IJHSR
ijhighschoolresearch.org
RESEARCH ARTICLE

Emerging Precision Therapy for Multiple Sclerosis Using Chimeric Autoantigen-T Cell Receptor (CATCR)

Aya Shammout

Arab International University, Al Midan, Damascus, Syria; aya.shammut@gmail.com

ABSTRACT: With the rise of precise cellular and immunotherapies for autoimmune diseases, multiple sclerosis presents a challenge for researchers due to its complexity, which includes multiple pathogens and the difficulty of detecting specific autoantibodies for this condition. As a result, current treatments rely on suppressive immunity, leading to a weakened immune system in patients, which increases the risk of infections and reduces anti-tumor immunity. In this review, we will focus on the role of B cells and autoantibodies in multiple sclerosis. We will discuss the efficacy of Chimeric Autoantigen T Cell Receptor Therapy in anti phospholipid syndrome, and suggest following the same approach to treat MS. We will discuss methodologies to identify the patient's specific auto-antigens to incorporate them into T cell receptors using CRISPR, and explore the potential therapeutic benefits as well as the associated side effects for CAR T Cell and CATCR therapies. Finally, we will highlight two in progress and approved immunotherapies for multiple sclerosis.

KEYWORDS: Biomedical and Health Sciences, Immunology, Multiple Sclerosis, B Cells; Immunotherapies.

Introduction

Multiple Sclerosis (MS) is a chronic, inflammatory autoimmune disease that affects the central nervous system (CNS). It occurs when the body's immune system mistakenly attacks the myelin sheaths that cover the nerves, leading to symptoms ranging from vision loss to muscle weakness and loss of sensation.[1] The medical term "multiple sclerosis" derives from the scars (or lesions) that appear in MRI scans of the brain and spinal cord. The etiology of the disease remains unknown, but it is believed to be influenced by environmental and genetic factors. Environmental factors include low vitamin D levels, reduced UV radiation exposure, smoking, and obesity.[2] Approximately 2.8 million people are affected by MS, and the disease typically occurs in young adults, usually females, between the ages of 20 and 40.[3]

MS is classified into types according to the progression of symptoms: Relapsing-Remitting MS, which is characterized by periods of exacerbation followed by long periods of remission; Secondary Progressive MS, which usually occurs after the relapsing-remitting form and is characterized by a steady progression of symptoms without clear relapses; and Primary Progressive MS, which is similar to Secondary Progressive MS but does not follow a relapsing-remitting phase.[4]

Under normal physiological conditions, our immune system consists of innate (general) immunity and adaptive (specialized) immunity. Innate immunity is the immunity we are born with and serves as the first line of defense. It includes components such as natural killer cells, which recognize and destroy infected cells, and phagocytes, which engulf and digest pathogens. The adaptive immune system includes T cells, B cells, and antibodies. T cells are produced in the bone marrow, travel through the bloodstream, and mature in the thymus (the "T" stands for "thymus"). There are two main types of T cells: T helper cells (also called CD4+ cells due to the presence of a CD4 co-receptor on their membranes) and cytotoxic T cells (also known as CD8+ cells because they have a CD8 co-receptor on their membranes). CD4+ T cells release proteins that serve as chemical messengers called cytokines, which regulate inflammation and immune responses, while CD8+ T cells recognize and kill infected cells. Some helper T cells differentiate into memory T cells, which remember past pathogens when they re-enter the body. B cells are produced and mature in the bone marrow (the "B" stands for "bone marrow"). Similar to T cells, there are two types of B cells: plasma cells and memory B cells. Plasma cells are responsible for producing proteins known as antibodies (or immunoglobulins). These antibodies can recognize and bind to specific substances on the surface of foreign cells, known as antigens, triggering immune cells to respond to these pathogens. Each antibody is specific to its corresponding antigen, functioning like a key in a lock.[5,6]

Various environmental or genetic factors may misdirect the immune system, leading it to attack self-antigens. MS has traditionally been viewed as a T-cell-mediated disease, triggered by the activation of pathogenic Th17 and Th1 cells, as well as CD8+ autoreactive T cells. Th cells play role in recognizing CNS antigens, producing inflammatory cytokines, and activating B cells, while CD8+ cells cause tissue damage.[7] However, the notable outcomes of B cell depletion therapies in reducing disease activity and demonstrating long-term efficacy have revealed that B cells also play a central and driving role in MS pathogenesis through antigen presentation, T cell regulation, and producing immunoglobulins.[8] Despite long-term studies, no specific targeted antigen has yet been identified.

