and their response to phosphoantigen in vitro. Cell Immunol. 2012 Dec;280(2):132-7.

Röring RJ, Debisarun PA, Botey-Bataller J, Suen TK, Bulut Ö, Kilic G, Koeken VA, Sarlea A, Bahrar H, Dijkstra H, Lemmers H, Gössling KL, Rüchel N, Ostermann PN, Müller L, Schaal H, Adams O, Borkhardt A, Ariyurek Y, de Meijer EJ, Kloet SL, Ten Oever J, Placek K, Li Y, Netea MG. MMR vaccination induces trained immunity via functional and metabolic reprogramming of γδ T cells. J Clin Invest. 2024 Jan 30;134(7):e170848.

Russo DM, Armitage RJ, Barral-Netto M, Barral A, Grabstein KH, Reed SG. Antigen-reactive gamma delta T cells in human leishmaniasis. J Immunol. 1993 Oct 1;151(7):3712-8.

Rutishauser T, Lepore M, Di Blasi D, Dangy JP, Abdulla S, Jongo S, Ramadhani K, Sim BKL, Hoffman SL, Tanner M, Daubenberger C, De Libero G. Activation of TCR Vδ1+ and Vδ1-Vδ2- γδ T Cells upon Controlled Infection with Plasmodium falciparum in Tanzanian Volunteers. J Immunol. 2020 Jan 1;204(1):180-191.

Ryg-Cornejo V, Ioannidis LJ, Ly A, Chiu CY, Tellier J, Hill DL, Preston SP, Pellegrini M, Yu D, Nutt SL, Kallies A, Hansen DS. Severe Malaria Infections Impair Germinal Center Responses by Inhibiting T Follicular Helper Cell Differentiation. Cell Rep. 2016 Jan 5;14(1):68-81.

Sage PT, Sharpe AH. T follicular regulatory cells in the regulation of B cell responses. Trends Immunol. 2015 Jul;36(7):410-8.

Saha A, Chakrabarti G, Sen S, Bandyopadhyay S. Leishmania donovani parasites interact with gamma/delta+ human peripheral blood T cells and induce susceptibility to NK cell-mediated lysis. Scand J Immunol. 1999 Dec;50(6):588-95.

Sant S, Jenkins MR, Dash P, Watson KA, Wang Z, Pizzolla A, Koutsakos M, Nguyen TH, Lappas M, Crowe J, Loudovaris T, Mannering SI, Westall GP, Kotsimbos TC, Cheng AC, Wakim L, Doherty PC, Thomas PG, Loh L, Kedzierska K. Human γδ T-cell receptor repertoire is shaped by influenza viruses, age and tissue compartmentalisation. Clin Transl Immunology. 2019 Sep 23;8(9):e1079.

Sanz M, Mann BT, Chitrakar A, Soriano-Sarabia N. Defying convention in the time of COVID-19: Insights into the role of γδ T cells. Front Immunol. 2022 Aug 11;13:819574.

Saura-Esteller J, de Jong M, King LA, Ensing E, Winograd B, de Gruijl TD, Parren PWHI, van der Vliet HJ. Gamma Delta T-Cell Based Cancer Immunotherapy: Past-Present-Future. Front Immunol. 2022 Jun 16;13:915837.

Schaerli P, Willimann K, Lang AB, Lipp M, Loetscher P, Moser B. CXC chemokine receptor 5 expression defines follicular homing T cells with B cell helper function. J Exp Med. 2000 Dec 4;192(11):1553-62.

Schmitt N, Liu Y, Bentebibel SE, Munagala I, Bourdery L, Venuprasad K, Banchereau J, Ueno H. The cytokine TGF-β co-opts signaling via STAT3-STAT4 to promote the differentiation of human TFH cells. Nat Immunol. 2014 Sep;15(9):856-65.

Sell S, Dietz M, Schneider A, Holtappels R, Mach M, Winkler TH. Control of murine cytomegalovirus infection by γδ T cells. PLoS Pathog. 2015 Feb 6;11(2):e1004481.

