IL-15/IL-15Rα HETERODIMERIC COMPLEX AS CANCER IMMUNOTHERAPY IN MURINE BREAST CANCER MODELS

1Siqi Guo*, 2Ronald Smeltz Smeltz, 1Anthony Nanajian, 3Richard Heller, 1Old Dominion University, Virginia Beach, VA, USA; 1Virginal Commonwealth University, Richmond, VA, USA; 2University of South Florida, Tampa, FL, USA

Background Interleukin 15 (IL-15) has been evaluated as a potential treatment for solid tumors in clinical trials, but the effectiveness of systemic IL-15 administration as a monotherapy has not been realized. IL-15 receptor alpha (IL-15Rα) can stabilize IL-15 and enhance its bioactivity. The goal of this study was to examine the activity of IL-15/IL-15Rα complex (IL-15cx) to CD8+ T cells and evaluate its potential efficacy in murine breast cancer models.

Methods The bioactivity of IL-15cx to CD8 T cells was assessed by ex vivo and in vivo cell proliferation assays. The antitumor efficacy was studied in mice mammary carcinoma models (Her2/neu transgenic and 4T1-luc mammary cancers) treated with systemic recombiant protein with/without the depletion of myeloid-derived suppressor cells or intratumoral gene electrotransfer (GET). Systemic and local changes of immune cells were examined by flow cytometry, and tumor-specific IFN-γ release from immune cells was measured by ELISA assays.

Results IL-15cx shows superior in vivo bioactivity to expand CD8 T cells in comparison to an equimolar single chain IL-15. T-bet is partially involved in CD8 T cell expansion ex vivo and in vivo due to IL-15 or IL-15cx. Intraperitoneal administration of IL-15cx results in a moderate inhibition of breast cancer growth that is associated with an increase in the frequency of cytotoxic CD8 T cells and the improvement of their function. The depletion of myeloid-derived suppressor cells (MDSCs) has no impact on mouse breast cancer growth. IL-15cx treatment diminishes MDSCs in murine tumors. However, it also antagonizes the effects of depletion antibody. Intratumoral GET with plasmid IL-15/IL-15Rα leads to a long-term survival benefit in 4T1 mammary carcinoma model. An early increase of local cytotoxic cells correlates with GET treatment and an increase of long-term memory T cells results from animals with complete tumor regression.

Conclusions Systemic and local administration of IL-15cx shows two distinct therapeutic responses, a moderate tumor growth inhibition or heterogeneous tumor regressions with survival improvement. Further studies are warranted to improve the efficacy of IL-15cx as an immunotherapy for breast cancer.

Acknowledgements This work was supported by funding from the National Cancer Institute grant R21 CA229939 to S. Guo and funding from the Thomas F. and Kate Miller Jeffress Memorial Trust to R. B. Smeltz.

Trial Registration N/A

Ethics Approval Experimental procedures were approved by the Institutional Animal Care and Use Committee (IACUC) at Old Dominion University (S. Guo) and by the IACUC at Virginia Commonwealth University (R.B. Smeltz).

REFERENCES

N/A

ANV419 IS A NOVEL CD122-SELECTIVE IL-2/ANTI-IL-2 ANTIBODY FUSION PROTEIN WITH POTENT CD8 T CELL AND NK CELL STIMULATORY FUNCTION IN VITRO AND IN VIVO

1Christoph Huber*, 1Andreas Katopodis, 2Barbara Branetti, 2Jean-Michel Rondeau, 2Simone Popp, 2Catherine Rengnier, 2Daniel Kaiser. 1Anaveon AG, Basel, Switzerland; 2NIBR, Cambridge, MA, USA

Background ANV419 is a uniquely engineered IL-2 fusion to an antibody selectively blocking the IL-2 receptor alpha (CD25) binding site. It signals selectively through the CD122/CD132 dimeric IL-2 receptor and stimulates the proliferation of CD8 T cells and NK cells while avoiding the proliferation of immunosuppressive regulatory T cells (Treg). ANV419 has the potential to substantially separate targeted T-cell and NK cell proliferation and anti-tumor responses from the dosing limiting toxicities of recombiant IL-2 (aldesleukin). ANV419 has antibody like stability and behavior and is currently in late preclinical development for tumor immunotherapy.

Methods The structural and functional structure of ANV419 have been solved and its binding affinity to CD25 and CD122 has been determined. In vitro and in vivo studies, including pharmacodynamics and toxicity, have been performed in rodents and non-human primates. The ability of ANV419 to inhibit tumor growth has been studied in mouse syngeneic models.

Results Structural analysis demonstrates that the CD25 binding site of IL-2 is completely blocked in ANV419 while the CD122/CD132 sites are available for binding. As a result, ANV419 lacks CD25 binding activity but retains IL-2 receptor beta (CD122) affinity comparable to native IL-2. In human peripheral blood monocyte cultures, ANV419 induces STAT5 phosphorylation with high selectivity for CD8 and NK cells but not Treg. Concordantly, it stimulates the proliferation of purified human CD8 T cells and NK cells but not CTLL-2 cells. A single injection of ANV419 in mice results in strong induction of the proliferation marker Ki67 specifically in CD8 T cells and NK cells but not Treg and a selective increase of the respective cell numbers in the spleen and peripheral blood of animals. Single agent anti-tumor activity was observed in checkpoint sensitive (H22) and resistant (Renca, B16F10) syngeneic mouse tumor models. Combination of ANV419 with trastuzumab in the gastric cancer N87 xenograft model in BALB/c nude mice led to significant tumor reduction relative to trastuzumab monotherapy. In non-human primates, ANV419 is well tolerated and induces expression of Ki67 and sustained expansion in CD8 T cells and NK cells with no signs of vascular leak syndrome observed with high dose aldesleukin in patients.

Conclusions The pre-clinical data suggest that ANV419 possesses a unique structure and is potent in expanding CD8 T-cells and NK cells with a marked safety window in non-human primates. This data warrants further translational development of ANV419 as an immune therapeutic in oncology.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0571