Currently, medications for treating multiple sclerosis (MS) primarily focus on suppressing the immune system and often lack specificity in targeting autoimmune cells. This broad im-

DOI: 10.36838/v7i1.7

munosuppression can increase patients' susceptibility to serious infections and diminish their body's ability to combat cancer. For instance, beta interferons are cytokines that reduce neuronal inflammation and decrease the frequency of MS relapses; however, they also lower the production of Th17 cells, leading to immunosuppressive effects. Cladribine, another treatment used for both B-cell lymphocytic leukemia and acute forms of relapsing-remitting MS in adults, works by depleting B and T cells to halt the immune cascade associated with MS. Similarly, alemtuzumab targets CD52, a protein found on the surface of B and T cells, resulting in their destruction and suppression of autoimmune responses. Many other therapies operate on this same principle of broad immunosuppression. While these treatments can effectively halt MS symptoms, they have the potential to suppress healthy immune function, putting patients at risk of severe infections. Therefore, there is an urgent need to develop more effective and precise therapies for MS that preserve the body's healthy immune response to external pathogens.

In this review, we will explore the potential for developing a precise therapy aimed at auto-reactive B cells in multiple sclerosis, given their critical role in regulating T cells and the promising outcomes associated with B cell depletion therapies for relapsing forms of MS. While much of the existing research has concentrated on T cell-targeted treatments, it is essential to investigate strategies that specifically address B cells—either as standalone therapies or in conjunction with other treatments. Our goal is to not only alleviate specific symptoms but also to halt or even reverse disease progression while preserving healthy immune cells.

Discussion

1. The Role of B Cells in Multiple Sclerosis

1.1. Antigen Presentation and T Cell Regulation:

During inflammation, a type of immune cell known as antigen presenting cells (APCs) can detect antigens, process them, and present them via the major histocompatibility complex (MHC), which functions as a cell surface marker and antigen-presenting molecule, to T cells to initiate the adaptive cellular immune response.[9,10] B cells are highly effective APCs. They can recognize conformational (folded) protein antigens and process them into short, linear peptides to present via MHC class II to antigen-specific T cells. Additionally, they have the ability to detect even low concentrations of antigens because of co-receptor complexes—molecules present on the surface of the majority of B cells that control their signaling—such as CD19, CD21, and CD81.[11,12]

The binding of helper T cells with MHC II on B cells activates helper T cells, which subsequently leads to the differentiation of B cells into memory cells and antibody-secreting plasma cells. The response of T cells is influenced by the nature of the interaction between B and T cells. Strong interactions lead to pro-inflammatory T cells, whereas weaker interactions promote regulatory T cell function. The activation of Th0 cells (naïve T cells), for example, requires additional signals from co-stimulatory molecules expressed by B cells, such as CD40, CD80, and CD86. Furthermore, the interaction between CD40 on B cells and CD40 ligand (CD40L) on T cells is crucial for the development of pro-inflammatory T cells; blocking this interaction has been shown to halt experimental autoimmune encephalomyelitis (EAE), a model of MS.

It has been noted that B cells in MS patients express elevated amounts of CD40 alongside increased levels of MHC II and CD80. Moreover, the strength of these interactions is also modulated by the cytokine milieu produced by the APCs. Interleukin (IL)-6 is a cytokine secreted by B cells that enhances the differentiation of Th17 cells while inhibiting the generation of regulatory T cells. In the context of MS, memory B cells secrete increased amounts of pro-inflammatory cytokines, including IL-6, lymphotoxin alpha, tumor necrosis factor alpha (TNF-α), and granulocyte-macrophage colony-stimulating factor (GM-CSF), while exhibiting decreased levels of anti-inflammatory IL-10. This imbalance contributes to the inflammatory effects of B cells in MS.[13]

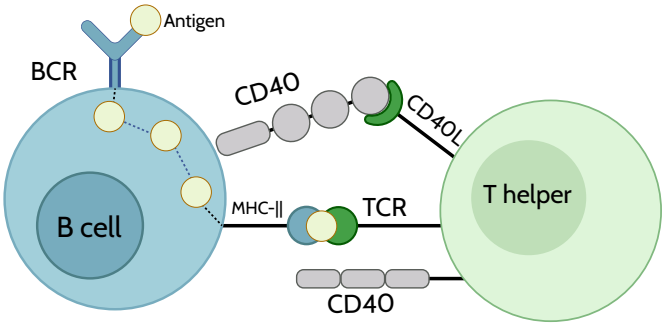

Figure 1: B cells in antigen presentation. B cells (blue) recognize antigens (yellow), process them, and present them via MHC-II to T cells (green). The interaction between CD40 on B cells and CD40 Ligand on T cells develops pro-inflammatory T cells.

1.2. Producing Immunoglobulins:

After B cells present antigens to T helper (Th) cells and the binding between MHC II and TCR activates these cells, B cells differentiate into memory B cells, which retain memory of the antigen, and plasma cells, which produce immunoglobulins (antibodies). In multiple sclerosis (MS), immunoglobulin G1 (IgG1) and immunoglobulin G3 (IgG3) are found more frequently than other immunoglobulin isotypes. These antibodies can be detected in the cerebrospinal fluid (CSF) as clusters identified through isoelectric focusing (IEF), known as intrathecal oligoclonal bands (OCBs). OCBs are observed in over 95% of multiple sclerosis patients, making them a hallmark for diagnosing the disease.