Semmes EC, Miller IG, Rodgers N, Phan CT, Hurst JH, Walsh KM, Stanton RJ, Pollara J, Permar SR. ADCC-activating antibodies correlate with decreased risk of congenital human cytomegalovirus transmission. JCI Insight. 2023 Jul 10;8(13):e167768.

Semmes EC, Nettere DR, Nelson AN, Hurst JH, Cain DW, Burt TD, Kurtzberg J, Reeves RK, Coyne CB, Fouda GG, Pollara J, Permar SR, Walsh KM. In utero human cytomegalovirus infection expands NK-like FcγRIII+CD8+ T cells that mediate Fc antibody functions. J Clin Invest. 2024 Nov 12;135(1):e181342.

Shen Y, Zhou D, Qiu L, Lai X, Simon M, Shen L, Kou Z, Wang Q, Jiang L, Estep J, Hunt R, Clagett M, Sehgal PK, Li Y, Zeng X, Morita CT, Brenner MB, Letvin NL, Chen ZW. Adaptive immune response of Vgamma2Vdelta2+ T cells during mycobacterial infections. Science. 2002 Mar 22;295(5563):2255-8.

Shen L, Frencher J, Huang D, Wang W, Yang E, Chen CY, Zhang Z, Wang R, Qaqish A, Larsen MH, Shen H, Porcelli SA, Jacobs WR Jr, Chen ZW. Immunization of Vγ2Vδ2 T cells programs sustained effector memory responses that control tuberculosis in nonhuman primates. Proc Natl Acad Sci U S A. 2019 Mar 26;116(13):6371-6378.

Shen H, Yang E, Guo M, Yang R, Huang G, Peng Y, Sha W, Wang F, Shen L. Adjunctive Zoledronate + IL-2 administrations enhance anti-tuberculosis Vγ2Vδ2 T-effector populations, and improve treatment outcome of multidrug-resistant tuberculosis1. Emerg Microbes Infect. 2022 Dec;11(1):1790-1805.

Silva-Barrios S, Stäger S. Hypergammaglobulinemia sustains the development of regulatory responses during chronic Leishmania donovani infection in mice. Eur J Immunol. 2019 Jul;49(7):1082-1091.

Singh U, Pawge G, Rani S, Hsiao CC, Wiemer AJ, Wiemer DF. Diester Prodrugs of a Phosphonate Butyrophilin Ligand Display Improved Cell Potency, Plasma Stability, and Payload Internalization. J Med Chem. 2023 Nov 23;66(22):15309-15325.

Slight SR, Rangel-Moreno J, Gopal R, Lin Y, Fallert Junecko BA, Mehra S, Selman M, Becerril-Villanueva E, Baquera-Heredia J, Pavon L, Kaushal D, Reinhart TA, Randall TD, Khader SA. CXCR5^{+} T helper cells mediate protective immunity against tuberculosis. J Clin Invest. 2013 Feb;123(2):712-26.

Soon MSF, Nalubega M, Boyle MJ. T-follicular helper cells in malaria infection and roles in antibody induction. Oxf Open Immunol. 2021 Apr 10;2(1):iqab008.

Spensieri F, Siena E, Borgogni E, Zedda L, Cantisani R, Chiappini N, Schiavetti F, Rosa D, Castellino F, Montomoli E, Bodinham CL, Lewis DJ, Medini D, Bertholet S, Del Giudice G. Early Rise of Blood T Follicular Helper Cell Subsets and Baseline Immunity as Predictors of Persisting Late Functional Antibody Responses to Vaccination in Humans. PLoS One. 2016 Jun 23;11(6):e0157066.

Spinozzi F, Agea E, Bistoni O, Forenza N, Monaco A, Falini B, Bassotti G, De Benedictis F, Grignani F, Bertotto A. Local expansion of allergen-specific CD30+Th2-type gamma delta T cells in bronchial asthma. Mol Med. 1995 Nov;1(7):821-6.

