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Driving CARs to new places: locally produced BCMA CAR T cells to treat multiple myeloma

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Chimeric antigen receptor (CAR) therapy is a novel immunotherapy that is based on the genetic targeting and reprogramming of immune cells to rapidly provide effective immunity. CARs are synthetic receptors for antigen that typically comprise an extracellular antigen-recognition domain (most often consisting in an scFv derived from an antibody specific for the targeted cell-surface molecule) and a dual-signaling intracellular domain that initiates T cell activation and augments T cell functions through costimulatory signals provided by CD28 or 4-1BB cytoplasmic domains[1]. Various extracellular scaffold and transmembrane elements may be interposed between the antigen-binding and signaling moieties. The targeting of CD19, a cell surface molecule found in most leukemias and non-Hodgkin lymphomas, has established in the clinic the formidable potency of CAR T cell therapy[2] and paved the way for a vast spectrum of potential CAR therapies for other hematological malignancies, solid tumors and several pathologies beyond cancer[3]. Six CAR therapies are presently approved in the US, four of which target CD19 and two B cell maturation antigen (BCMA), an antigen commonly found in multiple myeloma. BCMA binds to its ligands, BAFF (B cell activating factor) and APRIL (a proliferation-inducing ligand) and promotes survival in plasma cells. BCMA is a favorable CAR target owing to its restricted expression in B cells and plasma cells, including malignant plasma cells. The two CAR therapies that are approved for the treatment of refractory/relapsed multiple myeloma, idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel), consist in autologous T cells that are lentivirally transduced to express a CAR binding to BCMA through an scFv or two llama VHH elements and signaling through 4-1BB and CD3ζ cytoplasmic domains (Fig. 1A). The remarkable response rates following BCMA CAR treatment led to the FDA approval of ide-cel in March 2021 and cilta-cel in February 2022.

Challenges remain, in particular on the counts of efficacy and access to therapy. Although initial response rates are excellent, many patients will eventually relapse. Furthermore, since most CAR products require autologous manufacturing and are thus personalized for each patient, commercial production in centralized facilities is both expensive and prone to delays in CAR T cell availability.

In this issue of *Haematologica*, N. Asherie and co-workers describe their findings in a phase I dose escalation clinical trial with a BCMA CAR T cell product, HBI0101, developed in-house and locally manufactured for the first time in Israel[4]. The CAR molecule itself comprises an scFv derived from the C11D5.3 anti-BCMA monoclonal antibody, the hinge and transmembrane domains of CD8α and arrayed 4-1BB and CD3ζ cytoplasmic domains. The CAR design is similar in concept to idecabtagene vicleucel (ide-cel) but differs in using a γ-retroviral vector for its transduction to patient T cells. The clinical team enrolled 20 patients with relapsed and/or refractory multiple myeloma. The study shows a good safety profile,

overall similar to other BCAM CAR T cell phase I-II studies, and similar efficacy, albeit with shorter follow-up, to that initially reported with the later FDA-approved BCMA CAR T cells (75% overall response rate [85% ORR in the group given the highest CAR T cell dose[4]] compared with 85% in the phase I trial evaluating ide-cel[5] and 97% in the phase 1b/II trial for cilta-cel[6]). The Jerusalem trial included nine patients who had relapsed after treatment with an anti-BCMA antibody, belantamab mafodotin, prior to receiving HBI0101, which the authors suggested may be associated with a less favorable response to CAR therapy, although there were no differences in BCMA levels and frequency of positive plasma cells compared to patients who had not been treated with belantamab mafodotin. The authors further suggest that CD56 expression in plasma cells may be a favorable prognostic biomarker as 70% of responders were positive for CD56 while non-responders were all CD56-negative. The present study is a small study with a median follow-up of 136 days, wherein findings need to be substantiated in a larger cohort and with longer follow-up.

What makes this study so remarkable is how two academic groups came together to construct a CAR, set up a cGMP manufacturing facility and complete a clinical trial in record time. The laboratory of Cyrille Cohen at Bar-Ilan University built a BCMA CAR vector while Polina Stepensky and her team established at the Hadassah Medical Center the facilities and procedures for local CAR T cell manufacturing. Having hatched the project in 2018, they opened the trial in February 2021 and had infused 20 subjects by December 2021. This exploit will likely inspire others in the academic world who are tempted to part take in advancing CAR therapy and may have thought it not to be possible.

While there is a need to meet the increasing demand of CAR T cell therapy and shorten the vein-to-vein delivery time, it is also essential to improve CAR T cell designs for multiple myeloma since most of the patients treated with BCMA CARs will eventually relapse. One mechanism behind treatment failure is antigen-low relapse[7]. It is noteworthy that all current BCMA CARs in the clinic are of the 4-1BB type, which several studies have shown to be less sensitive to low antigen density than CD28-based CARs[8]. Other strategies are under evaluation to more effectively target BCMA (Fig. 1B). One is to stabilize BCMA on the cell surface by blocking its cleavage using a γ-secretase inhibitor[9]. Another is to increase the avidity of CAR T cells for BCMA-positive cells by co-expressing along with the BCMA CAR a second scFv or chimeric costimulatory receptor binding to CD38[10]. A bi-specific or tandem CAR engaging both BCMA and CD38 has also shown increased cytotoxicity against multiple myeloma cell lines[11]. Finally, novel CAR designs coopting the CD3 complex, such as the HIT receptor, also increase sensitivity to BCMA[12].