These immunoglobulins may play a secondary or enhancing role in the demyelination process of MS through several effector mechanisms by binding to antigens on the surface of target cells (e.g., myelin oligodendrocytes). One of these mechanisms is called antibody-dependent cellular cytotoxicity (ADCC), in which effector immune cells recognize the antibody-antigen complex and release cytotoxic substances that induce programmed cell death (apoptosis) in the target cells. Another important mechanism is opsonization and phagocytosis, in which phagocytes (such as macrophages and neutrophils) recognize the binding of antibodies on the surface of antigens, engulf them, and then fuse with lysosomes containing enzymes that digest the target cells.

There is controversy regarding the origin of these intrathecal immunoglobulins. While the central nervous system was once thought to be devoid of immune cells, a small number of B and T cells have been identified in healthy individuals, suggesting that these cells may contribute to the production of immunoglobulins in the CSF. Other studies propose that these antibodies originate from the periphery. By expressing specific chemokine receptors and adhesion molecules, B cells and immunoglobulins can cross the blood-brain barrier and recognize auto-antigens on astrocytes, neurons, axons, oligodendrocytes, and myelin.[14-17]

1.3. Common Autoantigens Among MS Patients:

Despite extensive studies aimed at identifying an autoantigen specific to multiple sclerosis that could serve as a diagnostic biomarker or therapeutic target, no such autoantigen has been definitively identified. While some target antigens have been found in certain multiple sclerosis cases, these antigens are not present across all MS patients and are not exclusive to the disease, as they have also been detected in patients with other neurologic diseases (OND) and even in healthy individuals.[18,19] For example, Myelin Oligodendrocyte Glycoprotein (MOG), Myelin Basic Protein (MBP) and Proteolipid Protein (PLP) are all important proteins of the myelin sheath and are commonly targeted by autoantibodies in MS—autoantibodies against these proteins involved in the demyelination process.[16] However, anti-MOG antibodies have also been found in Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD).[20] Another immune target in MS is Aquaporin-4 (AQP4), which is a water channel protein found on astrocytes, but it is more related to Neuromyelitis Optica Spectrum Disorder (NMOSD).[8] Antibodies against glycans like GAGA4 and glucose have been recently observed in some MS patients.[21] Additionally, while antibodies against other components of the central nervous system, such as anti-Inward-Rectifying Potassium Channel (KIR4.1), have been detected, their pathological role remains unconfirmed.[22] This complexity in identifying consistent autoantigens in MS complicates the development of effective therapies for the disease.

2. Chimeric Autoantigen-T Cell Receptor (CATCR)-T Cell Therapy—Suggested Treatment That Target The Autoreactive B Cells:

Recently, CATCR was first developed to treat antiphospholipid syndrome (APS) and rheumatoid diseases. The approach involves incorporating part or the entire peptide of the autoantigen into the patient's T cell receptors, enabling the autoreactive B cells to recognize and bind to the incorporated autoantigen, ultimately leading to their death.

This study employed CRISPR-Cas9/12a-based technology to integrate beta-2 glycoprotein I (β2GPI), an important autoantigen in APS, into the chimeric T cell receptor, specifically the TCR–CD3 complex, of a human cell. A homology-directed repair (HDR) template containing partial or complete nucleotide sequences of β2GPI, along with Cas-gRNA designed to modify the TCR-CD3 complex, were transfected into activated T cells. After transfection, the expression of these engineered receptors was measured using flow cytometry, a technique for analyzing cell counts and characteristics. β2GPI was effectively expressed as part of the CD3-gamma, CD3-epsilon, or TCR-beta/alpha chains.

To examine the specificity of CATCR, Ramos B cells (a type of lab-grown cell) were edited using CRISPR-Cas9 to replace their normal B cell receptors (BCRs) with monoclonal anti-β2GPI derived from APS patients. The efficiency and selectivity of β2GPI-CATCR-T cells were evaluated by exposing them to anti-β2GPI and unmodified Ramos B cells. Cytotoxicity was measured using flow cytometry, live-cell imaging for visualizing interactions in real-time, and cytokine assays to assess immune signaling molecules produced during the interaction.

The results were incredibly promising; β2GPI-CATCR-T cells precisely depleted anti-β2GPI B cells by inducing immune synapse formation via the perforin–granzyme effector pathway (perforin forms pores in the cell's membrane, allowing granzymes to enter and trigger the apoptotic process). This observation represents a significant advancement toward specific treatments for autoimmune diseases.[23-25]

