

Peer review

Waxman, Andrea. 2025. "Novel Cellular Engineered Therapeutics Targeting Autoreactive B Cells in Systemic Lupus Erythematosus." *Journal of High School Science* 9 (1): 321–36.

1. This manuscript leaves out a significant amount of content including drugs and signaling pathways/mechanisms such as JAK-STAT pathway inhibitors, mTOR inhibitors, calcineurin inhibitors, Transmembrane Activator and Calcium-modulator and cyclophilin ligand (CAML) Interactor (TACI), inducible T-cell co-stimulatory ligand (ICOSL) binders, Neutrophil extracellular traps and low density granulocyte reducers, spleen tyrosine kinase inhibitors, . See for example: <https://doi.org/10.1186/s43556-024-00217-8>, for a comprehensive presentation of SE medicines, both approved and in clinical trials, along with their mechanisms of action. The primary requirement of a review paper is to capture all the published literature as a start. However, this alone will not satisfy the Journal's requirements and expectations for a review paper; see here: <https://jhss.scholasticahq.com/for-authors>, types of manuscripts, review papers.
2. Your proposed bispecific CAR-T cell therapy had been realized and was on the verge of clinical trials, when the company ImmPACT bio was acquired by Lyell. Lyell, repurposed the CD19/20 bispecific CAR-T cell therapy, originally developed for SLE, into a large B-Cell lymphoma medicine. See: <https://www.empr.com/home/news/drugs-in-the-pipeline/impt-514-car-t-cell-sle-lupus-nephritis-fast-track-designation/>
3. Another BiTE study is underway that targets the CD3 antigen on T-cells as well as the CD19 on B cells that then is thought to effectuate killing only those B cells (including tissue resident B cells) that overexpress CD19. See: https://lupus.bmj.com/content/11/Suppl_3/A16 and reference 13 therein for the clinical trial.
4. CD19-BAFF CAR-T cells are in clinical trials for autoimmune disease, see: <https://clinicaltrials.gov/study/NCT06279923> and <https://doi.org/10.1038/s41375-021-01477-x>
5. In this context, it is interesting that CAR-T cells; sourced from cryopreserved leukapheresis products from patients with SLE despite their previous treatment with immunosuppressive therapies; targeting the B19 antigen were less likely to produce inflammatory cytokines and ICANS responses. These allogenic products may represent an advance over autologous products. See : <https://doi.org/10.1016/j.jtct.2024.03.023>. The mechanism for this serendipitous beneficial effect needs to be researched.
6. If successful, the CAR-T cells derived from point 5 can then be engineered further into BiTEs and/or logic gate activated multifunctional B cell engagers.
7. Allogenic CAR-T cells from induced Pluripotent Stem Cells (iPSCs) are in clinical trials ((NCT06308978) <https://ir.fatetherapeutics.com/news-releases/news-release-details/fate-therapeutics-presents-new-phase-1-clinical-data-ft819-shelf>
8. To be publishable as a review paper in this Journal, you must propose at least one idea or advancement that does not yet appear in the public domain. I propose that you combine the premises of point 5 and 7 and propose that iPSCs be engineered from SLE patients' B-Cells. These SLE derived iPSCs can then be engineered into allogenic CAR-T cells - either targeting one antigen or many. These may prove more effective in SLE patients. You can of-course, present your own idea or advancement. See this related publication and references therein: <https://doi.org/10.1186/s13287-022-03145-y>

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Calcium-modulator and cyclophilin ligand (CAML) Interactor (TACI), inducible T-cell co-stimulatory ligand (ICOSL) binders, Neutrophil extracellular traps and low density granulocyte reducers, spleen tyrosine kinase inhibitors, . See for example: <https://doi.org/10.1186/s43556-024-00217-8>, for a comprehensive presentation of SE medicines, both approved and in clinical trials, along with their mechanisms of action. The primary requirement of a review paper is to capture all the published literature as a start. However, this alone will not satisfy the Journal's requirements and expectations for a review paper; see here: <https://jhss.scholasticahq.com/for-authors>, types of manuscripts, review papers.

My review was intended to focus on cellular immunotherapies but I acknowledge that I should have provided a bigger picture of alternative treatments. I have added more information on this as suggested. I added information about Neutrophil extracellular traps in my antibodies paragraph in the "Immunology of Lupus" section. In my "Current Treatments for Lupus" section, I added information on antimalarials, nonsteroidal anti-inflammatory drugs, JAK-STAT inhibitors, mTOR inhibitors, BiTEs, and CD19/BAFF-R dual-targeted CAR T cells.

2. Your proposed bispecific CAR-T cell therapy had been realized and was on the verge of clinical trials, when the company ImmPACT bio was acquired by Lyell. Lyell, repurposed the CD19/20 bispecific CAR-T cell therapy, originally developed for SLE, into a large B-Cell lymphoma medicine. See: <https://www.empr.com/home/news/drugs-in-the-pipeline/impt-514-car-t-cell-sle-lupus-nephritis-fast-track-designation/>
3. *I did not propose an anti-CD19/20 CAR-T cell therapy. My proposed therapeutic is novel, and despite extensive searches, I have not found any articles about it. I proposed a CAR T cell therapy targeting CD11c, CD86, and CD40L.*
4. Another BiTE study is underway that targets the CD3 antigen on T-cells as well as the CD19 on B cells that then is thought to effectuate killing only those B cells (including tissue resident B cells) that overexpress CD19. See: https://lupus.bmj.com/content/11/Suppl_3/A16 and reference 13 therein for the clinical trial.

