396 ARTIFICIAL IMMUNE MODULATION (AIM) NANOPARTICLES EXPAND ANTIGEN SPECIFIC CD8 T CELLS FROM BOTH NAÏVE AND MEMORY T CELL POPULATIONS

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Background The NexImmune Artificial Immune Modulation (AIM) nanoparticle platform can be used to direct T cell responses by mimicking natural dendritic cell function. In cell therapy application, AIM nanoparticles (np) bearing peptide MHC dimers and anti-CD28 antibody are used *ex vivo* to enrich and expand (E+E) rare populations of multiantigen specific $CD8^+$ T cells as AIM adoptive cell therapy (AIM ACT).

Methods In this study, we used single cell sequencing based on the 10X Genomics platform to explore the clonotypes of AIM ACT cell products expanded from a healthy donor naïve T cell population (MART1 specific CD8s) or a memory T cell population (EBV specific CD8s) using MART1 peptide loaded AIM np or a cocktail of AIM np targeting 6 EBV peptides.

Results While 58% of $CD8^+$ T cells were positive for MART1 dimer staining following E+E, only 167 out of 11,936 sequenced TCRs (1.3%) are MART1/Melan-A associated with matching CDR3 sequences from Pathology-associated TCR database. By contrast, the EBV E+E $CD8^+$ T cells were ~100% dimer positive using 6 EBV antigen peptide-loaded dimers. A total of 758 out of 9,236 of sequenced TCR (8.2%) are associated with EBV antigen peptides from BMLF1, BRLF1, EBNA3, LMP1/2. Most antigen-specific TCRs were novel. The clonotype distribution was significantly different between MART1 E+E cells and EBV E+E cells. The top 10 clonotypes from MART1 E+E cells accounted for less than 2% of total TCRs sequenced, whereas the top 10 clonotypes from EBV E+E cells accounted for about 44% of total TCRs sequenced. The top 100 clonotypes from MART1 E+E cells accounted for 8% of total TCRs sequenced, whereas the top 100 clonotypes from EBV E+E cells accounted for 73% of total TCRs sequenced.

Conclusions About 95% of the human population is EBV positive, thus most healthy donors have an EBV-specific memory T cell population. By contrast, healthy donors have about 1000-fold lower frequency of naïve T cell precursors such as the MART1 antigen. Therefore, the clonotypic differences between MART1 and EBV antigen-expanded CD8 T cell populations observed using NexImmune's AIM ACT aAPC may be related to progenitor population frequencies in healthy donors, suggesting that AIM ACT nanoparticles expand antigen-specific CD8 T cells from both naïve and memory T cell populations. Overall, the single cell sequencing results demonstrated that NexImmune's AIM platform generates polyclonal, multi-antigen specific CD8 T cells for adoptive cell therapy. The AIM ACT platform also opens opportunities for antigen specific TCR screening of interest.

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