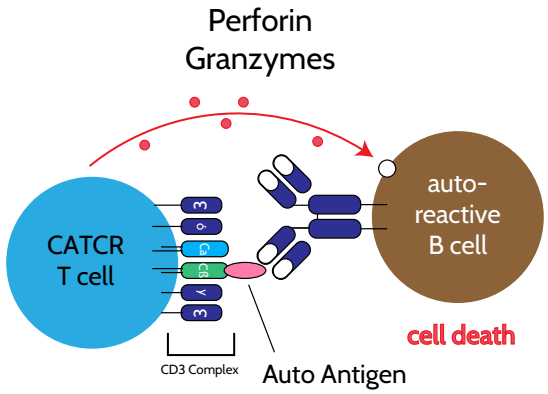

Figure 2: This figure explains what a Chimeric Autoantigen-T Cell Receptor (CATCR) is. A relevant autoantigen (pink) is incorporated into the beta chain (green) of the TCR-CD3 complex. These modified T cells (blue) can selectively kill autoreactive B cells (brown) through the perforin and granzyme pathway.
TCR: T Cell Receptor, CD3: Cluster of Differentiation[3]

3. Application on MS:

The success of CATCR Therapy in APS inspires further exploration of using a similar approach to design a precise therapy for MS, given the key role that B cells play in the production of autoantibodies in both conditions, and the significant results of preclinical and clinical trials of CAR T Cell therapy in MS, particularly CD19 CAR T Cell therapy, which targets B cells expressing the CD19 co-receptor.[26] This innovative therapy has received U.S. FDA approval for treatment in patients with refractory and progressive MS in phase 2 trial.[27] In a study involving patients with progressive MS, treatment with CD19 CAR T Cells resulted in a notable reduction of IgG levels in both the bloodstream and CSF.[28] This reduction suggests the potential to halt disease progression and offers promising prospects for the future application of CATCR therapy in the treating multiple sclerosis.

3.1. Potential Therapeutic Benefits and Side Effects:

Given that CATCR has shown specific and precise efficacy in APS, we hypothesize that similar outcomes could be

DOI: 10.36838/v7i1.7

achieved in MS. The comparable role of B cells in both conditions, along with the encouraging results from CAR T cell therapy on MS, supports this assumption. By selectively targeting and eliminating auto-reactive B cells, we aim to decrease the activity of pathogenic T cells and reduce auto antigen presentation. This will prevent the differentiation of autoreactive B cells into plasma cells that produce myelin-targeting autoantibodies. As a result, we anticipate a decrease in inflammation and demyelination, ultimately controlling disease progression. Importantly, this approach also seeks to preserve healthy immune cells, thereby protecting against severe infections and cancer. Additionally, this therapy may serve as a preventive strategy for individuals at risk of developing MS.

However, it is important to consider potential side effects, including:

- Cytokine release syndrome (CRS):

It is the most common CAR T Cell Therapy side effect (affects up to 9 in 10 patients who receive CAR T Cell therapy). It is an inflammatory response that causes rapid release of pro-inflammatory cytokines into the bloodstream, leading to symptoms that can range from mild flu-like symptoms to severe complications, including high fever, hypotension, hypoxia, and multi-organ dysfunction. CRS occurs when activated immune cells release large amounts of cytokines—the overproduction of these cytokines can lead to a cascade of inflammatory responses.[29]

- CAR T-Cell-related encephalopathy syndrome (CRES):

It is a neurological complication associated with CAR T-cell therapy, causing symptoms like confusion, agitation, seizures, and altered mental status. It typically occurs in the context of Cytokine Release Syndrome (CRS) but can also occur independently. CRES is thought to be related to the systemic inflammatory response triggered by the activation and proliferation of CAR T-cells, which leads to the release of cytokines that can affect the central nervous system. The exact pathophysiological mechanisms are still being studied.[30]

- Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS):

It is a neurological complication that can occur following the administration of immunotherapies such as CAR T-cell therapy. ICANS is characterized by a range of neurological symptoms that may include Confusion and altered mental status, headaches, and visual disturbances. The exact mechanisms behind ICANS still need to be investigated, but it is believed to be related to the systemic inflammatory response triggered by the activation of immune effector cells. This response can lead to the release of cytokines, which may affect the central nervous system.[30]

Immunosuppressive drugs can be used for managing CRS, CRES, and ICANS

3.2. Further Suggestions:

Further experimental research, both in vivo and in vitro, is needed to confirm the therapy's effectiveness and safety, monitor potential side effects, and develop strategies for managing them. Additionally, it is crucial to investigate the best route of administration for delivering the therapy across the blood-brain barrier to target auto-reactive B cells in the cerebrospinal fluid.[31] To halt and reverse the progression of MS, we will likely need to combine this therapy with additional treatments aimed at regulating the activity of auto-reactive T cells.[32,33] While specific targeted antigens for MS patients have not yet been identified, we propose developing personalized treatments tailored to each patient's unique autoantigens. Over the past decade, researchers have been investigating methods to identify these autoantigens, aiming to enhance diagnostic and therapeutic efficiency. A notable study conducted in 2011 analyzed patient-specific targeted antigens, following these steps:

1. Sample Collection: Cerebrospinal fluid (CSF) containing oligoclonal bands (OCBs) was collected from patients. The CSF was centrifuged at 500×g for 10 minutes to remove cellular debris. CSF and sera were stored at -80°C for later analysis.

