Background

T-cell attributes for adaptive cell therapy of patients with advanced cancer can be optimized during ex vivo expansion culture. Autologous TCR-engineered T-cells targeting the MAGE-A4 antigen with Specific Peptide Enhanced Affinity Receptors (SPEAR T-cells) have shown promise in the clinic. The highly variable leukocyte material obtained from individual patients during apheresis can present a manufacturing challenge for autologous T-cell therapies. The degree of ex vivo expansion and the functional attributes of the expanded T-cell product impact therapeutic efficacy and can be suboptimal for some patients apheresis material. Both TCR and cytokine growth factor signals used for ex vivo T-cell expansion promote robust activation of AKT (Protein Kinase B) signaling, which drives T-cell activation, proliferation, and terminal differentiation. It is hypothesized that inhibition of AKT signaling during T-cell expansion may uncouple proliferation and terminal differentiation, leading to the generation of less differentiated T-cells that may have functional benefit in vivo.

Methods

We evaluated use of an AKT inhibitor during SPEAR T-cell manufacturing to increase the yield of biomarkers of differentiation (CD27, CD161, and PD-1) in ex vivo-expanded T-cells.

Results

AKT inhibition resulted in the generation of a more consistent expansion and phenotype of the final T-cell product. This was observed using two SPEAR T-cell constructs, ADP-A2M4 and ADP-A2M4CD8. Ex vivo SPEAR T-cell expansion in the presence of an AKT inhibitor generated CD8+ T-cells that maintained a less differentiated phenotype (based on CCR7+CD45RA+ and CD62L+ expression). AKT inhibition was associated with enhanced antigen-specific responses of SPEAR T-cells in vitro, including effector cytokine production, target-cell killing, ability to proliferate in response to prolonged antigen-stimulation and maintenance of cytotoxic activity following antigen re-stimulation.

Conclusions

We plan to introduce AKT inhibition into the GMP manufacturing process, and evaluate the efficacy of the resulting products in ongoing clinical studies.

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Ethics Approval

The experimental study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines and was approved by local authorities. An independent ethics committee or institutional review board approved the clinical protocol at each participating center. All the patients provided written informed consent before study entry.

REFERENCES

3. van der Waart A, van de Weem N, Maas F, et al. DECIBATE gene modulation sensitizes human non-small-cell lung cancer (NSCLC) to NY-ESO-1 TCR immunotherapy (LETETRESGENE AUTOLEUCEL; GSK3377794) IN VIVO

Dmitry Pankov, Ioanna Eleftheriadou, Anna Domogala, Sara Brett, Lea Patock, Magdalena Kijewska, Gary Thripp, Jack Euesden, Jan Klapwijk, Katrina Soor, Miriam Dannm, Mark D Hill, Miraila Georgouli, Aiman Shalabi, Cedrik Britten, GSK3377794. Letetresgene autoleucel (TCR) incapable of recognizing NY-ESO-1 and LAGE-1a antigens in complex with human leukocyte antigen (HLA)-A*02. NY-ESO-1 (CTAG1B) and LAGE-1a (CTAG2) are tumor-associated antigens (TAA) that share the SLLMWITQF peptide bound to human leukocyte antigen HLA-A*02 and are expressed in various cancers. Emerging evidence suggests that TCR-engineered T cells targeting NY-ESO-1 hold promise for patients with solid tumors. Approximately 75% of synovial sarcomas can over-express NY-ESO-1 vs 12% of NSCLC, however, NSCLC expression of NY-ESO-1/LAGE-1a may have