Stankovic S, Davey MS, Shaw EM, von Borstel A, Cristiano Y, Levvey BJ, Rossjohn J, Westall GP, Snell GI, Brooks AG, Sullivan LC. Cytomegalovirus replication is associated with enrichment of distinct γδ T cell subsets following lung transplantation: A novel therapeutic approach? J Heart Lung Transplant. 2020 Nov;39(11):1300-1312.

Stanley AC, Engwerda CR. Balancing immunity and pathology in visceral leishmaniasis. Immunol Cell Biol. 2007 Feb-Mar;85(2):138-47.

Stavnezer J, Guikema JE, Schrader CE. Mechanism and regulation of class switch recombination. Annu Rev Immunol. 2008;26:261-92.

Stervbo U, Pohlmann D, Baron U, Bozzetti C, Jürchott K, Mälzer JN, Nienen M, Olek S, Roch T, Schulz AR, Warth S, Neumann A, Thiel A, Grützkau A, Babel N. Age dependent differences in the kinetics of γδ T cells after influenza vaccination. PLoS One. 2017 Jul 11;12(7):e0181161.

Stone E, Taylor J, Kiat H, McLachlan CS. Machine learning based deconvolution of microarray atrial samples from atrial fibrillation patients reveals increased fractions of follicular CD4+ T lymphocytes and gamma-delta T cells. J Physiol Pharmacol. 2021 Dec;72(6).

Suàrez-Fernández P, Utrero-Rico A, Sandonis V, García-Ríos E, Arroyo-Sánchez D, Fernández-Ruiz M, Andrés A, Polanco N, González-Cuadrado C, Almendro-Vázquez P, Pérez-Romero P, Aguado JM, Paz-Artal E, Laguna-Goya R. Circulatory follicular helper T lymphocytes associate with lower incidence of CMV infection in kidney transplant recipients. Am J Transplant. 2021 Dec;21(12):3946-3957.

Suen TK, Moorlag SJCFM, Li W, de Bree LCJ, Koeken VACM, Mourits VP, Dijkstra H, Lemmers H, Bhat J, Xu CJ, Joosten LAB, Schultze JL, Li Y, Placek K, Netea MG. BCG vaccination induces innate immune memory in γδ T cells in humans. J Leukoc Biol. 2024 Jan 5;115(1):149-163.

Swanson RV, Gupta A, Foreman TW, Lu L, Choreno-Parra JA, Mbandi SK, Rosa BA, Akter S, Das S, Ahmed M, Garcia-Hernandez ML, Singh DK, Esaulova E, Artyomov MN, Gommerman J, Mehra S, Zuniga J, Mitreva M, Scriba TJ, Rangel-Moreno J, Kaushal D, Khader SA. Antigen-specific B cells direct T follicular-like helper cells into lymphoid follicles to mediate Mycobacterium tuberculosis control. Nat Immunol. 2023 May;24(5):855-868.

Takamatsu HH, Denyer MS, Wileman TE. A sub-population of circulating porcine gammadelta T cells can act as professional antigen presenting cells. Vet Immunol Immunopathol. 2002 Sep 10;87(3-4):223-4.

Tanner R, Villarreal-Ramos B, Vordermeier HM, McShane H. The Humoral Immune Response to BCG Vaccination. Front Immunol. 2019 Jun 11;10:1317.

Terzoli S, Marzano P, Cazzetta V, Piazza R, Sandrock I, Ravens S, Tan L, Prinz I, Balin S, Calvi M, Carletti A, Cancellara A, Coianiz N, Franzese S, Frigo A, Voza A, Calcaterra F, Di Vito C, Della Bella S, Mikulak J, Mavilio D. Expansion of memory Vδ2 T cells following SARS-CoV-2 vaccination revealed by temporal single-cell transcriptomics. NPJ Vaccines. 2024 Mar 20;9(1):63.

Toyabe S, Harada W, Uchiyama M. Oligoclonally expanding gammadelta T lymphocytes induce IgA switching in IgA nephropathy. Clin Exp Immunol. 2001 Apr;124(1):110-7.

Tyler CJ, Doherty DG, Moser B, Eberl M. Human Vγ9/Vδ2 T cells: Innate adaptors of the immune system. Cell Immunol. 2015 Jul;296(1):10-21.

