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703.CELLULAR IMMUNOTHERAPIES: BASIC AND TRANSLATIONAL

CAR-T Cells for Systemic Lupus Erythematosus

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Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterized by an abnormal inflammatory response against nuclear antigens with consequent tissue damage. Autoreactive B cells and auto-antibodies have a fundamental role in SLE pathogenesis. Lupus nephritis (LN) has a great impact on patients' survival and quality of life and still represents and unmet clinical need due to the lack of specific treatments and to the poor response to conventional immunosuppression. Regulatory T cells (Tregs) physiologically maintain the immune tolerance and are impaired in SLE. Polyclonal Treg transfer obtained unsatisfactory results due to the low number of disease-relevant antigen-specific cells. Chimeric Antigen Receptors (CARs) are molecules capable of redirecting T cell specificity. CAR-Tregs proved effective in pre-clinical mouse models of autoimmunity. We aimed at developing a CAR-Treg based product to be employed in SLE in particular in LN.
We isolated Tregs from Healthy Donors Peripheral Blood Mononuclear Cells (PBMCs) and expanded them with IL-2 and rapamycin. We transduced Tregs with a Lentiviral Vector encoding for a second-generation anti-CD19 CAR, considering the relevant role of autoreactive B cells and autoantibodies in SLE. Engineered cells retained their immune suppressive capabilities upon polyclonal stimulation. Noticeably, they acquired new antigen-specific suppressive capacities, being able to block autologous B cell proliferation. We set up a humanized mouse model of SLE. In vivo, CAR-Tregs delayed the occurrence of B cell lymphopenia, producing immunomodulatory cytokines and without showing toxicity or reprogramming towards Th17 pro-inflammatory cells. In inflamed organs, CAR-Tregs restored the normal composition of the immune system.
In conclusion, we efficiently generated anti-CD19 CAR-Tregs and proved their efficacy both in vitro and in an in vivo humanized mouse model of lupus.

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