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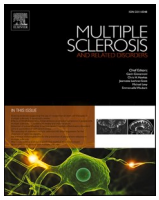

Review article

The impact of sphingosine-1-phosphate receptor modulators on COVID-19 and SARS-CoV-2 vaccination

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ABSTRACT

Background: Sphingosine-one phosphate receptor (S1PR) modulation inhibits S1PR1-mediated lymphocyte migration, lesion formation and positively-impacts on active multiple sclerosis (MS). These S1PR modulatory drugs have different: European Union use restrictions, pharmacokinetics, metabolic profiles and S1PR receptor affinities that may impact MS-management. Importantly, these confer useful properties in dealing with COVID-19, anti-viral drug responses and generating SARS-CoV-2 vaccine responses.

Objective: To examine the biology and emerging data that potentially underpins immunity to the SARS-CoV-2 virus following natural infection and vaccination and determine how this impinges on the use of current sphingosine-one-phosphate modulators used in the treatment of MS.

Methods: A literature review was performed, and data on infection, vaccination responses; S1PR distribution and functional activity was extracted from regulatory and academic information within the public domain.

Observations: Most COVID-19 related information relates to the use of fingolimod. This indicates that continuous S1PR1, S1PR3, S1PR4 and S1PR5 modulation is not associated with a worse prognosis following SARS-CoV-2 infection. Whilst fingolimod use is associated with blunted seroconversion and reduced peripheral T-cell vaccine responses, it appears that people on siponimod, ozanimod and ponesimod exhibit stronger vaccine-responses, which could be related notably to a limited impact on S1PR4 activity. Whilst it is thought that S1PR3 controls B cell function in addition to actions by S1PR1 and S1PR2, this may be species-related effect in rodents that is not yet substantiated in humans, as seen with bradycardia issues. Blunted antibody responses can be related to actions on B and T-cell subsets, germinal centre function and innate-immune biology. Although S1P1R-related functions are seeming central to control of MS and the generation of a fully functional vaccination response; the relative lack of influence on S1PR4-mediated actions on dendritic cells may increase the rate of vaccine-induced seroconversion with the newer generation of S1PR modulators and improve the risk-benefit balance

Implications: Although fingolimod is a useful asset in controlling MS, recently-approved S1PR modulators may have beneficial biology related to pharmacokinetics, metabolism and more-restricted targeting that make it easier to generate infection-control and effective anti-viral responses to SARS-COV-2 and other pathogens. Further studies are warranted.

Abbreviations: a.u, arbitrary units; COVID-19, coronavirus 2019; C_{max}, maximum concentration; CNS, central nervous system; mRNA, messenger ribonucleic acid; MS, Multiple sclerosis; SAR-CoV-2, severe acute respiratory corona virus two; S1PR, sphingosine-1-phosphate receptor, SmPC, Summary of Medical Product Characteristics; ELISA, enzyme-linked immunosorbent assay; ECLIA, electrochemiluminescent immunoassay; CLIA, chemiluminescent immunoassay.

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1. Multiple sclerosis and disease modifying treatments

Multiple sclerosis (MS) is an immune-mediated, demyelinating and neurodegenerative disease of the central nervous system (CNS) that is the major cause of non-traumatic disability in young adults (Dobson and Giovannoni, 2019). Relapsing disease is associated with mononuclear cell inflammation that enters and becomes sequestered in the CNS and supports the generation of innate immune/glial-cell based inflammation, which promotes the development of accumulating neurodegeneration and disability (Dobson and Giovannoni, 2019). Active inflammation, seen by new lesion activity on imaging and/or clinical relapse, can be targeted by a large number of disease modifying treatments (Dobson and Giovannoni, 2019; Lublin et al., 2014). Whilst MS is thought to be driven by pathogenic T cells, it is evident that all effective immunotherapies limit the capacity of B cell subsets to enter the CNS (Dobson and Giovannoni, 2019; Baker et al., 2017). These therapeutic monoclonal antibodies and small molecules target the adaptive immune response to act largely via inhibition of immune-activation, peripheral lymphocyte depletion or lymphocyte migration-inhibition (Dobson and Giovannoni, 2019).

Current migration inhibitors affect both T and B cells, which are central, interacting parts of the immune system that deals with infection and vaccination (Mehling et al., 2008; Gergely et al., 2012; Jurcevic et al., 2016; Petersone et al., 2018; Harris et al., 2020). Therefore, there was major concern at the beginning of the coronavirus 2019 (COVID-19) pandemic, caused by severe acute respiratory corona virus two (SAR--CoV-2) infection, about the risks posed to people taking immunosuppressive treatments, particularly as severe disease was associated with lymphopenia (Wang et al., 2020; Baker et al., 2020a). This led to treatment delays, cessation and switching of agents to avoid lymphopenia and to allow more rapid drug wash-outs in case of infection (Baker et al., 2020a). With time, SARS-CoV-2 vaccines and anti-viral agents have been developed to fight the disease that has killed millions of people and created economic havoc (Khoury et al., 2021; Wu et al., 2022; Gombolay et al., 2022; Sendi et al., 2022; Richards et al., 2022). However, this has created further challenges for use in immunosuppressed people (Baker et al., 2020a), especially as this is occurring within a landscape of global viral evolution and the generation of circulating SARS-CoV-2 variants that have different morbidities, contagion and immune-escape (Chen et al., 2022; Shrestha et al., 2022). However, as immune-escape is in part attributable to viral evolution in immunosuppressed individuals (Weigang et al., 2021; Scherer et al., 2022), it is important to optimise anti-viral therapy within the need to effectively control immune-mediated diseases.

2. Coronavirus-19 disease and issues with SARS-CoV-2 vaccination

As data emerged about COVID-19 pathogenesis it became evident that lymphopenia was largely a consequence of severe COVID-19 and that coagulation issues were central to pathology and morbidity (Baker et al., 2020b). The biology of the disease modifying MS treatments indicates that they have limited to no impact on coagulation and microthrombi formation and vice versa (Farrokhi et al., 2015). Furthermore, all MS treatments are largely targeted to the adaptive immune arm and seem to have limited activity on the innate system, which appears to be important in anti-viral immunity and some elements of pathology. This suggested that treatment of MS was less of a risk factor than initially feared (Baker et al., 2020a; Baker et al., 2020b). Indeed, it was found that susceptibility of people with MS to the SARS-CoV-2 virus was related largely to the risk factors seen within the general population, such as age and co-morbidities, with the addition of disability due to MS (Sormani et al., 2021; Simpson-Yap et al., 2021). Importantly, most disease modifying treatments were not associated with a worse prognosis following infection (Sormani et al., 2021; Simpson-Yap et al., 2021; Simpson-Yap et al., 2022). However, a modestly worse course of infection seemed to occur in some individuals who were continuously B cell depleted with either ocrelizumab or rituximab, CD20-depleting agents (Sormani et al., 2021; Simpson-Yap et al., 2021; Simpson-Yap et al., 2022; Reder et al., 2021). Furthermore, CD20-depletion was predicted to (Baker et al., 2020b) and subsequently shown to limit seroconversion to infection and SARS-CoV-2 vaccines, without major impact on T cell responses, until therapeutic-antibody disappears and B cell repopulation is allowed to occur (Wang et al., 2022; Gombolay et al., 2022; Madelon et al., 2021; Baker et al., 2021; Sormani et al., 2021b; Pitzalis et al., 2021; Tallantyre et al., 2022a; Tallantyre et al., 2022b). CD20-depletion prevents the generation of immature/naïve B cells capable of producing novel antibody-responses that may have included the inability to form protective, cross-reactive antibodies following natural infection with other (corona)viruses, which could prevent/protect against subsequent SARS-COV-2 infection (Baker et al., 2020b; Fraley et al., 2021; Klompus et al., 2021).

In contrast fingolimod (Fig. 1), which is a lymphocyte migration inhibitor, was not associated with a worse outcome following natural SARS-CoV-2 infection (Sormani et al., 2021; Simpson-Yap et al., 2021; Simpson-Yap et al., 2022; Reder et al., 2021; Sullivan et al., 2021). Perhaps consistent with this, the majority of people on fingolimod appeared to seroconvert, albeit sometimes with lower antibody titres following a natural SARS-CoV-2 infection (Bigaut et al., 2021; Bsteh et al., 2021; van Kempen et al., 2021; Zabalza et al., 2021; Louapre et al., 2022; Sormani et al., 2022a). Similarly, modest reductions in antibody titres notably with other vaccines, have been seen in fingolimod-treated individuals (Boulton et al., 2012; Kappos et al., 2015; Zoehner et al., 2019). However, fingolimod consistently inhibits both seroconversion and peripheral blood T cell responses following SARS-CoV-2 vaccination, although there was some variability between studies in part due to the: individuals, viral strain, past infection, vaccine type; time of assay relative to infection/vaccination, different assays and different functional and physical targets (Wu et al., 2022; Gombolay et al., 2022; Tallantyre et al., 2022a; Tallantyre et al., 2022b; Achiron et al., 2021; Meyer-Arndt et al., 2022). Importantly, this had biological impact because in comparison to other MS treatments, use of either fingolimod or CD20-depleting antibodies was sometimes associated with COVID-19 disease breakthrough following vaccination (Schiavetti et al., 2022; Garjani et al., 2022; Bsteh et al., 2022; Sormani et al., 2022). Importantly, this was seen even before the time when circulating SARS-CoV-2 variants of concern, notably omicron variants, required high vaccine-induced antibody titres to protect from infection compared to the initial SARS-CoV-2 variants (Chen et al., 2022; Sormani et al., 2022; Cheng et al., 2022; Tuekprakhon et al., 2022). As this breakthrough was associated with agents with poor seroconversion, it supports the view that viral neutralizing antibodies are particularly important in preventing infection/re-infection (Baker et al., 2020a; Sormani et al., 2022). This indicates that the clinical responses observed can be attributed to the chemistry and biology of the different agents. It therefore remained to be seen whether there could be any differences between fingolimod and the other sphingosine-one-phosphate receptor (S1PR) modulators, approved shortly before or during the COVID-19 pandemic (Fig. 1) (Al-Salama and Siponimod, 2019; Lamb, 2020; Markham, 2021), which may predict or explain likely COVID-19 infection and vaccine responses that may affect the risk-benefit balance.

3. Sphingosine-one-phosphate receptor modulators used in multiple sclerosis

Migration-inhibition ultimately limits entry of pathogenic cells into the CNS, which is an effective strategy to control relapsing MS (Dobson and Giovannoni, 2019; Lohmann et al., 2018). Sphingosine-1-phosphate acts via a number of G-protein-coupled S1P receptors (Fig. 1, Table 2). Fingolimod is likewise phosphorylated by sphingosine kinase enzymes to create an active molecule that performs important signalling function related notably to the vascular and immune systems (Scott, 2011; Grassi

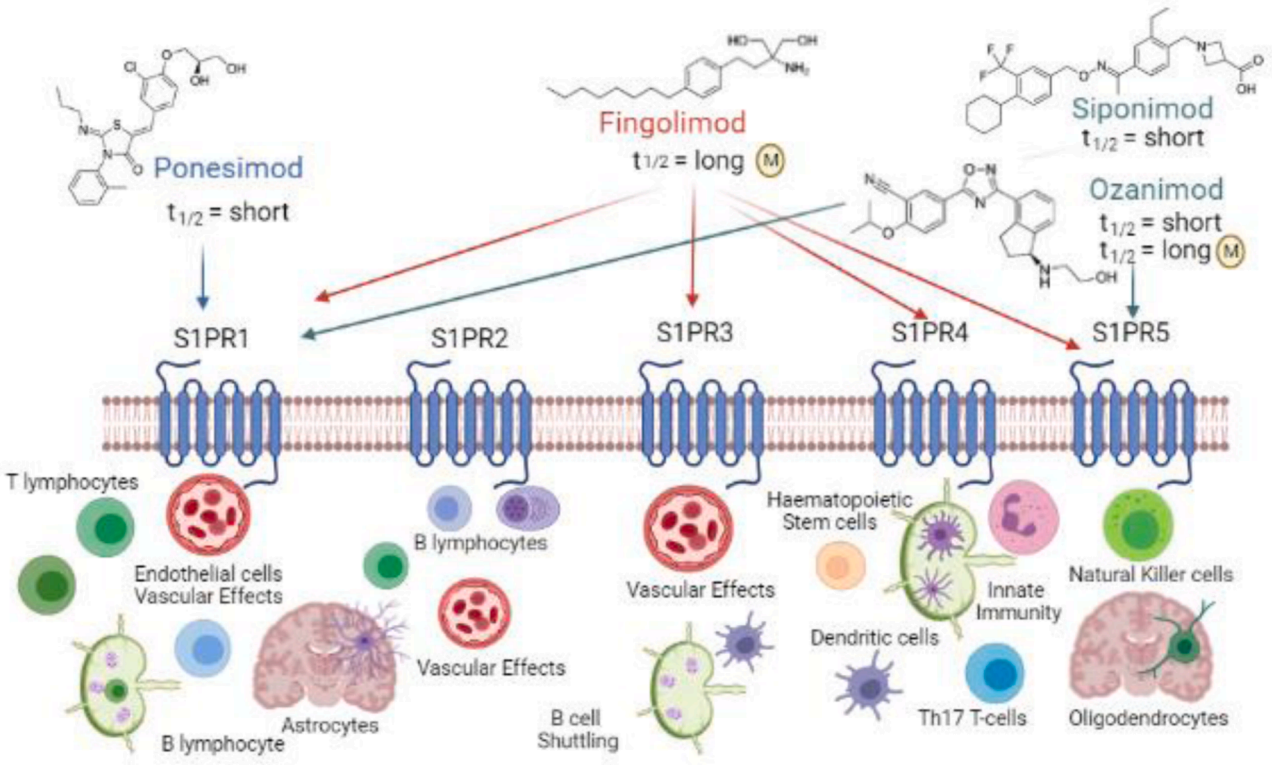

Fig. 1. Sphingosine-1-phosphate receptor modulators used in multiple sclerosis. Chemical structures, relative elimination half-lives, the presence of active metabolites (M) and receptor binding and distribution profiles were obtaining from the Summary of Medical Product Characteristic reported at the European Medicines Agency website and the literature. Ponesimod has low affinity for S1PR5. Created with Biorender.com.

et al., 2019). Different levels of S1P within tissues, lymph and the circulation and different cellular expression profiles of the S1PR creates gradients that can effect migration and influence the biology of cells (Cyster and Schwab, 2012). The current S1PR modulators have distinct S1PR binding affinities, pharmacokinetics and different use-indications (Fig. 1).

In the United States of America: fingolimod, siponimod, ozanimod and ponesimod all have a similar utility and are licensed for clinically-isolated syndrome, relapsing MS and active secondary progressive MS (Al-Salama and Siponimod, 2019; Lamb, 2020; Markham, 2021; Scott, 2011). These are all characterised by bout attacks and/or new T2 or gadolinium enhancing T1 lesion formation (Lublin et al., 2014). However, in Europe, differences in the licensing exist that may influence use in practice. As such, fingolimod is a second-line treatment for highly-active relapsing MS, siponimod is licenced for active, secondary progressive MS, whereas both ozanimod and ponesimod have recently been approved as first-line treatments for active relapsing MS (Al-Salama and Siponimod, 2019; Lamb, 2020; Markham, 2021; Scott, 2011). Fingolimod has been used and studied most extensively and forms the basis for most COVID-19- related information. Fingolimod exhibits a long half-life and so peripheral lymphocyte recover slowly after treatment cessation (Table 1). However, once cells repopulate, disease may relapse and therefore this requires an appropriately-timed switch to an alternative treatment (Barry et al., 2019). Although there were initial recommendations to stop fingolimod treatment following SARS-CoV-2 infection, the virus would be naturally cleared before therapeutic levels have been eliminated (Baker et al., 2020a). This probably prompted some people to switch to S1PR modulators with a more rapid clearance, in case people exhibited COVID-19 symptoms.

