Press Release

CAR T-REX Consortium announces prestigious €2.7M Pathfinder Open Grant awarded by the European Innovation Council (EIC) to develop novel, scalable CAR T cell therapies with increased efficacy for the treatment of solid tumours.

Guimarães (Portugal), 22 June 2023 – Partners in the international consortium CAR T-REX announce the awarding of a highly competitive EIC Pathfinder Open grant, following the positive evaluation of their project entitled '**CAR T** Cells **R**ewired to Prevent **EX**haustion in the Tumour Microenvironment'. One of 57 projects selected amongst 858 submissions, with a total funding of €2.7M, CAR T-REX was recognised for its radical and ambitious vision to improve the efficacy and safety of CAR T-based solid tumour-targeted cell therapies.

- By combining innovative methods of genome editing and non-viral gene delivery, CAR T-REX will explore the engineering of transcriptional networks in Chimeric Antigen Receptor (CAR) modified T lymphocytes (i.e., CAR T cells), to selectively circumvent T-cell exhaustion upon activation in the tumour microenvironment (TME).
- CAR T-REX aims to (i) build novel auto-regulated genetic circuits controlled by microRNAs (miRNAs) in immune cells, (ii) employ a novel high-performance non-viral gene delivery platform for delivery of the synthetic miRNA constructs, (iii) select and benchmark the best-performing construct(s) in preclinical settings, and (iv) execute GMP-like manufacturing run(s) for the final CAR T product.
- CAR T-REX consortium brings together a multidisciplinary group of internationally recognised experts and companies across Europe. The project will start in June 2023 and run for 4 years.

Cell and gene therapies (CGT) are at the forefront of healthcare innovation, with the potential to transform the current therapy toolbox. Indeed, highly personalised (autologous) CAR T cell therapies have dramatically changed the treatment landscape, achieving partial or, in a significant number of cases, long-lasting full remission for patients with blood cancers. However, while CAR T cell therapies have shown remarkable efficacy for the treatment of specific haematological malignancies, broad clinical use is limited by multiple factors, including high manufacturing costs and significant side effects. Moreover, treatment of patients with solid tumours has thus far failed to demonstrate clinical benefit, with antigen heterogeneity, limited infiltration into tumour tissue and (especially) T cell exhaustion/loss of function, negatively impacting clinical outcomes. In this regard, CAR T-REX aims to explore a novel paradigm for the generation of improved CAR T cells. By combining non-viral gene delivery with precise genome editing of T cell autoregulatory pathways, CAR T-REX proposes a strategy to overcome the mechanisms by which solid tumours (and the immunosuppressive TME) "switch off" the anti-tumoural immune response, potentially

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extending the utility and safety of current CAR T technologies.

György Vereb, Head of Chair at the Faculty of Medicine, University of Debrecen, adds: "For an ever-growing number of cancer patients, the current treatment options fail to provide a clear therapeutic benefit. Hence there is an unmet clinical need, which could be addressed by unleashing the curative potential of T cell-based therapies. It has therefore been an honour and an energizing yet humbling opportunity to be able to bring together this consortium which we expect to majorly contribute to the therapy of solid tumours."

Rui A. Sousa, CEO of Stemmatters & Coordinator, explains: "CAR T-REX brings together a multidisciplinary team with unique expertise and capabilities in genome editing, non-viral gene delivery, immunology and T cell therapy, as well as Quality-by-Design methodologies and cGMP manufacturing, providing the right mix of skills needed to achieve the proposed goals. Stemmatters will ensure that processes are designed in compliance with harmonised quality standards and applicable regulatory requirements, as well as state-of-the-art methodologies, thus supporting a faster translation into the clinic setting".

Overall, the CAR T-REX consortium expects to lay the foundation of an improved technology, with potential for significant scientific and societal impact, with recent estimations on the incidence and mortality for 25 major cancers across 40 European countries revealing 4 million new cases (excluding non-melanoma skin cancer) and 1.9 million cancer-related deaths in 2020[1].

