IEO
Istituto Europeo di Oncologia

Unlocking adoptive cell therapy by lipid-mediated metabolic reprogramming

Introduction

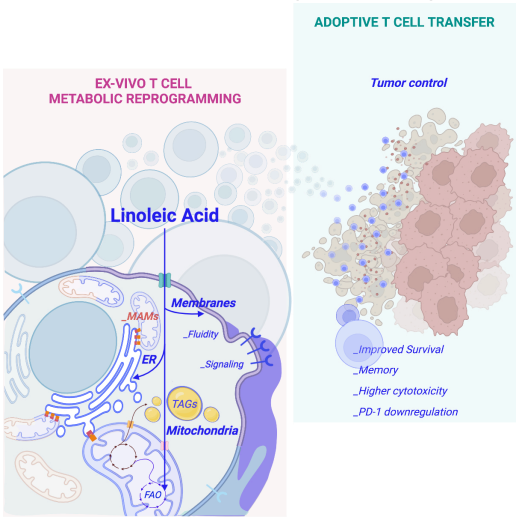
Adoptive cell therapy (ACT) holds the promise to precisely treat cancer by harnessing **T cells** to recognize tumor cells and carry out a productive **anti-tumor response**. This targeted cell therapy employs anti-tumor T cells expanded from tumor infiltrating lymphocytes (TILs) or autologous T cells engineered to express tumor-specific T cell receptors (TCR-Ts) or chimeric antigen receptors (CAR-Ts). ACT has demonstrated unparalleled clinical outcomes in the treatment of cancer, but its efficacy is still limited by T cell **persistence, function and infiltration**, especially in solid tumors. The group of **Dr. Teresa Manzo** is investigating the link between **T cell metabolism** and **immunity in cancer** and how T cells dysfunction can be reversed to **improve immunotherapeutic treatment of cancer.**

Medical Need

Therapeutic results have been heterogeneous and yet **marginal in solid tumors**. Common roadblocks limiting ACT efficacy include: 1) acquisition of **dysfunctional state** during the *ex vivo* manipulation and expansion steps of T cells; 2) **loss of metabolic functional plasticity**, which is fundamental to adapt and survive in the hostile nutrient-poor tumor microenvironment; 3) **immunosuppressive tumor microenvironment**, which limits T cell functions preventing tumor control. In this scenario, maintaining T cells in a **less-differentiated state**, **away from exhaustion** and with **high metabolic plasticity** during ***ex vivo*** production and manipulation **and after their infusion** into patients may have a strong therapeutic impact and raise the clinical efficacy of ACT.

Solution

The use of specific types of lipids to metabolically reprogram T cells and implement ACT efficacy, overcoming ACT current limitations. Specific lipids induce **T cells metabolic reprogramming** and shape their differentiation program away from the exhaustion and towards a **memory phenotype with improved effector functions**, resulting in ACT products with **productive and long-lasting anti-tumor response**. This strategy paves the way for a new generation of adoptive T cell-based therapies, where **lipids can be used during *ex vivo* T cells manufacturing** to achieve metabolic reprogramming and long-term functionality, broadening the therapeutic efficacy of ACT to a wide range of malignancies.

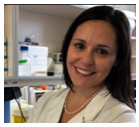


Advantages

- The method allows to produce **more efficient ACT products** for the treatment of **a large number of tumors**, including solid tumors.
- The method is **cost-effective** and includes **non-toxic** lipid compounds that can be **integrated in any established T cell manufacturing protocol**.
- The use of lipids **increases T cell yield after freezing and thawing** steps, thus maximizing the manufacturing and expansion processes.
- The results have been generated using **clinical grade protocols** in accordance with European and international guidelines for Good Manufacturing Practices.
- **Patent application filed** PCT/EP2022/081824.

Opportunity

IEO is seeking **industrial partners** interested in moving the method towards preclinical and clinic development.



Group Leader

Dr. Teresa Manzo is a Principal Investigator at IEO, head of the Immunometabolism and Cancer Immunotherapy Unit. In almost 15 years of research experience in the field of Cancer Immunotherapy, she made significant contributions on defining new strategies to overcome immunological tolerance that limits the protective immunity against solid tumors. Her laboratory - funded by an AIRC-StartUp Grant- aims to develop new strategies to foster and broaden the clinical efficacy of immunotherapy (teresa.manzo@ieo.it).

Relevant publications

Manzo et al., *Journal Experimental of Medicine* 2020.

Nava Lauson et al., *Cell Metabolism 2023.*

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