Siponimod, ozanimod and ponesimod have relatively short half-lives compared to fingolimod (Table 1) (Gardin et al., 2019; Brossard et al., 2013; Surapaneni et al., 2021), although individuals with the slow-metabolising cytochrome P450 variants for CYP2C9 (variant *3) are screened and excluded prior to commencement of siponimod treatment (Al-Salama and Siponimod, 2019; Gardin et al., 2019). Furthermore, as ozanimod is metabolised to compounds with long half-lives, it will exhibit similar issues to fingolimod in terms of slow lymphocyte recovery following treatment cessation (Table 2) (Lamb, 2020; Surapaneni et al., 2021). In contrast ponesimod has a relatively short life, with a relatively rapid repopulation of lymphocytes (Table 1) (Valenzuela et al., 2021) and therefore could offer advantages following infection or in using short treatment breaks to promote better vaccination responses. However, information on the time window before disease reactivation occurs after cessation is currently limited (Lublin et al., 2022), but effective vaccination following discontinuation that avoids disease breakthrough seems feasible with short-half live agents (Ufer et al., 2017; Ziemssen et al., 2022, Spiller et al., 2021).

Fingolimod binds to S1PR1, S1PR3, S1PR4, and S1PR5, which have distinct tissue distributions that will impact on its function (Fig. 1; Table 2) (Brinkmann et al., 2002). However, it is clear that the major

Table 1
Biological and pharmacokinetic characteristics of S1PR modulators.

Treatment	S1PR targeted	Time to Cmax	Approximate Elimination half-live	Median time lymphocyte recovery
Ponesimod	1	2–4h	33 h	1 week
Siponimod	1,5	4h	30 h	10 days
Ozanimod	1,5	6–8h	21 h/11days (CC112273)	30 days
Fingolimod	1,3,4,5	12–26h	6–9days	1–2 months

Information about the pharmacokinetics of sphingosine-1-phosphate receptor (S1PR) modulators were obtained from the Summary of Medical Product Characteristics from the European Medicines Agency website. CC112273 is a metabolite of ozanimod. C_{max} maximum concentration

Table 2
Receptors specific cities of approved S1PR modulators.

Treatment	Sphingosine-1-phophate (S1P) receptor binding affinities					
	S1PR1	S1PR2	S1PR3	S1PR4	S1PR5	Reference
S1P	0.47nM[a]	0.31nM[a]	0.17nM[a]	95 nM[a]	0.61nM[a]	Mandala et al., 2002
Fingolimod	300nM[a]	>10,000nM[a]	>10,000nM[a]	>5,000nM[a]	2623nM[a]	
Fingolimod-P	0.21nM[a]	>10,000nM[a]	5.0nM[a]	5.9 nM[a]	0.59nM[a]	
Fingolimod-P	8.2nM[b]	>10,000nM[b]	8.4nM[b]	7.2nM[b]	8.2nM[b]	Brinkmann et al., 2002
Siponimod	0.39nM[b]	>10,000nM[b]	> 1,000nM[b]	750nM[b]	0.98nM[b]	Gergely et al., 2012
OzanimodFingolimod-P	0.41nM[b]	>10,000nM[b]	>10,000nM[b]	>7,865nM[c]	11nM[b]	Scott et al., 2016
Siponimod	0.27nM[b]	>10,000nM[b]	0.90nM[b]	345nM[c]	0.5nM[b]	
	0.39nM[b]	>10,000nM[b]	>10,000nM[b]	920nM[c]	0.38nM[b]	
Ponesimod	5.7nM[b]	>10,000nM[b]	105nMa[b]	1,108nM[b,d]	59.1nM[b,d]	Bolli et al., 2010
S1P	25.3nM[b]	43.9M[b]	0.7nM[b]	164nM[b]	1.1nM[b]	

The S1P1R binding affinities of sphinogsine-1-phosphate (S1P) and the S1PR modulators were extracted from the literature. The results report the [a]IC_{50} or [b,c]EC_{50} binding levels using either.

[a] competitive radio-ligand binding.

[b] gamma GTPS or.

[c] beta-arrestin binding assays.

[d] Maximal effect at 10,000 nM on S1PR4/S1PR5 was 18/42%, respectively of the effect on S1P response, so was not only less efficacious but also less potent than S1P.

The standard daily doses are: 0.5 mg fingolimod, 1 mg siponimod, 0.92 mg ozanimod or 20 mg ponesimod.

therapeutic impact on lymphocyte migration is mediated by S1PR1 (Sanna et al., 2004). Ponesimod targets largely S1PR1, with lower affinities and partial activity for other receptors, notably S1PR5, and inhibits relapsing MS (Fig. 1, Table 2) (Markham, 2021; Bolli et al., 2010). Siponimod and ozanimod both target S1P1R and S1PR5, to notably to limit perceived S1PR3-mediated side effects encountered with fingolimod (Gergely et al., 2012; Sanna et al., 2004; Scott et al., 2016). They also target S1PR5 on oligodendrocytes and their precursors to potentially better influence remyelination (Fig. 1, Table 2) and do not require the action of phosphorylating S1P kinases for activity (Liu et al., 2000; Kharel et al., 2005; Roggeri et al., 2020). Although remyelination effects are largely unproven in MS, oligodendrocyte actions are unlikely to be of major importance to COVID-19, therefore targeting this pathway is unlikely to impact on SARS-CoV-2 infection or vaccination responses. However, S1PR5 modulators may affect natural killer cell function, which may influence COVID-19 biology (Walzer et al., 2007; Drouillard et al., 2018; Di Vito et al., 2022). However, given that the impact of these agents on natural killer cell numbers is often minimal (Harris et al., 2020) and that fingolimod, which also targets S1PR5 and is not associated with a worse prognosis following SARS-CoV-2 infection (Sormani et al., 2021; Simpson-Yap et al., 2021), indicates that likewise, siponimod, ozanimod and ponesimod are unlikely to cause a worse prognosis following COVID-19 infection. Indeed, this appears to be the case in the few individuals that are reported to be infected with SARS-CoV-2 who are taking these drugs (Sullivan et al., 2021; Czarnowska et al., 2021; Berger et al., 2022, Cree et al., 2022). Natural killer cells are unlikely to exhibit a major effect on the generation of T and B cell responses and this suggests that siponimod, ozanimod and ponesimod may behave similarly regarding vaccination.

4.1. Sphingosine-1-phopshate receptors controlling multiple sclerosis and COVID-19 infection and vaccine responses

Currently all approved S1PR modulators target S1P1R (Table 2). These may be agonists that trigger receptor internalisation and degradation (S1PR1) or internalization and recycling (S1PR3 and S1PR4) to be functional antagonists at S1PR1, S1PR3, S1PR4 and possibly agonists at S1PR5, which appears not to internalize (Grassi et al., 2019; Cyster and Schwab, 2012; Bigaud et al., 2018). Simplistically, S1PR1 is involved in lymphocyte egress from bone-marrow and some lymphoid tissues and therefore S1P1R modulators are associated with a rapid peripheral lymphopenia limiting entry of pathogenic cells into the CNS (Mehling et al., 2008; Jurcevic et al., 2016; Harris et al., 2020; Cyster and Schwab, 2012; Brossard et al., 2013; Mandala et al., 2002; Matloubian et al., 2004). In addition, S1PR1 is also expressed by the vascular system and brain endothelial cells, hence S1PR modulation can further inhibit leucocyte trafficking into the CNS to prevent disease (Zhao et al., 2018; Spampinato et al., 2015). This may be further influenced by astrocytic S1PR1/S1PR3 activity, as astrocytes are known to be involved in blood-brain barrier formation and targeting astrocytes probably serves to help inhibit disease (Choi et al., 2011; van Doorn et al., 2012; Spampinato et al., 2021).

Although it is clear that CD4, CD8 and CD19 expressing T and B lymphocytes are markedly inhibited following S1P1R internalization, it is evident that there is differential inhibition of lymphocyte subsets notably due to S1PR1 and CCR7 chemokine receptors (Mehling et al., 2008; Jurcevic et al., 2016; Harris et al., 2020; Lu and Cyster, 2019; Hjorth et al., 2020). This indicates that many studies showing diminished T cell responsiveness against SARS-CoV-2 vaccination are not measuring the same populations of T cells, which may have different stimulation thresholds and cytokine release profiles (Sallusto et al., 1999; Geginat et al., 2003). As such naïve (CD45RA+, CCR7+) and central memory [CD45RO+, CCR7+) populations, which are the cells that will generate new responses in lymph nodes are trapped and maintained in lymphoid tissues and bone marrow (Mehling et al., 2008; Hjorth et al., 2020). The effector memory (CD45RO+, CCR7+) and notably effector T-cells (CD45RA+, CCR7-), which will give the protective anti-viral responses in tissues can enter the circulation to promote defence against pathogens (Mehling et al., 2008; Jurcevic et al., 2016; Harris et al., 2020; Hjorth et al., 2020). Furthermore, as lymphoid tissue retention of CD8+ T-cell is less marked than seen with CD4+ T cells, peripheral effector CD8+ T-cells are enriched (Mehling et al., 2008; Jurcevic et al., 2016; Hjorth et al., 2020; Johnson et al., 2010). This will further aid anti-viral immune responses that promote recovery from COVID-19. However, this is a relative escape and there is an absolute reduction in effector memory cells, which are the major T-cell subset entering the CNS during MS (Hjorth et al., 2020; Mullen et al., 2012). Thus, this action could promote efficacy in MS, in addition to any effect on central memory T cells (Song et al., 2015).

Furthermore, the peripheral memory B cells are a major subsets of B cells implicated in MS pathogenesis and are affected along with naïve B cells, at least for fingolimod (Baker et al., 2017; Johansson et al., 2021; Kemmerer et al., 2020; Kowarik et al., 2021). Importantly, fingolimod, like most other MS-disease modifying treatments, targets the adaptive immune response and does not induce marked changes to the peripheral innate immune response, which are sentinels located within the affected tissues and appear to be central to SARS-CoV-2 removal (Baker et al., 2020a; Kemmerer et al., 2020; Amor et al., 2020). This is facilitated by

the cytotoxic T cell response and the subsequent generation of cytopathic and neutralizing antibodies that can help protect against re-infection (Baker et al., 2020a; Baker et al., 2020b; Sormani et al., 2022). Antibody responses can be generated within the lymphoid tissue from immature and naïve B cells, which seem to express many S1PR (Fig. 2) and thus may not require re-circulation to tissues to induce antibody-producing plasma cells that could facilitate removal of the SARS-CoV-2 virus (Turner et al., 2021; Kim et al., 2022). However, S1P1R is involved in the release of immature B cells from bone marrow and B cell migration within lymphoid tissues that involves shuttling of B cells from marginal zones and B cell follicles using S1PR1 and CXCR5, responding to CXCL13 (Lu and Cyster, 2019; Cinamon et al., 2008; Allende et al., 2010). This could contribute to the reduction of SARS-CoV-2 B cell responses as seen with fingolimod (Wu et al., 2022; Gombolay et al., 2022).

Vaccine responses during fingolimod treatment are blunted compared to untreated individuals with a seroconversion rate of 60.2% in a meta-analysis of $n = 785$ people treated with S1PR modulators, largely taking fingolimod $n = 764$ (Wu et al., 2022). This was supported in an additional meta-analysis examining only fingolimod treatment, which reported an antibody response in $n = 160/220$ (72.7%) vaccinated and $n = 152/198$ (76.8%) mRNA-vaccinated, fingolimod--treated individuals (Table 3) (Gombolay et al., 2022). In addition other S1PR modulators also exhibited a blunted vaccine response, seen as reduced antibody titres compared to untreated individuals following SARS-CoV-2 treated vaccination in animals or people with MS treated with either: siponimod ($n = 50$) (Ziemssen et al., 2022, Siddiqui et al., 2021; Krbot Skorić et al., 2022; Milo et al., 2022; Satyanarayan et al., 2022; Bar-Or et al., 2022), ozanimod ($n = 228$) (Satyanarayan et al., 2022; Kantor, 2022, Cree et al., 2022b, Akgün et al., 2022) or ponesimod ($n = 103$) (Spiller et al., 2021, Wong et al., 2022) (Table 3). This suggests an important impact of S1PR1 on vaccine-induced antibody responses.

Interestingly, although the numbers of studies on non-fingolimod, S1PR modulators are relatively small and the differences observed may be part of the variability between studies, including the nature of the vaccines and the immune-response detection assays used, it seems that there are better seroconversion rates seen in the majority of people treated with siponimod, ozanimod and ponesimod (Table 3). This contrasts with studies on fingolimod that often report that the minority of people seroconvert following vaccination (Wu et al., 2022; Gombolay et al., 2022; Ziemssen et al., 2022, Siddiqui et al., 2021; Krbot Skorić et al., 2022; Milo et al., 2022; Satyanarayan et al., 2022; Bar-Or et al.,

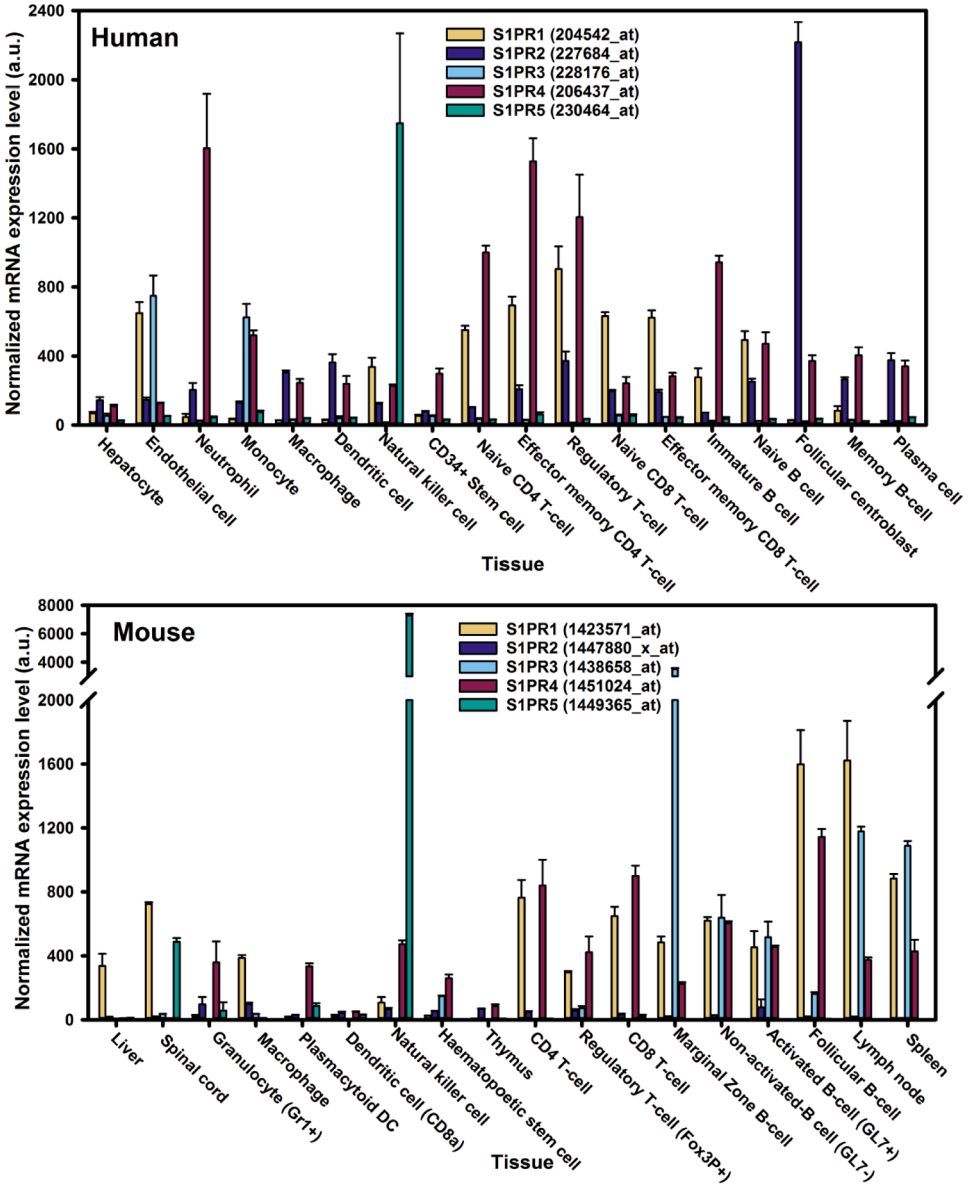

Fig. 2. Sphinogsine-1-phosphate receptor distribution in human and mouse cells. The S1PR mRNA expression distributions from cells and tissues were extracted from Affimetrix RNAseq data in the human Primary Cell Atlas or the mouse GeneAtlas MOE430 gcrma datasets at www.biogps.org, using the indicated S1PR-specific probes. The results represent the mean ± standard error of the mean expression of 2–21 individual samples of normalised expression data. Human macrophages and dendritic cells were monocyte-derived and the monocytes expressing S1PR3 were from the CD14+ subset (935±55a.u.) compared to the CD16+ (76 ±55a.u. $n = 3$). a.u. arbitrary units. The human natural killer cells subset examined, expressed CD56, CD62 antigens.

