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S104 DIFFERENTIAL TARGET PROFILES AND EFFICACY OF ADCLEC.SYN1 AND CD33-CARS IN HUMANIZED AML MODELS

Topic: Plenary Abstracts Session

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Background:

CAR therapy for AML faces efficacy challenges and on-target toxicity, owing to clonal heterogeneity and similarity to normal early hematopoiesis. We previously presented a novel IF-BETTER-gated combinatorial CAR concept targeting ADGRE2 and CLEC12A, termed ADCLEC.syn1, and demonstrated its potential to target ADGRE2-low AML by rescuing AML target engagement with a chimeric costimulatory receptor (CCR) specific for CLEC12A while sparing ADGRE2-low normal hematopoietic stem and progenitor cells (HSPC) that lack CLEC12A. Here we compare in humanized mouse models the efficacy of ADCLEC.syn1 to a conventional CAR targeting CD33.

Aims:

We aimed to gain insight into the efficacy of differently targeted CAR designs in the context of AML and normal hematopoiesis, using PDX or humanized AML mouse models, and quantifying target antigen expression in leukemic and normal cells.

Methods:

We performed quantitative target expression profiling for ADGRE2, CD33, CD123 and CLEC12A in AML and normal tissues of both hematopoietic and non-hematopoietic origin. Using flow cytometry, we determined the number of surface target molecules in relapsed/refractory (r/r) AML (n=39 patients) and normal hematopoietic cells (n=8 healthy donors). Target gene expression in non-hematopoietic cell types was also analyzed using single cell RNAseq datasets. Target findings were then correlated with ADCLEC.syn1 and CD33-CAR T cell *in vivo* efficacy in patient-derived or humanized AML xenograft models.

Results:

In the AML fraction enriched for leukemic stem cells (LSC), high ADGRE2 expression (>1.0x10^3 molecules/cell) was detected in 79% of patients, and high CD33 expression (>1.0x10^3) was detected in 87% of patients. In healthy donor bone marrow-derived normal hematopoietic cells, ADGRE2 was detected only in less abundant cell populations, at a maximum of 1.6x10^3 molecules/cell, while CD33 was ubiquitously expressed in all myeloid cells, at up to 2.4x10^4 molecules/cell, raising questions of a potential CAR target "antigen sink". ADGRE2, CD33 and CLEC12A expression was found to be restricted to hematologic cell types while CD123 was also expressed in endothelial cells.

We next compared the anti-leukemic efficacy of ADCLEC.syn1 vs a reference CD33-CAR in AML xenograft

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models of different AML engraftment patterns and additional normal bystander cells in a humanized model. In a MOLM13 xenograft NSG model, both ADCLEC.syn1 and CD33-CAR rapidly led to complete remissions even at a single low dose of $2x10^5$ CAR T cells per mouse, and successfully averted relapse upon late AML rechallenges. However, humanized NSG mice bearing the same MOLM13 AML xenograft and normal human bystander cells failed to respond to CD33-CAR T cells whereas ADCLEC.syn1 rapidly eliminated MOLM13 AML cells in the humanized setting.

In a r/r AML PDX model, both ADCLEC.syn1 and CD33-CAR led to CAR T cell *in vivo* expansion, however only ADCLEC.syn1 induced complete remissions. CD33-CAR-treated mice relapsed with a functional LSC pool as evidenced by serial AML transplantation. Importantly, post-CD33-CAR-relapsed AML was successfully eliminated by ADCLEC.syn1.

Summary/Conclusion:

Collectively, we link quantitative CAR target profiles in AML and normal tissues to pre-clinical CAR efficacy and compare a novel combinatorial CAR design, ADCLEC.syn1, vs a conventional CD33-targeted CAR. Our findings reveal potential challenges of a CAR target "antigen sink" limiting clinical efficacy when targeting antigens with high abundance in normal bystander cells. We are currently investigating ADCLEC.syn1 T cells for r/r AML in a first-in-human phase 1 clinical trial at MSKCC (NCT05748197).

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