Tyler CJ, McCarthy NE, Lindsay JO, Stagg AJ, Moser B, Eberl M. Antigen-Presenting Human γδ T Cells Promote Intestinal CD4$^+$ T Cell Expression of IL-22 and Mucosal Release of Calprotectin. J Immunol. 2017 May 1;198(9):3417-3425.

Tyler CJ, Hoti I, Griffiths DD, Cuff SM, Andrews R, Keisker M, Ahmed R, Hansen HP, Lindsay JO, Stagg AJ, Moser B, McCarthy NE, Eberl M. IL-21 conditions antigen-presenting human γδ T-cells to promote IL-10 expression in naïve and memory CD4+ T-cells. Discov Immunol. 2024 May 13;3(1):kyae008.

Ullrich L, Lueder Y, Juergens AL, Wilharm A, Barros-Martins J, Bubke A, Demera A, Ikuta K, Patzer GE, Janssen A, Sandrock I, Prinz I, Rampoldi F. IL-4-Producing Vγ1+/Vδ6+ γδ T Cells Sustain Germinal Center Reactions in Peyer's Patches of Mice. Front Immunol. 2021 Nov 3;12:729607.

Vantourout P, Hayday A. Six-of-the-best: unique contributions of γδ T cells to immunology. Nat Rev Immunol. 2013 Feb;13(2):88-100.

Vermijlen D, Ellis P, Langford C, Klein A, Engel R, Willimann K, Jomaa H, Hayday AC, Eberl M. Distinct cytokine-driven responses of activated blood γδ T cells: insights into unconventional T cell pleiotropy. J Immunol. 2007 Apr 1;178(7):4304-14.

Vermijlen D, Brouwer M, Donner C, Liesnard C, Tackoen M, Van Rysselberge M, Twité N, Goldman M, Marchant A, Willems F. Human cytomegalovirus elicits fetal gammadelta T cell responses in utero. J Exp Med. 2010 Apr 12;207(4):807-21.

Vermijlen D, Gatti D, Kouzeli A, Rus T, Eberl M. γδ T cell responses: How many ligands will it take till we know? Semin Cell Dev Biol. 2018 Dec;84:75-86.

Victora GD, Nussenzweig MC. Germinal centers. Annu Rev Immunol. 2012;30:429-57.

Vidovic D, Dembic Z. Qa-1 restricted gamma delta T cells can help B cells. Curr Top Microbiol Immunol. 1991;173:239-44.

Vinuesa CG, Linterman MA, Yu D, MacLennan IC. Follicular Helper T Cells. Annu Rev Immunol. 2016 May 20;34:335-68.

Vlahava VM, Murrell I, Zhuang L, Aicheler RJ, Lim E, Miners KL, Ladell K, Suárez NM, Price DA, Davison AJ, Wilkinson GW, Wills MR, Weekes MP, Wang EC, Stanton RJ. Monoclonal antibodies targeting nonstructural viral antigens can activate ADCC against human cytomegalovirus. J Clin Invest. 2021 Feb 15;131(4):e139296.

von Borstel A, Chevour P, Arsovski D, Krol JMM, Howson LJ, Berry AA, Day CL, Ogongo P, Ernst JD, Nomicos EYH, Boddey JA, Giles EM, Rossjohn J, Traore B, Lyke KE, Williamson KC, Crompton PD, Davey MS. Repeated Plasmodium falciparum infection in humans drives the clonal expansion of an adaptive γδ T cell repertoire. Sci Transl Med. 2021 Dec;13(622):eabe7430.

von Borstel A, Nguyen TH, Rowntree LC, Ashhurst TM, Allen LF, Howson LJ, Holmes NE, Smibert OC, Trubiano JA, Gordon CL, Cheng AC, Kent SJ, Rossjohn J, Kedzierska K, Davey MS. Circulating effector γδ T cell populations are associated with acute coronavirus disease 19 in unvaccinated individuals. Immunol Cell Biol. 2023 Apr;101(4):321-332.