Table 3
Influence of S1PR modulation on SARS-CoV-2 vaccine responses.

S1PR modulator	No. seroconversion/ Total (% response) & subgroup	SARS-CoV-2 Assay (Source)	T cell Response assessed	Reference
Fingolimod	160/220 (72.7%) Varied	Multiple	Yes	Gombolay et al., 2022
	152/198 (76.8%) mRNA	"	"	"
	20/37 (54.1%) mRNA	ECLIA (Abbott)	Yes	Milo et al., 2022
	11/18 (61.1%) Varied	Multiple	No	Satyanarayan et al., 2022
	$n = 86$ (27.9%) mRNA	CLIA (DiaSorin)	Yes	Akgün et al., 2022*
Siponimod	15/21 (71.4%) mRNA	Neutralization assay	Yes	Rauser et al., 2022*
	1/1 (100%) mRNA	ECLIA (Roche)	No	Siddiqui et al., 2021
	11/13 (84.6%) Varied	ECLIA (Roche)	No	Krbot Skorić et al., 2022
	3/3 (100%) mRNA	ECLIA (Abbott)	No	Milo et al., 2022
	7/8 (87.5%) Varied	Multiple	No	Satyanarayan et al., 2022
	4/5 (80.0%) mRNA	SARS-CoV IgG	No	Bar-Or et al., 2022*
Ozanimod	3/3 (100%) Varied	Multiple	No	Satyanarayan et al., 2022
	30/30 (100%) Varied	ECLIA (Roche)	Yes	Kantor, 2022*
	137/148 (92.6%) Varied	ECLIA (Roche)	No	Cree et al., 2022b*
	39/39 (100%) Exposed	"	"	"
	98/109 (89.9%) Naïve	"	"	"
	80/80 (100%) mRNA	"	"	"
	$n = 47$ (84.2%) mRNA	CLIA (DiaSorin)	Yes	Akgün et al., 2022*
Ponesimod	89/103 (86.4%) Varied	ELISA (Nexelis)	No	Wong et al., 2022*
	11/11 (100%) Exposed	"	"	"
	33/38 (86.8%) Naïve	"	"	"
	29/32 (90.6%) mRNA	"	"	"

Information was extracted from data tables from a meta-analysis of 31 studies on the influence fingolimod treatment on SARS-CoV-2 vaccination (two doses). This was contrasted with individual public domain studies of SARS-CoV-2 vaccination in people treated with either siponimod, ozanimod or ponesimod. The results show the number of serological responders, defined within their studies, from the total analysed in response to any Index SARS-CoV-2 vaccine (varied) or stratified into those receiving only mRNA vaccines. Data was also stratified into those potentially previously exposed to COVID-19 infection, indicated by serological responses to SARS-CoV-2 nucleocapsid, or were considered to be infection-naïve in the absence of nucleocapsid serology. Where defined the SARS-Cov-2, antibody detection assay and manufacturer was indicated and these included electro-chemiluminescent immunoassay (ECLIA) and enzyme-linked immunosorbent assays (ELISA). It is indicated whether SARS-CoV-2 T-cell recall responses were performed. The source references are indicated.

* Indicates that the public domain information may not have been peer-reviewed.

2022; Kantor, 2022, BAC Cree et al., 2022, Akgün et al., 2022, Wong et al., 2022). This could suggest that S1PR3 and S1PR4, which are widely expressed by the immune system (Fig. 2), contribute to lower antibody titres following vaccination, as suggested by the underlying biology.

Consistent with other studies (Khoury et al., 2021), the level of seroconversion is influenced by the nature of administered vaccine (Table 3) (Khoury et al., 2021). As such, mRNA vaccines induce better seroconversion than seen following viral vector use (Wu et al., 2022; Gombolay et al., 2022; Tallantyre et al., 2022a). Meta-analysis indicates responses in $n = 152/198$ (76.8%) mRNA vaccinated individuals vs. $n = 8/22$ (36.4%) individuals vaccinated with SARS-CoV-2 viral vectors administered during fingolimod (Wu et al., 2022) and was seen with ozanimod and ponesimod (Table 3) (Cree et al., 2022b, Wong et al., 2022). Likewise, as anticipated there were more marked vaccine responses in people who have seroconverted following natural SARS-CoV-2 infection (Table 3) (BAC Cree et al., 2022, Wong et al., 2022). Therefore, the demographics of individuals vaccinated will potentially influence study outcome.

Furthermore, it could also be argued that the possible subtle differences reported between fingolimod and the more recently approved variants may relate to biology created by the changing circulating SARS-CoV-2 variants of concern and thresholds of immunity required for immune protection (Sormani et al., 2022; Ohashi et al., 2022). However, the information reported here was largely based on full vaccination (typically two cycles) with the original index-SARS-CoV-2 virus-based vaccines. This was also collected during periods when SARS-COV-2 alpha and delta variants of concern were prevalent (Looi, 2022 Sep 15) and most people appeared to be natural-infection naïve (Table 3) and respond consistently over time and between vaccine cycles (Tallantyre et al., 2022a; Tallantyre et al., 2022b; König et al., 2022). Therefore, the circulating SARS-CoV-2 variant, may have had limited impact on the vaccine responses seen (Table 3).

However, it is likely that the threshold of assay detection of SARS-CoV-2 antibodies is important in determining the level of seroconversion. Therefore, it is perhaps of interest that the high frequency of seroconversion seen notably in ozanimod-treated individuals was largely detected in studies using the SARS-CoV-2 receptor binding domain ECLIA *Elecsys*® assay (Table 3) (Kantor, 2022,(BAC Cree et al., 2022). This seems to detect higher levels of seroconversion in fingolimod-treated, infection-naive (SARS-CoV-2 nucleocapsid antibody negative) individuals in comparison to the many different assays used (Wu et al., 2022; Sormani et al., 2021b; Pitzalis et al., 2021).These large studies may help skew the level of seroconversion observed, which can be quite heterogenous between fingolimod-related studies (Wu et al., 2022). As such a high level of seroconversion ($n = 58/64$. (90.6%)) was detected following tozinameran (BNT162b2) vaccination using the *Elecsys*® receptor binding domain antibody assay (Sormani et al., 2021b). However, the median titre detected was only about 20 U/ml (Sormani et al., 2021b). Likewise, in another similar fingolimod study, again a median antibody titre of only 26.7 U/ml ($n = 71$) was reported in infection-naïve, tozinameran-vaccinated individuals (Pitzalis et al., 2021). Importantly, it was reported that only 14/71 (19.1%) fingolimod-treated, infection-naïve individuals developed an index SARS-CoV-2 strain neutralizing titre of >133 U/ml occurred in fingolimod-treated individuals (Pitzalis et al., 2021). In contrast, the median SARS-CoV-2 receptor binding domain-specific antibody in ozanimod-treated, infection-naïve individuals was 138 U/ml (BAC Cree et al., 2022). Although caution is needed in comparing different studies, this supports the view that at least ozanimod and perhaps other S1PR modulators, may allow a higher antibody titre to develop and thus create a potentially more effective vaccination response. Larger studies, meta-analysis of numerous smaller studies (Wu et al., 2022; Gombolay et al., 2022) or ideally clinical or experimental head to head studies will be required to determine whether there are indeed any real differences between the vaccine responses of the different S1PR modulators. However so far, this idea is suggested by some recent studies that contain responses to multiple different S1PR modulators (Table 3) (Milo et al., 2022; Satyanarayan et al., 2022; Akgün et al., 2022).

Whilst the majority on SARS-CoV-2 vaccine responses have focused

on antibody responses, reduced T-cell recall responses have also repeatedly been reported during fingolimod treatment in many small studies that are perhaps consistent with the induced T cell lymphopenia (Wu et al., 2022; Gombolay et al., 2022; Tallantyre et al., 2022a; Meyer-Arndt et al., 2022; Wolf et al., 2022). The peripheral blood T cell responses in people treated with the more recent S1PR modulators have been inconsistent and further study is required (Ziemssen et al., 2022; Kantor, 2022; Akgün et al., 2022). However, as memory T and B cell recall responses require stimulation and are maintained even after antibody titres are diminished (Tallantyre et al., 2022a; König et al., 2022; Moore et al., 2022), the threshold level needed for immune protection requires further study and may vary with time, notably related to the changing circulating SARS-CoV-2 variant of concern, as seen with antibody protection from infection (Khoury et al., 2021; Sormani et al., 2022; Ohashi et al., 2022).

4.2. *Influence of non-sphingosine-1-phopshate 1 receptors controlling antibody responses*

None of the current S1PR modulators target S1PR2 (Table 2) and this may be beneficial for vaccine responses as SP1R2 and the CXCR5 chemokine regulate the localization of follicular helper T cells into the B cell follicles to promote antibody responses and are particularly important for germinal centre reactions, where they can function to help antibody responses to novel antigens, through production of cytokines and co-stimulatory molecules (Moriyama et al., 2014; Cohan et al., 2021). Furthermore, S1PR2 is expressed by B cells within follicles (Fig. 2) and this regulates entry into a plasma cell or recycling germinal centre cell fate and maintains the homoeostasis of germinal centre B cells (Cattoretti et al., 2009; Green et al., 2011; Green and Cyster, 2012; Ise et al., 2018; Al-Kawaaz et al., 2019). As such, S1PR2 may inhibit some S1PR1-mediated functions (Sic et al., 2014).

In contrast, it is also possible to speculate that potential differences between fingolimod and the other S1P modulators could occur due to an activity on S1PR3. Indeed, it has been suggested that S1PR3 controls B cell function (Cinamon et al., 2008; Tedford et al., 2017; Donovan et al., 2010). Notably, this receptor has been associated with the development of progenitor cells; positioning of immature B cells within bone marrow sinusoids and migration of B cells within the bone marrow and lymphoid tissues (Donovan et al., 2010; Muppidi et al., 2015; Ogle et al., 2017). Importantly, it is involved in B cell capture of antigens in the marginal zones and shuttling to B cell follicles for the development of antibodies (Cinamon et al., 2008; Tedford et al., 2017). However, this view may only reflect the case in rodents, as there is a paucity of evidence to suggest an S1PR3-mediated B cell activity in humans. As such, there may be subtle differences in the migration cues between rodent and humans (Park et al., 2021). Importantly, whilst mouse B cells express S1PR3 (Donovan et al., 2010; Wu et al., 2009) it appears that human B cells express limited S1PR3 mRNA (Wu et al., 2009; Kassambara et al., 2015) (Fig. 2). This may have parallels with the cardiac side-effect activity that was originally attributed to S1PR3, based on rodent studies (Gergely et al., 2012; Sanna et al., 2004). It is now evident that these issues are mediated by S1PR1 in humans (Gergely et al., 2012). As such all approved S1P modulators, including those with no/limited S1PR3 activity can induce cardiac arrhythmias (Al-Salama and Siponimod, 2019; Lamb, 2020; Markham, 2021; Scott, 2011). However, S1PR3 can be pathologically regulated within lymphoid tissues and may have some element to play in B cell development, notably as it has been suggested that S1PR3 contributes to vascular and dendritic cell function within B cell areas (Muppidi et al., 2015; Girkontaite et al., 2004; Middle et al., 2015; Nussbaum et al., 2015). As such S1PR3 can control dendritic cell migration into secondary lymphoid tissues and monocyte activity (Maeda et al., 2007; Keul et al., 2011) and may influence the generation of primary immune responses that ultimately lead to a vaccination response (Fig. 2).

Indeed, it is evident that S1PR4 is widely expressed by immune cells subsets (Fig. 2), including platelets (Golfier et al., 2010) (Fig. 2) and that S1PR4 modulation may mediate effects on T and B cell migration and may modulate S1PR1 function (Sic et al., 2014; Wang et al., 2005; Xiong et al., 2019; Olesch et al., 2020; Riese et al., 2021), *S1pr4*-gene deficient mice have normal lymphocyte numbers and regular architecture of secondary lymphoid organs (Schulze et al., 2011). In contrast, there was a marked impact of S1PR4 depletion on dendritic cell migration and cytokine secretion leading to reduced Th17 T-cell differentiation and inhibition of mouse and human dendritic cell activity (Schulze et al., 2011; Mosheimer et al., 2005; Olesch et al., 2017). There is S1PR-mediated control of dendritic (Langerhans) cell migration from the skin (Bock et al., 2016). This could impact antigen-presenting cell function in vaccine-induced responses and may affect progenitor development in the bone marrow that limit the occurrence of dendritic cells (Olesch et al., 2017; Dillmann et al., 2015). Furthermore, S1PR4 is required for plasmacytoid dendritic cell differentiation (Dillmann et al., 2015). Plasmacytoid dendritic cells secrete high levels of interleukin-6 and type I interferons in response to infection, which are protective against the SARS-CoV-2 virus and can help induce the differentiation of B cells into IgG-secreting plasma cells (Le Bon et al., 2001; Jego et al., 2003; Poeck et al., 2004). The innate immune system and endothelial express the S1P kinases, notably SPHK1 and can respond to fingolimod (Schwiebs et al., 2016; Mohammed et al., 2019). However, it is important to note that the affinity of fingolimod for S1PR4 may be low in some functional assays (Table 2) and therefore differences between this and other agents may only be incremental. Likewise, it is possible that differences between fingolimod and other agents could relate to the requirement for phosphorylation that may vary due to the potential differential expression of SPKH1 and SPKH2 in tissues influencing fingolimod activity (Brinkmann et al., 2002; Liu et al., 2000)

The potential differences observed between seroconversion after infection or vaccination during fingolimod use may simply reflect variability between studies and it is important to note in both cases the level of response is often diminished compared to untreated individuals. However, whilst vaccination is induced via the skin, natural infection with SARS-COV-2 occurs via the pulmonary and mucosal surfaces over time and so the range of antigen-presenting cells and lymphoid tissues involved may be broader and may account for potentially better seroconversion in these immunosuppressed people (Poeck et al., 2004; Schwiebs et al., 2016; Mohammed et al., 2019). We hypothesise that the apparent, subtle, differences between fingolimod and the newer generation S1PR modulators are most likely due to differences on SIPR3 and notably SP1R4 modulation on the germinal centre formation and function, which are critical for neoantigen antibody responses (Fig. 3).

