More than a Bridging Therapy: Targeting CD123 with Rapidly Switchable Universal CAR-T Cells for Treatment of Acute Leukemia

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Abstract

Chimeric antigen receptor T-cell (CAR-T) therapy targeting CD123 or BCMA is highly effective in treating hematological malignancies. However, the application of CAR-T beyond certain B-cell malignancies such as ALL, MM, lymphoma and CLL remains challenging due to the lack of tumor-specific antigens and the limited ability to control acute and potential long-term CAR-T adverse effects in patients. Therefore, a rapidly switchable universal CAR T-platform (UniCAR-T) was developed. Standard CAR-T cells depend on the presence and direct binding of cancer antigens for activation and proliferation. An inherent key feature of the UniCAR platform is a rapidly switchable on/off mechanism enabled by the short pharmacokinetic half-life and fast internalization of suitable adaptors termed targeting modules (TM). These TM provide the antigen-specificity to activate UniCAR gene-modified T-cells (UniCAR-T) and consist of a highly flexible antigen-binding moiety, linked to a motif recognized by UniCAR-T, allowing for excellent controllability of CAR-T reactivity while maintaining the high anti-tumor activity of CAR-T cells. Here we present results from the late stage pre-clinical characterization of UniCAR-T targeting CD123 (UniCAR-T-CD123) for treatment of acute leukemia. Pre-clinical characterization confirmed specificity and safety. UniCAR-T proved to be per se an important clinically relevant in vivo toxicity models. Activation of UniCAR-T occurs solely in the presence of the CD123-specific TM (TM123) and upon cross-linkage to CD123 expressing leukemic cells. Specific loss of leukemic target cells and primary patient material is induced in a dose-dependent manner at post-molar TM123 concentrations. Notably, induction of cytotoxic release occurs at higher TM doses than on-set of target cell loss, opening a potentially enhanced therapeutic window for clinical application. In vivo efficacy of UniCAR-T directed against CD123 was proven in CDK and PDX mouse models. In contrast to conventional CD123 CAR-T, CD123-specific toxicity of TM-activated UniCAR-T towards hematopoietic progenitors was reversible and could be abrogated by withdrawal of TM, allowing for normal development of hematopoietic progenitors in a xenograft model. In summary, in vitro and in vivo evidence suggests that UniCAR-T-CD123 could provide strong efficacy against CD123 expressing hematological malignancies while providing excellent control and ensuring recovery of normal hematopoiesis post treatment. A Phase I dose-finding study is ongoing (NCT04320205).

References:

Fig. 1 The Universal CAR (UniCAR) Platform

Fig. 2 Switchable UniCAR-T Triggered by TM123 Are Highly Active Against Acute Leukemia

Fig. 3 Leukemia Eradication by CD123-Redirected UniCAR-T in CDX and PDX in Vivo Models

Fig. 4 The Rapid Switch-on/off Mechanism Prevents Durable Hematotoxic Effects of UniCAR-T

Fig. 5 UniCAR-T-CD123 Phase IIA Study – UniCAR & TM Dosing and Scheduling

Conclusion

• Highly effective anti-tumor response of UniCAR-T against primary acute leukemia
• Precise control of UniCAR-T reactivity for improved patient safety
• A Phase IIA dose-finding study in patients with CD123+ mAML/ALL is ongoing