In all, BCMA targeted CAR T cell therapy offers the prospect for improved outcome in heavily pre-treated patients with multiple myeloma. Increased accessibility to this therapy will benefit patients world-wide. Novel CAR designs introduced into T cells and other immune cell types that avert late relapse have the potential to further improve the efficacy of this therapy and will shape the future of CAR therapy for multiple myeloma.

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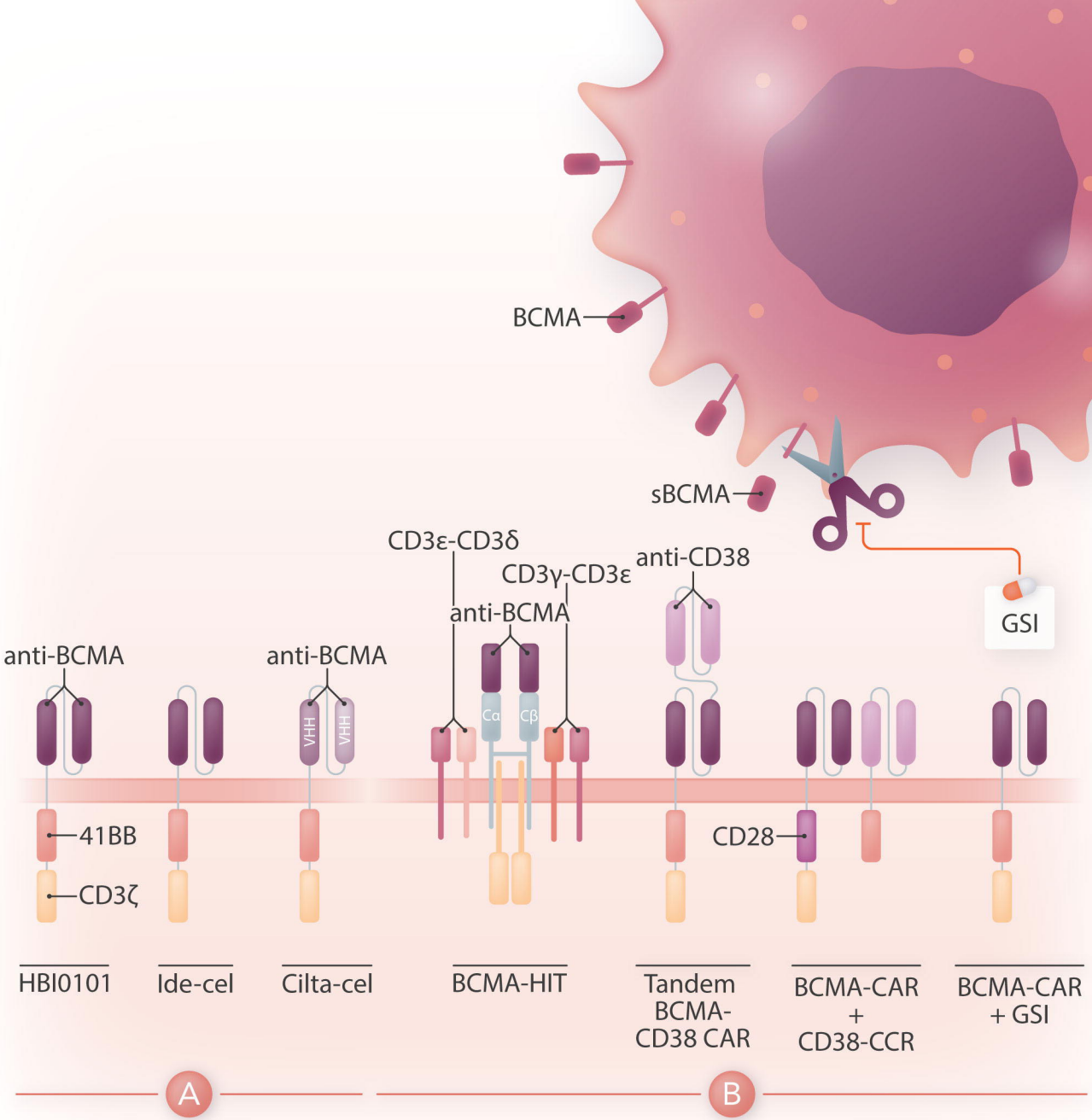
Design of HBI0101 and new CAR strategies to target BCMA-low multiple myeloma. (A). HBI0101 is a novel CAR that incorporates 4-1BB and CD3ζ signaling moieties, similar to both FDA-approved BCMA CARs (see text). Cilta-cel comprises two llama-based VHH regions that bind to two different epitopes of BCMA and thereby increase overall binding affinity. (B) To minimize BCMA-low escape, several new CAR designs have been proposed. These include, from left to right, the use of a BCMA HIT receptor, a tandem CAR engaging CD38 and BCMA, a BCMA CAR co-expressed with a CD38 CCR and the use of γ-secretase inhibitors to block the shedding of soluble BCMA. Ide-cel = idecabtagene vicleucel, cilta-cel = ciltacabtagene autoleucel, CCR = chimeric co-stimulatory receptor, VHH = Variable domain on a heavy-chain, GSI = γ-secretase inhibitor, sBCMA = soluble BCMA, HIT = HLA (Human Leucocyte Antigen)-Independent T cell receptor, Cα/β = Constant regions of αβ-TCRs.


BCMA
sBCMA
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CD3ε-CD3δ
CD3γ-CD3ε
anti-BCMA
anti-CD38
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VHH
Cα
Cβ
41BB
CD3ζ
CD28
HBI0101
Ide-cel
Cilta-cel
BCMA-HIT
Tandem BCMA-CD38 CAR
BCMA-CAR + CD38-CCR
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