5. Influence of SARS-CoV-2 antiviral agents on S1PR modulators

5.1. *Anti-viral antibodies*

From SARS-CoV-2 vaccination have the potential to provide protection from infection and disease-related morbidity, but it is not infallible (Sormani et al., 2021b; Tuekprakhon et al., 2022; Peng et al., 2022; Cho et al., 2021; Gazit et al., 2022; Antonelli et al., 2022). This may especially be the case as viral variants have evolved that are relatively resistant to the original SARS-CoV-2 spike-based serology and vaccines (Tuekprakhon et al., 2022; Schiavetti et al., 2022b, Planas et al., 2022; Wang et al., 2022). However, blocking the serological responses to infection and/or vaccination in immunosuppressed-individuals have supported the need for effective anti-viral treatments. Monoclonal antibodies often generated from COVID-19 convalescent individuals have shown promise in protecting individuals from infection (Planas et al., 2022; Wang et al., 2022; Focosi et al., 2022; Woopen et al., 25). There, is limited expression of S1PR receptors, except for S1PR4, by polymorphonuclear neutrophils and neutropenia is not typically associated with S1PR modulation and may control egress from inflamed tissues (Harris et al., 2020; Sehr et al.,

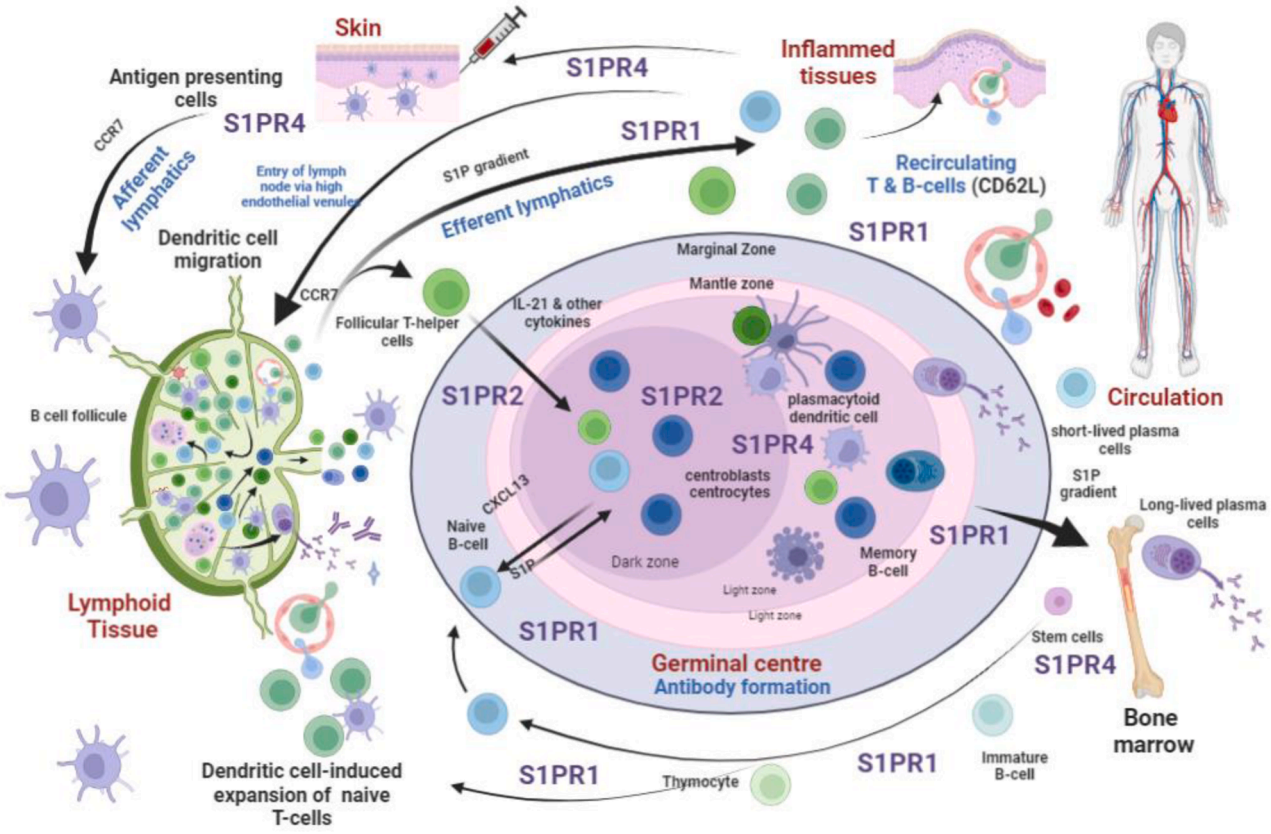

Fig. 3. The germinal centre reaction to generate vaccine responses. Hypothetical activity of S1PR in generating vaccine-induced antibody responses. This involves S1PR4-related migration of dendritic/Langerhans cells from blood to tissues and from sites of inflammation to lymphoid tissues. T cells are activated, expanded and differentiated prior to recirculation to lymphoid (CD62L+) or inflamed tissue (CD44+, CD49d). CD4+ follicular T-helper cells migrate into and stay in B-cell follicles to support B-cell development and maturation and the formation of germinal centre cells. Naïve B cells capture antigens from the marginal zone become activated and differentiate to memory B cells, plasmablasts and long-lived plasma cells that reside in the bone marrow and secrete antibody. Short-lived plasma cells may be formed from extra-germinal centre B-cell areas. Created with Biorender.com.

2020; Mao-Draayer et al., 2017). Although fingolimod, siponimod and ozanimod could perhaps influence natural killer (NK) cell function secondary to effects notably on S1P5R, and in the case of fingolimod S1P4R, associated migration (Walzer et al., 2007; Drouillard et al., 2018). Again, peripheral NK depletion is modest following S1PR modulation (Harris et al., 2020; Mehling et al., 2015; Michel et al., 2016). This probably reflects a more limited activity on the CD16+, $CD56^{dim}$ NK cell subset that are dominant in the periphery and are important for antibody-mediated cytotoxicity (Harris et al., 2020; Mao-Draayer et al., 2017; Mehling et al., 2015). There is therefore limited reason to believe that S1PR would directly influence viral activity via antibodies or a direct effect on viral activity. However, poor viral elimination in SARS-CoV-2 neutralizing antibody-treated and immunosuppressed people can support the selection of immune escape variants that can render SARS-CoV-2-specific neutralizing antibodies such as casirivimab/imdevimab, tixagevimab/cilgavimab and sotrovimab to become rather ineffective as the SARS-CoV-2 virus evolves (Shrestha et al., 2022; Scherer et al., 2022; Ohashi et al., 2022; Planas et al., 2022; Wang et al., 2022; Woopen et al., 25; Magnè et al., 2022). Therefore, alternative strategies are needed.

5.2. *Small molecule anti-viral agents*

Have been identified and/or generated to block essential viral function that are distinct from SARS-CoV-2 receptor-binding domain targeting antibodies. These chemicals currently include: remdesivir infusions for hospitalised individuals (Beckerman et al., 2022) and oral molnupiravir (Jayk Bernal et al., 2022; Khoo et al., 2022, (Wen et al., 2022) and ritonavir-enhanced nirmatrelvir (Wen et al., 2022; Sun et al., 2022) that are used for COVID-19 prophylaxis or for a rapid, post-infection application (Sun et al., 2022). Remdesivir prodrug is metabolised by the cytochrome P450 CYP3A4 variant leading to increased bioavailability of other CYP3A4 substrates that include some MS-related drugs (Deb and Reeves, 2021; Hirai et al., 2022). Molnupiravir, is another prodrug and is rapidly converted to active drug in plasma, which is excreted with limited hepatic metabolism (Painter et al., 2021). This should not unduly influence S1PR modulators. In contrast, ritonavir-enhanced nirmatrelvir may augment the pharmacokinetics of many drugs, including nirmatrelvir, because ritonavir is a potent inhibitor of CYP3A4, CYP2D6 and a number of drug transporters (Heskin et al., 2022). Ponesimod is metabolised by a number of cytochrome enzymes including: CYP2J2, CYP3A4, CYP3A5, CYP4F3A, and CYP4F12 without major contribution by any single enzyme and as such is considered unlikely that any major impact on ponesimod metabolism will occur (Anon 2021). Likewise, fingolimod is metabolised mainly by CYP4F2 and CYP4F3B enzymes and specific CYP3A4 inhibition did not impact fingolimod distribution (Jin et al., 2011). Ozanimod is extensively metabolised, notably by CYP2C8 and to a small extent by CYP3A4, as such CYP3A4 inhibition had limited impact on ozanimod levels (Tran et al., 2020). However, ozanimod and its active metabolites (notably CC112273) are substrates for p-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2), which can be inhibited by ritonavir and could increase ozanimod exposure. However, this would be within safe limits observed in ozanimod trials (Heskin et al., 2022). Siponimod carries a warning that it should be avoided with CYP2C9 and CYP3A4 inhibitors (Huth et al., 2019). Whilst this may lead some people to avoid

use of nirmatrelvir/ritonavir, the contraindication is based on the combination of both CYP2C9 and CYP3A4 inhibition, whereas CYP3A4 inhibition alone exhibits limited impact on siponimod concentrations (Gardin et al., 2019). Likewise, as with ozanimod, any enhanced levels of siponimod would be within safe limits tested in trials. Whilst ritonavir can induce CYP2C9 (Heskin et al., 2022), problems will be avoided as people sensitive to the influences of CYP2C9 alleles, notably *CYP2C9×3* homozygotes as poor metabolizers, are excluded from siponimod treatment as part of drug screening and those with CY2C9×2*3 and *CYPC9×1*3* genotypes are differentially dosed (Huth et al., 2019). Currently there is no information to determine whether CYP2C9 genotypes influences vaccine responses. However, given the short course of anti-viral and the half-lives of the agents, there does not seem to be a major risk-benefit barrier to offering anti-viral agents to people taking S1PR modulators, if considered to be useful.

6. Conclusions

The success of fingolimod as a therapeutic in MS, has led to the development of a number of other S1PR modulators for the treatment of MS and other immune conditions, which have different binding and pharmacokinetic activities. Whilst their selection may in part be hampered by their licence/label, from a biological perspective these differences can influence: dosing and activity; the strategy required to switch to other agents in case of treatment failure and, as highlighted here, the ability to facilitate vaccination and infection control. Whilst vaccination issues have become evident due to the COVID-19 pandemic, annual vaccinations such as with the current influenza vaccines, mean that this element of S1P and S1PR biology will remain an issue. Therefore, ways to improve/optimize vaccination responses will be beneficial (Sullivan et al., 2022). Although, repeated boosting can increase the titres of SARS-CoV-2 specific-antibodies in some people (Tallantyre et al., 2022a; Milo et al., 2022; Capuano et al., 2022; Achtnichts et al., 2022), uninterrupted S1PR modulator treatment is currently often associated with a blunted vaccination response (Pitzalis et al., 2021; Tallantyre et al., 2022a; Louapre et al., 2022, Meyer-Arndt et al., 2022; Akgün et al., 2022; Achiron et al., 2022). A long-period of fingolimod discontinuation, to allow recovery of lymphocytes, may increase the chance of a vaccine-induced antibody response, but risks disease breakthrough that can occur within a few weeks of discontinuation (Barry et al., 2019; Achtnichts et al., 2022). Short treatment breaks with ponesimod may be feasible without disease breakthrough (Lublin et al., 2022). Good vaccine responses have been seen with other immunosuppressive agents, with short half-lives, following short-term interruption of treatment in other immune conditions (Schnuelle et al., 2021; Abhishek et al., 2022). This was seen in animals treated with ponesimod (Spiller et al., 2021) and people given other vaccines during siponimod treatment and potentially in a small number of people given the SARS-CoV-2 vaccine (Ufer et al., 2017; Ziemssen et al., 2022). This is consistent with the observations that vaccine-responsiveness correlated with lymphocyte numbers, notably CD19+, CD27- B cell numbers (Schiavetti et al., 2022b, Achiron et al., 2022). However, the primary aim should be to effectively control disease and with anti-viral agents available, potentially less virulent and vaccine immune-escape SARS-COV-2 variants circulating, thought/evidence is needed to justify any change to standard practice (Giovannoni, 2022). However, more extensive studies to optimise responses whilst ensuring efficacy and safety are needed to avoid disease-breakthrough and cardiac issues for all S1P modulators (Orrico et al., 2021). This is important as the power to rapidly generate vaccines to infections is likely to increase in the future.

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Declaration of Competing Interest

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References

Abhishek, A., Boyton, R.J., Peckham, N., McKnight, Á., Coates, L.C., Bluett, J., Barber, V., Cureton, L., Francis, A., Appelbe, D., Eldridge, L., Julier, P., Valdes, A.M., Brooks, T., Rombach, I., Altmann, D.M., Nguyen-Van-Tam, J.S., Williams, H.C., Cook, J.A., VROOM study investigators, 2022. Effect of a 2-week interruption in methotrexate treatment versus continued treatment on COVID-19 booster vaccine immunity in adults with inflammatory conditions (VROOM study): a randomised, open label, superiority trial. Lancet Respir. Med. S2213-2600(22)00186-2.

Achiron, A., Mandel, M., Dreyer-Alster, S., Harari, G., Magalashvili, D., Sonis, P., Dolev, M., Menascu, S., Flechter, S., Falb, R., Gurevich, M., 2021. Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies. Ther. Adv. Neurol. Disord. 14, 17562864211012835.

Achiron, A., Mandel, M., Gurevich, M., Dreyer-Alster, S., Magalashvili, D., Sonis, P., Dolev, M., Menascu, S., Harari, G., Flechter, S., Falb, R., 2022. Immune response to the third COVID-19 vaccine dose is related to lymphocyte count in multiple sclerosis patients treated with fingolimod. J. Neurol. 269, 2286–2292.

Achtnichts, L., Ovchinnikov, A., Jakopp, B., Oberle, M., Nedeltchev, K., Fux, C.A., Sellner, J., Findling, O., 2022. SARS-CoV-2 mRNA vaccination in people with multiple sclerosis treated with fingolimod: protective humoral immune responses may develop after the preferred third shot. Vaccines (Basel) 10, 341.

Akgün, K., Dunsche, M., Katoul Al Rahbani, G., Woopen, C., Ziemssen, T, 2022. Different type and timing of S1P receptor modulator therapy impacts T and B cell response after SARS-CoV2 vaccination P316. Multip. Scler. J. 28 (3S), 347–348. *.

Al-Kawaaz, M., Sanchez, T., Kluk, M.J., 2019. Evaluation of S1PR1, pSTAT3, S1PR2, FOXP1 expression in aggressive, mature B cell lymphomas. J. Hematop. 12, 57–65.

Al-Salama, Z.T., Siponimod, 2019. First global approval. Drugs. 79, 1009–1015.

Allende, M.L., Tuymetova, G., Lee, B.G., Bonifacino, E., Wu, Y.P., Proia, R.L., 2010. S1P1 receptor directs the release of immature B cells from bone marrow into blood. J. Exp. Med. 207, 1113–1124.

Amor, S., Fernández Blanco, L., Baker, D, 2020. Innate immunity during SARS-CoV-2: evasion strategies and activation trigger hypoxia and vascular damage. Clin. Exp. Immunol. 202, 193–209.

Ponvory Summary of Medical Product Characteristics, 2021. European Union. www.ema.europa.eu.

Antonelli, M., Penfold, R.S., Merino, J., Sudre, C.H., Molteni, E., Berry, S., Canas, L.S., Graham, M.S., Klaser, K., Modat, M., Murray, B., Kerfoot, E., Chen, L., Deng, J., Österdahl, M.F., Cheetham, N.J., Drew, D.A., Nguyen, L.H., Pujol, J.C., Hu, C., Selvachandran, S., Polidori, L., May, A., Wolf, J., Chan, A.T., Hammers, A., Duncan, E.L., Spector, T.D., Ourselin, S., Steves, C.J., 2022. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. Lancet Infect. Dis. 22, 43–55.

Baker, D., Marta, M., Pryce, G., Giovannoni, G., Schmierer, K, 2017. Memory B cells are major targets for effective immunotherapy in relapsing multiple sclerosis. EBioMedicine 16, 41–50.

Baker, D., Amor, S., Kang, A.S., Schmierer, K., Giovannoni, G., 2020a. The underpinning biology relating to multiple sclerosis disease modifying treatments during the COVID-19 pandemic. Mult. Scler. Relat. Disord. 43, 102174.

Baker, D., Roberts, C.A.K., Pryce, G., Kang, A.S., Marta, M., Reyes, S., Schmierer, K., Giovannoni, G., Amor, S, 2020b. COVID-19 vaccine-readiness for anti-CD20-depleting therapy in autoimmune diseases. Clin. Exp. Immunol. 202, 149–161.

Baker, D., MacDougall, A., Kang, A.S., Schmierer, K., Giovannoni, G., Dobson, R., 2021. Seroconversion following COVID-19 vaccination: can we optimize protective response in CD20-treated individuals? Clin. Exp. Immunol. 207, 263–271.

Bar-Or, A., Mao-Draayer, Y., Delgado, S.R., Fox, R.J., Cruz, L.A., Meng, X., Mavrikis Cox G5, 2022. Evaluating humoral immune response to mRNA COVID-19 vaccines in siponimod-treated patients with advancing forms of relapsing multiple sclerosis: a COVID-19 vaccine sub-study of phase 3b EXCHANGE trial. ACTRIMS Forum. *. https://www.medcommshydhosting.com/MSKnowledgecenter/actrims/2022/posters/Evaluating_Humoral_Immune_Response_Poster.pdf.

Barry, B., Erwin, A.A., Stevens, J., Tornatore, C., 2019. Fingolimod rebound: a review of the clinical experience and management considerations. Neurol. Ther. 8, 241–250.

Beckerman, R., Gori, A., Jeyakumar, S., Malin, J.J., Paredes, R., Póvoa, P., Smith, N.J., Teixeira-Pinto, A., 2022. Remdesivir for the treatment of patients hospitalized with COVID-19 receiving supplemental oxygen: a targeted literature review and meta-analysis. Sci. Rep. 12, 9622.

Berger, J., Sullivan, R., Kilaru, A., Hemmer, B., Cree, B.A.C., Greenberg, B.M., DeLasHeras, V., Ward, B.J., 2022. COVID-19 outcomes in fingolimod- or siponimod-treated patients: clinical trial and post marketing cases P726. Mult. Scler. 28 (3S), 637. *.

