OPTIMISED ACHILLES VELOSTM PROCESS 2B MANUFACTURING PLATFORM GENERATES A SIGNIFICANT DOSE BOOST OF REACTIVE CD8 AND CD4 CLONAL NEOANTIGEN-REACTIVE T CELLS FOR THE TREATMENT OF SOLID CANCER


Background Clonal neoantigens are formed early in cancer evolution and have been identified as a subset of patient specific mutations that are associated with improved clinical benefit, representing great promise as targets for next generation T cell therapies. Cell therapies targeting multiple clonal neoantigens represent a unique personalised approach to treating solid cancer, as they are present on all cancer cells, minimising the risk of tumour escape, and absent from healthy tissue. Process 2 of the VELOSTM manufacturing platform has successfully demonstrated the feasibility of generating clonal neoantigen-reactive T cell (cNeT) products for the treatment of advanced NSCLC, (NCT04032847) and melanoma (NCT03997474) in two first-in-human studies. Here we demonstrate that implementation of an optimised VELOSTM platform (Process 2b) in clinical manufacturing can generate a significant dose boost of highly potent and reactive CD8+ and CD4+ cNeT for clinical use compared to both Process 1 and Process 2.

Method Briefly, tumour-infiltrating lymphocytes (TIL) were isolated from tumour fragments and Dendritic Cells (DCs) generated from whole blood, prior to cryopreservation. Patient-specific clonal neoantigens were predicted using our proprietary PELEUS™ bioinformatic platform, enabling manufacture of synthetic peptides for each patient. The co-culture of TIL and peptide loaded DCs allows the selective expansion of cNeT, prior to a polyclonal T cell boost step.

Results Here we present clinical manufacturing data on 21 tumour samples (13 NSCLC and 8 melanoma) generated with Process 2b and demonstrate a 5-fold increase in the median CD3+ TIL yield compared to 33 TIL intermediates (13 NSCLC and 20 melanoma) generated with Process 2 (30M vs. 147M). Improvements in TIL yield at the pre-expansion step have driven a 10-fold increase in the median cNeT dose (17M vs. 167M) following co-culture in 15 clinical batches manufactured with VELOSTM Process 2b (14 – 6,347M) compared to 17 batches manufactured with Process 2 (1.4 – 6,409M). Median clonal reactivity was 16% (0.2 – 96%) with products manufactured with Process 2b compared to 10% (0 – 97.6%) with Process 2. Furthermore, peptide deconvolution identified products with multiple single T cell reactivities to clonal neoantigens demonstrating a highly polyclonal product (mean number of unique variants: 7, range 0 – 90).

Conclusions We demonstrate that optimised VELOSTM Process 2b incorporating the PELEUS™ platform for prediction of clonal neoantigens can generate significantly higher cNeT doses and in some cases >1B in concert with accurately identifying the active drug component for the treatment of advanced NSCLC and melanoma.

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