UNIL | Université de Lausanne

European Research Council
Established by the European Commission

PROF. GEORGE COUKOS
(FBM / DOF)

PROJECT TYPE ERC Advanced Grant (FP7)

TITLE Development of Vascular-Disrupting Lymphocyte Therapy for Tumours

ACRONYM Antivessel-T-Cells

DURATION 01.08.2013 – 31.07.2018

BUDGET 2 500 000 €

In recent years the adoptive transfer of T-cells gene-engineered to express tumor targeting receptors, so-called chimeric antigen receptors (CARs), has emerged as a potent immunotherapy against advanced liquid tumors. In the case of treatment-refractive chronic lymphoid leukaemia patients, for example, complete response rates of greater than 90% have been reported.

CARs typically comprise an extracellular single chain variable fragment (scFv) that binds to a tumor cell-surface epitope, fused to a linker, transmembrane region, and various combinations of intracellular signaling domains associated with T cell activation and co-stimulation. Solid tumors, however, remain an important challenge to CAR T-cell therapy. Barriers include impaired homing and transendothelial migration via an aberrant vasculature into the tumor bed, along with a wide range of immunometabic obstacles such as an insufficient supply of oxygen and nutrients, the upregulation of suppressive receptors like PDL1 on the surface of tumor cells, and inhibitory immune infiltrate including regulatory T cells. A promising approach to overcome several of these barriers, along with the unstable nature of antigen expression by tumor cells, is to target CAR T-cells against molecules highly and widely upregulated by the tumor vasculature, but weakly, if at all, by healthy tissues. We have developed several such CARs and have demonstrated important tumor control in pre-clinical tumor models.

Moreover, we have shown that co-engineering of the CAR T-cells to express molecules to either support T-cell function (like cytokines), or to block inhibitory mechanisms (such as the PD1/PDL1 checkpoint pathway), and/or the combinatorial application of anti-tumor drugs and monocolonal antibodies, enhances survival. Our work has strong clinical translation that we believe will bring important benefit to patients suffering a range of solid tumor-types.