Bigaud, M., Nuesslein-Hildesheim, B., Tran, T.T.T., Guerini, D., 2018. Siponimod and fingolimod down regulate S1P1 but no effect on S1P5. Neurology (15 Supplement), 90. P3.404.

Bigaut, K., Kremer, L., Fabacher, T., Lanotte, L., Fleury, M.C., Collongues, N., de Seze, J., 2021. Impact of disease-modifying treatments of multiple sclerosis on anti-SARS-CoV-2 antibodies: an observational study. Neurol. Neuroimmunol. Neuroinflamm. 8, e1055.

Bock, S., Pfalzgraff, A., Weindl, G., 2016. Sphingosine 1-phospate differentially modulates maturation and function of human Langerhans-like cells. J. Dermatol. Sci. 82, 9–17.

Bolli, M.H., Abele, S., Binkert, C., Bravo, R., Buchmann, S., Bur, D., Gatfield, J., Hess, P., Kohl, C., Mangold, C., Mathys, B., Menyhart, K., Müller, C., Nayler, O., Scherz, M., Schmidt, G., Sippel, V., Steiner, B., Strasser, D., Treiber, A., Weller, T., 2010. 2-imino-thiazolidin-4-one derivatives as potent, orally active S1P1 receptor agonists. J. Med. Chem. 53, 4198–4211.

Boulton, C., Meiser, K., David, O.J., Schmouder, R., 2012. Pharmacodynamic effects of steady-state fingolimod on antibody response in healthy volunteers: a 4-week, randomized, placebo-controlled, parallel-group, multiple-dose study. J. Clin. Pharmacol. 52, 1879–1890.

Brinkmann, V., Davis, M.D., Heise, C.E., Albert, R., Cottens, S., Hof, R., Bruns, C., Prieschl, E., Baumruker, T., Hiestand, P., Foster, C.A., Zollinger, M., Lynch, K.R., 2002. The immune modulator FTY720 targets sphingosine 1-phosphate receptors. J. Biol. Chem. 277, 21453–21457.

Brossard, P., Derendorf, H., Xu, J., Maatouk, H., Halabi, A., Dingemanse, J., 2013. Pharmacokinetics and pharmacodynamics of ponesimod, a selective S1P1 receptor modulator, in the first-in-human study. Br. J. Clin. Pharmacol. 76, 888–896.

Bsteh, G., Dürauer, S., Assar, H., Hegen, H., Heschl, B., Leutmezer, F., Pauli, F.D., Gradl, C., Traxler, G., Zulehner, G., Rommer, P., Wipfler, P., Guger, M., Höftberger, R., Enzinger, C., Berger, T., 2021. Humoral immune response after COVID-19 in multiple sclerosis: a nation-wide Austrian study. Mult. Scler. 27, 2209–2218.

Bsteh, G., Gradl, C., Heschl, B., Hegen, H., F, Di Pauli, Assar, H., Leutmezer, F., Traxler, G., Krajnc, N., Zulehner, G., Hiller, M.S., Rommer, P., Wipfler, P., Guger, M., Enzinger, C., Berger, T., investigators, AUT-MuSC, 2022. Impact of vaccination on COVID-19 outcome in multiple sclerosis. Eur. J. Neurol. https://doi.org/10.1111/ene.15488.

Capuano, R., Altieri, M., Conte, M., Bisecco, A., d'Ambrosio, A., Donnarumma, G., Grimaldi, E., Coppola, N., Medici, N., Galdiero, M., Tedeschi, G., Gallo, A., 2022. Humoral response and safety of the third booster dose of BNT162b2 mRNA COVID-19 vaccine in patients with multiple sclerosis treated with ocrelizumab or fingolimod. J. Neurol. https://doi.org/10.1007/s00415-022-11296-4.

Cattoretti, G., Mandelbaum, J., Lee, N., Chaves, A.H., Mahler, A.M., Chadburn, A., et al., 2009. Targeted disruption of the S1P 2 sphingosine 1-phosphate receptor gene leads to diffuse large B-cell lymphoma formation. Cancer Res. 69, 886–8692.

Chen, Z., Zhang, Y., Wang, M., Islam, M.S., Liao, P., Hu, Y., Chen, X., 2022. Humoral and cellular immune responses of COVID-19 vaccines against SARS-CoV-2 omicron variant: a systemic review. Int. J. Biol. Sci. 18, 4629–4641.

Cheng, S.M.S., Mok, C.K.P., Leung, Y.W.Y., Ng, S.S., Chan, K.C.K., Ko, F.W., Chen, C., Yiu, K., Lam, B.H.S., Lau, E.H.Y., Chan, K.K.P., Luk, L.L.H., Li, J.K.C., Tsang, L.C.H., Poon, L.L.M., Hui, D.S.C., Peiris, M., 2022. Neutralizing antibodies against the SARS-CoV-2 Omicron variant BA.1 following homologous and heterologous CoronaVac or BNT162b2 vaccination. Nat. Med. 28, 486–489.

Cho, A., Muecksch, F., Schaefer-Babajew, D., Wang, Z., Finkin, S., Gaebler, C., Ramos, V., Cipolla, M., Mendoza, P., Agudelo, M., Bednarski, E., DaSilva, J., Shimeliovich, I., Dizon, J., Daga, M., Millard, K.G., Turroja, M., Schmidt, F., Zhang, F., Tanfous, T.B., Jankovic, M., Oliveria, T.Y., Gazumyan, A., Caskey, M., Bieniasz, P.D., Hatziioannou, T., Nussenzweig, M.C., 2021. Anti-SARS-CoV-2 receptor-binding domain antibody evolution after mRNA vaccination. Nature 600, 517–522.

Choi, J.W., Gardell, S.E., Herr, D.R., Rivera, R., Lee, C.W., Noguchi, K., Teo, S.T., Yung, Y.C., Lu, M., Kennedy, G., Chun, J., 2011. FTY720 (fingolimod) efficacy in an animal model of multiple sclerosis requires astrocyte sphingosine 1-phosphate receptor 1 (S1P1) modulation. Proc. Natl. Acad. Sci. USA. 108, 751–756.

Cinamon, G., Zachariah, M.A., Lam, O.M., Foss Jr, F.W., Cyster, J.G., 2008. Follicular shuttling of marginal zone B cells facilitates antigen transport. Nat. Immunol. 9, 54–62.

Cohan, S.L., Baumjohann, D., Fazilleau, N., 2021. Antigen-dependent multistep differentiation of T follicular helper cells and its role in SARS-CoV-2 infection and vaccination. Eur. J. Immunol. 51, 1325–1333166.

Cree B.A., Selmaj K.W., Steinman L., Comi G., Bar-Or A., Arnold D.L., Hartung H.P., Montal X., Havrdova E.K., Desai H., Sheffield J.K., Minton N., Cheng C.Y., Silva D., Kappos L., Cohen J.A. COVID-19 infections and vaccinations among patients receiving ozanimod in the daybreak open-label extension study P387. Mult. Scler. 2022*, 28 (3S):401–402.

Cree, B.A.C., Maddux, R., Bar-Or, A., Hartung, H.P., Kaur, A., Brown, E., Hu, S., Sheffield, J.K., Silva, D., Harris, S., 2022b. Serologic response and clinical outcomes of sars-cov-2 infection and vaccination in ozanimod-treated participants with relapsing multiple sclerosis. P1199 Mult. Scler. 28 (3S), 973–974. *.

Cyster, J.G., Schwab, S.R., 2012. Sphingosine-1-phosphate and lymphocyte egress from lymphoid organs. Annu. Rev. Immunol. 30, 69–94.

Czarnowska, A., Brola, W., Zajkowska, O., Rusek, S., Adamczyk-Sowa, M., Kubicka-Bączyk, K., Kalinowska-Łyszczarz, A., Kania, K., Słowik, A., Wnuk, M., Marona, M., Podlecka-Piętowska, A., Nojszewska, M., Zakrzewska-Pniewska, B., Jasińska, E., Gołuch, K., Lech, B., Noga, M., Perenc, A., Popiel, M., Lasek-Bal, A., Puz, P., Maciejowska, K., Kucharska-Lipowska, M., Lipowski, M., Kapica-Topczewska, K., Chorąży, M., Tarasiuk, J., Kochanowicz, J., Kulikowska, J., Wawrzyniak, S., Niezgodzińska-Maciejek, A., Pokryszko-Dragan, A., Gruszka, E., Budrewicz, S., Białek, M., Kurkowska-Jastrzębska, I., Kurowska, K., Stępień, A., Włodek, A., Ptasznik, V., Pawełczyk, M., Sobolewski, P., Lejmel, H., Strzalińska, K., Maciejowski, M., Tutaj, A., Zwiernik, J., Litwin, A., Lewańczyk, B., Paprocka, I., Zwiernik, B., Pawlos, A., Borysowicz, A., Narożnik, A., Michałowska, A., Nosek, K., Fudala, M., Milewska-Jędrzejczak, M., Kułakowska, A., Bartosik-Psujek, H., 2021. Clinical course and outcome of SARS-CoV-2 infection in multiple sclerosis patients treated with disease-modifying therapies - the Polish experience. Neurol. Neurochir. Pol. 55, 212–222.

Deb, S., Reeves, A.A, 2021. Simulation of remdesivir pharmacokinetics and its drug interactions. J. Pharm. Pharm. Sci. 24, 277–291.

Di Vito, C., Calcaterra, F., Coianiz, N., Terzoli, S., Voza, A., Mikulak, J., Della Bella, S., Mavilio, D., 2022. Natural killer cells in SARS-CoV-2 infection: pathophysiology and therapeutic implications. Front. Immunol. 13, 888248.

Dillmann, C., Mora, J., Olesch, C., Brüne, B., Weigert, A., 2015. S1PR4 is required for plasmacytoid dendritic cell differentiation. Biol. Chem. 396, 775–782.

Dobson, R., Giovannoni, G., 2019. Multiple sclerosis - a review. Eur. J. Neurol. 26, 27–40.

Donovan, E.E., Pelanda, R., Torres, R.M., 2010. S1P3 confers differential S1P-induced migration by autoreactive and non-autoreactive immature B cells and is required for normal B-cell development. Eur. J. Immunol. 40, 688.

Drouillard, A., Mathieu, A.L., Marçais, A., Belot, A., Viel, S., Mingueneau, M., Guckian, K., Walzer, T., 2018. S1PR5 is essential for human natural killer cell migration toward sphingosine-1 phosphate. J. Allergy Clin. Immunol. 141, 2265–2268 e1.

Farrokhi, M., Beni, A.A., Etemadifar, M., Rezaei, A., Rivard, L., Zadeh, A.R., Sedaghat, N., Ghadimi, M., 2015. Effect of fingolimod on platelet count among multiple sclerosis patients. Int. J. Prev. Med. 6, 125.

Focosi, D., McConnell, S., Casadevall, A., Cappello, E., Valdiserra, G., Tuccori, M., 2022. Monoclonal antibody therapies against SARS-CoV-2. Lancet Infect. Dis. S1473-3099(22)00311-5.

Fraley, E., LeMaster, C., Banerjee, D., Khanal, S., Selvarangan, R., Bradley, T., 2021. Cross-reactive antibody immunity against SARS-CoV-2 in children and adults. Cell Mol. Immunol. 18, 1826–1828.

Gardin, A., Ufer, M., Legangneux, E., Rossato, G., Jin, Y., Su, Z., Pal, P., Li, W., Shakeri-Nejad, K, 2019. Effect of fluconazole coadministration and CYP2C9 genetic polymorphism on siponimod pharmacokinetics in healthy subjects. Clin. Pharmacokinet. 58, 349–361.

Garjani, A., Patel, S., Bharkhada, D., Rashid, W., Coles, A., Law, G.R., Evangelou, N., 2022. Impact of mass vaccination on SARS-CoV-2 infections among multiple sclerosis patients taking immunomodulatory disease-modifying therapies in England. Mult. Scler. Relat. Disord. 57, 103458.

Gazit, S., Shlezinger, R., Perez, G., Lotan, R., Peretz, A., Ben-Tov, A., Herzel, E., Alapi, H., Cohen, D., Muhsen, K., Chodick, G., Patalon, T., 2022. SARS-CoV-2 naturally acquired immunity vs. vaccine-induced immunity, reinfections versus breakthrough infections: a retrospective cohort Study. Clin. Infect. Dis. ciac262.