Wan F, Hu CB, Ma JX, Gao K, Xiang LX, Shao JZ. Characterization of γδ T Cells from Zebrafish Provides Insights into Their Important Role in Adaptive Humoral Immunity. Front Immunol. 2017 Jan 9;7:675.

Wang X, Lin X, Zheng Z, Lu B, Wang J, Tan AH, Zhao M, Loh JT, Ng SW, Chen Q, Xiao F, Huang E, Ko KH, Huang Z, Li J, Kok KH, Lu G, Liu X, Lam KP, Liu W, Zhang Y, Yuen KY, Mak TW, Lu L. Host-derived lipids orchestrate pulmonary γδ T cell response to provide early protection against influenza virus infection. Nat Commun. 2021 Mar 26;12(1):1914.

Wang C, Lai AY, Baiu DC, Smith KA, Odorico JS, Wilson K, Schreiber T, de Silva S, Gumperz JE. Analysis of Butyrophilin-Mediated Activation of γδ T Cells from Human Spleen. J Immunol. 2024 Jan 15;212(2):284-294.

Welton JL, Morgan MP, Martí S, Stone MD, Moser B, Sewell AK, Turton J, Eberl M. Monocytes and γδ T cells control the acute-phase response to intravenous zoledronate: insights from a phase IV safety trial. J Bone Miner Res. 2013 Mar;28(3):464-71.

Wen L, Roberts SJ, Viney JL, Wong FS, Mallick C, Findly RC, Peng Q, Craft JE, Owen MJ, Hayday AC. Immunoglobulin synthesis and generalized autoimmunity in mice congenitally deficient in alpha beta(+) T cells. Nature. 1994 Jun 23;369(6482):654-8.

Wen L, Pao W, Wong FS, Peng Q, Craft J, Zheng B, Kelsoe G, Dianda L, Owen MJ, Hayday AC. Germinal center formation, immunoglobulin class switching, and autoantibody production driven by "non alpha/beta" T cells. J Exp Med. 1996 May 1;183(5):2271-82.

Wesch D, Glatzel A, Kabelitz D. Differentiation of resting human peripheral blood gamma delta T cells toward Th1- or Th2-phenotype. Cell Immunol. 2001 Sep 15;212(2):110-7.

WHO. Global tuberculosis report 2024. Geneva: World Health Organization; 2024a. ISBN 978-92-4-010153-1 (electronic version).

WHO. World malaria report 2024: addressing inequity in the global malaria response. Geneva: World Health Organization; 2024b. ISBN 978-92-4-010444-0 (electronic version).

WHO. Implementing the global health sector strategies on HIV, viral hepatitis and sexually transmitted infections, 2022–2030: report on progress and gaps 2024, second edition. Geneva: World Health Organization; 2024c. ISBN 978-92-4-009787-2 (electronic version).

Wiesner J, Borrmann S, Jomaa H. Fosmidomycin for the treatment of malaria. Parasitol Res. 2003 Jun;90 Suppl 2:S71-6.

Willcox CR, Pitard V, Netzer S, Couzi L, Salim M, Silberzahn T, Moreau JF, Hayday AC, Willcox BE, Déchanet-Merville J. Cytomegalovirus and tumor stress surveillance by binding of a human γδ T cell antigen receptor to endothelial protein C receptor. Nat Immunol. 2012 Sep;13(9):872-9.

Xia M, Blazevic A, Fiore-Gartland A, Hoft DF. Impact of BCG vaccination on the repertoire of human γδ T cell receptors. Front Immunol. 2023 Mar 28;14:1100490.

Workalemahu G, Wang H, Puan KJ, Nada MH, Kuzuyama T, Jones BD, Jin C, Morita CT. Metabolic engineering of Salmonella vaccine bacteria to boost human Vγ2Vδ2 T cell immunity. J Immunol. 2014 Jul 15;193(2):708-21.

