Overcoming *ex vivo* cell therapy manufacturing challenges through an *in vivo* lentiviral platform

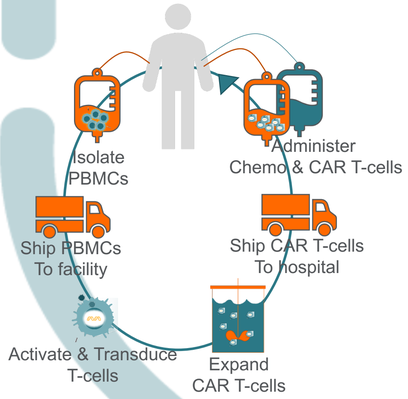
Sarah Gould, Ph.D.*; Sarah Dickerson, Ph.D.; Jessica Freeman; Branden Salinas, Ph.D.; Rich Getto, MBA; and Ryan Crisman, Ph.D.

*Contact author: sarah.gould@umoja-biopharma.com

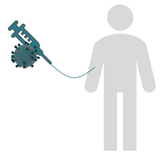
Introduction

Ex vivo CAR T-cell therapies have shown significant clinical success in treating hematological cancers. However, access to these life saving therapeutics has been severely limited due to the critical challenges in supply chain and manufacturing. Significant capital investments and costly overhead are required to produce these products, driving the cost to unattainable levels. With almost 200,000 new blood cancer diagnoses per year in the US[1], demand for life saving CAR T-cell therapies will undoubtedly continue to grow to levels unachievable with the current ex vivo manufacturing platforms and strategies, and skilled administration requirements. Umoja is pioneering a transformative in vivo CAR T-cell platform that would mitigate these challenges associated with ex vivo therapies, by using a universal, off-the-shelf, direct injection lentiviral vector to harness the patient's own immune system to create cancer targeting CAR T-cells in vivo, thereby removing the complex ex vivo CAR T-cell generation.

Ex Vivo CAR T-cell Therapy
1 batch = 1 patient



Umoja's In Vivo CAR T-cell Platform
1 batch = thousands of patients



Cuts out the patient T-cell isolation, activation, transduction, expansion, and lympho-depleting chemotherapy, and takes the lentiviral vector directly to the patient to create CAR T-cells inside their own body!

To highlight the advantages of Umoja's in vivo CAR T-cell generation platform via direct injection lentivirus over ex vivo autologous or allogenic CAR T-cell therapies in the below areas:

1. Expediting treatment for critically ill patients
2. Decouples batch failure from patient outcomes
3. Reducing supply chain, process, storage, and distribution complexity
4. Reducing cost through batch scale up to thousands of doses

Umoja's in vivo CAR T-cell platform allows for immediate treatment without the need for lympho-depleting chemo

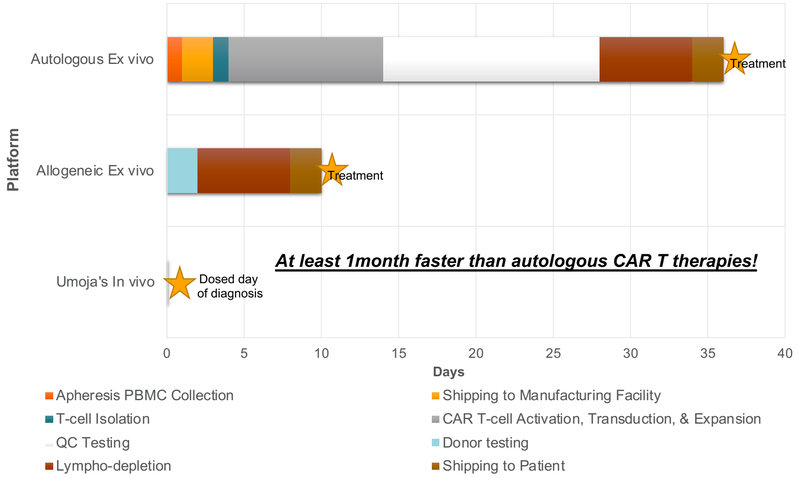


Figure 1: The difference in time to treatment between autologous and allogeneic ex vivo vs. in vivo CAR T-cell therapies.[2,3]