2. Phage Display Peptide Library: This technology utilizes bacteriophages that carry random peptides on their surfaces. Two specific libraries, Ph.D.-7™ and Ph.D.-C7C™, were employed to identify peptides that bind to the antibodies in the CSF. The CSF IgG was mixed with the phage libraries, and phages that adhered to the IgG were retained while unbound phages were washed away. This process was repeated multiple times to enrich for binding phages.

3. ELISA Confirmation: To verify that the selected peptides specifically bind to CSF IgG, an ELISA test was performed. Individual phage clones were tested for reactivity with the CSF IgG, with a control using pre-immune human IgG to ensure specificity in binding.

4. Western Blotting: This technique was used to visualize interactions between the peptides and IgG. Proteins in the CSF and serum were separated based on charge using isoelectric focusing (IEF), followed by probing with phage peptides to identify specific bands that corresponded to the antibodies.

5. Alanine Scan Mutagenesis: To determine which amino acids are crucial for binding to IgG, alanine scan mutagenesis was applied, systematically replacing each amino acid in the peptide with alanine. This method helped identify which residues are essential for maintaining strong binding affinity.

6. Protein Identification: To ascertain the proteins corresponding to the identified peptides, databases such as BLAST were utilized to identify potential proteins involved in the immune response.[34,35]

4. In Progress and Approved Immunotherapies for MS

4.1. CD 19 CAR T Cell Therapy —In Progress Therapy:

This therapy targets the CD19 antigen, a protein expressed on the surface of B cells that increases during their maturation and disappears when they differentiate into plasma cells.[36,37] CD19 plays a crucial role in controlling B cell receptor signaling by regulating MHC-II expression, and it lowers the activation threshold for B cells which enhances their response to lower levels of antigens.[11] Studies have shown that MS patients have an increased number of B cells expressing CD19.[38] In this context, elevated CD19 levels make B cells more sensitive to antigens, contributing to autoimmunity and the production of autoantibodies. Consequently, developing therapies for targeting CD19 has been considered to suppress autoimmunity. Notably, CD19 CAR T cell therapy has yielded

fully decreased autoantibodies in the bloodstream and in the CSF which contribute to inflammation. This therapy demonstrated a favorable safety profile, with no ICANS observed. Although cytokine release syndrome (CRS) took place, it was manageable with Tocilizumab and Dexamethasone (immunosuppressant drugs).[28] However, this therapy lacks specificity in targeting autoreactive immune cells, as CD19 is also present on normal B cells. In advanced stages of the disease, depleting B cells may be beneficial for halting disease progression.

4.2. Anti-CD20 Monoclonal Antibodies (Ocrelizumab)—FDA-Approved Therapy:

Monoclonal antibodies (mAbs) are laboratory-engineered antibodies designed to target specific antigens.[39] CD20 is a protein expressed on immature B cells, naïve B cells, memory B cells, and germinal center B cells, but it is absent in pre–B cells and plasma cells.[40] While the specific function of CD20 remains unclear, it is believed to serve as a calcium ion channel, playing a role in B cell activation, proliferation, and differentiation into plasma cells.[41,42] Studies have shown a significant presence of plasma cells and CD20+ B cells in the perivenular areas of patients with advanced courses of MS,[43,15] suggesting their pathological involvement. Targeting CD20 has proven effective in eliminating B cells (including autoreactive B cells), making this approach useful for treating relapsing forms of MS (RMS) and primary progressive MS (PPMS). The treatment has demonstrated clear benefits in reducing inflammation and relapse rates. The long-term safety profile of these therapies is still under investigation, with potential side effects including infusion reactions and immune suppression due to the depletion of normal CD20+ B cells.[44,15]

Conclusion

In summary, B cells play a significant pathological role in multiple sclerosis, underscoring the critical need for treatments. Current therapies lack precision in depleting autoimmune cells, leading to an increased risk of serious infections. Therefore, developing precise therapies that target the autoimmune cells is essential. Chimeric Auto-antigen T Cell receptor (CATCR)-T Cell therapy represents a promising approach for treating autoimmune diseases like multiple sclerosis by selectively targeting and eliminating autoreactive B cells while preserving the patient's healthy immune system against infections and cancer. Further research is necessary to evaluate its therapeutic benefits and identify potential side effects. Additionally, strategies must be developed to effectively manage these side effects to ensure patient safety. We remain optimistic that the outcomes of this therapy will mirror the positive results observed in using CATCR T Cell Therapy in Anti phospholipid syndrome, paving the way for more effective management of multiple sclerosis and improving the quality of life for those affected by this challenging disease.

Acknowledgments

I want to send special thanks to my research mentor, Dr. Hamidreza Shaye and my teacher assistant, Taylor Hailstock for their guidance and support throughout this invaluable research journey.

