Charging towards the CAR-T cells of tomorrow

The rise of chimeric antigen receptor (CAR)-T cell therapies has dramatically changed the landscape and outlook for patients with certain haematological cancers. More than five years have passed since the United States Food and Drug Administration approval of the first such therapy in 2017. Since then, autologous CAR-T therapies have been tested and approved for use in a range of indications.

The development trajectory of CAR-T holds substantial promise for patients worldwide, but challenges remain in bringing autologous CAR-T therapies to the full range of patients who could benefit from them. Some challenges are related to the product itself – for instance, the risk of T cell exhaustion leading to incomplete or brief responses in patients. Others are related to the complexity of manufacturing and delivering the product.

As scientists leading research at Novartis, the first pharmaceutical company to significantly invest in developing and commercializing CAR-T therapies, we aim to meet these challenges. Most recently, we developed the T-Charge™ platform for investigational autologous CAR-T cell therapies, introduced at the 63rd American Society of Hematology Annual Meeting & Exposition (ASH) in 2021, and currently advancing in clinical development. T-Charge is designed so that CAR-T cell expansion occurs primarily in vivo, eliminating the need for extended ex vivo culture time. This design essentially enables the body to act as its own bioreactor, which may offer benefits for patients1,2.

Conventional CAR-T products consist mostly of central memory (Tcm) T cells and also include some more mature effector (Teff) and effector memory (Tem) cells with a higher degree of senescence and effector function and a shorter potential lifespan. In contrast, a goal of T-Charge is to preserve T cell stemness - the ability to self-renew and differentiate - resulting in a product containing fewer exhausted Tcm cells and more naive T cells (Tn) and T memory stem cells (Tscm). (Fig. 1). Naive and Tscm cells have greater proliferative potential. Naive and Tscm cells are more durable than mature T cells, a characteristic that could ultimately provide more powerful and long-lasting responses for patients, reduce risk of severe adverse events, and improve long-term outcomes1,2.

The T-Charge platform is designed to implement important process efficiencies and practical improvements. Its manufacturing and quality control processes have been simplified and streamlined, giving it improved potential for fast and reliable delivery. With a manufacturing process time of less than two days, and efforts to continue to reduce the release time, T-Charge aims to deliver a product in less than half the time of conventional products – a potential benefit for patients with rapidly progressing haematological cancers who need treatment quickly1,2.

Early data from first-in-human dose-escalation trials of the first Novartis CAR-T cell therapies developed using the T-Charge platform have shown the investigational CD19-directed and BCMA-directed CAR-T cell therapies preserve T cell stemness, which may result in a highly proliferative CAR-T product with improved efficacy and safety outcomes. Findings presented at recent haematology medical congresses showed the CD19-directed CAR-T expanded in vivo and persisted, despite the fact that a lower number of CAR-T cells were initially administered compared to conventional products. The BCMA-directed CAR-T also showed rapid in vivo expansion, and initial immunophenotypic characterization shows an increase in Tscm in the cellular product compared to paired apheresis material2,4. Novartis is further testing these therapies in larger clinical trials.

While much remains to be learned, we are hopeful that next-generation CAR-T treatments will be delivered to patients faster and benefit a broader patient population than ever before. We aim to go beyond incremental advances: to revolutionize CAR-T cell therapy with new products that have the potential to offer patients what they deserve – durable responses with the ultimate potential for a cure.

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REFERENCES

Cell phenotype of CD4 and CD8 subsets in leukapheresis (N=13) and BCMA-directed final product (N=13) measured by flow cytometry. Phenotype percentages are expressed as a percentage of CD4 or CD8 for paired patient samples: Naive = CD3+CD45RO-CD95-, TSCM = CD3+CD45RA+CD95+, Central Memory = CD3+CD45RO+CCR7+, Effector Memory = CD3+CD45RO-CCR7-, and Effector=CD3+CD45RO-. APH, apheresis; CDF, cluster of differentiation; FP, final product; TSCM, stem cell memory T cells.

Figure 1. T-Charge preserves `stemness', which is important for therapeutic potential4.