Novel CAR-T Cell Therapy that can be Activated, Silenced, and Reprogrammed In Vivo with Soluble Protein Adapters in Dose Dependent Manner

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Introduction

Arcellx has developed a novel gene-modified cell therapy engineered to address a number of current CAR-T cell limitations such as:
- Fixed antigen-targeting is unable to address tumor heterogeneity and antigen escape
- Inability to control rate of cell killing that may result in side-effects such as severe CDIs, neurotoxicity, and/or ‘on-target, off-tumor’ toxicities
- Cell exhaustion from being constitutively active
- Limited persistence due to immunogenicity

The ARC-sparX platform is designed to give physicians control of the target specificity and rate of cell killing to potentially increase efficacy and manage toxicities.

The ARC-sparX Platform

The ARC-sparX platform enables the antigen-recognition and killing functions of conventional CAR-T therapy and is comprised of two key components:
1. sparX technology provides antigen-recognition in living protein binds specific antigens on diseased cells and targets them for destruction.
2. ARC-T Cells deliver antigen Recognition Complex (ARC) to bind sparX proteins and kill flagged cells.

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Novel Binding Domains and TAG are Foundational to ARC-sparX Platform

Novel Binding Domains

- Non-self-binding domains are based on ‘off-the-shelf’ randomized at 13-14 amino acid binding regions
- Incorporates binding domains for both ARC-T and sparX that are: high affinity, low nanomolar range
- Only achieved active form of daughter of ARC-T + sparX = doped cell
- Gene-seq vector regardless of antigen target enables production of antigen-specific based therapies

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Results

ARC-sparX Tumor Killing is Dose Dependent

- sparX concentration dependent killing of GFP/Luciferase expressing H929 target cells dependent on the dose of mono-valent sparX-BCMA (top)
- ARC-T cells in combination with sparX-BCMA demonstrate dose dependent elimination of tumors generated with BCMA expressing NALM6 cells or use of daily CAR-T administration (bottom)

Bivalency Improves on Mono-valent sparX-BCMA Efficacy in vitro and in vivo

- Affinity measurements by surface plasmon resonance (SPR) using Biotin, shows 50-fold improvement in the affinity of sparX in vivo eptargets in vivo. BCRMA binding (red down) → sparX dosing controls ARC-T cell killing in a dose-dependent manner

Conclusions

- ARC-sparX is a novel, adoptive, and controllable cell therapy platform
- sparX proteins can be engineered to target different antigens
- Uniform ARC-T cell product can be paired with any sparX
- ARC-sparX activity can be tuned through engineering sparX valency and titration
- sparX targeting BCMA or CD123 potently induce ARC-T activity to eliminate tumors
- ARC-sparX performs on-par with traditional scFv-based CAR-T with the following differences:
  - ARC-T cells are not constitutively active
  - sparX dosing controls ARC-T cell killing in a dose-dependent manner
  - ARC-T cells can be reprogrammed in vivo by switching sparX

Future Plans

- Use current collection of sparX to treat hematologic malignancies, solid tumors, and autoimmune diseases
- Ongoing Phase II clinical trial of CART-ddBCMA for the treatment of multiple myeloma (MM) is designed to validate the functional properties of our novel non-scFv binding domain
- Planned Clinical Trials
  - Phase I trial for ARC-T + sparX-BCMA for MM
  - Phase I trial for ARC-T + sparX-CD123 for AML/MDS
  - Continue to expand collection of sparX proteins to bind different antigens, including novel targets
  - Pursue allogeneic ARC-T program

References

- 2018 Sep;180(1):134-42. Blood.