Xu H, Li X, Liu D, Li J, Zhang X, Chen X, Hou S, Peng L, Xu C, Liu W, Zhang L, Qi H. Follicular T-helper cell recruitment governed by bystander B cells and ICOS-driven motility. Nature. 2013 Apr 25;496(7446):523-7

Wu M, Liu J, Liu L, Yang Y, Liu H, Yu L, Zeng H, Yuan S, Xu R, Liu H, Jiang H, Qu S, Wang L, Chen Y, Wang J, Zhang Y, He S, Feng L, Han J, Zeng W, Wang H, Huang Y. Autologous Peripheral Vγ9Vδ2 T Cell Synergizes with αβ T Cell Through Antigen Presentation and BTN3A1 Blockade in Immunotherapy of Cervical Cancer. Adv Sci (Weinh). 2025 Mar 17:e2401230.

Xu W, Zhao X, Wang X, Feng H, Gou M, Jin W, Wang X, Liu X, Dong C. The Transcription Factor Tox2 Drives T Follicular Helper Cell Development via Regulating Chromatin Accessibility. Immunity. 2019 Nov 19;51(5):826-839.e5.

Xu Q, Sharif M, James E, Dismorr JO, Tucker JHR, Willcox BE, Mehellou Y. Phosphonodiamidate prodrugs of phosphoantigens (ProPAgens) exhibit potent Vγ9/Vδ2 T cell activation and eradication of cancer cells. RSC Med Chem. 2024 Jun 3;15(7):2462-2473.

Yamamoto T, Lynch RM, Gautam R, Matus-Nicodemos R, Schmidt SD, Boswell KL, Darko S, Wong P, Sheng Z, Petrovas C, McDermott AB, Seder RA, Keele BF, Shapiro L, Douek DC, Nishimura Y, Mascola JR, Martin MA, Koup RA. Quality and quantity of TFH cells are critical for broad antibody development in SHIVAD8 infection. Sci Transl Med. 2015 Jul 29;7(298):298ra120.

Yang XW, Li H, Feng T, Zhang W, Song XR, Ma CY, Nie M, Wang L, Tan X, Kang Y, Liao X. Impairment of antigen-presenting function of peripheral γδ T cells in patients with sepsis. Clin Exp Immunol. 2022 Jan 28;207(1):104-112.

Yared N, Papadopoulou M, Barennes P, Pham HP, Quiniou V, Netzer S, Kaminski H, Burguet L, Demeste A, Colas P, Mora-Charrot L, Rousseau B, Izotte J, Zouine A, Gauthereau X, Vermijlen D, Déchanet-Merville J, Capone M. Long-lived central memory γδ T cells confer protection against murine cytomegalovirus reinfection. PLoS Pathog. 2024 Jul 8;20(7):e1010785.

Yonekawa M, Shimizu M, Kaneko A, Matsumura J, Takahashi H. Suppression of R5-type of HIV-1 in CD4+ NKT cells by Vδ1+ T cells activated by flavonoid glycosides, hesperidin and linarin. Sci Rep. 2019 May 17;9(1):7506.

Young C, Brink R. The unique biology of germinal center B cells. Immunity. 2021 Aug 10;54(8):1652-1664.

Yu D, Ye L. A Portrait of CXCR5+ Follicular Cytotoxic CD8+ T cells. Trends Immunol. 2018 Dec;39(12):965-979.

Yu D, Walker LSK, Liu Z, Linterman MA, Li Z. Targeting TFH cells in human diseases and vaccination: rationale and practice. Nat Immunol. 2022 Aug;23(8):1157-1168.

Yuan L, Ma X, Yang Y, Qu Y, Li X, Zhu X, Ma W, Duan J, Xue J, Yang H, Huang JW, Yi S, Zhang M, Cai N, Zhang L, Ding Q, Lai K, Liu C, Zhang L, Liu X, Yao Y, Zhou S, Li X, Shen P, Chang Q, Malwal SR, He Y, Li W, Chen C, Chen CC, Oldfield E, Guo RT, Zhang Y. Phosphoantigens glue butyrophilin 3A1 and 2A1 to activate Vγ9Vδ2 T cells. Nature. 2023 Sep;621(7980):840-848.

