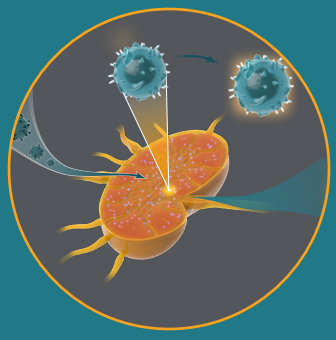
Umoja BIOPHARMA

The Next Step Forward in CAR T Development

Umoja's Integrated, In Vivo Approach

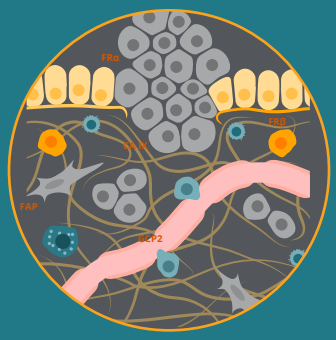
Contents

At Umoja Biopharma, we are addressing the challenges preventing broader use of CAR T therapy by:



Mass producing treatment to induce CAR T production within the body

Eliminating the need for lymphodepletion



Labeling solid tumors in a new way for T cell attack

INTRODUCTION

With the first approved product in 2017, CAR T (chimeric antigen receptor T-cell) therapy was hailed as "a new frontier in medical innovation."[1] The promise of genetic engineering to program the body's own immune system to fight cancer had finally come to fruition after almost 40 years in development. Real world experience in rare and treatment-resistant B cell lymphomas and leukemia, demonstrated CAR T therapy's promise – treatment in patients with these cancers showed response rates of 82% to 90%, with a complete response rate (defined as no signs of cancer after treatment) of 64% to 85.5%.[2-4]

The success of CAR T therapy in blood cancers has motivated further development of such treatments for broader use in more patients with diverse types of cancer. However, to achieve effective wider use, there are several challenges to overcome. Operational and logistical improvements are needed so manufacturing can be scaled to meet patients' needs in a cost-effective manner. In addition, current CAR T treatments exhibit treatment-limiting adverse effects and their utility is limited to a small number of blood cancers.[5-9]

At Umoja Biopharma, we are re-envisioning the path forward for transformative cancer treatments by addressing the aforementioned challenges to broaden use of CAR T therapy. Umoja's platforms allow for a streamlined CAR T therapy that is scalable and circumvents the need for the most problematic aspects of traditional CAR T regimens. Our approach also provides the means to expand the benefits of CAR T beyond blood cancers to include solid tumors where the need for new therapies is greatest.

Our approach directly addresses gaps in CAR T product safety and activity, manufacturing and scaling, targeting and delivery, to improve efficacy, cost-effectiveness, and accessibility of treatment.[5,9-13]

SAFETY AND EFFICACY

Autologous (Patient-Derived) Approaches

Current CAR T therapy begins with collecting immune cells from the patient by removing blood from one arm, filtering out and retaining white blood cells (i.e., leukocytes) and returning blood into the other arm – an hours-long process called ***leukapheresis***.[14,15]

After extraction, the patient's leukocytes are transported (usually by air) to a central manufacturing facility, where the DNA encoding the chimeric antigen receptor, which is the "CAR" in CAR T, is transfected into those T cells. The genetically modified cells are then allowed to grow and divide, in a process termed expansion, so that a large number of CAR T cells—specific to the individual patient—can be re-transfused into that patient. This process of making precision therapy and delivering it back to the patient can take 3 to 6 weeks for each individual.[2] Clinical experience suggests the wait time is psychologically difficult for patients and their social-support networks. Wait time may also increase mortality, especially for those with aggressive cancers who may experience clinical decline and require bridge chemotherapy or radiation therapy, become ineligible for the treatment, or die.[16] There is also evidence that CAR T cells may lose activity when days of expansion are increased to grow sufficient number of cells to achieve the target dose level.[17]

The advantage of autologous CAR T therapies is that the patient's immune system does not recognize the re-transfused cells as foreign and is not activated to attack them. The incoming CAR T cells are, therefore, able to attack the cancer without hindrance from host immune cells. To extend persistence of CAR T cells, which correlates with increased length of remission,[18-20] patients also undergo ***lymphodepletion***—chemotherapy to eliminate most of their white blood cells—before re-transfusion.[18,21]

