393 REJUVENATION OF TUMOR-INFILTRATING LYMPHOCYTES (TIL) THROUGH PARTIAL REPROGRAMMING

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Background TIL therapy is a promising approach to the treatment of advanced solid tumors, but efficacy is limited by T-cell exhaustion and terminal differentiation. In addition, recent studies highlight the detrimental effects of aging in T cells. Reprogramming T cells into induced pluripotent stem cells (iPSC) and then differentiating back to T-cell lineage has proven complex and time-consuming. In particular for TIL applications, rejuvenation via iPSCs requires each TCR in the final product to be derived from an individual iPSC clone. To overcome these barriers, we developed a novel technology called rejuvenation, which do not need full reprogramming to iPSCs. Rejuvenated TIL (TIL_{RJ}) retain polyclonality, and have reduced T-cell age and improved cellular function.

Methods TIL from melanoma and epithelial cancers (CRC and NSCLC) were used for this study. TIL_{RJ} were generated by the transient expression of transcription factors for one week in a process called 'Partial Reprogramming' and returned back to a T-cell lineage phenotype by a process called 'Redirection'. Cytometric, metabolic and TCR repertoire phenotypes of TIL_{RJ} were analyzed. *In vitro* characteristics and anti-tumor properties were analyzed using several surrogate models including PBMC, TCR and CAR T- cell Rejuvenation. *In vivo* anti-tumor efficacy was evaluated using the NY-ESO-1 specific TCR in a xenograft NSG mouse model.

Results Partially reprogrammed TIL showed an altered morphology resembling adherent stromal cells and down-regulated conventional T-cell markers including CD3, CD4, and CD8. After Redirection, T cells reacquired a conventional phenotype including morphology, surface markers and function, while decreasing epigenetic age (>7 years younger, N =3), higher proliferation capacity (M=630-fold, SEM=447, N=3), improved metabolic state, and increased expression of biomarkers associated with T-cell stemness, including CCR7 and CD62L. Both CD4 and CD8 TIL_{RJ} populations expanded while retaining a polyclonal TCR repertoire. These results were confirmed in several other surrogate models confirming the reliability of Rejuvenation technology. Finally, TCR-specific functionality was analyzed by NY-ESO-1 TCR and CD19 CAR transduced T cells. Rejuvenated T cells persisted and killed target cell lines longer (at least two times more) upon repeated encounter with target cells *in vitro* and showed improved anti-tumor effect and survival benefit ($P < 0.05$ by log-rank test) *in vivo*.

Conclusions TIL Rejuvenation improves the function and anti-tumor properties of T cells while retaining broad TCR repertoire. This technology has the potential to develop into the first rejuvenated autologous polyclonal TIL therapy in advanced solid tumors.

Ethics Approval Animal studies were conducted in Labcorp's vivariums and are approved by Labcorp's IACUC (EB17–010).

All the human donor material that was obtained from commercial vendors. These vendors use their own IRB-approved protocol and consent process.

Tumor tissues were obtained from patients through a procurement protocol approved by WCG IRB, tracking number 20210857.

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