Zaidi I, Diallo H, Conteh S, Robbins Y, Kolasny J, Orr-Gonzalez S, Carter D, Butler B, Lambert L, Brickley E, Morrison R, Sissoko M, Healy SA, Sim BKL, Doumbo OK, Hoffman SL, Duffy PE. γδ T Cells Are Required for the Induction of Sterile Immunity during Irradiated Sporozoite Vaccinations. J Immunol. 2017 Dec 1;199(11):3781-3788.

Zander RA, Guthmiller JJ, Graham AC, Pope RL, Burke BE, Carr DJ, Butler NS. Type I Interferons Induce T Regulatory 1 Responses and Restrict Humoral Immunity during Experimental Malaria. PLoS Pathog. 2016 Oct 12;12(10):e1005945.

Zhou D, Lai X, Shen Y, Sehgal P, Shen L, Simon M, Qiu L, Huang D, Du GZ, Wang Q, Letvin NL, Chen ZW. Inhibition of adaptive Vgamma2Vdelta2+ T-cell responses during active mycobacterial coinfection of simian immunodeficiency virus SIVmac-infected monkeys. J Virol. 2003 Mar;77(5):2998-3006.

Box 1: Open questions and potential avenues of research.

- ✓ How do γδ T cells affect the level, specificity, affinity and/or class of antibodies in infection and autoimmunity?
- ✓ How, when and where do γδ T cells modulate the differentiation and activity of Tfh cells and B cells?
- ✓ Are the molecular mechanisms involved in the γδ T cell crosstalk with Tfh cells and B cells conserved across species?
- ✓ Do non-Vγ9/Vδ2 T cells present antigens to naïve $CD4^+$ T cells and trigger differentiation into distinct effector subsets, including Tfh cells?
- ✓ Does targeted manipulation of γδ T cells *in vivo* affect the level, specificity, affinity and/or class of antibodies?
- ✓ Does co-administration of cytokines such as IL-4 or IL-21 improve γδ T cell-driven humoral immune responses?
- ✓ Will novel vaccines benefit from γδ T cell-stimulating adjuvants?
- ✓ Will novel γδ T cell targeting therapies dampen autoantibody production in patients with autoimmune disorders?

Table

Table 1. Strategies to target Vγ9/Vδ2 T cells in the clinic. Approaches include both the activation of Vγ9/Vδ2 T cells as novel adjuvants in order to boost humoral immunity and the potential inhibition of Vγ9/Vδ2 T cells to suppress overshooting immune responses.

Approach	Example	Key references
γδ T cell activation		
Phosphoantigens	HMB-PP and derivatives	Ali et al., 2007; Cendron et al., 2007
	Prodrugs	Singh et al., 2023; Xu et al., 2024
Aminobisphosphonates	Zoledronate	Welton et al., 2013; Shen et al., 2022
Agonist antibodies	ICT01 (anti-BTN3A1)	de Gassart et al., 2021
	107G3B5 (anti-BTN2A1)	Le Floch et al., 2024
Attenuated bacteria	BCG vaccine	Shen et al., 2002
	Listeria monocytogenes	Shen et al., 2019
Enhanced microbial HMB-PP production	Δ*lytB Salmonella enterica*	Workalemahu et al., 2014
Cytokines	IL-21	Li et al., 2024; Kvistad et al., 2021
γδ T cell inhibition		
Blocking antibodies	103.2 (anti-BTN3A1)	Harly et al., 2012
	anti-Vγ9	Davey et al., 2011
Inhibition of microbial HMB-PP production	Fosmidomycin	Davey et al., 2011
	Δ*gcpE Listeria monocytogenes*	Frencher et al., 2014