Adverse effects of lymphodepletion and autologous CAR T transfusion treatment are significant and can be severe. Lymphodepletion can cause prolonged low white blood cell count with increased risk of severe infection.[20-24] Cytokine release syndrome (CRS), associated with the dose of lymphodepleting agents and thought to occur in response to rapid increases in cytokine levels,[25] is among the most common side effects of CAR T therapy and can be life-threatening but is generally treatable with tocilizumab.[2-4,26] Immune effector cell-associated neurotoxicity (ICANs) is another serious side effect common with approved CAR T therapies for blood cancers.[2-4,26,27]

Allogeneic (Donor-Derived) Approaches

Allogeneic CAR T therapy—making T cells from healthy donors rather than the patient's own cells—is one approach to overcome the challenges of current CAR T therapies.[5-9] In particular, the allogeneic CAR T strategy reduces wait times by mass-producing CAR T cells for off-the-shelf use, a clear advantage over the autologous process driven by an individual patient's need.[16] High-quality standardized mass production could provide cost advantages and also allow for a more defined treatment paradigm that does not depend on the success of autologous cell production. These changes alone are likely to expand patient eligibility and treatment equity. Despite this, an allogeneic approach does not address all of the limitations of autologous CAR T therapy.

Whether through allogeneic therapies, localized production, or other methods, there is a clear need for more cost-effective, highly active, safer, and more accessible CAR T therapy for blood and solid cancers. By unifying all aspects of CAR T therapy into a platform that is more cost effective, more directed and potentially safer while maximizing potential efficacy, Umoja hopes to bring the immense benefits of this therapy to the many people who need it.

Allogeneic CAR T therapy, as with autologous treatments, requires specialized lymphodepletion prior to CAR T cell infusion and thus shares the significant risks of infection, CRS, and ICANS. Allogeneic therapy also carries the added risk of rejection and graft-vs-host-disease (GVHD),[5-9,28,29] and even in the absence of full rejection or GVHD the patient's immune system may act to rid the body of allogeneic cells as foreign, an action likely to decrease the length of time, or persistence, of allogeneic CAR T cells remaining active. Although decreased persistence could be overcome by repeat treatments, each transfusion of new cells has to come from a different donor and requires repeat lymphodepletion, potentially reducing the cost and safety benefits of allogeneic CAR T.[30-32] While allogeneic treatments are likely to be of value for select indications, they do not represent a panacea for the shortcomings of autologous CAR T therapy.[32]

The VivoVec and RACR/TagCAR platforms are designed to deliver the potential treatment benefits of autologous CAR T therapy, using a patient's own immune cells to generate durable responses without the complex and difficult to scale manufacturing and logistics of current autologous CAR T transplant (Figure 1).

The Umoja Approach – Integrated Technologies May Offer A Better Way

Umoja is developing a unique integrated technology platform using genetic modification of a patient's own cells without extraction or external cell culture and expansion. Our VivoVec technology delivers genetic payloads directly to a patient's T cells in vivo and allows these cells to expand in a manner that resembles a natural immune response comprising a range of anti-tumor activities. This eliminates multiple steps in the process of creating individualized CAR T therapy, including leukapheresis, transport of cells, transfection, and expansion at a cell culture facility. Activation and expansion occur within the body through the activity of the small molecule-gated synthetic receptors TagCAR and RACR,[33-35] eliminating the delay between autologous cell harvesting and engineered CAR T cell infusion.[17] CAR signaling synergizes with RACR signaling to support maximal cell expansion and persistence. With no T-cell extraction, manipulation, or culture, there is also no need for lymphodepletion with chemotherapy, eliminating the risks of that process. Risks of CRS and ICANs may also be reduced when the patient's immune system shifts into cancer-fighting mode. A gradual accumulation of cancer fighting CAR T-cells from normal baseline levels, rather than an abrupt step function via engraftment of a large population of activated T-cells into an immunodepleted host, could have the potential to decrease these adverse effects.[25]

