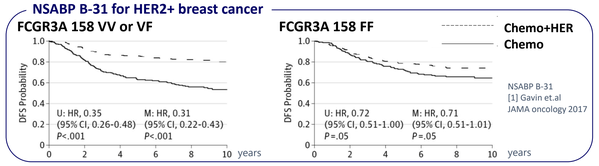
An IL- 15 superagonist enhances antibody-dependent cell-mediated cytotoxicity against breast cancer cells regardless of *FCGR3A* (CD16) genotype and rescues NK cell from TGF-b1-induced immunosuppression

Rika Fujii[1], Hing Wong[2], Jeffrey Schlom[1], James W. Hodge[1]

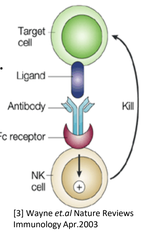
1) Laboratory of Tumor Immunology and Biology, NCI, NIH, Bethesda, MD 2) Altor bioscience corporation, Miramar, FL

Introduction

- Some clinical studies suggest that the genotype of *FCGR3A* is associated with differential response to IgG1 monoclonal Ab (mAb) therapy such as trastuzumab, rituximab, and cetuximab, by modulating Antibody-dependent cell-mediated cytotoxicity (ADCC) effects [1, 2].



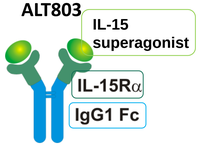
- ADCC is mediated by an IgG1 antibody bound to tumor cells and the Fc receptor (FcγIIIa) on natural killer (NK) cells [3].



- NK cells express 3 types of polymorphisms [4-6].

The polymorphisms in the FcγIIIa of NK cells				
phenotype	**Position 158 of FCGR3A**		**Affinity to IgG1**	**Popularity (vary with ethnics)**
FcγIIIa 158 VV	V (val)	V	High	10-30 %
FcγIIIa 158 FF	F (phe)	F	low	20-45 %
FcγIIIa 158 VF	V	F	High-med	45-55 %

- It is a clinical challenge to improve outcomes in patients with the *FCGR3A* 158FF genotype whose NK cells have lower affinity to mAb and mediate poor ADCC activity.
- NK cells of cancer patients exhibit impaired function mediated by immunosuppressive factors released from the tumor microenvironment, such as transforming growth factor (TGF)-β1 [7,8].
- An IL- 15 superagonist/IL-15Rα Sushi-Fc fusion complex (ALT803) activates the IL-15 receptor on CD8+ T cells and NK cells, inducing their expansion and cytotoxicity [9]. ALT803 has shown encouraging results in several *in vivo* studies [10, 11], leading to multiple clinical trials against hematological and solid cancers.

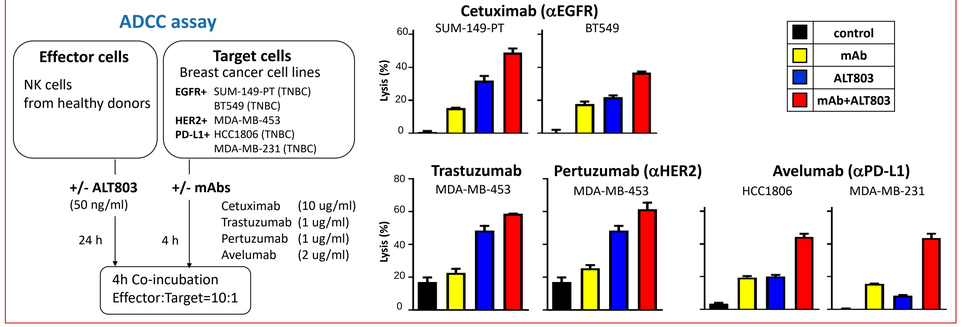


Here, we examined the potential of ALT803 for NK cells eliminating breast cancer cells in terms of;

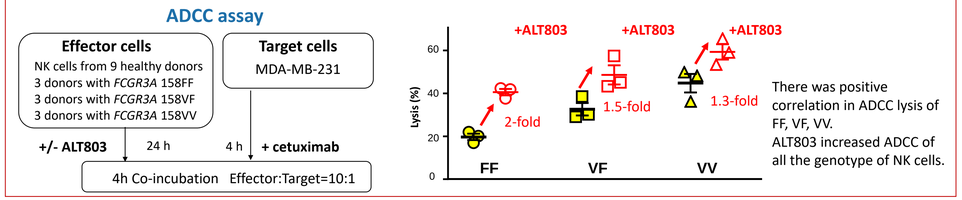
1) The strategy for patients with *FCG3A* 158 FF genotype
2) The rescue of TGF-β1-suppressed NK cell cytotoxic function

Results 1

IgG1 mAbs induced NK cell lysis of breast cancer cells via ADCC. ALT803 further upregulated ADCC.