Figure

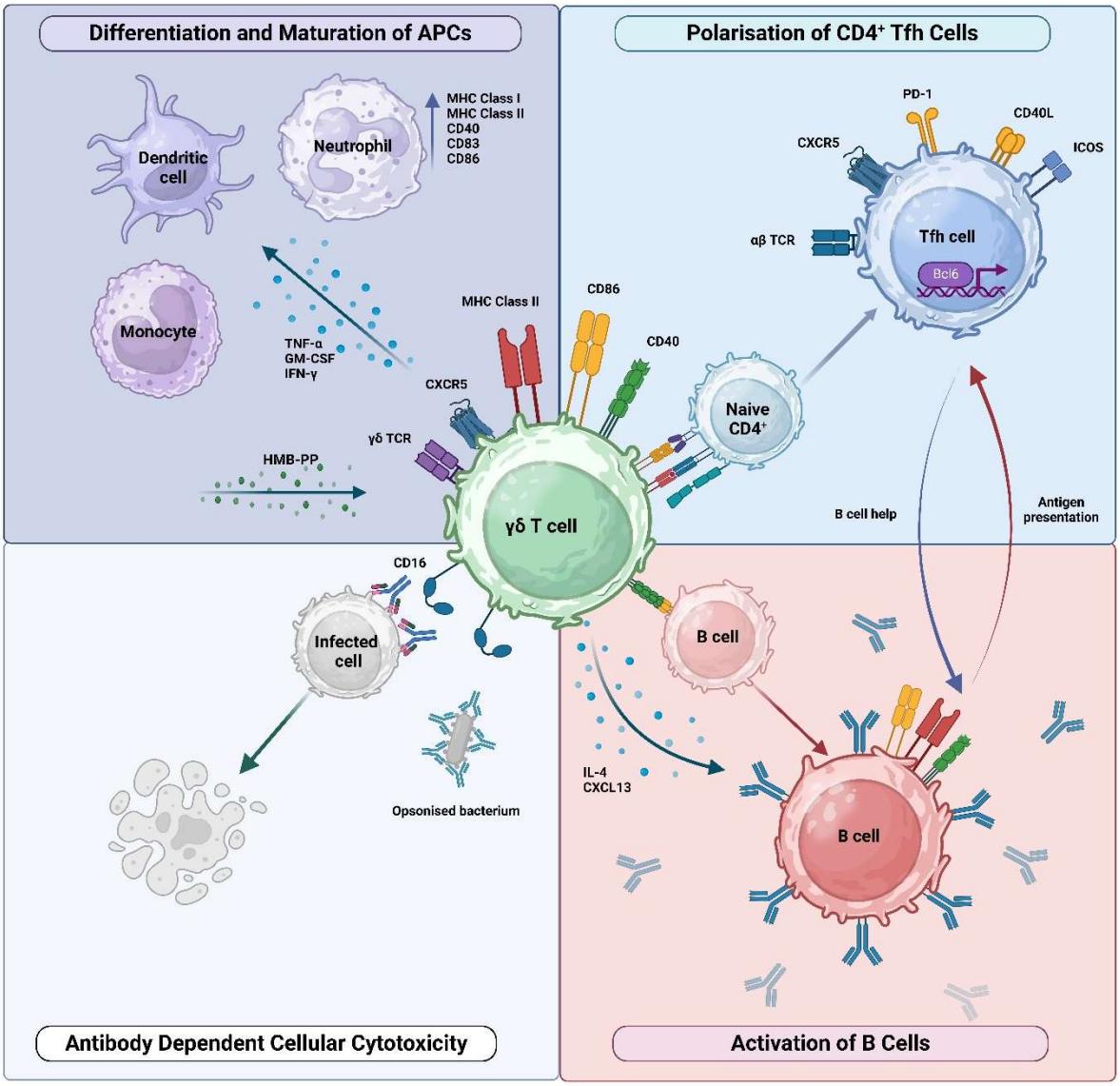

Figure 1. Modulation of humoral immunity by human Vγ9/Vδ2 T cells. γδ T cells can modulate humoral immunity both by presenting antigens to naïve CD4⁺ T cells and inducing their differentiation into Tfh cells, and by providing direct help to B cells. At the same time they can trigger differentiation and maturation of different types of APCs, thereby further amplifying adaptive immune responses. Antibodies produced upon infection or as a result of vaccination can trigger protective immunity against

infected targets via ADCC. Created in BioRender. Eberl, M. (2025) https://BioRender.com/j0lk18q.