

THE ACHILLES VELOS™ PROCESS 2 BOOSTS THE DOSE OF HIGHLY FUNCTIONAL CLONAL NEOANTIGEN-REACTIVE T CELLS FOR PRECISION PERSONALIZED CELL THERAPIES

¹Eleni Kotsiou*, ¹Joe Robinson*, ¹Amber Rogers, ¹Daisy Melandri, ¹Amy Baker, ¹Anabel Ramirez Aragon, ¹Sidra Nawaz, ¹Michael Epstein, ¹Shreenal Patel, ¹Jennine Mootien, ¹Andrew Craig, ¹Satwinder Kaur-Lally, ¹Hinal Patel, ²Andreas Schmitt, ³Farah Islam, ³Mariam Jamal-Hanjani, ³David Lawrence, ³Martin Foster, ⁴Samra Turajlic, ¹Sergio Quezada, ¹Katy Newton. ¹*Achilles Therapeutics, London, UK*; ²*Royal Marsden Hospital, London, UK*; ³*University College London Hospital, London, UK*; ⁴*The Francis Crick Institute, London, UK*

Background Adoptive transfer of ex-vivo expanded tumor-infiltrating lymphocytes (TIL) has shown promise in the clinic. However, the non-specific expansion of TIL and the lack of understanding of the active component of TIL has resulted in poor correlation between clinical response and dose as well as poor understanding of response and resistance mechanisms. The VELOS™ manufacturing process generates a precision and personalized treatment modality by targeting clonal neoantigens with the incorporation of an antigen-specific expansion step to enrich the product for these specificities. Achilles has developed a second generation manufacturing process (VELOS™ Process 2) to boost the neoantigen-reactive cell dose while maintaining key qualitative features associated with function. Here we report the in-depth characterization of clonal neoantigen-reactive T cells (cNeT) products expanded using the two VELOS™ processes.

Methods Matched tumors and peripheral blood from patients undergoing routine surgery were obtained from patients with primary NSCLC or metastatic melanoma (NCT03517917). TIL were expanded from tumor fragments and peptide pools corresponding to the clonal mutations identified using the PELEUS™ bioinformatics platform were synthesized. cNeT were expanded by co-culture of TIL with peptide-pulsed autologous dendritic cells, with an optimized cytokine cocktail and co-stimulation for Process 2. Neoantigen reactivity was assessed using our proprietary potency assay with peptide pool re-challenge followed by intracellular cytokine staining. Single peptide reactivities were identified using ELISPOT and flow cytometric analysis for in-depth phenotyping of cNeT was performed.

Results CD3⁺ T cells displayed higher fold expansion in Process 2 (median 77.4) compared to Process 1 (median 3.8) (n=5). Both processes showed similar CD3⁺ T cell content (median Process 1=91.3%, Process 2=96.9% n=5) and contained both CD4⁺ and CD8⁺ T cells showing reactivity to clonal neoantigens. Proportion of cells responding to neoantigen re-challenge was similar across both processes (median Process 1=19.9% and Process 2=18.2%) leading to higher reactive dose when coupled with higher T cell doses in Process 2. Phenotypically T cells were predominantly effector memory for both processes and Process 2 had lower frequencies of terminally differentiated T cells.

Conclusions Achilles' proprietary potency assay enables the optimization of new processes that deliver high cNeT doses to patients by detecting the active drug component. We have generated proof of concept data that supports the transfer of the VELOS™ Process 2 to clinical manufacture for two first-in-human studies for the treatment of solid cancers.

Ethics Approval The samples for the study were collected under an ethically approved protocol (NCT03517917)

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.193>