Geginat, J., Lanzavecchia, A., Sallusto, F., 2003. Proliferation and differentiation potential of human CD8+ memory T-cell subsets in response to antigen or homeostatic cytokines. Blood 101, 4260–4266.
Gergely, P., Nuesslein-Hildesheim, B., Guerini, D., Brinkmann, V., Traebert, M., Bruns, C., Pan, S., Gray, N.S., Hinterding, K., Cooke, N.G., Groenewegen, A., Vitaliti, A., Sing, T., Luttringer, O., Yang, J., Gardin, A., Wang, N., Crumb Jr, W.J., Saltzman, M., Rosenberg, M., Wallström, E., 2012. The selective sphingosine 1-phosphate receptor modulator BAF312 redirects lymphocyte distribution and has species-specific effects on heart rate. Br. J. Pharmacol. 167, 1035–1047.
Giovannoni, G., 2022. How important are COVID-19 vaccine responses in patients with MS on disease-modifying therapies? Mult. Scler. Relat. Disord. 63, 103803183.
Girkontaite, I., Sakk, V., Wagner, M., Borggrefe, T., Tedford, K., Chun, J., Fischer, K.D., 2004. The sphingosine-1-phosphate (S1P) lysophospholipid receptor S1P3 regulates MAdCAM-1+ endothelial cells in splenic marginal sinus organization. J. Exp. Med. 200, 1491–1501.
Golfier, S., Kondo, S., Schulze, T., Takeuchi, T., Vassileva, G., Achtman, A.H., Gräler, M. H., Abbondanzo, S.J., Wiekowski, M., Kremmer, E., Endo, Y., Lira, S.A., Bacon, K.B., Lipp, M., 2010. Shaping of terminal megakaryocyte differentiation and proplatelet development by sphingosine-1-phosphate receptor S1P4. FASEB J. 24, 4701–4710.
Gombolay, G.Y., Dutt, M., Tyor, W., 2022. Immune responses to SARS-CoV-2 vaccination in multiple sclerosis: a systematic review/meta-analysis. Ann. Clin. Transl. Neurol. 8, 1321–1331.
Grassi, S., Mauri, L., Prioni, S., Cabitta, L., Sonnino, S., Prinetti, A., Giussani, P., 2019. Sphingosine 1-phosphate receptors and metabolic enzymes as druggable targets for brain diseases. Front. Pharmacol. 10, 807.
Green, J.A., Cyster, J.G., 2012. S1PR2 links germinal center confinement and growth regulation. Immunol. Rev. 247, 36–51.
Green, J.A., Suzuki, K., Cho, B., Willison, L.D., Palmer, D., Allen, C.D., Schmidt, T.H., Xu, Y., Proia, R.L., Coughlin, S.R., Cyster, J.G., 2011. The sphingosine 1-phosphate receptor $S1P_2$ maintains the homeostasis of germinal center B cells and promotes niche confinement. Nat. Immunol. 12, 672–680.
Harris, S., Tran, J.Q., Southworth, H., Spencer, C.M., Cree, B.A.C., Zamvil, S.S., 2020. Effect of the sphingosine-1-phosphate receptor modulator ozanimod on leukocyte subtypes in relapsing MS. Neurol. Neuroimmunol. Neuroinflamm. 7, e839.
Heskin, J., Pallett, S.J.C., Mughal, N., Davies, G.W., Moore, L.S.P., Rayment, M., Jones, R., 2022. Caution required with use of ritonavir-boosted PF-07321332 in COVID-19 management. Lancet 399, 21–22.
Hirai, T., Mizuta, A., Sasaki, T., Nishikawa, K., Inoue, T., Iwamoto, T., 2022. Drug-drug interaction between remdesivir and immunosuppressant agents in a kidney transplant recipient. Int. J. Clin. Pharmacol. Ther. doi: 10.5414/CP204239.
Hjorth, M., Dandu, N., Mellergård, J., 2020. Treatment effects of fingolimod in multiple sclerosis: selective changes in peripheral blood lymphocyte subsets. PLoS One 15, e0228380.
Huth, F., Gardin, A., Umehara, K., He, H., 2019. Prediction of the impact of cytochrome P450 2C9 genotypes on the drug-drug interaction potential of siponimod with physiologically-based pharmacokinetic modeling: a comprehensive approach for drug label recommendations. Clin. Pharmacol. Ther. 106, 1113–1124.
Ise, W., Fujii, K., Shiroguchi, K., Ito, A., Kometani, K., Takeda, K., Kawakami, E., Yamashita, K., Suzuki, K., Okada, T., Kurosaki, T., 2018. T Follicular Helper Cell-Germinal Center B cell interaction strength regulates entry into plasma cell or recycling germinal center cell fate. Immunity 48, 702–715 e4.
Jayk Bernal, A., Gomes da Silva, M.M., Musungaie, D.B., Kovalchuk, E., Gonzalez, A., Delos Reyes, V., Martín-Quirós, A., Caraco, Y., Williams-Diaz, A., Brown, M.L., Du, J., Pedley, A., Assaid, C., Strizki, J., Grobler, J.A., Shamsuddin, H.H., Tipping, R., Wan, H., Paschke, A., Butterton, J.R., Johnson, M.G., De Anda, C., MOVe-OUT Study Group, 2022. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. N. Engl. J. Med. 386, 509–520.
Jego, G., Palucka, A.K., Blanck, J.P., Chalouni, C., Pascual, V., Banchereau, J., 2003. Plasmacytoid dendritic cells induce plasma cell differentiation through type I interferon and interleukin 6. Immunity 19, 225–234.
Jin, Y., Zollinger, M., Borell, H., Zimmerlin, A., Patten, C.J., 2011. CYP4F enzymes are responsible for the elimination of fingolimod (FTY720), a novel treatment of relapsing multiple sclerosis. Drug Metab. Dispos. 39, 191–198.
Johansson, D., Rauld, C., Roux, J., Regairaz, C., Galli, E., Callegari, I., Raad, L., Waldt, A., Cuttat, R., Roma, G., Diebold, M., Becher, B., Kuhle, J., Derfuss, T., Carballido, J.M., Sanderson, N.S.R., 2021. Mass cytometry of CSF identifies an MS-associated B-cell population. Neurol. Neuroimmunol. Neuroinflamm. 8, e943.
Johnson, T.A., Lapierre, Y., Bar-Or, A., Antel, J.P., 2010. Distinct properties of circulating CD8+ T cells in FTY720-treated patients with multiple sclerosis. Arch. Neurol. 67, 1449–1455.
Jurcevic, S., Juif, P.E., Hamid, C., Greenlaw, R., D'Ambrosio, D., Dingemanse, J, 2016. Effects of multiple-dose ponesimod, a selective S1P1 receptor modulator, on lymphocyte subsets in healthy humans. Drug Des. Devel. Ther. 11, 123–131.
König, M., Torgauten, H.M., Tran, T.T., Holmøy, T., Vaage, J.T., Lund-Johansen, F., Nygaard, G.O., 2022. Immunogenicity and Safety of a Third SARS-CoV-2 Vaccine Dose in Patients With Multiple Sclerosis and Weak Immune Response After COVID-19 Vaccination. JAMA Neurol. 79, 307–309.
Kantor, D., 2022. SARS-CoV-2 vaccine response in RMS patients treated with ozanimod and other DMTs P13-4.008. Neurology 98 (18 Suppl), 3849. *.
Kappos, L., Mehling, M., Arroyo, R., Izquierdo, G., Selmaj, K., Curovic-Perisic, V., Keil, A., Bijarnia, M., Singh, A., von Rosenstiel, P, 2015. Randomized trial of vaccination in fingolimod-treated patients with multiple sclerosis. Neurology 84, 872–879.
Kassambara, A., Rème, T., Jourdan, M., Fest, T., Hose, D., Tarte, K., Klein, B, 2015. GenomicScape: an easy-to-use web tool for gene expression data analysis. Application to investigate the molecular events in the differentiation of B cells into plasma cells. PLoS Comput. Biol. 11, e1004077.
Kemmerer, C.L., Pernpeintner, V., Ruschil, C., Abdelhak, A., Scholl, M., Ziemann, U., Krumbholz, M., Hemmer, B., Kowarik, M.C., 2020. Differential effects of disease modifying drugs on peripheral blood B cell subsets: a cross sectional study in multiple sclerosis patients treated with interferon-β, glatiramer acetate, dimethyl fumarate, fingolimod or natalizumab. PLoS One 15, e0235449.
Keul, P., Lucke, S., von Wnuck Lipinski, K., Bode, C., Gräler, M., Heusch, G., Levkau, B., 2011. Sphingosine-1-phosphate receptor 3 promotes recruitment of monocyte/macrophages in inflammation and atherosclerosis. Circ. Res. 108, 314–323.
Kharel, Y., Lee, S., Snyder, A.H., Sheasley-O'neill, S.L., Morris, M.A., Setiady, Y., Zhu, R., Zigler, M.A., Burcin, T.L., Ley, K., Tung, K.S., Engelhard, V.H., Macdonald, T.L., Pearson-White, S., Lynch, K.R, 2005. Sphingosine kinase 2 is required for modulation of lymphocyte traffic by FTY720. J. Biol. Chem. 280, 36865–36872.
Khoo, S.H., FitzGerald, R., Saunders, G., Middleton, C., Ahmed, S., Edwards, C.J., Hasdjiyiannaskis, D., Walker, L., Rebecca Lyon, R., Shaw, V., Mozgunov, P., Periselneris, J., Woods, C., Bullock, K., Hale, C., Reynolds, H., Downs, N., Ewings, S., Buadi, A., Cameron, D., Edwards, T., Knox, E., Donovan-Banfield, I., Greenhalf, W., Chiong, J., Lavelle-Langham, L., Jacobs, M., Painter, W., Holman, W., Lalloo, D.G., Tetlow, M., Hiscox, J.A., Jaki, T., Fletcher, T., Griffiths, G., AGILE CST-2 Study Group, 2022. A randomised -controlled phase 2 trial of molnupiravir in unvaccinated and vaccinated individuals with early SARS-CoV-2. MedRxiv. https://doi.org/10.1101/2022.07.20.22277797. *.
Khoury, D.S., Cromer, D., Reynaldi, A., Schlub, T.E., Wheatley, A.K., Juno, J.A., Subbarao, K., Kent, S.J., Triccas, J.A., Davenport, M.P., 2021. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat. Med. 27, 1205–1211.
Kim, W., Zhou, J.Q., Horvath, S.C., Schmitz, A.J., Sturtz, A.J., Lei, T., Liu, Z., Kalaidina, E., Thapa, M., Alsoussi, W.B., Haile, A., Klebert, M.K., Suessen, T., Parra-Rodriguez, L., Mudd, P.A., Whelan, S.P.J., Middleton, W.D., Teefey, S.A., Pusic, I., O'Halloran, J.A., Presti, R.M., Turner, J.S., Ellebedy, A.H, 2022. Germinal centre-driven maturation of B cell response to mRNA vaccination. Nature 604, 141–145.
Klompus, S., Leviatan, S., Vogl, T., Mazor, R.D., Kalka, I.N., Stoler-Barak, L., Nathan, N., Peres, A., Moss, L., Godneva, A., Kagan Ben Tikva, S., Shinar, E., Dvashi, H.C., Gabizon, R., London, N., Diskin, R., Yaari, G., Weinberger, A., Shulman, Z., Segal, E, 2021. Cross-reactive antibodies against human coronaviruses and the animal coronavirome suggest diagnostics for future zoonotic spillovers. Sci. Immunol. 6, eabe9950.
Kowarik, M.C., Astling, D., Lepennetier, G., Ritchie, A., Hemmer, B., Owens, G.P., Bennett, J.L., 2021. Differential effects of Fingolimod and natalizumab on B cell repertoires in multiple sclerosis patients. Neurotherapeutics 18, 364–377.
Krbot Skorić, M., Rogić, D., Lapić, I., Šegulja, D., Habek, M, 2022. Humoral immune response to COVID-19 vaccines in people with secondary progressive multiple sclerosis treated with siponimod. Mult. Scler. Relat. Disord. 57, 103435.
Lamb, Y.N., 2020. Ozanimod: first Approval. Drugs 80, 841–848.
Le Bon, A., Schiavoni, G., D'Agostino, G., Gresser, I., Belardelli, F., Tough, D.F, 2001. Type interferons potently enhance humoral immunity and can promote isotype switching by stimulating dendritic cells in vivo. Immunity 14, 461–470.
Liu, H., Sugiura, M., Nava, V.E., Edsall, L.C., Kono, K., Poulton, S., et al., 2000. Molecular cloning and functional characterization of a novel mammalian sphingosine kinase type 2 isoform. J. Biol. Chem. 275, 19513–19520.
Lohmann, L., Janoschka, C., Schulte-Mecklenbeck, A., Klinsing, S., Kirstein, L., Hanning, U., Wirth, T., Schneider-Hohendorf, T., Schwab, N., Gross, C.C., Eveslage, M., Meuth, S.G., Wiendl, H., Klotz, L., 2018. Immune cell profiling during switching from natalizumab to fingolimod reveals differential effects on systemic immune-regulatory networks and on trafficking of non-t cell populations into the cerebrospinal fluid-results from the ToFingo Successor Study. Front. Immunol. 9, 1560.
Looi, M.K., 2022 Sep 15. Is covid-19 settling into a pattern? BMJ 378, o2183.
Louapre, C., Ibrahim, M., Maillart, E., Abdi, B., Papeix, C., Stankoff, B., Dubessy, A.L., Bensa-Koscher, C., Créange, A., Chamekh, Z., Lubetzki, C., Marcelin, A.G., Corvol, J. C., Pourcher, V., COVISEP and Bio-coco-neuroscience study group, 2022. Anti-CD20 therapies decrease humoral immune response to SARS-CoV-2 in patients with multiple sclerosis or neuromyelitis optica spectrum disorders. J. Neurol. Neurosurg. Psychiatry. 93, 24–31.
Lu, E., Cyster, J.G., 2019. G-protein coupled receptors and ligands that organize humoral immune responses. Immunol. Rev. 289, 158–172.
Lublin, F.D., Reingold, S.C., Cohen, J.A., Cutter, G.R., Sørensen, P.S., Thompson, A.J., Wolinsky, J.S., Balcer, L.J., Banwell, B., Barkhof, F., Bebo Jr, B., Calabresi, P.A., Clanet, M., Comi, G., Fox, R.J., Freedman, M.S., Goodman, A.D., Inglese, M., Kappos, L., Kieseier, B.C., Lincoln, J.A., Lubetzki, C., Miller, A.E., Montalban, X., O'Connor, P.W., Petkau, J., Pozzilli, C., Rudick, R.A., Sormani, M.P., Stüve, O., Waubant, E., Polman, C.H, 2014. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 83, 278–286.
Lublin, F., Ait-Tihyaty, M., Keenan, A., Gandhi, K., Turkoz, I., Sidorenko, T., Wong, J., Kappos, L., 2022. Disease activity after short-term interruption of ponesimod versus teriflunomide in relapsing multiple sclerosis patients. P386. Mult. Scler. 28 (S3), 400. *.
Madelon, N., Lauper, K., Breville, G., Sabater Royo, I., Goldstein, R., DO, Andrey, Grifoni, A., Sette, A., Kaiser, L., Siegrist, C.A., Finckh, A., Lalive, P.H., Didierlaurent, A.M., Eberhardt, C.S., 2021. Robust T cell responses in anti-CD20 treated patients following COVID-19 vaccination: a prospective cohort study. Clin. Infect. Dis. ciab954.
Maeda, Y., Matsuyuki, H., Shimano, K., Kataoka, H., Sugahara, K., Chiba, K., 2007. Migration of CD4 T cells and dendritic cells toward sphingosine 1-phosphate (S1P) is

