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Developing Cross-reactive B7H3-targeting CAR-T Cells for Enhanced Preclinical Cancer Models

Stanford scientists have developed species cross-reactive B7H3-targeting CAR-T cells that can effectively target both human and mouse tumors, enabling more accurate preclinical testing in immunocompetent models. This breakthrough allows researchers to use a single CAR sequence throughout development—from initial testing in immune-competent mouse models to clinical trials—dramatically improving the predictive value of preclinical studies and reducing the risk of clinical trial failures.

CAR-T cell therapies have shown remarkable success in blood cancers, but extending this success to solid tumors remains challenging. Current preclinical development relies heavily on testing human CAR-T cells against human tumors in immunocompromised mouse models, which cannot accurately predict clinical performance because they fail to account for the complex tumor immune microenvironment and potential off-target toxicities. This limitation has contributed to mixed results for solid tumor CAR-T therapies, including early B7H3-targeting approaches that have shown limited efficacy and some adverse events. B7H3 represents a particularly attractive pan-cancer target, as it is highly expressed across multiple solid tumor types with minimal expression in healthy tissues, making it a priority for pharmaceutical companies investing heavily in cellular therapy platforms. However, existing B7H3 CAR-T cells lack species cross-reactivity, preventing meaningful preclinical testing in immunocompetent models that could better predict clinical outcomes and identify potential safety issues before human trials.

Engineering B7H3-targeting CAR-T cells with species cross-reactivity through directed evolution resulted in variants that maintain high affinity for both human and

mouse B7H3. In preclinical studies, the cross-reactive CAR-T cells demonstrated effective tumor control in both human and mouse models, with superior *in vivo* performance and no observed toxicity at high doses. Consequently, this species cross-reactive approach has the potential to significantly improve preclinical testing accuracy, reduce development risks, and enhance the clinical translation success of B7H3-targeting CAR-T therapies across multiple solid tumor types.

Stage of Development:
Research: in-vivo
Continued research: expanding efficacy testing across additional tumor models and exploring combination therapeutic approaches

Applications

- Development of B7H3-targeting CAR-T therapies for solid tumors
- Enhanced preclinical testing in immunocompetent mouse models
- Pan-cancer therapeutic platform for multiple solid tumor types

Advantages

- Species cross-reactive binding enables testing in immunocompetent models that better predict clinical outcomes
- Single CAR sequence can be used from preclinical development through clinical trials
- Superior safety profile with no observed toxicity at high doses
- Reduced development risk and improved clinical translation potential compared to existing B7H3 CAR approaches

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