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CRISPR-CAS INDUCED IMMUNOSUPPRESSANT RESISTANCE IN ANTI-VIRAL T CELL PRODUCTS FOR CLINICAL APPLICATION

Keywords: CRISPR-Cas, immunotherapy, tacrolimus, T cells, FKBP12, solid organ transplantation, GMP manufacturing, TReAT

INVENTION NOVELTY

The present invention provides an innovative approach for the treatment of life-threatening immunopathology caused by virus reactivation, such as CMV, induced by immunosuppressants, and viral infections like SARS-CoV-2. The approach involves using specific anti-viral T cells that are resistant to calcineurin inhibitors (anti-viral T cell warriors). These T cell warriors remain their critical anti-viral functions but restore sensitivity to other calcineurin inhibitors, such as Cyclosporine A, as a safety measure.

VALUE PROPOSITION

T cell responses play a vital role in both protecting against and causing immunopathology from viral infections. The challenge arises in immunosuppressed patients (transplant, autoimmunity), where reduced virus control by T cells abolishes immune balance and induces tissue-damaging inflammation. Viral infections in such patients require the treatment with anti-viral drugs that harbor toxic side-effects. This new technology circumvents the need for toxic and insufficient anti-viral drug treatment by replacing it with GMP-compliant manufactured anti-viral T cell warriors.

TECHNOLOGY DESCRIPTION

Using CRISPR-CaS-9 technology the coding sequence of FKBP12, the adaptor protein of the calcineurin inhibitor Tacrolimus, is knocked out, allowing the manufacturing of GMP-compliant, Tacrolimus-resistant T cell warriors with different viral specificities. The highly pure, virus-specific T cell products are manufactured in small semi-enclosed bioreactors using GMP-compliant media and supplements. This allows for rapid cell expansion and efficient translation to the patient's bedside.

As part of TReAT (https://treat-project.com), funded by the Federal Ministry of Education and Research (BMBF) antiviral T cell warriors will be tested for safety and efficacy in human-based organoid/organ-on-a-chip test systems, that show improved reproducibility and translatability especially in the context of viral pathogenesis.

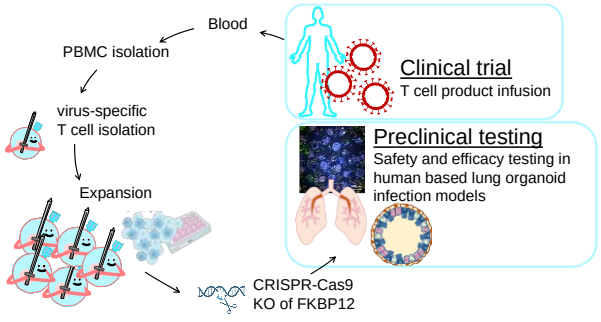

Fig 1. Testing of CRISPR-Cas9-Edited Tacrolimus-Resistant Antiviral T Cells for ATT in human based lung organoids (modified after Amini et al., 2021)

DEVELOPMENT STATUS

T cell warriors specific to CMV and SARS-CoV-2 have been manufactured using a GMP-compatible process and characterized in-depth using CITEseq, proteomics, epigenomics and off-target sequencing. GMP-compatible production of T cell warriors specific to EBV and IAV is planned for the near future.

In addition, a phase I/IIa clinical trial with CMV-specific Tacrolimus-resistant anti-viral T cell products in lung transplant recipients is in preparation.

COMMERCIAL OPPORTUNITY

In-licensing or collaboration for further development.
Investments for clinical trials.

PATENT SITUATION

Priority filed in 2020, International application published in 2022 (WO2022034233A1). EP EP4196572A1 published in 2023, national applications pending in US, CN, CA.

FURTHER READING

1. Amini L, et al. CRISPR-Cas9-Edited Tacrolimus-Resistant Antiviral T Cells for Advanced Adoptive Immunotherapy in Transplant Recipients. Molecular Therapy 2021 Jan 6; https://doi.org/10.1016/j.ymthe.2020.09.011
2. Peter et al., Tacrolimus-resistant SARS-CoV-2-specific T cell products to prevent and treat severe COVID-19 in immunosuppressed patients. Mol Ther Methods Clin Dev 2022. https://doi.org/10.1016/j.omtm.2022.02.012

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CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

Ascenion GmbH
Herzogstraße 64
D-80803 München
info@ascenion.de
www.ascenion.de

Licensing Contact
Dr Heidi Zinecker
Technology Scout
T: +49 30 450 543078
zinecker@ascenion.de