mediated by different receptor subtypes: S1P regulates the functions of murine mature dendritic cells via S1P receptor type 3. J. Immunol. 178, 3437–3446.
Magnè, F., Cellerino, M., Balletto, E., Aluan, K., Inglese, M., Mikulska, M., Bassetti, M., 2022. Anti-SARS-CoV-2 monoclonal antibodies for the treatment of active COVID-19 in multiple sclerosis: an observational study. Mult. Scler., 13524585221103787
Mandala, S., Hajdu, R., Bergstrom, J., Quackenbush, E., Xie, J., Milligan, J., Thornton, R., Shei, G.J., Card, D., Keohane, C., Rosenbach, M., Hale, J., Lynch, C.L., Rupprecht, K., Parsons, W., Rosen, H., 2002. Alteration of lymphocyte trafficking by sphingosine-1-phosphate receptor agonists. Science 296, 346–349.
Mao-Draayer, Y., Wu, Q., Wang, Q., Dowling, C., Lundy, S., Fox, D., 2017. Basic immunological profile changes of secondary progressive multiple sclerosis patients treated with BAF312 (Siponimod). J. Neurol. Sci. 381 (suppl), 783.
Markham, A., 2021. Ponesimod: first approval. Drugs 81, 957–962.
Matloubian, M., Lo, C.G., Cinamon, G., Lesneski, M.J., Xu, Y., Brinkmann, V., Allende, M. L., Proia, R.L., Cyster, J.G., 2004. Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. Nature 427, 355–360.
Mehling, M., Brinkmann, V., Antel, J., Bar-Or, A., Goebels, N., Vedrine, C., Kristofic, C., Kuhle, J., Lindberg, R.L., Kappos, L., 2008. FTY720 therapy exerts differential effects on T cell subsets in multiple sclerosis. Neurology 71, 1261–1267.
Mehling, M., Burgener, A.V., Brinkmann, V., Bantug, G.R., Dimeloe, S., Hoenger, G., Kappos, L., Hess, C., 2015. Tissue distribution dynamics of human NK cells inferred from peripheral blood depletion kinetics after Sphingosine-1-phosphate receptor blockade. Scand. J. Immunol. 82, 460–466.
Meyer-Arndt, L., Braun, J., Fauchere, F., Vanshylla, K., Loyal, L., Henze, L., Kruse, B., Dingeldey, M., Jürchott, K., Mangold, M., Maraj, A., Braginets, A., Böttcher, C., Nitsche, A., de la Rosa, K., Ratswohl, C., Sawitzki, B., Holenya, P., Reimer, U., Sander, L.E., Klein, F., Paul, F., Bellmann-Strobl, J., Thiel, A., Giesecke-Thiel, C., 2022. SARS-CoV-2 mRNA vaccinations fail to elicit humoral and cellular immune responses in patients with multiple sclerosis receiving fingolimod. J. Neurol. Neurosurg. Psychiatry 93, 960–971.
Michel, T., Poli, A., Cuapio, A., Briquemont, B., Iserentant, G., Ollert, M., Zimmer, J., 2016. Human CD56bright NK cells: an update. J. Immunol. 196, 2923–2931.
Middle, S., Coupland, S.E., Taktak, A., Kidgell, V., Slupsky, J.R., Pettitt, A.R., Till, K.J., 2015. Immunohistochemical analysis indicates that the anatomical location of B-cell non-Hodgkin's lymphoma is determined by differentially expressed chemokine receptors, sphingosine-1-phosphate receptors and integrins. Exp. Hematol. Oncol. 4, 10.
Milo, R., Staun-Ram, E., Karussis, D., Karni, A., Hellmann, M.A., Bar-Haim, E., Miller, A., Israeli Neuroimmunology study group on COVID-19 vaccination in multiple sclerosis, 2022. Humoral and cellular immune responses to SARS-CoV-2 mRNA vaccination in patients with multiple sclerosis: an Israeli multi-center experience following 3 vaccine doses. Front. Immunol. 13, 86891.
Mohammed, S., Vineetha, N.S., James, S., Aparna, J.S., Lankadasari, M.B., Allegood, J.C., Li, Q.Z., Spiegel, S., Harikumar, K.B., 2019. Examination of the role of sphingosine kinase 2 in a murine model of systemic lupus erythematosus. FASEB J. 33, 7061–7071.
Moore, T., Hossain, R., Doores, K.J., Shankar-Hari, M., Fear, D.J., 2022. SARS-CoV-2-specific memory B cell responses are maintained after recovery from natural infection and postvaccination. Viral Immunol. 35, 425–436.
Moriyama, S., Takahashi, N., Green, J.A., Hori, S., Kubo, M., Cyster, J.G., Okada, T., 2014. Sphingosine-1-phosphate receptor 2 is critical for follicular helper T cell retention in germinal centers. J. Exp. Med. 211, 1297–1305.
Mosheimer, B., Mayer, G., Konwalinka, G., Heufler, C., Tiefenthaler, M., 2005. The immunomodulator FTY720 interferes with effector functions of human monocyte-derived dendritic cells. Eur. J. Immunol. 35, 533–545.
Mullen, K.M., Gocke, A.R., Allie, R., Ntranos, A., Grishkan, I.V., Pardo, C., Calabresi, P.A, 2012. Expression of CCR7 and CD45RA in CD4+ and CD8+ subsets in cerebrospinal fluid of 134 patients with inflammatory and non-inflammatory neurological diseases. J. Neuroimmunol. 249, 86–92.
Muppidi, J.R., Lu, E., Cyster, J.G., 2015. The G protein-coupled receptor P2RY8 and follicular dendritic cells promote germinal center confinement of B cells, whereas S1PR3 can contribute to their dissemination. J. Exp. Med. 212, 2213–2222.
Nussbaum, C., Bannenberg, S., Keul, P., Gräler, M.H., Gonçalves-de-Albuquerque, C.F., Korhonen, H., von Wnuck Lipinski, K., Heusch, G., de Castro Faria Neto, H.C., Rohwedder, I., Göthert, J.R., Prasad, V.P., Haufe, G., Lange-Sperandio, B., Offermanns, S., Sperandio, M., Levkau, B, 2015. Sphingosine-1-phosphate receptor 3 promotes leukocyte rolling by mobilizing endothelial P-selectin. Nat. Commun. 6, 6416.
Ogle, M.E., Olingy, C.E., Awojoodu, A.O., Das, A., Ortiz, R.A., Cheung, H.Y., Botchwey, E.A., 2017. Sphingosine-1-phosphate receptor-3 supports hematopoietic stem and progenitor cell residence within the bone marrow niche. Stem Cell. 35, 1040–1052.
Ohashi, H., Hishiki, T., Akazawa, D., Kim, K.S., Woo, J., Shionoya, K., Tsuchimoto, K., Iwanami, S., Moriyama, S., Kinoshita, H., Yamada, S., Kuroda, Y., Yamamoto, T., Kishida, N., Watanabe, S., Hasegawa, H., Ebihara, H., Suzuki, T., Maeda, K., Fukushi, S., Takahashi, Y., Iwami, S., Watashi, K, 2022. Different efficacies of neutralizing antibodies and antiviral drugs on SARS-CoV-2 Omicron subvariants, BA.1 and BA.2. Antiviral Res. 205, 105372.
Olesch, C., Ringel, C., Brüne, B., Weigert, A., 2017. Beyond immune cell migration: the emerging role of the sphingosine-1-phosphate receptor s1pr4 as a modulator of innate immune cell activation. Mediators Inflamm. 2017, 6059203.
Olesch, C., Sirait-Fischer, E., Berkefeld, M., Fink, A.F., Susen, R.M., Ritter, B., Michels, B. E., Steinhilber, D., Greten, F.R., Savai, R., Takeda, K., Brüne, B., Weigert, A., 2020. S1PR4 ablation reduces tumor growth and improves chemotherapy via CD8+ T cell expansion. J. Clin. Invest. 130, 5461–5476.
Orrico, M., Nozzolillo, A., Gelibter, S., Sangalli, F., Preziosa, P., Filippi, M., Moiola, L., 2021. Atrioventricular block after fingolimod resumption: a consequence of sphingosine-1-phosphate axis alteration due to COVID-19? J. Neurol. 268, 3975–3979.
Painter, W.P., Holman, W., Bush, J.A., Almazedi, F., Malik, H., Eraut, N.C.J.E., Morin, M. J., Szewczyk, L.J., Painter, G.R., 2021. Human safety, tolerability, and pharmacokinetics of molnupiravir, a novel broad-spectrum oral antiviral agent with activity against SARS-CoV-2. Antimicrob. Agents Chemother. 65 e02428-20.
Park, S.M., Brooks, A.E., Chen, C.J., Sheppard, H.M., Loef, E.J., McIntosh, J.D., Angel, C. E., Mansell, C.J., Bartlett, A., Cebon, J., Birch, N.P., Dunbar, P.R., 2021. Migratory cues controlling B-lymphocyte trafficking in human lymph nodes. Immunol. Cell Biol. 99, 49–64.
Peng, P., Deng, H., Li, Z., Chen, Y., Fang, L., Hu, J., Wu, K., Xue, J., Wang, D., Liu, B., Long, Q., Chen, J., Wang, K., Tang, N., Huang, A.L., 2022. Distinct immune responses in the early phase to natural SARS-CoV-2 infection or vaccination. J. Med. Virol. https://doi.org/10.1002/jmv.28034.
Petersone, L., Edner, N.M., Ovcinnikovs, V., Heuts, F., Ross, E.M., Ntavli, E., Wang, C.J., Walker, L.S.K., 2018. T Cell/B cell collaboration and autoimmunity: an intimate relationship. Front. Immunol. 9, 1941.
Pitzalis, M., Idda, M.L., Lodde, V., Loizedda, A., Lobina, M., Zoledziewska, M., Virdis, F., Delogu, G., Pirinu, F., Marini, M.G., Mingoia, M., Frau, J., Lorefice, L., Fronza, M., Carmagnini, D., Carta, E., Orrù, V., Uzzau, S., Solla, P., Loi, F., Devoto, M., Steri, M., Fiorillo, E., Floris, M., Zarbo, I.R., Cocco, E., Cucca, F., 2021. Effect of different disease-modifying therapies on humoral response to BNT162b2 vaccine in sardinian multiple sclerosis patients. Front. Immunol. 12, 781843.
Planas, D., Saunders, N., Maes, P., Guivel-Benhassine, F., Planchais, C., Buchrieser, J., Bolland, W.H., Porrot, F., Staropoli, I., Lemoine, F., Péré, H., Veyer, D., Puech, J., Rodary, J., Baele, G., Dellicour, S., Raymenants, J., Gorissen, S., Geenen, C., Vanmechelen, B., Wawina-Bokalanga, T., Martí-Carreras, J., Cuypers, L., Sève, A., Hocqueloux, L., Prazuck, T., Rey, F.A., Simon-Loriere, E., Bruel, T., Mouquet, H., André, E., Schwartz, O., 2022. Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. Nature 602, 671–675.
Poeck, H., Wagner, M., Battiany, J., Rothenfusser, S., Wellisch, D., Hornung, V., Jahrsdorfer, B., Giese, T., Endres, S., Hartmann, G., 2004. Plasmacytoid dendritic cells, antigen, and CpG-C license human B cells for plasma cell differentiation and immunoglobulin production in the absence of T-cell help. Blood 103, 3058–3064.
Reder, A.T., Centonze, D., Naylor, M.L., Nagpal, A., Rajbhandari, R., Altincatal, A., Kim, M., Berdofe, A., Radhakrishnan, M., Jung, E., Sandrock, A.W., Smirnakis, K., Popescu, C., de Moor, C, 2021. COVID-19 in patients with multiple sclerosis: ssociations with disease-modifying therapies. CNS Drug. 35, 317–330.
Richards, F., Kodjamanova, P., Chen, X., Li, N., Atanasov, P., Bennetts, L., Patterson, B.J., Yektashenas, B., Mesa-Frias, M., Tronczynski, K., Buyukkaramikli, N., El Khoury, A. C., 2022. Economic burden of COVID-19: a systematic review. Clinicoecon. Outcome. Res. 14, 293–307.
Riese, J., Gromann, A., Lührs, F., Kleinwort, A., Schulze, T., 2021. Sphingosine-1-phosphate receptor type 4 (S1P4) is differentially regulated in peritoneal B1 B cells upon TLR4 stimulation and facilitates the egress of peritoneal B1a B cells and subsequent accumulation of splenic IRA B cells under inflammatory conditions. Int. J. Mol. Sci. 22, 3465.
Roggeri, A., Schepers, M., Tiane, A., Rombaut, B., van Veggel, L., Hellings, N., Prickaerts, J., Pittaluga, A., Vanmierlo, T., 2020. Sphingosine-1-phosphate receptor modulators and oligodendroglial cells: beyond immunomodulation. Int. J. Mol. Sci. 21, 7537.
Sallusto, F., Lenig, D., Förster, R., Lipp, M., Lanzavecchia, A., 1999. Two subsets of memory T ymphocytes with distinct homing potentials and effector functions. Nature 401, 708–712.
Sanna, M.G., Liao, J., Jo, E., Alfonso, C., Ahn, M.Y., Peterson, M.S., Webb, B., Lefebvre, S., Chun, J., Gray, N., Rosen, H, 2004. Sphingosine 1-phosphate (S1P) receptor subtypes S1P1 and S1P3, respectively, regulate lymphocyte recirculation and heart rate. J. Biol. Chem. 279, 13839–13848.
Satyanarayan, S., Safi, N., Sorets, T., Filomena, S., Zhang, Y., Klineova, S., Fabian, M., Horng, S., Tankou, S., Miller, A., Krieger, S., Lublin, F., Sumowski, J., Katz Sand, I., 2022. Mult. Scler. Relat. Disord. 62, 103737.
Scherer, E.M., Babiker, A., Adelman, M.W., Allman, B., Key, A., Kleinhenz, J.M., Langsjoen, R.M., Nguyen, P.V., Onyechi, I., Sherman, J.D., Simon, T.W., Soloff, H., Tarabay, J., Varkey, J., Webster, A.S., Weiskopf, D., Weissman, D.B., Xu, Y., Waggoner, J.J., Koelle, K., Rouphael, N., Pouch, S.M., Piantadosi, A., 2022. SARS-CoV-2 evolution and immune escape in immunocompromised patients. N. Engl. J. Med. 386, 2436–2438.
Schiavetti, I., Cordioli, C., Stromillo, M.L., Teresa Ferrò, M., Laroni, A., Cocco, E., Cola, G., Pasquali, L., Rilla, M.T., Signoriello, E., Iodice, R., Di Sapio, A., Lanzillo, R., Caleri, F., Annovazzi, P., Conte, A., Liberatore, G., Ruscica, F., Docimo, R., Bonavita, S., Ulivelli, M., Cavalla, P., Patti, F., Ferraro, D., Clerico, M., Immovilli, P., Di Filippo, M., Salvetti, M., Sormani, M.P, 2022. Breakthrough SARS-CoV-2 infections in MS patients on disease-modifying therapies. Mult. Scler. 23, 13524585221102918.
Schiavetti, L., Barcellini, C., Lapucci, F., Tazza, M., Cellerino, E., Capello, D., Franciotta, M., Inglese Sormani, M.P., Uccelli, A., Laroni, A, 2022b. CD19+ B cell numbers predict the increase of anti-SARS CoV2 antibodies in fingolimod-treated and COVID-19-vaccinated patients with multiple sclerosis. MedrXiv. https://doi.org/10.1101/2022.07.02.22277178. *.
Schnuelle, P., Kölling, S., Müller, A., Schmitt, W.H., 2021. Short-time interruption of second-line mycophenolate treatment in a patient with renal sarcoidosis enabled a marked antibody response to SARS-CoV-2 messenger RNA vaccine. Clin. Kidney J. 15, 584–586.

Schulze, T., Golfier, S., Tabeling, C., Räbel, K., Gräler, M.H., Witzenrath, M., Lipp, M., 2011. Sphingosine-1-phospate receptor 4 (S1P$_4$) deficiency profoundly affects dendritic cell function and TH17-cell differentiation in a murine model. FASEB J. 25, 4024–4036.

Schwiebs, A., Friesen, O., Katzy, E., Ferreirós, N., Pfeilschifter, J.M., Radeke, H.H., 2016. Activation-induced cell death of dendritic cells is dependent on Sphingosine Kinase 1. Front. Pharmacol. 7, 94.

Scott, F.L., Clemons, B., Brooks, J., Brahmachary, E., Powell, R., Dedman, H., Desale, H. G., Timony, G.A., Martinborough, E., Rosen, H., Roberts, E., Boehm, M.F., Peach, R. J., 2016. Ozanimod (RPC1063) is a potent sphingosine-1-phosphate receptor-1 (S1P1) and receptor-5 (S1P5) agonist with autoimmune disease-modifying activity. Br. J. Pharmacol. 173, 1778–1792.

Scott, L.J., 2011. Fingolimod: a review of its use in the management of relapsing-remitting multiple sclerosis. CNS Drugs 25, 673–698.

Sehr, T., Akgün, K., Haase, R., Ziemssen, T., 2020. Fingolimod leads to immediate immunological changes within 6 h after first administration. Front. Neurol. 11, 39.

Sendi, P., Razonable, R.R., Nelson, S.B., Soriano, A., Gandhi, R.T., 2022. First-generation oral antivirals against SARS-CoV-2. Clin. Microbiol. Infect. S1198-743X(22)00223-3.

Shrestha, L.B., Foster, C., Rawlinson, W., Tedla, N., Bull, R.A., 2022. Evolution of the SARS-CoV-2 omicron variants BA.1 to BA.5: implications for immune escape and transmission. Rev. Med. Virol. e2381.

Sic, H., Kraus, H., Madl, J., Flittner, K.A., von Münchow, A.L., Pieper, K., Rizzi, M., Kienzler, A.K., Ayata, K., Rauer, S., Kleuser, B., Salzer, U., Burger, M., Zirlik, K., Lougaris, V., Plebani, A., Römer, W., Loeffler, C., Scaramuzza, S., Villa, A., Noguchi, E., Grimbacher, B., Eibel, H., 2014. Sphingosine-1-phosphate receptors control B-cell migration through signaling components associated with primary immunodeficiencies, chronic lymphocytic leukemia, and multiple sclerosis. J. Allergy Clin. Immunol. 134, 420–428.

Siddiqui, G., Maloni, H., Nava, V.E., 2021. Adequate antibody response to BioNTech COVID vaccine in a multiple sclerosis patient treated with siponimod. Egypt J. Neurol. Psychiatr. Neurosurg. 57, 171.

Simpson-Yap, S., De Brouwer, E., Kalincik, T., Rijke, N., Hillert, J.A., Walton, C., Edan, G., Moreau, Y., Spelman, T., Geys, L., Parciak, T., Gautrais, C., Lazovski, N., Pirmani, A., Ardeshirdavanai, A., Forsberg, L., Glaser, A., McBurney, R., Schmidt, H., Bergmann, A.B., Braune, S., Stahmann, A., Middleton, R., Salter, A., Fox, R.J., van der Walt, A., Butzkueven, H., Alroughani, R., Ozakbas, S., Rojas, J.I., van der Mei, I., Nag, N., Ivanov, R., Sciascia do Olival, G., Dias, A.E., Magyari, M., Brum, D., Mendes, M.F., Alonso, R.N., Nicholas, R.S., Bauer, J., Chertcoff, A.S., Zabalza, A., Arrambide, G., Fidao, A., Comi, G., Peeters, L., 2021. Associations of disease-modifying therapies with COVID-19 severity in multiple sclerosis. Neurology 97, e1870–e1885.

Simpson-Yap, S., Pirmani, A., Kalincik, T., De Brouwer, E., Geys, L., Parciak, T., Helme, A., Rijke, N., Hillert, J.A., Moreau, Y., Edan, G., Sharmin, S., Spelman, T., McBurney, R., Schmidt, H., Bergmann, A.B., Braune, S., Stahmann, A., Middleton, R. M., Salter, A., Bebo, B., Van der Walt, A., Butzkueven, H., Ozakbas, S., Boz, C., Karabudak, R., Alroughani, R., Rojas, J.I., van der Mei, I.A., Sciascia do Olival, G., Magyari, M., Alonso, R.N., Nicholas, R.S., Chertcoff, A.S., de Torres, A.Z., Arrambide, G., Nag, N., Descamps, A., Costers, L., Dobson, R., Miller, A., Rodrigues, P., Prčkovska, V., Comi, G., Peeters, L.M, 2022. Updated results of the COVID-19 in MS Global Data Sharing Initiative: anti-CD20 and other risk factors associated with COVID-19 severity. Neurol. Neuroimmunol. Neuroinflamm. 29 (9), e200021048.

Song, Z.Y., Yamasaki, R., Kawano, Y., Sato, S., Masaki, K., Yoshimura, S., Matsuse, D., Murai, H., Matsushita, T., Kira, J., 2015. Peripheral blood T cell dynamics predict relapse in multiple sclerosis patients on fingolimod. PLoS One 10, e0124923.