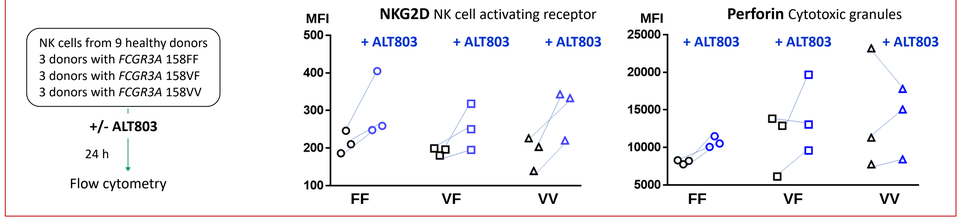


ALT803 increased cetuximab-mediated ADCC in NK cells regardless of the genotype of *FCGR3A*.



There was positive correlation in ADCC lysis of FF, VF, VV.
ALT803 increased ADCC of all the genotype of NK cells.

ALT803 upregulated the expression of NKG2D and perforin in NK cells regardless of the genotype of *FCGR3A*.

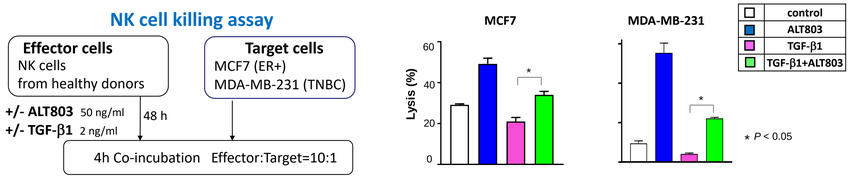


Conclusion 1

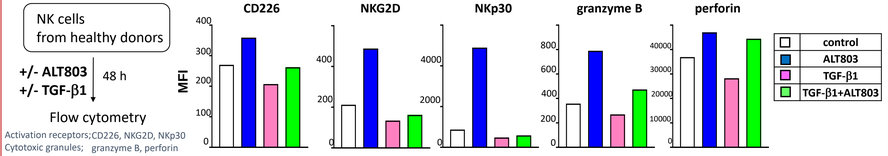
ALT803 can potentially increase the clinical benefit of ADCC-based mAb therapy for breast cancer patients, regardless of the genotype of *FCGR3A*.

Results 2

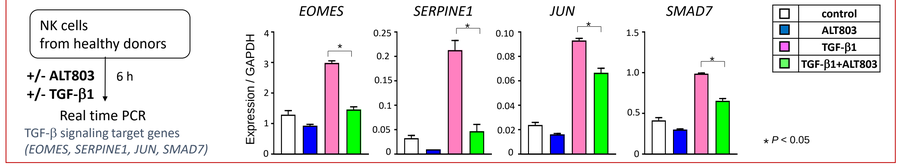
ALT803 protected NK cell-cytotoxicity from TGF-β1-induced functional suppression.



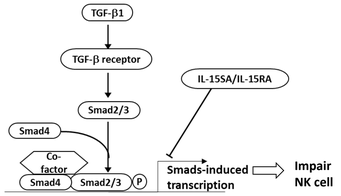
ALT803 inhibited TGF-β1 from decreasing the expression of NK cell activation receptors and cytotoxic granules.



ALT803 significantly decreased TGF-β1-induced transcription activity.



Conclusion 2



TGF-β1 decreased the expression of NK cell activation receptors and cytotoxic granules, resulting in impaired NK cell cytotoxic function. ALT803 can function as an inhibitor of TGF-β1 signaling, providing a potential remedy for NK cell dysfunction in the immunosuppressive tumor microenvironment.

References

[1] Gavin et al. JAMA Oncol.2017;3(3) [2] Mellor et al. J Hematol Oncol 2013;6(1) [3] Wayne *et.al* Nat Rev Immunol 2003;3(4) [4] Koene et al. Blood 1997;90(3) [5] Oboshi et al. Hum Immunol 2016;77(2) [6] Musolino et al. J Clin Oncol 2008;26(11) [7] Yu et al. Immunity 2006;24(5) [8] Trotta et al. J Immunol 2008;181(6) [9] Zhu et al. J Immunol 2009;183(6) [10] Xu et al. Cancer Res 2013;73(10) [11] Kim et al. Oncotarget 2016;7(13)