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FceR1g negative NK-cells (g-nNK) enhance antibody dependent cellular cytotoxicity and in vivo efficacy of therapeutic monoclonal antibodies against hematologic malignancies

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Abstract

Monoclonal antibodies (mAbs) are a central component of therapy for hematologic malignancies. Widely used mAb agents in multiple myeloma (MM) include daratumumab and elotuzumab. However, not all patients respond to these agents and resistance is a significant clinical issue. A recently discovered subset of human NK-cells lacking expression of Fc□R1□ ("g-NK cells") was found to have a multi-fold increase in antibody-dependent effector functions after CD16 crosslinking. In this study, we tested the capacity of g-NK cells to enhance efficacy of therapeutic mAbs against MM. In vitro, we found that that g-NK cells have strikingly superior anti-myeloma cytotoxicity compared to conventional NK-cells (cNK) when combined with daratumumab or elotuzumab (~6-fold, $p<0.001$). In addition, g-NK cells naturally expressed minimal surface CD38 and SLAMF7, reducing incidence of therapeutic "fratricide". In tumor-naïve murine models, g-NK persistence in blood, spleen, and bone marrow was markedly improved (>90%) relative to cNK cells over 31 days ($p<0.001$). In vivo efficacy studies showed the combination of daratumumab and g-NK cells led to a >99% tumor reduction (by flow cytometry analysis) as compared to the combination of daratumumab and cNK cells ($p<0.001$). Moreover, treatment with daratumumab and g-NK cells led to complete elimination of myeloma burden in 5 of 7 mice. Collectively, these results underscore the unique ability of g-NK cells to potentiate the activity of therapeutic mAbs and overcome limitations of current "off-the-shelf" NK-cell therapies, without the need for cellular irradiation or genetic engineering.

Biography

Austin Bigley is the V.P. Director of Research & Development at Indapta Therapeutics where he developed the donor screening and cellular expansion protocols for Indapta's g-NK cell platform. Austin has been extensively published in the NK-cell space over the past 12 years and has worked with major players, such as Dr. Nina Shah and Dr. Katy Rezvani at M.D. Anderson Cancer Center in Houston, TX. Austin's primary research goal is to harness adaptive NK-cell responses for cancer immunotherapy against a variety of hematologic malignancies and solid tumors. In addition to his work in cancer immunotherapy, Austin was the first to demonstrate that NK-cell anti-tumor activity is elevated during exercise recovery and that NK-cell activity is impaired during spaceflight.

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