MANUFACTURING OF A CLINICAL SCALE CD8 TIL PRODUCT, AGX148, WITH AND WITHOUT GENE SILENCING OF PD-1 USING SELF-DELIVERING RNAI INTASYL™ PH-762

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Background Adoptive Cell Therapy (ACT) with Tumor Infiltrating Lymphocytes (TIL) can induce durable clinical responses in a percentage of patients with melanoma, however, the efficacy of standard TIL therapy (Bulk TILs) can be limited. We hypothesize that the therapeutic efficacy of TIL therapy is dependent on the abundance of tumor-reactive T cells in the ACT product, as well as the functionality of the T cells in the product. Our approach enriches for tumor-reactive TIL by sorting CD8+ T cells from patient tumors that co-express CD103 and CD39 prior to expansion of the ACT product,1 termed AGX148. To mitigate PD-1-induced immune suppression in the Tumor Microenvironment (TME) and further enhance the therapeutic potential of AGX148 we have utilized Phio Pharmaceuticals’ self-delivering RNAi INTASYL™ PH-762 to knock down PD-1 during the expansion.

Methods Surgically resected human tumor samples were provided through a collaboration with the Earle A. Chiles Research Institute’s clinical research program at the Providence Cancer Institute. We have adapted our research expansion method into an optimized clinical manufacturing process. In collaboration with the Providence Cancer Institute’s Cell Processing Facility and Phio Pharmaceuticals, we have completed three full scale IND-enabling manufacturing runs of our ACT product AGX148 w/wo PH-762 INTASYL™.

Results Our data demonstrate that the AGX148 ACT product can be successfully manufactured at a clinical scale and that AGX148 treated with PH-762 during the expansion process is effective at reducing the steady-state level of PD-1 protein. We also tested AGX148 ACT product for autologous tumor recognition and killing in co-culture assays in vitro and in vivo. AGX148 combined with PH-762 were able to recognize and kill autologous tumor lines in vitro and PH-762-treated cells had increased 4-1BB expression in TIL/tumor cocultures. PH-762 induced knockdown of PD-1 was observed in circulating T cells after ACT in a xenograft model with autologous tumor.

Conclusions We have generated a potent tumor-specific ACT TIL product (AGX148) at clinical scale through the isolation and selective expansion of tumor-reactive T cells. Knocking down PD-1 with PH-762 INTASYL™ has the potential to further enhance the function of the AGX148 product and this ACT product will soon be tested in cancer patients.

REFERENCE

Ethics Approval Human sample collection for this study was approved by the institutional review board, Providence St. Joseph Health IRB (FWA00029175), Study ID: PDX06-108. All patients provided informed consent for participation in this study. Experimental animal studies were performed according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals and in accordance with the EACRI Institutional Animal Care and Use Committee (Animal Welfare Assurance No. A3913-01) protocol# 51.

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