References

1. Hauser, S. L.; Oksenberg, J. R. The Neurobiology of Multiple Sclerosis: Genes, Inflammation, and Neurodegeneration. Neuron 2006, 52 (1), 61–76. https://doi.org/10.1016/j.neuron.2006.09.011.
2. Baecher-Allan, C.; Kaskow, B. J.; Weiner, H. L. Multiple Sclerosis: Mechanisms and Immunotherapy. Neuron 2018, 97 (4), 742–768. https://doi.org/10.1016/j.neuron.2018.01.021.
3. Walton, C.; King, R.; Rechtman, L.; Kaye, W.; Leray, E.; Marrie, R. A.; Robertson, N.; Rocca, N. L.; Uitdehaag, B.; Mei, I. van der; Wallin, M.; Helme, A.; Napier, C. A.; Rijke, N.; Baneke, P. Rising Prevalence of Multiple Sclerosis Worldwide: Insights from the Atlas of MS, Third Edition. Multiple Sclerosis (Houndmills, Basingstoke, England) 2020, 26 (14), 1816. https://doi.org/10.1177/1352458520970841.
4. Multiple sclerosis - Symptoms and causes. https://www.mayoclinic.org/diseases-conditions/multiple-sclerosis/symptoms-causes/syc-20350269 (accessed 2024-11-13).
5. In Brief: The Innate and Adaptive Immune Systems; Institute for Quality and Efficiency in Health Care (IQWiG), 2023.
6. Alberts, B.; Johnson, A.; Lewis, J.; Raff, M.; Roberts, K.; Walter, P. T Cells and MHC Proteins; Garland Science, 2002.
7. Derdelinckx, J.; Cras, P.; Berneman, Z. N.; Cools, N. Antigen-Specific Treatment Modalities in MS: The Past, the Present, and the Future. Front. Immunol. 2021, 12. https://doi.org/10.3389/fimmu.2021.624685.
8. Pröbstel, A.-K.; Sanderson, N. S. R.; Derfuss, T. B Cells and Autoantibodies in Multiple Sclerosis. International Journal of Molecular Sciences 2015, 16 (7), 16576. https://doi.org/10.3390/ijms160716576.
9. Antigen Presenting Cell - an overview | ScienceDirect Topics. https://www.sciencedirect.com/topics/medicine-and-dentistry/antigen-presenting-cell (accessed 2024-11-13).
10. Human leukocyte antigens (HLA): A roadmap - UpToDate. https://www.uptodate.com/contents/human-leukocyte-antigens-hla-a-roadmap/print (accessed 2024-11-13).
11. Wang, K.; Wei, G.; Liu, D. CD19: A Biomarker for B Cell Development, Lymphoma Diagnosis and Therapy. Experimental Hematology & Oncology 2012, 1 (1), 36. https://doi.org/10.1186/2162-3619-1-36.
12. Charles A Janeway, J.; Travers, P.; Walport, M.; Shlomchik, M. J. B-Cell Activation by Armed Helper T Cells; Garland Science, 2001.
13. Häusser-Kinzel, S.; Weber, M. S. The Role of B Cells and Antibodies in Multiple Sclerosis, Neuromyelitis Optica, and Related Disorders. Front. Immunol. 2019, 10. https://doi.org/10.3389/fimmu.2019.00201.
14. Yu, X.; Graner, M.; Kennedy, P. G. E.; Liu, Y. The Role of Antibodies in the Pathogenesis of Multiple Sclerosis. Front. Neurol. 2020, 11. https://doi.org/10.3389/fneur.2020.533388.
15. de Sèze, J.; Maillart, E.; Gueguen, A.; Laplaud, D. A.; Michel, L.; Thouvenot, E.; Zephir, H.; Zimmer, L.; Biotti, D.; Liblau, R. Anti-CD20 Therapies in Multiple Sclerosis: From Pathology to the Clinic. Front. Immunol. 2023, 14. https://doi.org/10.3389/fimmu.2023.1004795.
16. Weber, M. S.; Hemmer, B.; Cepok, S. The Role of Antibodies in Multiple Sclerosis. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease 2011, 1812 (2), 239–245. https://doi.org/10.1016/j.bbadis.2010.06.009.
17. van Langelaar, J.; Rijvers, L.; Smolders, J.; van Luijn, M. M. B and T Cells Driving Multiple Sclerosis: Identity, Mechanisms and Potential Triggers. Front. Immunol. 2020, 11. https://doi.org/10.3389/fimmu.2020.00760.
18. Höftberger, R.; Lassmann, H.; Berger, T.; Reindl, M. Pathogenic Autoantibodies in Multiple Sclerosis — from a Simple Idea to a

