A NOVEL TARGETED, TYPE I INTERFERON PRODUCING, INNATE LYMPHOCYTE THERAPY WITH POTENT ANTI-TUMOR ACTIVITY

1Anders Laustsen, 1Tobias W Bjerg, 1Aida S Hansen, 1Ditte Jahger, 1Trine I Jensen, 1Mette-Louise Trepenau, 1Kasper M Jensen, 1Nicolai O Haahr, 1Marcus N Rosendal, 1Jonas B Vejlebo, 1Julia Diaconu, 1Rasmus O Bak, 1Martin R Jakobsen*. 1UNIKUM Therapeutics, Copenhagen, Denmark; 2Aarhus University, Aarhus C, Denmark

Background Plasmacytoid Dendritic Cells (pDCs) - sometimes referred to as type I interferon producing innate lymphocyte cells - are known as a master regulator of the immune system. The pDCs are responsible for the body’s Interferon (IFN) α production, and contain multiple direct effector functions that can mount strong anti-tumor responses. The low number of pDCs in tissues and their frailness have, however, impeded their use in the clinic as adoptive cell therapy. Here we present a first-in-class pDC cell therapy engineered for antigen-dependent activation that results in release of IFNs, direct killing of tumor cells, and recruitment of other innate and adaptive immune cells.

Methods Hematopoietic stem and progenitor cells (HSPCs) were used as source material in a GMP-compliant manufacturing process of human pDCs. During early differentiation, HSPCs were genetically engineered with a Synthetic Notch (SynNotch) receptor by lentiviral transduction. In this system, tumor specificity was provided by a single-chain fragment variant (scFv) targeting tumor antigen (here used CD19) and antigen-dependent activation of using a genetic response element, based on gain-of-function STING gene (STINGGoF). In vitro co-culture assays including different CD19+ cancer cell lines (REH, NALM6, RAJI) with genetic modified pDCs were used to assess functionality. An in vivo xenograft model of NOG (NOD.Cg-PrkdcscidIl2rgtm1Sug/JicTac) mice subcutaneously engrafted with NALM6 cells to mimic a solid tumor, was used to study the potency of the cell product.

Results From bulk RNA-seq we demonstrate that in vitro co-cultures of pDC-STINGGoF with cancer cell lines elicit a strong and broad gene signature including Type I IFNs and a spectrum of inflammatory cytokines. In cytotoxicity assays, pDC-STINGGoF elicit antigen-dependent killing of all tested cancer cell lines to levels beyond that of NK cells (up to 80% in a 1:2 (T:E) ratio). In NOG mice xenografted with NALM6 tumors and receiving a single intravenous infusion of pDC-STINGGoF we observed pDC tumor infiltration 48hrs post-injection which was supported by strong tumor regression. Mice treated with non-targeted pDCs exhibit tumor growth similar to control mice.

Conclusions Our genetic engineered pDC is a novel cell therapy that may change the paradigm of solid tumor treatment by the inhibitory effects on tumor cells of Type I interferons, combined with the release of pro-inflammatory cytokines, resulting in recruitment and engagement of other immune cells. This activity is further complemented by pDCs direct tumor cell killing effects. We are currently moving toward phase I to evaluate the safety and efficacy of autologous pDCs.

Ethics Approval Human cord blood was collected from Aarhus University Hospital by consent from donors that the material could be used for research under complete anonymisation. The animal experiments have been approved by Danish ethics committee in Region Midt with the ID#2020-15-0201-00394

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0442-E