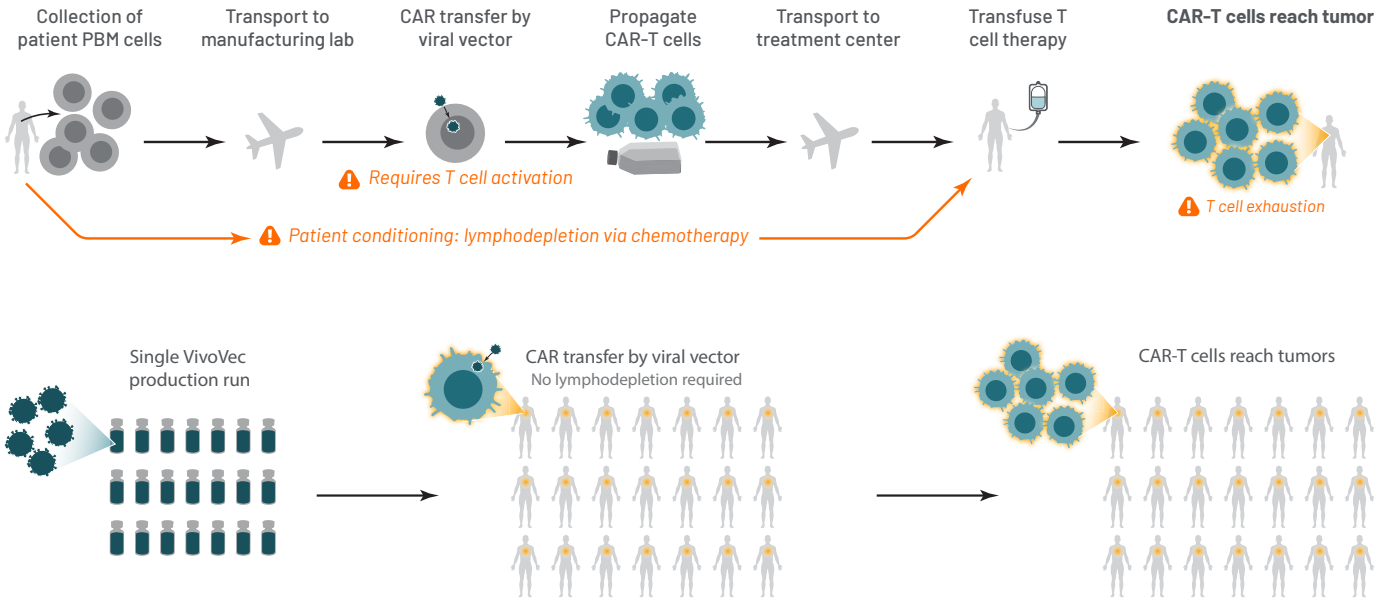


Figure 1. TOP: current manufacturing of CAR T therapy for one person requires 1) leukapheresis, 2) transport of cells to a manufacturing facility, 3) viral vector transfection, 4) cell expansion, 5) transport back to the health care facility, 6) lymphodepletion, 7) transfusion, and 8) CAR T cells encountering and fighting cancer cells. BOTTOM: the Umoja technology platform in development produces a 2000 L batch of VivoVec to treat approximately 1,000 people by 1) administering VivoVec to prompt the immune system to create CAR T therapy so that it can 2) encounter and fight cancer cells. For solid tumors, a third step involves adaptive targeting with Umoja's TumorTag. Tumor targeting of some form is also requisite for autologous or allogeneic cell treatments of solid tumors.

MANUFACTURING, SCALING & COST

More Efficient Processes Needed

Current autologous CAR T therapy is hampered by a complex multi-step manufacturing process that is primarily manual, labor-intensive, and requires transportation of a patient's cells to and from a centralized manufacturing facility (Figure 1). This process requires complex logistics and supply-chain management support, estimated to account for over 10% of labor costs.[36] The same estimate suggests labor costs account for 71% of the cost of producing a single treatment for one person that is priced at $375,000 to $475,000. Additional care costs of evaluation, leukapheresis, lymphodepletion, post-infusion care, and management of side effects, are estimated at an average $125,000 in the US and $60,000 (50,000 Euro) in European countries.[5,11,36-39] Although treatment with CAR T is cost effective considering the quality-adjusted life years (QALYs) saved,[36-39]

the costs are among the highest of any treatment and raise questions of accessibility and health care equity.[5-9]

The cost associated with scaling CAR T products out and up (for both autologous and allogeneic approaches respectively) is substantial, as facilities with large footprints are required to develop treatments. In addition, the cost and resources required to make one product for one patient is high and hard to scale accordingly.[32]

Allogeneic CAR T therapy, derived from healthy donors and manufactured in large batches that could treat many more patients, would have significant costs savings—primarily because of scalability. As noted earlier, it could also reduce wait times and potentially increase efficacy. Leukapheresis of T cells from many healthy donors would provide T cells to generate CAR T therapy that could be transported, transformed, and expanded in large batches. This can be expected to decrease the cost of these labor-intensive steps significantly. None of the process steps, however, would be entirely eliminated. There would still be costs associated with each step as well as added risks of adverse events with allogeneic CAR T therapy.[5-9,28,33]