Sormani, M.P., Salvetti, M., Labauge, P., Schiavetti, I., Zephir, H., Carmisciano, L., Bensa, C., De Rossi, N., Pelletier, J., Cordioli, C., Vukusic, S., Moiola, L., Kerschen, P., Radaelli, M., Théaudin, M., Immovilli, P., Casez, O., Capobianco, M., Ciron, J., Trojano, M., Stankoff, B., Créange, A., Tedeschi, G., Clavelou, P., Comi, G., Thouvenot, E., Battaglia, M.A., Moreau, T., Patti, F., De Sèze, J., Louapre, C., Musc-19, Covisep study groups, 2021. DMTs and Covid-19 severity in MS: a pooled analysis from Italy and France. Ann. Clin. Transl. Neurol. 8, 1738–1744.

Sormani, M.P., Inglese, M., Schiavetti, I., Carmisciano, L., Laroni, A., Lapucci, C., Da Rin, G., Serrati, C., Gandoglia, I., Tassinari, T., Perego, G., Brichetto, G., Gazzola, P., Mannironi, A., Stromillo, M.L., Cordioli, C., Landi, D., Clerico, M., Signoriello, E., Frau, J., Ferrò, M.T., Di Sapio, A., Pasquali, L., Ulivelli, M., Marinelli, F., Callari, G., Iodice, R., Liberatore, G., Caleri, F., Repice, A.M., Cordera, S., Battaglia, M.A., Salvetti, M., Franciotta, D., Uccelli, A., 2021b. CovaXiMS study group on behalf of the Italian Covid-19 Alliance in MS. Effect of SARS-CoV-2 mRNA vaccination in MS patients treated with disease modifying therapies. EBioMedicine 72, 103581.

Sormani, M.P., Schiavetti, I., Inglese, M., Carmisciano, L., Laroni, A., Lapucci, C., Visconti, V., Serrati, C., Gandoglia, I., Tassinari, T., Perego, G., Brichetto, G., Gazzola, P., Mannironi, A., Stromillo, M.L., Cordioli, C., Landi, D., Clerico, M., Signoriello, E., Cocco, E., Frau, J., Ferrò, M.T., Di Sapio, A., Pasquali, L., Ulivelli, M., Marinelli, F., Pizzorno, M., Callari, G., Iodice, R., Liberatore, G., Caleri, F., Repice, A. M., Cordera, S., Battaglia, M.A., Salvetti, M., Franciotta, D., Uccelli, A., CovaXiMS study group, 2022. Breakthrough SARS-CoV-2 infections after COVID-19 mRNA vaccination in MS patients on disease modifying therapies during the Delta and the Omicron waves in Italy. EBioMedicine 80, 104042.

Sormani, M.P., Schiavetti, I., Landi, D., Carmisciano, L., De Rossi, N., Cordioli, C., Moiola, L., Radaelli, M., Immovilli, P., Capobianco, M., V, Brescia Morra, Trojano, M., Tedeschi, G., Comi, G., Battaglia, M.A., Patti, F., Fragoso, Y.D., Sen, S., Siva, A., Furlan, R., Salvetti, M., MuSC-19 Study Group, 2022a. SARS-CoV-2 serology after COVID-19 in multiple sclerosis: an international cohort study. Mult. Scler. 28, 1034–1040.

Spampinato, S.F., Obermeier, B., Cotleur, A., Love, A., Takeshita, Y., Sano, Y., Kanda, T., Ransohoff, R.M., 2015. Sphingosine 1 phosphate at the blood brain barrier: can the modulation of S1P receptor 1 influence the response of endothelial cells and astrocytes to inflammatory stimuli? PLoS One 10, e0133392.

Spampinato, S.F., Merlo, S., Costantino, G., Sano, Y., Kanda, T., Sortino, M.A., 2021. Decreased astrocytic CCL2 accounts for BAF-312 effect on pbmcs transendothelial migration through a blood brain barrier in vitro model. J. Neuroimmune. Pharmacol. https://doi.org/10.1007/s11481-021-10016-5.

Spiller, K., Aras, R., DeGuzman, M., Ramsburg, E., Bhattacharya, A., 2021. A short pause in ponesimod treatment completely restores the ability to mount post-vaccination antibody titers in mice P646. Mult. Scler. 27 (2 Suppl), 557–558. *.

Sullivan, R., Kilaru, A., Hemmer, B., Cree, B.A.C., Greenberg, B.M., Kundu, U., Hach, T., DeLasHeras, V., Ward, B.J., Berger, J., 2021. COVID-19 infection in fingolimod- or siponimod-treated patients: case series. Neurol. Neuroimmunol. Neuroinflamm. 9, e1092.

Sullivan, D.J., Focosi, D., Hanley, D., Franchini, M., Ou, J., Casadevall, A., Paneth, N., 2022. Effective antiviral regimens to reduce COVID-19 hospitalizations: a systematic comparison of randomized controlled trials. medRxiv. https://doi.org/10.1101/2022.05.24.22275478.

Sun, F., Lin, Y., Wang, X., Gao, Y., Ye, S., 2022. Paxlovid in patients who are immunocompromised and hospitalised with SARS-CoV-2 infection. Lancet Infect. Dis. S1473-3099(22)00430-3.

Surapaneni, S., Yerramilli, U., Bai, A., Dalvie, D., Brooks, J., Wang, X., Selkirk, J.V., Yan, Y.G., Zhang, P., Hargreaves, R., Kumar, G., Palmisano, M., Tran, J.Q., 2021. Absorption, metabolism, and excretion, in vitro pharmacology, and clinical pharmacokinetics of ozanimod, a novel sphingosine 1-phosphate receptor modulator. Drug. Metab. Dispos. 49, 405–419.

Tallantyre, E.C., Vickaryous, N., Anderson, V., Asardag, A.N., Baker, D., Bestwick, J., Bramhall, K., Chance, R., Evangelou, N., George, K., Giovannoni, G., Godkin, A., Grant, L., Harding, K.E., Hibbert, A., Ingram, G., Jones, M., Kang, A.S., Loveless, S., Moat, S.J., Robertson, N.P., Schmierer, K., Scurr, M.J., Shah, S.N., Simmons, J., Upcott, M., Willis, M., Jolles, S., Dobson, R., 2022a. COVID-19 vaccine response in people with multiple sclerosis. Ann. Neurol. 91, 89–100.

Tallantyre, E.C., Scurr, M.J., Vickaryous, N., Richards, A., Anderson, V., Baker, D., Chance, R., Evangelou, N., George, K., Giovannoni, G., Harding, K.E., Hibbert, A., Ingram, G., Jolles, S., Jones, M., Kang, A.S., Loveless, S., Moat, S.J., Robertson, N.P., Rios, F., Schmierer, K., Willis, M., Godkin, A., Dobson, R., 2022b. Response to COVID-19 booster vaccinations in seronegative people with multiple sclerosis. Mult. Scler. Relat. Disord. 64, 103937.

Tedford, K., Steiner, M., Koshutin, S., Richter, K., Tech, L., Eggers, Y., Jansing, I., Schilling, K., Hauser, A.E., Korthals, M., Fischer, K.D., 2017. The opposing forces of shear flow and sphingosine-1-phosphate control marginal zone B cell shuttling. Nat. Commun. 8, 2261.

Tran, J.Q., Zhang, P., Ghosh, A., Liu, L., Syto, M., Wang, X., Palmisano, M., 2020. Single-Dose Pharmacokinetics of ozanimod and its major active metabolites alone and in combination with gemfibrozil, itraconazole, or rifampin in healthy subjects: a randomized, parallel-group, open-label study. Adv Ther. 37, 4381–4395.

Tuekprakhon, A., Nutalai, R., Dijokaite-Guraliuc, A., Zhou, D., Ginn, H.M., Selvaraj, M., Liu, C., Mentzer, A.J., Supasa, P., Duyvesteyn, H.M.E., Das, R., Skelly, D., Ritter, T. G., Amini, A., Bibi, S., Adele, S., Johnson, S.A., Constantinides, B., Webster, H., Temperton, N., Klenerman, P., Barnes, E., Dunachie, S.J., Crook, D., Pollard, A.J., Lambe, T., Goulder, P., Paterson, N.G., Williams, M.A., Hall, D.R., , OPTIC Consortium, ISARIC4C Consortium, Fry, E.E., Huo, J., Mongkolsapaya, J., Ren, J., Stuart, D.I., Screaton, G.R, 2022. Antibody escape of SARS-CoV-2 Omicron BA.4 and BA.5 from vaccine and BA.1 serum. Cell 185, 2422–2433 e13.

Turner, J.S., O'Halloran, J.A., Kalaidina, E., Kim, W., Schmitz, A.J., Zhou, J.Q., Lei, T., Thapa, M., Chen, R.E., Case, J.B., Amanat, F., Rauseo, A.M., Haile, A., Xie, X., Klebert, M.K., Suessen, T., Middleton, W.D., Shi, P.Y., Krammer, F., Teefey, S.A., Diamond, M.S., Presti, R.M., Ellebedy, A.H., 2021. SARS-CoV-2 mRNA vaccines induce persistent human germinal centre responses. Nature 596, 109–113.

Ufer, M., Shakeri-Nejad, K., Gardin, A., Su, Z., Paule, I., Marbury, T.C., Legangneux, E, 2017. Impact of siponimod on vaccination response in a randomized, placebo-controlled study. Neurol. Neuroimmunol. Neuroinflamm. 4, e398.

Valenzuela, B., Pérez-Ruixo, J.J., Leirens, Q., Ouwerkerk-Mahadevan, S., Poggesi, I., 2021. Effect of ponesimod exposure on total lymphocyte dynamics in patients with multiple sclerosis. Clin. Pharmacokinet. 60, 1239–1250.

van Doorn, R., Nijland, P.G., Dekker, N., Witte, M.E., Lopes-Pinheiro, M.A., van het Hof, B., Kooij, G., Reijerkerk, A., Dijkstra, C., van van der Valk, P., van Horssen, J., de Vries, H.E., 2012. Fingolimod attenuates ceramide-induced blood-brain barrier dysfunction in multiple sclerosis by targeting reactive astrocytes. Acta Neuropathol. 124, 397–410.

van Kempen, Z.L.E., Strijbis, E.M.M., Al, M.M.C.T., Steenhuis, M., Uitdehaag, B.M.J., Rispens, T., Killestein, J, 2021. SARS-CoV-2 antibodies in adult patients with multiple sclerosis in the Amsterdam MS cohort. JAMA Neurol. 78, 880–882.

Walzer, T., Chiossone, L., Chaix, J., Calver, A., Carozzo, C., Garrigue-Antar, L., Jacques, Y., Baratin, M., Tomasello, E., Vivier, E., 2007. Natural killer cell trafficking in vivo requires a dedicated sphingosine 1-phosphate receptor. Nat. Immunol. 8, 1337–1344.

Wang, W., Graeler, M.H., Goetzl, E.J., 2005. Type 4 sphingosine 1-phosphate G protein-coupled receptor (S1P4) transduces S1P effects on T cell proliferation and cytokine secretion without signaling migration. FASEB J. 19, 1731–1733.

Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., Wang, B., Xiang, H., Cheng, Z., Xiong, Y., Zhao, Y., Li, Y., Wang, X., Peng, Z., 2020. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 323, 1061–1069.

Wang, Q., Guo, Y., Iketani, S., Nair, M.S., Li, Z., Mohri, H., Wang, M., Yu, J., Bowen, A.D., Chang, J.Y., Shah, J.G., Nguyen, N., Chen, Z., Meyers, K., Yin, M.T., Sobieszczyk, M. E., Sheng, Z., Huang, Y., Liu, L., Ho, D.D., 2022. Antibody evasion by SARS-CoV-2 Omicron subvariants BA.2.12.1, BA.4, & BA.5. Nature. https://doi.org/10.1038/s41586-022-05053-w.

Weigang, S., Fuchs, J., Zimmer, G., Schnepf, D., Kern, L., Beer, J., Luxenburger, H., Ankerhold, J., Falcone, V., Kemming, J., Hofmann, M., Thimme, R., Neumann-Haefelin, C., Ulferts, S., Grosse, R., Hornuss, D., Tanriver, Y., Rieg, S., Wagner, D., Huzly, D., Schwemmle, M., Panning, M., Kochs, G., 2021. Within-host evolution of SARS-CoV-2 in an immunosuppressed COVID-19 patient as a source of immune escape variants. Nat. Commun. 12, 6405.

Wen, W., Chen, C., Tang, J., Wang, C., Zhou, M., Cheng, Y., Zhou, X., Wu, Q., Zhang, X., Feng, Z., Wang, M., Mao, Q., 2022. Efficacy and safety of three new oral antiviral treatment (molnupiravir, fluvoxamine and Paxlovid) for COVID-19:a meta-analysis. Ann. Med. 54, 516–523.

Wolf, A.S., Ravussin, A., König, M., Øverås, M.H., Solum, S., Fadum Kjønstad, I., Chopra, A., Holmøy, T., Harbo, H.F., Watterdal, S.S., Kaasen Jørgensenn, K., August Høgestøl, F., Torgils Vaage, J., Celius, E.G., Lund-Johansen, F., Munthe, L.A., Owren Nygaard, G., Mjaaland, S, 2022. T cell responses to SARS-CoV-2 vaccination in people with multiple sclerosis differ between disease-modifying therapies. MedRXiv. https://doi.org/10.1101/2022.08.25.22279202. *.

Wong, J., Hertoghs, N., Lemle, A., Linscheid, P., Raghavan, N., Singh, A., Sidorenko, T.., 2022. COVID-19 antibody response by vaccine type and lymphocyte count in RMS patients on ponesimod: results from Phase 2 long-term extension study AC-058B202. Mult. Scler. 28 (3S), 396–397. *.

Woopen, C., Konofalska, U., Akgün, K., Ziemssen, T., 2022 Jul 25. Case report: variant-specific pre-exposure prophylaxis of SARS-CoV-2 infection in multiple sclerosis patients lacking vaccination responses. Front. Immunol. 13, 897748.

Wu, C., Orozco, C., Boyer, J., Leglise, M., Goodale, J., Batalov, S., Hodge, C.L., Haase, J., Janes, J., Huss 3rd, J.W., Su, A.I., 2009. BioGPS: an extensible and customizable portal for querying and organizing gene annotation resources. Genome Biol. 10, R130.

Wu, X., Wang, L., Shen, L., Tang, K., 2022. Response of COVID-19 vaccination in multiple sclerosis patients following disease-modifying therapies: a meta-analysis. EBioMedicine 81, 104102.

Xiong, Y., Piao, W., Brinkman, C.C., Li, L., Kulinski, J.M., Olivera, A., Cartier, A., Hla, T., Hippen, K.L., Blazar, B.R., Schwab, S.R., Bromberg, J.S., 2019. CD4 T cell sphingosine 1-phosphate receptor (S1PR)1 and S1PR4 and endothelial S1PR2 regulate afferent lymphatic migration. Sci. Immunol. 4, eaav1263.

Zabalza, A., Cárdenas-Robledo, S., Tagliani, P., Arrambide, G., Otero-Romero, S., Carbonell-Mirabent, P., Rodriguez-Barranco, M., Rodríguez-Acevedo, B., JL, Restrepo Vera, Resina-Salles, M., Midaglia, L., Vidal-Jordana, A., Río, J., Galan, I., Castillo, J., Á, Cobo-Calvo, Comabella, M., Nos, C., Sastre-Garriga, J., Tintore, M., Montalban, X, 2021. COVID-19 in multiple sclerosis patients: susceptibility, severity risk factors and serological response. Eur. J. Neurol. 28, 3384–3395.

Zhao, Y., Shi, D., Cao, K., Wu, F., Zhu, X., Wen, S., You, Q., Zhang, K., Liu, L., Zhou, H., 2018. Fingolimod targets cerebral endothelial activation to block leukocyte recruitment in the central nervous system. J. Leukoc. Biol. 103, 107–118.

Ziemssen, T., Groth, M., Rauser, B., Bopp, T., 2022. Assessing the immune response to SARS-CoV-2 mRNA vaccines in siponimod-treated patients: a nonrandomized controlled clinical trial (AMA-VACC). Ther. Adv. Neurol. Diord. 15 https://doi.org/10.1177/17562864221135305.

Zoehner, G., Miclea, A., Salmen, A., Kamber, N., Diem, L., Friedli, C., Bagnoud, M., Ahmadi, F., Briner, M., Sédille-Mostafaie, N., Kilidireas, C., Stefanis, L., Chan, A., Hoepner, R., Evangelopoulos, M.E., 2019. Reduced serum immunoglobulin G concentrations in multiple sclerosis: prevalence and association with disease-modifying therapy and disease course. Ther. Adv. Neurol. Disord. 12, 1756286419878340.