Proyecto CPP2021-008350 financiado por MCIN/AEI /10.13039/501100011033 y por la Unión Europea NextGenerationEU/ PRTR

Identificación del proyecto:

Off-the-Shelf iPSC-derived next generation CAR-NK cells for solid tumor allogenic immunotherapy

Descripción del proyecto:

Autologous CAR-T therapies have been a game changer for cancer treatment, especially for hematological tumors, but they still present some limitations: production is too long for critically ill patients, some patients cannot provide good quality starting T-cells and they have a high economic cost. New allogeneic approaches are being developed to help overcome these obstacles. In this context, natural killer (NK) cells are advantageous over T-cells as they do not cause graft-versus-host disease (GVHD), are well tolerated, and show positive results in clinical trials. In the case of solid tumors, CAR therapies present additional difficulties: the hostile tumor microenvironment (TME), immunosuppressive and refractory to infiltration and the lack of targets specific enough to ensure low off target toxicity.
Our goal is to produce a new generation of ready-to-use allogenic CAR-NK cells equipped to overcome TME countermeasures. The new CAR-NK cells will be derived from induced pluripotent stem cells (iPSCs) reprogrammed from donors naturally homozygous for widely compatible HLA haplotypes (haplolines). The practically unlimited in vitro expandability of iPSCs will enable large-scale production of CAR-iNK cells covering most of the population. The iPSC haplolines will be genetically modified to carry not only CARs, but also a full complement of the genes necessary to ensure the proper function of the NKs derived from them in the specific circumstances of a solid tumor.
To do so, OSCAR-iNK will use a novel and proprietary technology based on a multiload Docking Platform (DP) The DP will be installed in a predetermined Genome Safe Harbor (GSH) locus of the iPSCs, and use a fast, highly specific and reproducible, transposon-based system to upload CARs and any other adjuvant gene (suicide genes, immunosuppression blockers, cytokines, etc.,) that might be deemed necessary to improve the anti-tumor activity of the final iNK cells. This versatility will allow tailoring the therapy to specific tumor types or to the genetic background and physiology of each patient. The resulting DP-haplo-iPSCs will integrate an intermediate cell bank ready for cell expansion and differentiation into the mature effector cell population.
In order to demonstrate the efficacy of this new system in solid tumor immunotherapy we have chosen, as an efficient and low toxicity CAR target, the p95HER2 truncated variant of the HER2 gene. This truncated form of HER2 is expressed in some gastroesophageal and breast tumors, among others, and not in nontransformed tissues, and thus circumvents the toxicity commonly associated with standard CAR-HER2 therapies. The p95HER2 target represents a breakthrough for CAR therapies in this tumor type and will be tested here, for the first time, in the context of N cells. In addition to the p95HER2 CAR, iPSC-derived NKs will be equipped with other genes

designed to enhance their efficacy in the TME: IL-15 to promote NK proliferation and activation, CXCR1 to enhance tumor infiltration, and a bicistronic suicide construct with built-in redundancy as an additional system safety switch.
Upon completion of the project, a fully characterized CARp95-iPSC-derived NK line will be produced under scalable and GMP conditions and, following the recommendations of the regulatory authorities, the Investigational Medicinal Product Dossier (IMPD) will be completed. This will provide the necessary basis for the approval of the first-in-human clinical trial, scaling up in a clinical environment and immediate commercial exploitation.
In summary, OSCAR-iNK will validate a new technology with the potential to overcome most of the limitations of current CAR immunotherapies in solid tumors. This will lead to increased efficacy and lower treatment prices, making CAR immunotherapies available for a wider range of applications and a much larger patient population.

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