

important. Our diet affects our metabolism. So too do the myriad metabolic processes of our own cells and those of the millions of bacteria that live in our mouth, stomach, and gut.<sup>6</sup> In the future, it will be important to map the metabolite interactions between food intake and the gut microbiome composition, and thereby enable prediction of how the gut microbiome can engage in converting bioactive metabolites in our food to compounds that cause increased risk of disease development. This is a complex endeavor. However, through combined blood metabolome and gut microbiome analyses of very large cohorts and standardizing data collection, we will gain greater mechanistic insight into how the gut microbiome impacts human health.

#### DECLARATION OF INTERESTS

J.N. is a shareholder in Chrysea, Inc. that produces bioactive metabolites through synthetic biology.

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## CAR T therapy extends its reach to autoimmune diseases

Daniel J. Baker<sup>1,2,3,4,\*</sup> and Carl H. June<sup>1,2,3,\*</sup>

<sup>1</sup>Center for Cellular Immunotherapies, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104, USA

<sup>2</sup>Department of Pathology and Laboratory Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104, USA

<sup>3</sup>Parker Institute for Cancer Immunotherapy at University of Pennsylvania, Philadelphia, PA 19104, USA

<sup>4</sup>Cardiovascular Institute, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, PA 19104, USA

\*Correspondence: [bakerda@pennmedicine.upenn.edu](mailto:bakerda@pennmedicine.upenn.edu) (D.J.B.), [cjune@upenn.edu](mailto:cjune@upenn.edu) (C.H.J.)

<https://doi.org/10.1016/j.cell.2022.10.026>

**CAR T therapy has revolutionized the treatment of hematologic cancers. In their recent *Nature Medicine* paper, Mackensen et al. report the use of CAR T cells to treat systemic lupus erythematosus in five patients. This provides enthusiasm to further explore CAR T therapy beyond oncology.**

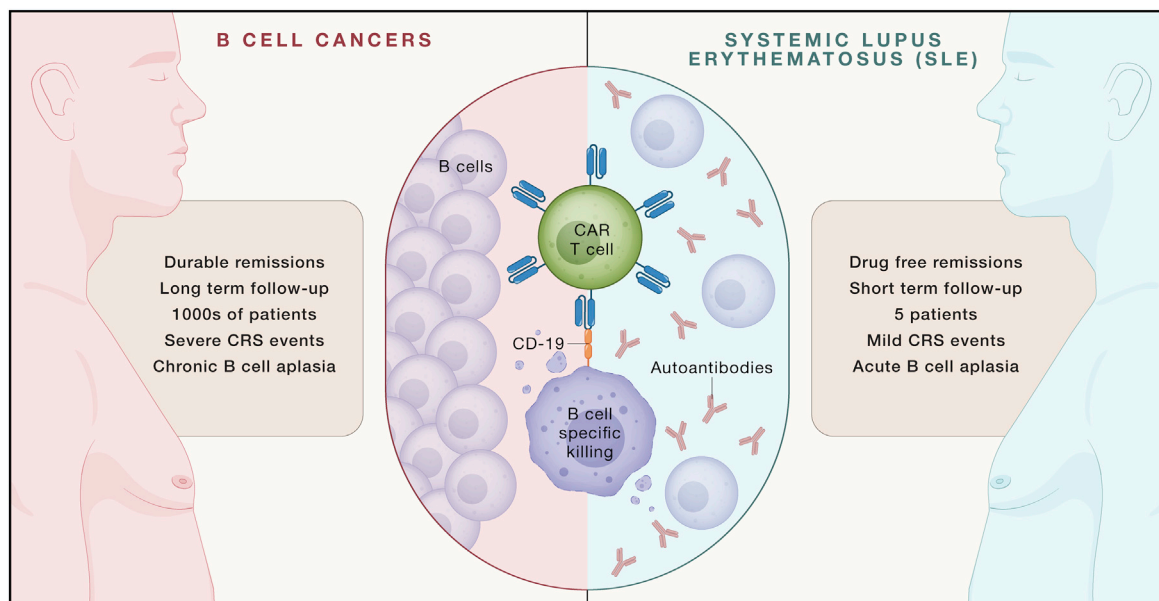
Engineering chimeric antigen receptors (CARs) into T cells has been transformative for the field of oncology. This approach allows these synthetic immune cells to recognize and eliminate cancer in a powerful and precise manner. CAR T therapy has shown remarkable and lasting therapeutic effects in leukemia, lymphoma, and multiple myeloma.<sup>1</sup> This has resulted in multiple regulatory approvals over the last 5 years. These exciting results have incited substantial effort to expand CAR T therapy throughout cancer treatment and beyond. Recently, Mackensen et al. reported using CAR T therapy to treat five young adults diag-

nosed with systemic lupus erythematosus (SLE).<sup>2</sup>

SLE is an autoimmune disease where the body recognizes self-antigens as foreign, resulting in the activation of autoreactive B and T cells. This self-targeting can result in fatigue, inflammation, and in severe cases, death. Several clinical strategies target B cells with therapeutic effects; however, these approaches are limited as severe forms of SLE are resistant to treatment and no long-term strategy to achieve drug-free remission has been realized. CAR T cells targeting CD19 have shown ability to eliminate pathologic B cells in cancer, leading to

durable remissions and even cures (Figure 1). We, and others, have proposed CAR T therapy may have applications in treating autoimmune diseases such as SLE.<sup>3,4</sup> Building on an exciting case report from last year where CD19 CAR T products were repurposed to deplete B cells in a patient with SLE,<sup>5</sup> Mackensen et al. expand on this and report this approach in five patients (Figure 1). In all five patients, these CAR T cells engrafted, expanded, and eliminated B cells. This was accompanied by a resolution of SLE symptoms in the three months following CAR T infusion. Impressively, these patients have been declared





**Figure 1. CAR T cells approved to target B cells in cancer can be used to treat SLE**

CAR T cells that have been used to treat B cell leukemias and lymphomas are able to eliminate pathologic B cells in five patients with systemic lupus erythematosus. The short-term results demonstrate drug-free remissions with manageable CRS and temporary B cell aplasia.

to be in remission with a discontinuation of their immunosuppressive drugs.

