A Humanizing Rewrite for CAR T Cells in Autoimmune Disease: A Step Toward Repeatable, Durable Therapy

By Samia Chergui

Can the immunogenicity challenges of traditional CD19 CAR T cells be solved by replacing the murine antibody component with a human analog? In their 2024 Molecular Therapy – Methods & Clinical Development study, Peng et al. present CABA-201, a fully human anti-CD19 CAR T therapy aimed at treating autoimmune disease with greater persistence and safety.[1]

Autoimmune diseases affect more than 4% of the global population and often require chronic treatments that carry serious side effects.[2] Conditions such as systemic lupus erythematosus (SLE), multiple sclerosis (MS), and pemphigus vulgaris (PV) involve aberrant B cell activity and the production of self-reactive antibodies.[3] While anti-CD20 monoclonal therapies like rituximab have provided clinical relief, they fall short in fully eliminating tissue-resident B cells and often necessitate repeated dosing.[4,5] These limitations have driven interest in the use of chimeric antigen receptor (CAR) T cell therapies targeting CD19, a B cell marker, to achieve deeper, more durable immunomodulation.[6,7,8]

Recent clinical reports suggest that CD19 CAR T cells may induce long-lasting remission in SLE and other autoimmune disorders.[7,8] Yet most CD19 CAR constructs in use today contain murine-derived antigen-binding regions, which can trigger immune responses that compromise therapeutic persistence and limit the feasibility of retreatment.[9,10] This raises a key question: Can a fully human anti-CD19 CAR T cell preserve therapeutic efficacy while reducing immunogenicity, particularly in patients who may need repeated dosing?

A schematic of this therapeutic strategy is presented in **Figure 1** to illustrate the proposed mechanism of B cell depletion in autoimmune disease. The authors evaluate CABA-201 across a series of preclinical models using both healthy donors and patients with autoimmune diseases, comparing it to the widely used murine-based FMC63 CAR T cell.

Both CABA-201 and FMC63 CARs demonstrated robust surface expression and equivalent CD4/CD8 T cell subset composition after *ex vivo* manufacturing. In cytotoxicity assays, CAR T cells from both constructs showed >70% killing efficiency against $CD19^+$ leukemia cells across a range of effector-to-target ratios. Cytokine profiling revealed high levels of IFN-γ, TNF-α, IL-2, and GM-CSF, with CABA-201 eliciting slightly higher output in some conditions.[1] These results align with previous work showing that fully human CAR constructs can elicit potent cytotoxic and cytokine responses *in vitro*.[11,12]

In vivo, both CAR T products induced strong tumor clearance in NSG mice bearing CD19+ leukemia xenografts. Bioluminescent imaging and flow cytometry confirmed CAR T cell trafficking to lymphoid organs and prolonged persistence, especially in the spleen. Importantly, CABA-201 did not bind or lyse CD19-negative epithelial cells in co-culture assays, indicating minimal off-target toxicity.[1]

To extend relevance to autoimmune disease, Peng *et al.* tested CABA-201 using T cells from patients with SLE, RA, MS, PV, scleroderma, and inflammatory myopathy. In all cases, CAR T cells maintained high surface expression, displayed antigen-specific activation markers (CD25, CD69), and eliminated autologous $CD19^+$ B cells without affecting healthy epithelial cells.[1] These findings support the versatility of CABA-201 across disease settings and patient backgrounds.

By eliminating the murine antibody domain, CABA-201 may offer a path toward more durable treatments without eliciting immune responses against the construct, which would allow for future retreatments that are critical in attenuating autoimmunity[1,11,12] While Peng *et al.* convincingly demonstrate the preclinical efficacy and selectivity of this platform, questions remain about how these effects will translate in human autoimmune settings. Disease heterogeneity, antigen escape, and T cell exhaustion may complicate long-term outcomes. Nonetheless, CABA-201 represents a significant step forward in humanizing CAR T cell platforms for safer and more sustainable use in chronic immune disorders.

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University of Kansas
Corresponding Author jtreml@@ku.edu

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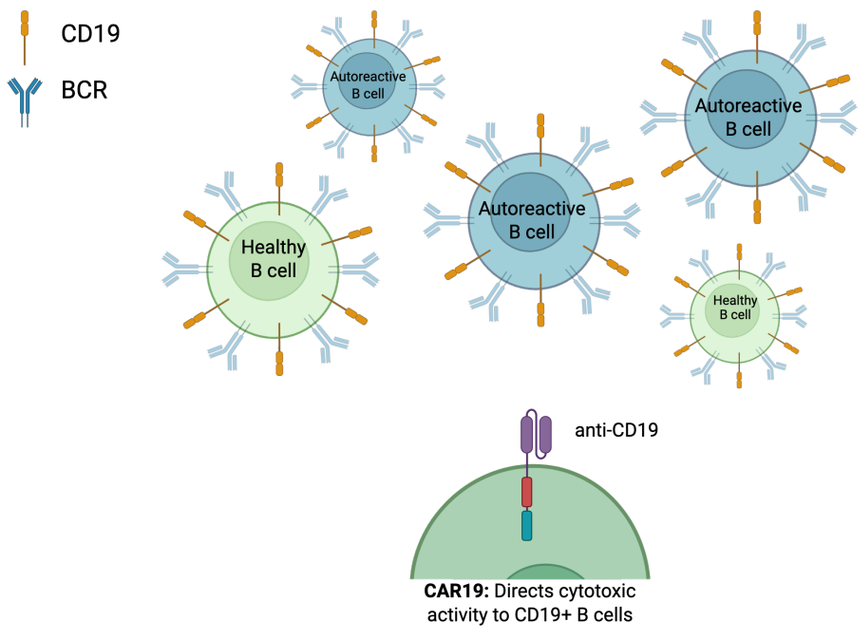

Figure 1 | Anti-CD19 CAR T Cells improve antibody-mediated autoimmune disorders | CABA-201 CAR T cell therapy utilizes fully human anti-CD19 CAR (IC78 scFv with 4-1BB), to target and eliminate over-represented autoreactive $CD19^{+}$ B cells, helping restore immune balance.

Armored CARs rooting out cancer cells in a hostile tumor microenvironment