

887 **IN VIVO EVALUATION OF THE ROLE OF T CELL HELP IN NK CELL MEDIATED ADCC**

¹Jyoti Arora*, ¹Caitlin D Lemke-Miltner, ²George J Weiner. ¹University of Iowa, Iowa City, IA, USA; ²Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA, USA

Background A number of anti-cancer monoclonal antibodies (mAbs), including the anti-CD20 mAb rituximab, are thought to mediate their antitumor effect, in large part, through NK cell Antibody-Dependent Cellular Cytotoxicity (ADCC). These mAb are standard of care for multiple types of cancer, but some patients are resistant to therapy. *In vitro* studies in our laboratory suggest longer term activation of NK cells by mAb is dependent on T cell help *via* IL2.¹ Therefore, the lack of T cell help in the tumor microenvironment (TME) could limit longer term NK cell viability and activation following mAb therapy, and so be a possible mechanism of resistance.

Methods Syngeneic mouse models are of limited value for studying this potential mechanism of resistance to mAb therapy *in vivo* due to biological differences in NK cell biology, and the mechanisms of mAb action between mice and humans. Therefore, a humanized mouse model was developed that allows for control of immune cells in the TME. This model involves mixing Raji lymphoma cells with consistent numbers of NK cells, but varying number of T cells obtained from normal donor PBMCs and inoculating this mixture into NCG immunodeficient mice.² Using this model, pre-therapy fine needle aspirates (FNAs) were collected when tumors developed 20 days after tumor inoculation. A single dose of rituximab or control mAb (trastuzumab) was given after the pre-therapy FNA was obtained, followed one week later by a post-treatment FNA of the tumor.

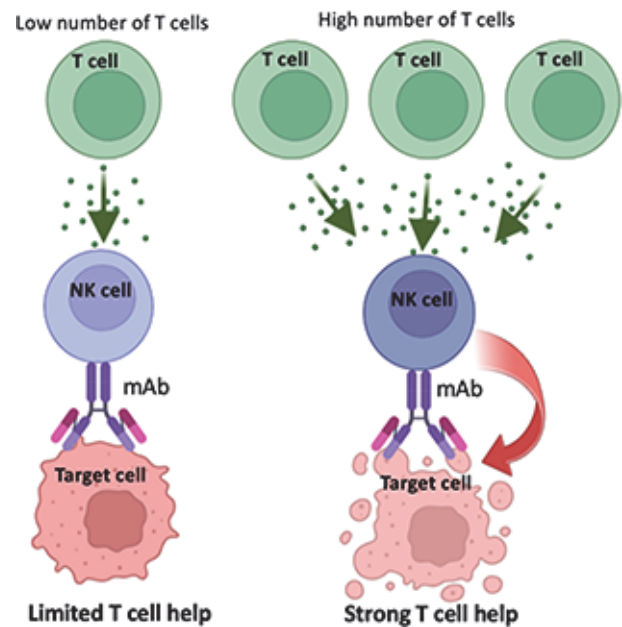
Results Flow cytometric analysis of pre-therapy FNAs (20 days after tumor-PBMCs mix injection) demonstrated the tumors contained consistent numbers of NK cells but variable numbers of T cells as would be expected based on the cell mixtures at the time of inoculation. Comparison of the post- to the pre-treatment FNA revealed a T cell-dependent increase in NK cell viability and CD16 expression on NK cells in mice treated with rituximab but not those treated with trastuzumab. Because the primary goal was to assess changes in the TME, rituximab therapy was not given until tumors were large and growing rapidly. Nevertheless, there was a trend towards slowing of tumor growth in mice treated with RTX bearing tumors with a larger number of T cells compared to other groups.

Conclusions These *in vivo* studies support the hypothesis that T cells provide help that enhances the viability and activation of NK cells following mAb therapy, and so may contribute to the efficacy of that therapy (figure 1).

REFERENCES

1. Wang Z, Chimenti MS, Strouse C, Weiner GJ. T cells, particularly activated CD4 (+) cells, maintain anti-CD20-mediated NK cell viability and antibody dependent cellular cytotoxicity. *Cancer Immunol Immunother.* 2022;**71**(2):237–49.
2. Arora J, Lemke-Miltner CD, Weiner GJ. Abstract 4: A novel humanized mouse model for study of T cells and NK cells in the tumor microenvironment. *Cancer Research.* 2023;**83**(7_Supplement):4

Ethics Approval Mouse studies were approved and performed according to guidelines established by the University of Iowa Institutional Animal Care and Use Committee (IACUC) under the approved Protocol #1011236.



Abstract 887 Figure 1 Graphical abstract of hypothesis

<http://dx.doi.org/10.1136/jitc-2023-SITC2023.0887>