Technology Offer

Therapeutic composition to combat CAR-T cell unresponsiveness and method of rejuvenation

CAR-T cells, while promising in immunotherapy as a key strategy for cancer treatment, often become unresponsive, especially in elderly patients or in solid tumors. One fundamental characteristic that determine the CAR-T therapy efficacy is the maintenance of mitochondrial fitness.

The inventors have proved that both murine and human aged T cells exhibited remarkable defects in mitochondrial activity, which correlated with less functional CAR T cell activity *in vitro* and *in vivo*. This dysfunctional mitochondrial profile stems from the age-related decline in pools of NAD+ (nicotinamide adenine dinucleotide), a molecule of critical importance to energy production, metabolism and mitochondrial function *(Nat Cancer (May 2025))*. This unresponsiveness compromise the efficacy of CAR-T therapy in aging population and in longevity treatment.

TECHNOLOGY OVERVIEW

In order to address this exhaustion, the inventors have identified a composition and methods to identify, predict, and restore the functionality of CAR-T cells by targeting NAD metabolism:

- Identification of unresponsive CAR-T cells via NAD levels and CD38 expression.
- Rejuvenation of CAR-T cells through ex vivo treatment with a composition comprising
  - NAD boosters
  - CD38 inhibitors (e.g. 78c), PARP inhibitors (e.g. Olaparib), or NAMPT activators (e.g. SBI-797812)
- Predictive methods for CAR-T or ICB therapy efficacy based on NAD/CD38 levels.

APPLICATIONS

The composition are suitable for use in:

- **CAR-T therapies:** enhanced persistence, memory, and anti-tumor efficacy.
- **Personalized medicine:** patient selection based on NAD/CD38 profile.
- **Bioproduction:** improved ex vivo CAR-T manufacturing processes.
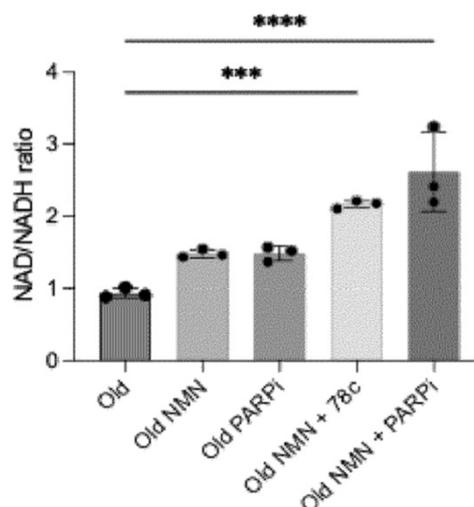
COMPETITIVE ADVANTAGES

- First-in-Class Approach to CAR-T Rejuvenation
- Applicable to both CAR-T cell therapies and immune checkpoint blockade (ICB).
- Improves manufacturing quality of CAR-T cells by restoring mitochondrial fitness and stem-like properties

STAGE OF DEVELOPMENT

- Robust Preclinical Validation with murine models and functional rescue
- Alternative NAD Restoration Strategies
- Human Data correlation: Treatment with NMN + CD38 inhibitor restored mitochondrial fitness to levels comparable to younger donors
- Biomarker Validation

INTELLECTUAL PROPERTY

PCT application : WO2025/093707, Pub. May 5, 2025

KEY PUBLICATIONS:

Hope, H.C., de Sostoa, J., Ginefra, P. et al. Age-associated nicotinamide adenine dinucleotide decline drives CAR-T cell failure. **Nat Cancer (2025)**.
https://doi.org/10.1038/s43018-025-00982-7

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