DEVELOPMENT OF POTENT IPSC-DERIVED MACROPHAGES (IMACS) FOR OFF-THE-SHELF CANCER IMMUNOTHERAPY – A NEW CELL TYPE IN THE EVOCELLS PLATFORM

Background Cellular immunotherapy has transformed the oncology landscape and provided promising treatment options for patients suffering from hematological malignancies in the form of chimeric antigen receptor (CAR)-T therapies, which involve the adoptive transfer of autologous patient-derived ab T cells equipped with a CAR for enhanced tumor cell targeting. However, the manufacturing complexity and logistical hurdles associated with such autologous products have shifted the focus to the development of allogenic therapies including off-the-shelf immune cells derived from induced pluripotent stem cells (iPSCs). Whilst CAR-Ts have been effective in treating a range of different blood cancers, they have demonstrated limited efficacy to date in solid tumors, which represent approximately 90% of all adult human cancers. Recently, CAR-directed autologous macrophages have emerged as a new potential treatment for solid tumors, as they carry many inherent characteristics beneficial for the penetration into and reprogramming of an immunosuppressive tumor microenvironment (TME). We aim to generate genetically modified iPSC-derived macrophages (iMACs) as an innovative, off-the-shelf cell source for cancer immunotherapy.

Methods Using a validated GMP iPSC line as starting material, we have established a proprietary feeder- and cell sorting-free 3D differentiation protocol that enables robust and large-scale production of iMACs. To ensure reproducible high quality and safety of our cells, we perform stringent monitoring of all process stages using flow cytometry, transcriptome analysis (scRNAseq), as well as an array of analytical methods to ensure genetic integrity of the cells. iMACs were polarized towards an M1-like phenotype and compared to blood-derived counterparts in functional assays, including antibody-dependent cellular phagocytosis (ADCP) and cytokine release.

Results Our iMACs exhibited the typical cell morphology and marker expression of fully differentiated macrophages at a homogeneous level. Transcriptome analysis confirmed the complete switch of iPSCs to cells with a macrophage-specific gene profile. The iMACs responded to M1 polarization by inducing expression of classic pro-inflammatory macrophage markers, showed a cytokine profile comparable to blood-derived macrophages and exhibited high phagocytic activity. In combination with clinically well-validated monoclonal antibodies, iMACs could be directed to target tumor cell lines as well as primary patient samples in vitro.

Conclusions Using our proprietary EVOcells iMAC differentiation process we were able to generate highly pure iMACs that can be polarized to M1-like macrophages with a pro-inflammatory phenotype and a high phagocytic capacity against cancer cell lines and primary tumor samples, indicating their great potential as a cell source for cancer immunotherapies.