Driving CAR-T Into the Future: What Are the Right B Cell Targets in Systemic Lupus Erythematosus and Beyond?

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THE AMERICAN College of Rheumatology (ACR) 2025 Convergence was an epicenter for discussion, collaboration, and celebration of the advancements in rheumatology. This session, 'Driving CAR-T Into the Future: What is the Right B Cell Targets in Systemic Lupus Erythematosus and Beyond?' was a program highlight, exploring the various B cell subsets, their role in autoimmunity, and examining novel pathways and targets that might promote the selective targeting of autoreactive B cells in autoimmune disease. It was moderated by Jeremy Tilstra, University of Pittsburgh School of Medicine, Pennsylvania, USA; and Anne Davidson, Feinstein Institute for Medical Research, Manhasset, New York, USA, and featured notable panelists including Nan Shen, Shanghai Jiao Tong University School of Medicine, China; and Inaki Sanz, Emory University School of Medicine, Atlanta, Georgia, USA.

A BACKGROUND ON CAR-T CELL THERAPY

Opening the discussion, Tilstra gave some background on the history of CAR-T cell therapy. First developed for prostate cancer in 2002, it was followed by the first CAR-T cell trial just over 10 years later in 2013, and the first FDA-approved CAR-T cell therapy in 2017. So, how are CAR-T cells manufactured? As summarized by Tilstra, T cells or natural killer cells are isolated from a patient's blood sample, and the *CAR* gene, encoding the CAR receptor, is inserted inside the isolated immune cells via a vector, then expanded and infused back into the patient.

Tilstra then drew the audience's attention to a case series published in 2024 that assessed the effect of a cluster of differentiation (CD)19 CAR-T cell therapy for three different types of autoimmune diseases: systemic lupus erythematosus (SLE), idiopathic inflammatory myositis, and systemic sclerosis.[1] The study enrolled 15 patients: eight with SLE, three with idiopathic inflammatory myositis, and four with systemic sclerosis, and administered a single infusion of CD19 CAR-T cell therapy after preconditioning with two types of chemotherapy: fludarabine and cyclophosphamide. Interestingly, after a median follow-up of 15 months, all patients achieved disease remission or major clinical response specific to their condition, allowing complete discontinuation of immunotherapy.

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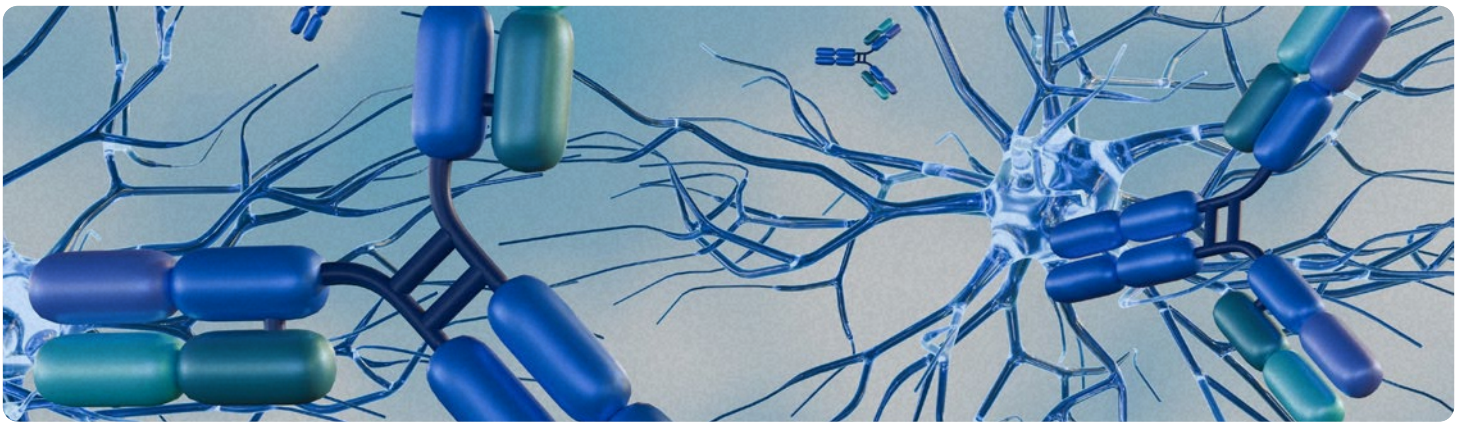
Tilstra then recapped the activation pathway from naïve B cells to CD27+ antibody-secreting memory B cells. Naïve B cells become activated via toll-like receptor (TLR) 7 and TLR9, with TLR9 directing activation via the germinal center; however, B cells can also become activated in the extrafollicular space. Once activated, these naïve B cells migrate to the germinal center, driven by cytokines such as IL-21 and IL-4. There, they interact with T follicular helper cells in the dark zone and undergo expansion and somatic hypermutation, generating both CD27+ memory cells and long-lived plasma cells. Although this process is well established, Tilstra highlighted growing research interest in the alternative extrafollicular pathway, where cytokines IL-12 and interferon gamma interact with activated naïve B cells to drive the production of several cell types, notably double-negative (DN)1-3, plasmablasts, and long-lived plasma cells.