About CAR T-REX

The consortium comprises three (3) academic and two (2) industrial partners from five (5) European countries. CAR T-REX is led by **Stemmatters** (Portugal), a regenerative medicine CDMO with expertise in the development and manufacturing of cell therapies under current Good Manufacturing Practice (cGMP). The company will adopt Quality-by-design (QbD) and risk assessment methodologies during product/process development, while levering its scientific and regulatory know-how to ensure a faster clinical translation of the CAR T cell therapy into the clinical setting. **TargetGene Biotechnologies** (Israel) brings expertise in new technologies for gene editing human cells. The company has developed a unique genome editing technology – T-GEE – which displays higher specificity and lower off-target events compared to the gold-standard CRISPR/Cas9, improving the safety of gene delivery systems. The CiQUS at **Universidade de Santiago de Compostela** (Spain) will employ its versatile delivery technology for non-toxic delivery of relevant cargos to immune cells, a high-value asset for industrial stakeholders working on the development of advanced therapies and nucleic acid-based therapeutics. The **University of Debrecen** (Hungary) and **Leibniz-Institut für Immuntherapie** (Germany), provide expertise in immunology, CAR T cell design and development, as well as preclinical models of solid tumours - critical areas in a project focused on the development of a new CAR T technology. This multidisciplinary collaboration brings together a unique set of researchers that encompass all the skills and resources needed to achieve the ambitious objectives of this project.

[1] Dyba T, Randi G, Bray F, et al. The European cancer burden in 2020: Incidence and mortality estimates for 40 countries and 25 major cancers. Eur J Cancer. 2021;157:308-347. doi:10.1016/j.ejca.2021.07.039

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About EIC

The European Innovation Council (EIC) was created as part of the **EU Horizon Europe** program. With a €10.1 billion budget, it aims to support game-changing ideas from early-stage research to proof of concept, technology transfer, and the financing and scaling-up of start-ups and SMEs. The EIC Pathfinder Open provides funding for projects in any field of science or technology based on high-risk/high-gain science-towards-technology breakthrough interdisciplinary research.

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About Stemmatters

Stemmatters is a contract development and manufacturing organisation (CDMO) operating in the manufacturing of regenerative medicine (RM) products such as cell therapies and cell-derived biologicals. The company addresses needs in product development and cGMP production, supporting the clinical translational and future commercialisation of high-impact medicinal products.

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About TargetGene Biotechnologies

TargetGene, founded 2012 in Israel, is a pioneer in the gene-editing field with its proprietary best-in-class T-GEE platform. TargetGene is leveraging T-GEE's advantages to develop safe and effective cell-therapies for cancer and immune-related diseases via its proprietary "genetic-circuit rewiring" concept.
T-GEE is an ultra-precise dual-RNA guided genome-editing platform enabling modification of the patient's own DNA, whereby genes can be deleted, replaced or added in specific cells, allowing cures as opposed to chronic treatment. T-GEE, with its superior mode of action is fundamentally more specific than CRISPR-cas9, eliminating the severe safety concerns due to the latter's alarming "off-target" frequency and could potentially replace this transformative technology altogether.

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About CiQUS - Universidade de Santiago de Compostela

Since 2011, the Centro Singular de Investigación en Química Biolóxica y Materiais Moleculares (CiQUS) of the Universidade de Santiago de Compostela is the first member of a network of singular research centres with a new model of scientific organization. CiQUS is certified as a Research Centre of the Galician University System (2019-2022) and is supported by the Consellería de Educación and co-financed by the European Regional Development Fund (FEDER Galicia 2014-2020). The research developed at the centre adresses, from a multidisciplinary perspective, current challenges in the fields of health, materials science and the development of new transformative and sustainable technologies.

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In addition, CiQUS aims to create socio-economic progress of the region through the training of new scientists and professionals, technology transfer and the social transfer of knowledge.

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About University of Debrecen

With its past of more than 450 years, the University of Debrecen is the oldest institution of higher education in continuous operation in Hungary. Its 14 faculties and 24 graduate schools host a student body of 30,000, making it the most versatile and one of the largest higher education institutions in Hungary. This outstanding intellectual center with vast research and development capacity has growing importance in the socioeconomic development and cultural life of the region. The institution also provides high quality patient care at all levels for the city, and advanced health services progressively up to national level, which underpins its excellence in biomedical research.

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About Leibniz Institute for Immunotherapy

The central aim of the Leibniz Institute for Immunotherapy (LIT) is research, development and application of innovative cellular therapies for the treatment of cancer, chronic inflammatory and auto-immune diseases, and organ and stem cell transplantation. Within this framework, the division of Genetic Immunotherapy headed by Prof Abken is focusing on the development of novel formats of chimeric antigen receptors (CARs) for redirecting T cells and for the modulation of cellular functions and the tissue environment through the delivery of immune modulatory products. For translation to clinical application the LIT runs a GMP facility, to manufacture cell products in close cooperation with the University Hospital Regensburg.

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