A NOVEL SMALL MOLECULE INHIBITOR OF CBL-B SHOWS POTENT ANTITUMOR ACTIVITY IN COMBINATION WITH PMEL-1 ADOPTIVE CELL TRANSFER IN AN AGGRESSIVE MOUSE MELANOMA MODEL

Marilena Gallotta*, Jose Gomez Romo, Serena Ranucci, Austin Tenn-McClellan, Frederick Cohen, Gwenn Hansen, Arthur Sands, Ryan Rountree, Cristiana Guiducci. Nurix Therapeutics, San Francisco, CA, USA

Background Adoptive cell transfer (ACT) involving engineered T cells (CAR-T) or autologous tumor-specific lymphocytes (TIL) induces effective antitumor response in advanced cancer patients. However, tumors frequently relapse after an initial response due to suboptimal T-cell activation and expansion within the tumor microenvironment. Moreover, current ACT treatment paradigms require application of high dose bolus infusions of IL-2 which are associated with acute toxicities restricting the use of ACT in the clinic. The E3 ubiquitin ligase Casitas B-lineage lymphoma B (CBL-B) is highly expressed in T cells, where it functions as an intracellular checkpoint that constrains T-cell activation following T cell receptor (TCR) engagement, therefore limiting T cell-mediated antitumor responses.

Methods We have developed two highly potent small molecule inhibitors of CBL-B to increase T-cell antitumor function both in vitro (NX-0255) and in vivo (NX-1607).

Results We previously reported that addition of NX-0255 during in vitro treatment of tumor-specific T cells increases the frequency and absolute numbers of less exhausted CD8+ memory T cells, profoundly improving their functionality and ability to control tumor growth following ACT in tumor-bearing mice. Here, we hypothesized that CBL-B inhibition could reduce the requirement for IL-2 bolus and utilized the Pmel-1 ACT/B16 melanoma tumor model to compare the antitumor effect of post infusion in vivo treatments with NX-1607 to high dose IL-2. C57BL/6 mice were implanted with B16-OVA and received Pmel-1 CD8+ T cells activated in vitro using anti-CD3 stimulation and NX-0255 combined with IL-2, followed by systemic treatment with either IL-2 (IP, 150000 IU for three days, BID) or oral NX-1607 (30 mg/kg, QD). We found that ACT supported by in vivo treatment with NX-1607 increased the antitumor activity of Pmel-1 cells when compared to ACT alone. Importantly, the increased antitumor activity of NX-1607-supported ACT was comparable to IL-2. Spectral cytometry analysis performed at 7 and 14 days after ACT showed that following NX-1607, a larger fraction of circulating Pmel-1 cells had a central-memory phenotype and expressed high levels of Granzyme B. Interestingly, both in vivo treatments induced increased 4-1BB/CD137 expression that significantly correlates with antitumor response.

Conclusions These findings demonstrated that oral dosing of NX-1607 in combination with ACT can support the functionality of transferred cells providing a robust antitumor response in the aggressive B16-OVA model. Treatment with NX-1607 induces a more favorable T cell phenotype compared to IL-2 treatment and is well tolerated. The observed antitumor effects of NX-1607 support its potential use in combination with cell-based therapeutics.