DOI: 10.36838/v7i1.7

Complex Concept. Nat Rev Neurol 2022, 18 (11), 681–688. https://doi.org/10.1038/s41582-022-00700-2.
19. DeMarshall, C.; Goldwaser, E. L.; Sarkar, A.; Godsey, G. A.; Acharya, N. K.; Thayasivam, U.; Belinka, B. A.; Nagele, R. G. Autoantibodies as Diagnostic Biomarkers for the Detection and Subtyping of Multiple Sclerosis. Journal of Neuroimmunology 2017, 309, 51–57. https://doi.org/10.1016/j.jneuroim.2017.05.010.
20. Lerch, M.; Bauer, A.; Reindl, M. The Potential Pathogenicity of Myelin Oligodendrocyte Glycoprotein Antibodies in the Optic Pathway. Journal of Neuro-Ophthalmology 2022, 43 (1), 5. https://doi.org/10.1097/WNO.0000000000001772.
21. Brettschneider, J.; Jaskowski, T. D.; Tumani, H.; Abdul, S.; Huseboye, D.; Seraj, H.; Hill, H. R.; Fire, E.; Spector, L.; Yarden, J.; Dotan, N.; Rose, J. W. Serum Anti-GAGA4 IgM Antibodies Differentiate Relapsing Remitting and Secondary Progressive Multiple Sclerosis from Primary Progressive Multiple Sclerosis and Other Neurological Diseases. Journal of Neuroimmunology 2009, 217 (1), 95–101. https://doi.org/10.1016/j.jneuroim.2009.07.017.
22. Brill, L.; Goldberg, L.; Karni, A.; Petrou, P.; Abramsky, O.; Ovadia, H.; Ben-Hur, T.; Karussis, D.; Vaknin-Dembinsky, A. Increased Anti-KIR4.1 Antibodies in Multiple Sclerosis: Could It Be a Marker of Disease Relapse? Mult Scler 2015, 21 (5), 572–579. https://doi.org/10.1177/1352458514551779.
23. Chimeric Autoantigen-T Cell Receptor (CATCR)-T Cell Therapies to Selectively Target Autoreactive B Cells. https://acrabstracts.org/abstract/chimeric-autoantigen-t-cell-receptor-catcr-t-cell-therapies-to-selectively-target-autoreactive-b-cells/ (accessed 2024-11-13).
24. Konig, M. F. The Rise of Precision Cellular Therapies. Nat Rev Rheumatol 2024, 20 (2), 69–70. https://doi.org/10.1038/s41584-023-01073-6.
25. Finkel, T. H.; Radic, M. Chimeric Receptors Broaden the Therapeutic Landscape for Autoimmune Disease. Nat Rev Rheumatol 2023, 19 (6), 327–328. https://doi.org/10.1038/s41584-023-00968-8.
26. Dieudonné, Y.; Guffroy, A.; Poindron, V.; Sprauel, P. S.; Martin, T.; Korganow, A.-S.; Gies, V. B Cells in Primary Antiphospholipid Syndrome: Review and Remaining Chlenges. Autoimmunity Reviews 2021, 20 (5), 102798. https://doi.org/10.1016/j.autrev.2021.102798.
27. Kyverna's KYV-101 Receives U.S. FDA Clearance for Treatment of Patients With Refractory, Progressive Multiple Sclerosis in the KYSA-7 Phase 2 Trial. https://ir.kyvernatx.com/news-releases/news-release-details/kyvernas-kyv-101-receives-us-fda-clearance-treatment-patients (accessed 2024-11-13).
28. Fischbach, F.; Richter, J.; Pfeffer, L. K.; Fehse, B.; Berger, S. C.; Reinhardt, S.; Kuhle, J.; Badbaran, A.; Rathje, K.; Gagelmann, N.; Borie, D.; Seibel, J.; Ayuk, F.; Friese, M. A.; Heesen, C.; Kröger, N. CD19-Targeted Chimeric Antigen Receptor T Cell Therapy in Two Patients with Multiple Sclerosis. Med 2024, 5 (6), 550-558.e2. https://doi.org/10.1016/j.medj.2024.03.002.
29. Shimabukuro-Vornhagen, A.; Gödel, P.; Subklewe, M.; Stemmler, H. J.; Schlößer, H. A.; Schlaak, M.; Kochanek, M.; Böll, B.; Bergwelt-Baildon, M. S. von. Cytokine Release Syndrome. Journal for Immunotherapy of Cancer 2018, 6, 56. https://doi.org/10.1186/s40425-018-0343-9.
30. Neelapu, S. S.; Tummala, S.; Kebriaei, P.; Wierda, W.; Gutierrez, C.; Locke, F. L.; Komanduri, K. V.; Lin, Y.; Jain, N.; Daver, N.; Westin, J.; Gulbis, A. M.; Loghin, M. E.; de Groot, J. F.; Adkins, S.; Davis, S. E.; Rezvani, K.; Hwu, P.; Shpall, E. J. Chimeric Antigen Receptor T-Cell Therapy — Assessment and Management of Toxicities. Nat Rev Clin Oncol 2018, 15 (1), 47–62. https://doi.org/10.1038/nrclinonc.2017.148.