This is useful to include, although I did mention CLN-978, which is another T cell engager, already. I have added it in the "Current Treatments for Lupus" section.

5. CD19-BAFF CAR-T cells are in clinical trials for autoimmune disease, see: <https://clinicaltrials.gov/study/NCT06279923> and <https://doi.org/10.1038/s41375-021-01477-x>

This is useful to include. I have included it in the "Current Treatments for Lupus" section under the paragraph discussing belimumab.

6. In this context, it is interesting that CAR-T cells; sourced from cryopreserved leukapheresis products from patients with SLE despite their previous treatment with immunosuppressive therapies; targeting the B19 antigen were less likely to produce inflammatory cytokines and ICANS responses. These allogenic products may represent an advance over autologous products. See : <https://doi.org/10.1016/j.jtct.2024.03.023>. The mechanism for this serendipitous beneficial effect needs to be researched.

7. *The paper linked seems to be for an autologous method, but I do find it interesting that products from these patients produced fewer cytokines. I have addressed this by proposing engineering strategies to limit additional inflammation at the bottom paragraph of concerns with my proposed treatment. However, I had already mentioned the risk of cytokine release syndrome in my table of treatments.*
8. If successful, the CAR-T cells derived from point 5 can then be engineered further into BiTEs and/or logic gate activated multifunctional B cell engagers.

Do you mean that the CAR T cells should secrete BiTEs or engagers? I like the idea of a logic gate, but there are complexities associated with adding too many edits to an engineered cell therapy, so I would like to keep my proposal simple and realistic.

9. Allogenic CAR-T cells from induced Pluripotent Stem Cells (iPSCs) are in clinical trials (NCT06308978)
<https://ir.fatetherapeutics.com/news-releases/news-release-details/fate-therapeutics-presents-new-phase-1-clinical-data-ft819-shelf>

iPSCs are known to result in a less mature and functional product than their true adult cell counterparts, which is why no iPSC-derived immunotherapy has yet received FDA approval despite years of attempts and many clinical trials. Given the success of allogeneic CAR T cell companies, such as Poseida, which was just bought by Roche for over 1 billion dollars, I would prefer to use adult immune cells rather than iPSCs.

10. To be publishable as a review paper in this Journal, you must propose at least one idea or advancement that does not yet appear in the public domain. I propose that you combine the premises of point 5 and 7 and propose that iPSCs be engineered from SLE patients' B-Cells. These SLE derived iPSCs can then be engineered into allogenic CAR-T cells - either targeting one antigen or many. These may prove more effective in SLE patients. You can of-course, present your own idea or advancement. See this related publication and references therein:
<https://doi.org/10.1186/s13287-022-03145-y>

My proposal does not yet appear in the public domain, so I would prefer to stick with this proposal - but I do agree with the concern about cytokine release, so I have modified it to address this potential issue in two different ways (in the paragraph introducing CAR T cell therapies and the bottom paragraph of concerns with my proposed treatment).

Note: I adjusted my "Discussion" section and treatments table with the additional information I added.

Thank you for addressing my comments. I have three outstanding concerns.

1. I would still like to see point 5 addressed explicitly in the manuscript because it can be applied to allogenic cells and may well render your proposed treatment less likely to produce CRS and ICANS responses if (at least some of) those allogenic cells are derived from SLE patients. Please insert in the manuscript (change as necessary) with the relevant reference. "...In this context, it is interesting that CAR-T cells; sourced from cryopreserved leukapheresis products from patients with SLE despite their previous treatment with immunosuppressive therapies; targeting the B19 antigen were less likely to

produce inflammatory cytokines and ICANS responses. These allogenic products may represent an advance over autologous products.....”

2.Include your response to point 7 in the manuscript as a rationale for not discussing iPSC related treatments. Also include the Fate therapeutics phase I reference plus a reference for “... iPSCs are known to result in a less mature and functional product than their true adult cell counterparts, which is why no iPSC-derived immunotherapy has yet received FDA approval.....”

3.If your treatment targets cellular therapeutics, maybe you should say so in the changed title: Novel cellular engineered therapeutics targeting autoreactive B cells in Systemic Lupus Erythematosus

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I added this under “Proposed Treatment” in the paragraph regarding concerns that could arise with my proposed treatment.

11. Include your response to point 7 in the manuscript as a rationale for not discussing iPSC related treatments. Also include the Fate therapeutics phase I reference plus a reference for “... iPSCs are known to result in a less mature and functional product than their true adult cell counterparts, which is why no iPSC-derived immunotherapy has yet received FDA approval.....”

I added this in my discussion section, where I mention current treatment limitations.

12. If your treatment targets cellular therapeutics, maybe you should say so in the changed title:
Novel cellular engineered therapeutics targeting autoreactive B cells in Systemic Lupus Erythematosus

I changed my title to reflect this. Thank you!

Thank you for addressing my comments. I can now recommend accepting the manuscript. Note that copyediting cannot proceed until:

- 1.You submit a word document of the manuscript, 12 font Times New Roman, single column text.
 - 2.You reformat the references to include the first 6 authors (if > 6 authors) followed by an et al. Remove the ‘and’ symbol (ampersand &) between the penultimate and last authors and generally ensure that references are consistently formatted. Do NOT use the software’s numbering system to number the references; instead number them manually.
- Please upload your word doc to the communications thread. Once this is received, we will begin copyediting.