ARTIFICIAL IMMUNE MODULATION ADOPTIVE CELL THERAPIES FOR VIRALLY DRIVEN MALIGNANCIES

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Background NexImmune is developing novel, antigen-specific immunotherapies to meet serious unmet clinical needs. Here we report on the development of adoptive cell therapies (ACT) for virally driven malignancies. The proprietary Artificial Immune Modulation (AIM™) platform mimics natural T cell biology to target, activate and expand antigen-specific CD8+ T cells. EBV, HPV, and HTLV are estimated to contribute to 6-7% of global cancer cases. The targeted antigens are implicated in multiple malignancies including B cell lymphomas (EBV), adult T cell leukemia/lymphoma (HTLV1) as well as multiple HPV related malignancies such as oropharyngeal, cervical, and anal cancers.

Methods Using the paramagnetic AIM nanoparticle as an artificial antigen presenting cell (aAPC), in two-weeks T cells were enriched and expanded from HLA-A*02:01 donor apheresis material against immunodominant antigens of EBV, HTLV, and HPV. The memory phenotype of these cells was determined by CD45RA, CD62L, and CD95 expression. Antigen specific killing was observed on HLA-A2+ cell lines and polyfunctional activity characterized by an intracellular cytokine staining assay.

Results Greater than 90% of the total resulting CD8+ T cells display a phenotype of effector, central, or long-lived stem-like memory. From 8 independent healthy donor clinical scale manufacturing runs of NEXI-003, a pentavalent specific AIM ACT against the E6 and E7 antigens of both HPV-16 and HPV-18, as well as the tumor-associated antigen Survivin, 0.28E9 to 3.79E9 cells were generated. These cells showed dual HPV-16+ and HPV-18+ cancer antigen specificity and cytotoxic activity against HLA-A2+ cell lines, without significant cytotoxic activity against autologous PBMCs. With respect to EBV, using HLA-A2+ cell lines we further show antigen specific killing directed at LMP2, BRLF1, BMLF1, EBNA3, and LMP1 from a single healthy donor AIM ACT selected on 6 EBV antigens. In addition, these expanded memory T cells demonstrate a high degree of polyfunctional activity upon stimulation.

Conclusions NEXI-003 is an immunotherapy for HPV cancers in HLA-A*02:01 patients that recently received IND clearance and it is anticipated to begin clinical trials in 2022. In addition to B cell lymphomas, B cells that are present in the plaques of multiple sclerosis patients have been found to express EBV antigens. Therefore, by directing a multivalent EBV T cell response there is the potential to treat other EBV-associated diseases using one AIM ACT product. Results reported here, will support the expansion of the AIM platform modalities for use in the treatment of virally driven malignancies, as well as potential virally associated autoimmune and infection diseases.