A major safety concern associated with CAR T therapy is an inflammatory response intrinsically linked to high amounts of cell killing. In cancer, where pounds of cells are eliminated, patients can experience severe cases of cytokine release syndrome (CRS) that may include high fevers, respiratory dysfunction, or even major organ failure. Mackensen et al. observed a small rise in cytokines upon CAR T infusion in these five SLE patients; however, this was accompanied by mild CRS, which was routinely managed. This low amount of CRS is likely because the number of B cells targeted in SLE is significantly lower than in cancer, where large numbers of malignant target cells can be encountered. This smaller target burden not only has advantages as it pertains to CRS but may also decrease the number of CAR T cells needing to be infused, thus limiting potential unwanted CAR T cell toxicity. These preliminary results in SLE suggest that other noncancerous diseases may have a superior safety profile due to the smaller proportion of targeted cells.

In leukemia, the early reappearance of normal B cells is correlated with patient relapse. Interestingly, Mackensen et al.

report reemergence of B cells in all patients after a few months; however, there was no relapse of SLE symptoms at the time of the report. For 60% of the patients, less than a year has passed since CAR T treatment and it is too early to tell whether these patients will remain in remission. It is promising that B cell aplasia was rescued without the return of disease symptoms in the short term. The fact that B cells return strongly suggests that functional CAR T cells do not persist in these patients. The authors suggest the resolution of symptoms accompanied with only acute B cell aplasia could be a result of a “deep reset” and present immune phenotyping data to show that the new B cell receptor repertoire is significantly altered compared to the repertoire prior to CAR T infusion. This is in contrast to what we have seen in leukemia with CAR T cells circulating a decade following infusion, and this generally is accompanied by long-term B cell aplasia.<sup>6</sup> It is tempting to speculate that the differential persistence of CAR T cells in leukemia and lupus (if confirmed in larger cohorts) likely relates to distinct cellular niches for memory CAR T cells.<sup>7</sup> Where these memory CAR T cells reside plays a significant

role in their persistence. It is possible that the reason for the lack of persistence in lupus is due to CAR T cells situated in secondary lymphoid organs, whereas in leukemia memory CAR T cells reside in the bone marrow. Further work should be done to quantify if CAR T cells are still present and functional in the five SLE patients. Additionally, kinetic studies should be conducted to elucidate the therapeutic window for such a strategy.

Another issue arising is the requirement for lymphodepletion and the therapeutic role that it may have had. The patients were treated with fludarabine and cyclophosphamide prior to CAR T infusion, using the same regimen as for cancer patients. Lymphodepletion has been shown to increase CAR T engraftment and proliferation, and it may have potentiated the effects of CAR T in SLE patients. However, this raises a question that the lymphodepletion per se may have mediated beneficial effects on SLE. Notably, previous studies have shown that high dose chemotherapy and autologous hematopoietic stem cell transplantation can be beneficial in SLE.<sup>8</sup> Further studies are necessary to determine whether lymphodepletion is required for CAR T therapy of SLE.

Though exciting, these results are limited to a handful of patients and long term follow up will reveal the full spectrum of potential safety concerns. It must be stressed that these results are still preliminary, and longer studies with greater number of patients are needed to validate them. Until then, we should use caution applying CAR Ts to other diseases. Nonetheless, this clinical report is encouraging: it suggests that CAR T therapy could have clinical potential in a wide range of disease contexts. Recent preclinical studies demonstrate that CAR T therapy may prove effective in other autoimmune settings and in infectious diseases.<sup>9,10</sup> CAR Ts have also shown potential more broadly in the contexts of heart failure, liver disease, and diabetes.<sup>11</sup> The success of CAR T therapy in blood cancer highlights the potential of this modality in other contexts. In cancer, clearance of nearly all neoplastic cells is necessary, whereas in most other disease contexts clearance of a subset of pathologic cells is therapeutic. Similarly, the tumor microenvironment in cancer has proved a significant hurdle for CAR T therapy, whereas in most other diseases target cells are not localized in such an inaccessible and inhospitable environment. The results from this report signals the possibility of a new paradigm for this living drug and, ultimately, new hope for patients.

#### ACKNOWLEDGMENTS

We would like to thank members of the June lab for their helpful comments. This work was supported by P01CA214278 and the Parker Institute for Cancer Immunotherapy (C.H.J.)

#### DECLARATION OF INTERESTS

C.H.J. is an inventor on patents and/or patent applications licensed to Novartis Institutes of Biomedical Research and receives license revenue from such licenses. C.H.J. is a scientific founder of Tmunity Therapeutics and Capstan Therapeutics. C.H.J. is a member of the scientific advisory boards of AC Immune, Alauos, Blue-sphereBio, Cabaletta, Carisma, Cartography, Cellares, Celldex, Decheng, Poseida, Verismo, and WIRB-Copernicus.

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