It has also been suggested that instead of shipping extracted cells to a manufacturing site, health care facilities could have an in-house facility to transfect and expand a patient's T cells into CAR T therapy.[12,40,41] This would eliminate the transportation and facility costs of current CAR T therapy and slightly reduce wait time, but questions of scalability remain.[5]

The technology platform we are developing at Umoja takes an entirely different approach. Rather than upscaling or dispersing transformation and expansion of T cells into CAR T therapy, we aim to eliminate those steps altogether. The element of our platform that is produced at scale is our VivoVec technology, which induces a person's immune system to produce their own bespoke CAR T therapy. Scalable production of other viral vectors has been accomplished,[42-45] and three drugs delivered on viral vectors have been approved by the FDA.[46] We estimate the cost of producing a viral vector treatment to induce in vivo CAR T therapy to be a fraction of the cost associated with current autologous CAR T manufacturing. The cost per person is also expected to be lower than some of the approved viral vector-associated treatments because of the larger need for cancer treatments.

TARGETING, DELIVERY AND ACCESS

Targeted Directly to the Tumor

The success of CAR T therapy for blood cancers has, in part, resulted from a shared biology – as "liquid" tumors, the tumor cells are dispersed in the vascular and lymphoid compartments allowing them to be readily accessible to targeting by T cells that traffic efficiently through those same compartments. In addition, because blood tissues are regenerated constantly, we are able to transiently target both the tumor and the normal blood cells from which the tumor is derived – once the tumor cells are eradicated, the normal tissue compartment is naturally restored. This is not the case for solid tumors, which account for approximately 90% of new cancer cases each year. With solid tumors, targeting of antigens shared between the tumor and normal tissue could be fatal because we cannot even transiently go without (e.g. kidney, lung or liver function). In addition, solid tumors evolve through a mechanism in which the tumor cells recruit normal helper cells called "stroma" to build a protective environment around themselves to evade immune cell attack.Thus, there is a need to develop CAR T cells which can both modify the protective microenvironment and selectively target tumor cells vs. normal tissue.[6, 9,28,47]

The Umoja platforms under development address this challenge with our unique TumorTag technology, which may represent a universal approach to cancer therapy by targeting both the tumor and stromal elements. TumorTags are bispecific molecules that consist of a moiety that selectively bind to tumor cells or immunosuppressive tumor stromal cells. They can be designed to have a tumor-binding moiety that is antigen-specific or antigen-independent. The latter is a novel breakthrough targeting concept which circumvents the limitations of targeting cell surface proteins by exploiting metabolic alterations associated with malignant cell transformation to label tumors. Upon labeling, tumor cells become marked for recognition and destruction by TagCAR T cells, which are universal CAR T cells expressing a TagCAR that is engineered to bind to a fluorescein Tag. Zeroing in on stromal elements also is a key part of being able to effectively attack cancers, as tumors can stay hidden in these structures. Proof-of-concept in vivo studies have shown that the TumorTag combinatorial approach is a feasible means of directing therapy specifically to a malignant tumor.[48-50]

REACHING PATIENTS

The high rate of potentially serious adverse events with CAR T therapy and intensive nature of the treatment require as high as 31 days in the hospital and a price tag that can quickly reach $1 million U.S. dollars if complications occur. The FDA requires specialized training for teams who administer the therapy at certified centers with capability to manage the known side effects if they occur.[5-9] These limitations on who can administer and where therapy can be provided make treatment safer but also increase wait times, potentially lowering the benefit of treatment.[16] Location, cost, and time all significantly limit access to effective CAR T therapy. As a result, despite estimates confirming the cost-effectiveness of the existing CAR T regime,[37-39] questions have been raised about the ethics of these treatments because of the disparities in access. According to data shared by approved CAR T therapy drug manufacturers, as of 2019, it is estimated that likely less than 2,000 patients in the U.S. have been treated.[51]

CONCLUSION

CAR T has incredible promise and has delivered lifesaving therapy outcomes to a small but growing number of people with hematologic cancer. To make CAR T more accessible and more broadly useful, scaling manufacturing and reducing logistical complexities are critical next steps. Variability in outcomes and mitigation of safety concerns also need to be addressed. Other limitations on use requiring solutions include the complicated administration and high cost of therapy and the inability, as yet, to reach and treat solid tumors with specificity. At Umoja, our platforms are each designed to overcome these challenges. We aim to produce a safer, more efficacious, and more accessible therapy that can be used to treat both hematologic and solid cancers.

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