Patients treated per batch

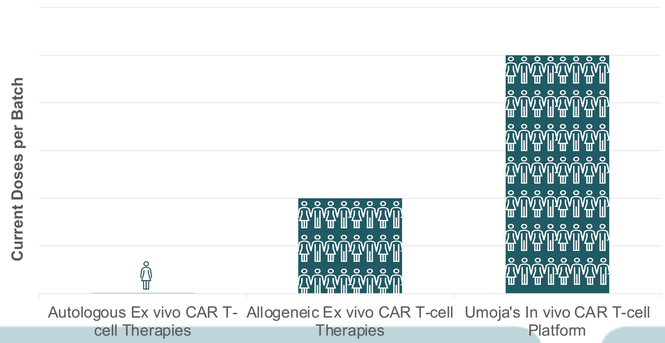


Figure 2: The number of patients that can be treated per batch using current platforms for ex vivo autologous and allogeneic therapies vs. Umoja's in vivo CAR T-cell therapy.[3,4]

Discussion

Eliminating the ex vivo CAR T-cell generation through use of Umoja's in vivo lentiviral vector has significant advantages to the patient, including immediate, on-demand treatment and no harsh, lymphodepleting chemotherapy is required. The lentiviral vector can be made and stocked in hospitals well in advance to ensure rapid treatment.

Further, the in vivo lentiviral vector manufacturing process uses a more consistent starting cell line as compared to variable patient cells in ex vivo autologous and allogeneic donor cell therapies, meaning a faster and less complex manufacturing process more similar to that of a traditional therapeutic. In addition to a more reliable supply chain, each batch of direct injection lentiviral vector can potentially treat thousands of patients, instead of one or hundreds of patients as in ex vivo autologous or allogeneic therapies, respectively, making them a fraction of the cost. Lastly, ex vivo CAR-T cell therapies must be held on liquid nitrogen for storage and shipment, which is significantly reduced with in vivo lentivirus suspension drug product, simplifying distribution complexity and cost.[5]

Taken together, the advantages of Umoja's in vivo CAR T-cell platform not only disrupt the autologous ex vivo CAR T-cell space, but also the off-the-shelf allogeneic CAR T-cell therapies as well.

Conclusions

1. In vivo CAR T-cell, direct injection lentivirus therapies can be manufactured prior to diagnosis and do not require harsh, lympho-depleting chemo prior to administration, which allows for immediate treatment.
2. The lentivirus production process is much faster and less complex than ex vivo CAR T-cell therapies and are more scalable; potentially creating enough doses to treat thousands of patients per batch instead of just one or hundreds.
3. The lentiviral drug product can be more easily and widely distributed on dry ice instead of the liquid nitrogen required for cell therapies, reaching a larger percentage of the population.

1. "Statistics on Leukemia and Other Blood Cancers." All Blood Cancers, 3 May 2021, allbloodcancers.org/statistics/.
2. V. Picanço-Castro, *et al., Establishment of a simple and efficient platform for car-t cell generation and expansion: from lentiviral production to in vivo studies*. Hematology, Transfusion and Cell Therapy. 42:2 (2020) pp150-158.
3. B.T. Aftab, B. Sasu, J. Krishnamurthy, E. Gschweng, V. Alcazer, S. Depil. *Toward "off-the-shelf" allogeneic CAR T cells*. Advances in Cell and Gene Therapy. 3:3 (2020) https://doi.org/10.1002/acg2.86
4. A.P. Manceur, *et. al., Scalable Lentiviral Vector Production Using Stable HEK293SF Producer Cell Lines*. Human Gene Therapy Methods. 28:6 (2017) pp330-339.
5. B.C. Simpson. *Managing Refrigerated vs. Frozen Drug Product: What's The Big Deal?* Bioprocess Online.