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Pharmacological enhancement of CD8 T cell effector function using TEPP46

A clinically viable strategy for preventing mitochondria-mediated T cell exhaustion and enhancing effector T cell function.

IP Status: PCT Pending; Application No. PCT/US2024/061566

Applications

- Immunotherapy
- Research tool

Key Benefits & Differentiators

- **Enhanced efficacy:** By preventing mitochondria-mediated exhaustion and enhancing effector T cell function, this technology potentially improves the efficacy of immunotherapy treatments.
- **Extended longevity:** By preventing T cell exhaustion, this technology potentially extends the longevity of effector T cell function, leading to more sustained therapeutic effects.

Technology Overview

Effector T cells show promise in immunotherapy, but their efficacy is hindered by the progressive loss of mitochondrial structure, function, and cell metabolism, directly contributing to T cell exhaustion and therapeutic failures. Currently, there are no clinically viable strategies to prevent mitochondria-mediated exhaustion and to enhance effector T cell function. This gap in clinically viable strategies not only hampers the effectiveness of immunotherapies but also prolongs treatment duration, increases costs, and exacerbates the risk of adverse side effects. As a result, there is an urgent need for clinically viable strategies that can address these challenges and unlock the full therapeutic potential of effector T cells in combating disease.

Researchers at the University of Minnesota have developed a clinically viable strategy for preventing mitochondria-mediated exhaustion and enhancing effector T cell function. This approach focuses on inducing tetrameric pyruvate kinase isoform M2 (tet-PKM2) using the TEPP46 agonist, regulating gene expression, whole genome methylome, and metabolome while boosting CD8 T cell effector functions both in vitro and in vivo. TEPP46 treatment upregulated key genes linked to mitochondrial biogenesis and structure, leading to denser cristae, increased mass, and improved interaction with the endoplasmic reticulum. Metabolomics studies showed a redirection of glucose-derived carbon flux, enhancing mitochondrial metabolism and effector functions. In preclinical melanoma and colon cancer models, TEPP46 treatment significantly delayed tumor growth and altered the tumor immune-environment with increased infiltration of activated CD8 cells having higher mitochondrial mass. These findings highlight the clinical promise of targeting PKM2 to enhance effector T cell activation, prevent exhaustion, and improve outcomes in immunotherapy.

Phase of Development

TRL: 3-4
TEPP46 has been tested in in vitro and in vivo models, showing enhancement of T cell effector function.

Technology ID

2022-294

Category

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Researchers

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