31. Turk, O.; Woodall, R. C.; Gutova, M.; Brown, C. E.; Rockne, R. C.; Munson, J. M. Delivery Strategies for Cell-Based Therapies in the Brain: Overcoming Multiple Barriers. Drug delivery and translational research 2021, 11 (6), 2448. https://doi.org/10.1007/s13346-021-01079-1.
32. Baecher-Allan, C.; Kaskow, B. J.; Weiner, H. L. Multiple Sclerosis: Mechanisms and Immunotherapy. Neuron 2018, 97 (4), 742–768. https://doi.org/10.1016/j.neuron.2018.01.021.
33. Islam, M. A.; Kundu, S.; Hassan, R. Gene Therapy Approaches in an Autoimmune Demyelinating Disease: Multiple Sclerosis. Curr Gene Ther 2020, 19 (6), 376–385. https://doi.org/10.2174/1566523220766620030609255 6.
34. Graner, M.; Pointon, T.; Manton, S.; Green, M.; Dennison, K.; Davis, M.; Braiotta, G.; Craft, J.; Edwards, T.; Polonsky, B.; Fringuello, A.; Vollmer, T.; Yu, X. Oligoclonal IgG Antibodies in Multiple Sclerosis Target Patient-Specific Peptides. PLoS ONE 2020, 15 (2), e0228883. https://doi.org/10.1371/journal.pone.0228883.
35. Yu, X.; Burgoon, M.; Green, M.; Barmina, O.; Dennison, K.; Pointon, T.; Davis, M.; Gilden, D. Intrathecally Synthesized IgG in Multiple Sclerosis Cerebrospinal Fluid Recognizes Identical Epitopes over Time. Journal of Neuroimmunology 2011, 240–241, 129–136. https://doi.org/10.1016/j.jneuroim.2011.10.009.
36. Scheuermann, R. H.; Racila, E. CD19 Antigen in Leukemia and Lymphoma Diagnosis and Immunotherapy. Leuk Lymphoma 1995, 18 (5–6), 385–397. https://doi.org/10.3109/10428199509059636.
37. Kegyes, D.; Jitaru, C.; Ghiaur, G.; Ciurea, S.; Hoelzer, D.; Tomuleasa, C.; Gale, R. P. Switching from Salvage Chemotherapy to Immunotherapy in Adult B-Cell Acute Lymphoblastic Leukemia. Blood Reviews 2023, 59, 101042. https://doi.org/10.1016/j.blre.2023.101042.
38. Abbadessa, G.; Miele, G.; Cavalla, P.; Valentino, P.; Marfia, G. A.; Signoriello, E.; Landi, D.; Bosa, C.; Vercellino, M.; De Martino, A.; Missione, R.; Sparaco, M.; Lavorgna, L.; Lus, G.; Bonavita, S. CD19 Cell Count at Baseline Predicts B Cell Repopulation at 6 and 12 Months in Multiple Sclerosis Patients Treated with Ocrelizumab. Int J Environ Res Public Health 2021, 18 (15), 8163. https://doi.org/10.3390/ijerph18158163.
39. Malik, B.; Ghatol, A. Understanding How Monoclonal Antibodies Work; StatPearls Publishing: Treasure Island (FL), 2024.
40. Looney, R. J.; Anolik, J.; Sanz, I. New Therapies for Systemic Lupus Erythematosus: Cellular Targets. Rheumatic Disease Clinics of North America 2006, 32 (1), 201–215. https://doi.org/10.1016/j.rdc.2005.09.007.
41. Béné, M. C. Immunophenotyping of Acute Leukaemias. Immunology Letters 2005, 98 (1), 9–21. https://doi.org/10.1016/j.imlet.2004.10.008.
42. Payandeh, Z.; Bahrami, A. A.; Hoseinpoor, R.; Mortazavi, Y.; Rajabibazl, M.; Rahimpour, A.; Taromchi, A. H.; Khalil, S. The Applications of Anti-CD20 Antibodies to Treat Various B Cells Disorders. Biomedicine & Pharmacotherapy 2019, 109, 2415–2426. https://doi.org/10.1016/j.biopha.2018.11.121.
43. Carlson, A. K.; Amin, M.; Cohen, J. A. Drugs Targeting CD20 in Multiple Sclerosis: Pharmacology, Efficacy, Safety, and Tolerability. Drugs 2024, 84 (3), 285–304. https://doi.org/10.1007/s40265-024-02011-w.
44. Lin, M.; Zhang, J.; Zhang, Y.; Luo, J.; Shi, S. Ocrelizumab for Multiple Sclerosis. The Cochrane Database of Systematic Reviews 2022, 2022 (5), CD013247. https://doi.org/10.1002/14651858.CD013247.pub2.

Author

Aya recently graduated from Al Awael School and is now studying pharmacy at Arab International University in Syria. She has a strong passion for immunobiology and genetics, and she aspires to further

her education and work in the field of pharmacogenetics, with the goal of developing treatments for autoimmune diseases.

DOI: 10.36838/v7i1.7