QUESTION 1: CAN WE AND SHOULD WE CONSIDER MORE SPECIFIC B CELL TARGETS?

Tilstra then posed an important question: "Which subset of B cells may be targeted by unique CAR-T cells?" He presented a slide illustrating the various B cell subtypes, from pro- and pre-B cells in the bone marrow to transitional, naïve, germinal centre, memory, and plasmablast populations in the periphery, spleen, and lymph nodes, and finally plasma cells back in the bone marrow. While CAR-T cell therapy commonly targets CD19 due to its widespread expression across most B cell types, Tilstra noted that CD19 expression is reduced in plasmablasts and plasma cells. CD20 is another frequently used target, but it is more restricted, as it is present only from the pre-B cell stage through to some memory B cells. CD38 is expressed across all B cell types, though its expression is variable and tends to be highest in later-stage populations. Additional targets discussed included B cell maturation antigen (BCMA) and B cell activating factor receptor.[2]

The question was then posed to the panellists. Sanz responded first, cautioning that much remains to be understood in this field and that this foundational knowledge is essential before refining treatment targets. He



emphasized that treatment specificity should consider not only B cell subtypes but also differences between patient populations, depending on which pathway, germinal centre or extrafollicular, is most relevant to their disease.

"Different patients are going to be different, so when we talk about which B cells, specific B cells, might be the target, I would argue that there are going to be some groups of patients for which the germinal center pathway may be a better target, or the extrafollicular pathway, and the other way around."

Shen added that more disease-specific context is needed, particularly in identifying the pathogenic clone in each case. He also noted that further research is required to determine whether precursor B cell populations should also be targeted. In conclusion, Shen recommended a broad approach to B cell targeting for CAR-T therapy at this stage, given current knowledge and evidence.

QUESTION 2: IF WE WERE TO BE MORE SPECIFIC, WHAT SHOULD OUR B CELL TARGETS BE? ARE THERE DIFFERENT TARGETS FOR DIFFERENT DISEASES?

Building on this, Tilstra then posed another thought-provoking question: "If we were to consider being more specific, what should our B cell targets be?" He introduced the concept of 'precision immunotherapy', asking whether different diseases may require distinct targets. Tilstra suggested several cell populations for targeted CAR-T therapies, in addition to CD19 and CD20. These included 1) plasma cells using BCMA-CAR-T and anti-CD38 CAR-T; 2) autoimmune or age-associated B cells or DN2 B cells; and 3) autoreactive B cells.

Focusing on plasma cells, many autoimmune diseases are characterized by autoantibody production, with plasma cells and plasmablasts as the major producers of these autoantibodies. As Tilstra highlights, if CAR-T cell therapy becomes more targeted by B cell subtype, plasma cells would be an ideal population to pursue. For example, daratumumab, which targets CD38 expressed on plasma cells, has demonstrated efficacy in lupus nephritis.

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When this concept was presented to the panel, Sanz urged caution, noting: "I think it is hard to think that the plasma cells alone, or the autoantibodies alone, are responsible for the entire burden of disease." Shen agreed, adding that targeting only plasma cells may not result in a sustainable clinical remission. "If we have not eliminated upstream control and determined these very critical extrafollicular pathogenic cells, [then] we have not cut the upstream origin of these cells."

QUESTION 3: IS THERE UTILITY IN TARGETING SPECIFIC B CELL AFFINITY POPULATIONS?

Tilstra then shifted the discussion toward whether therapy should target specific B cell populations that express known pathogenic markers. For instance, it is known that some autoimmune diseases show high levels of antibodies produced by B cells with the VH4-34 heavy chain segment.[3] Additionally, anti-Sm and anti-Jo-1 are autoantibodies found mainly in SLE and polymyositis, respectively. Sanz explained that, "for those who might not be familiar with it, typically, the VH4-34 B cells are anywhere from 5–10% of all naïve cells, including in healthy people, but they are heavily central in the germinal centers, and thus, effective in lupus." While he acknowledged the potential of targeting B cells that express known pathogenic markers, such as VH4-34, he cautioned that this approach would require selecting patients in whom the marker is not only pathogenic but also the sole pathogenic B cell population, something that is challenging to determine in practice.

ANTIBODY REPERTOIRES AFTER CAR-T CELL THERAPY

Tilstra then drew attention to two studies from 2022 and 2025. The first study demonstrated that autoantibody profiles measured using a 57-antigen microarray could reliably detect patients who will later develop SLE, identifying 53% of pre-diagnosis cases with high specificity (94%), highlighting their potential as early diagnostic biomarkers to prevent irreversible organ damage.[4] The second study was a Phase I trial that showed that dual anti-CD19/anti-BCMA CAR-T cell therapy was safe and highly effective in treatment-refractory SLE, inducing remission in 80% of patients and eliminating autoreactive B cell and plasma cell clones, with sustained immune reconstitution and potential long-term cure.[5]

CONCLUSION

The session highlighted that while CAR-T therapy targeting broad B cell populations shows strong promise in SLE and other autoimmune conditions, the future lies in refining targets based on individual disease mechanisms and pathogenic cell subsets. Continued research into B cell biology and autoantibody profiles will be crucial to advancing precision immunotherapy and improving long-term treatment outcomes.

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