Activating innate immune response as strategy for endometrial cancer treatment

M. Pia Morelli[1], Massimo Fantini[2], Alexandra Diggs[1], Philip M. Arlen[2], Kwong Y. Tsang[2] and Christina M. Annunziata[1]

[1]Women's Malignancies Branch National Cancer Institute, National Institutes of Health, Bethesda, MD, USA. [2]Precision Biologics, Inc., Bethesda MD, USA

PRECISION BIOLOGICS

NIH NATIONAL CANCER INSTITUTE Center for Cancer Research

Poster #3315

Background: Uterine cancer is the 6th most common cause of death for women in the USA, and about 10,000 women will die from this disease every year. A better understanding of the disease biology has opened the door for more individualized treatment approaches. In the present study we focused on new strategies to potentiate the innate immune response against endometrial cancer. To direct NK cell activity, we used a monoclonal antibody NEO-201 which targets a tumor specific form of CEACAM-5 and -6, in combination with IL-15. We hypothesized that the expression of tumor associated neo-antigen for NEO-201 correlates with specific tumor biological characteristics, with a goal of designing new rational combinations to potentiate the anti-tumor immune response.

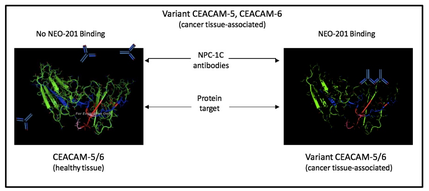
Method: NEO-201 is a humanized monoclonal antibody developed through vaccine, and is currently being evaluated in a first-in-human Phase I study currently ongoing at the NCI (NCT03476681). This antibody exerts anti-tumor activity via NK-mediated ADCC. To establish the biological relevance of this antigen, we screened a Tissue Microarray (TMA) of endometrial cancer patient tissues by IHC. To identify relevant cell line models, we screened 11 endometrial cancer cell lines for NEO-201 expression by IHC, WB and FACS; and studied the biological characteristics of the same cell lines by whole exome and RNA sequencing. Next, we evaluated NEO-201 anti-tumor activity in combination with IL-15 using ADCC assay *in vitro*.

Result: The expression of NEO-201 was confirmed in the patient TMA, where the antigen was detected predominantly on cells membrane and apical surface in 10% of samples. ACI-158 cell line was strongly positive for NEO-201 antigen by WB, FACS and IHC. To evaluate ADCC, NK were isolated from healthy donor PBMC and incubated with IL15 for 48hours, before performing a chromium release assay. The stimulation with IL-15 increased NK mediated ADCC by 2.5 fold, regardless of the donor genotype. Addition of NEO-201 to facilitate NK mediated ADCC further increased activation by 1.5 to 6 fold. Preliminary sequencing data showed that 5 cell lines express MMR gene mutations, 3 NRAS/KRAS/ERK1-2 mutations, 1 AKT and 1 CTNNB1 mutation, and 2 cell lines carry HER2+ amplification.

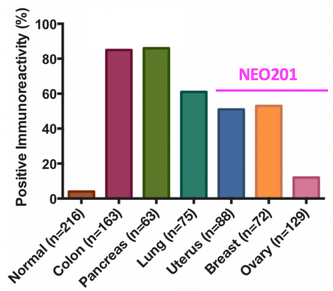
Conclusion: NEO-201 and IL15 showed promising results in activating innate immune system against endometrial cancer cells in vitro. Additional *in vitro* and *in vivo* studies are ongoing to optimize the combination and to correlate its activity with cells' biological characteristics.

Background

TAA derived mAb NEO-201 selectively binds tumor tissue

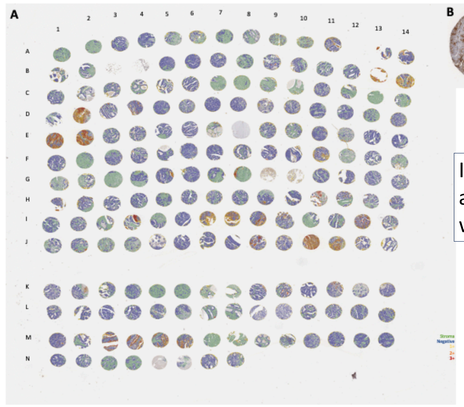


NEO antigen is highly expressed across different tumor types



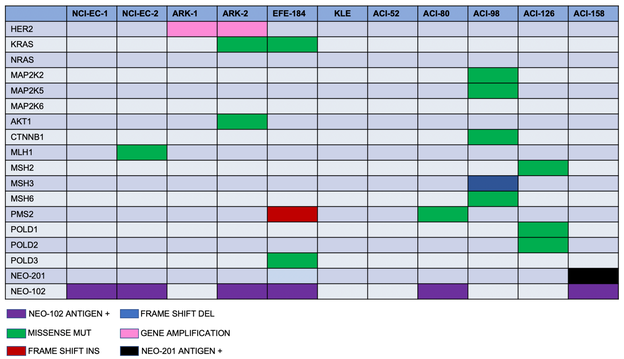
Results

TMA shows NEO201 expressed in 10% of the cases, with predominantly on cell surface staining



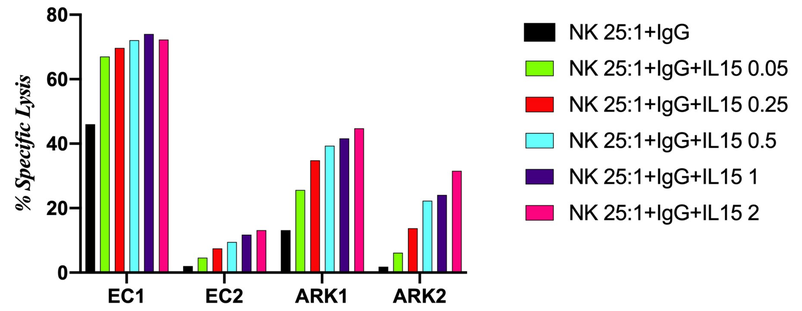
Interestingly, intraluminal (C) and immune cell (D) staining was detected as well.

EC Cell lines mutational profile and expression of Tumor Associated Neo-Antigen

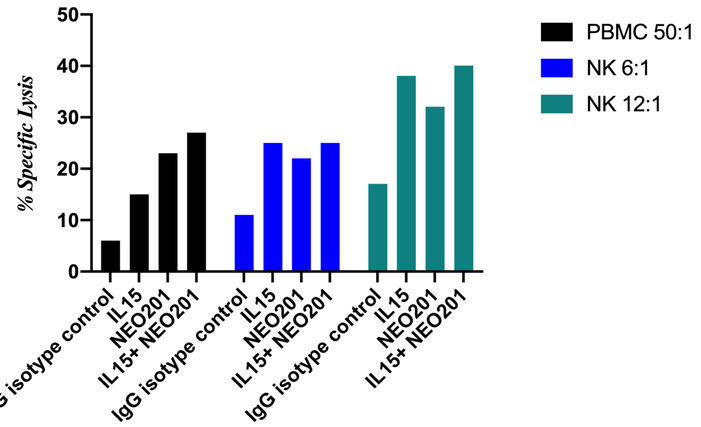


Results

Endometrial Cancer Cell Lines have a different degree of sensitive to NK killing, which is potentiated by IL15 stimulation



IL15 increase specific lysis of ACI-158 by PBMC, NK, and NEO-201 mediated ADCC. No clear synergistic effect were observed for the combination of NEO201 and IL15



Conclusions

1. EC cells are vulnerable to NK killing, which makes strategy to activity innate immune system very appealing for the treatment of this disease.
2. Studies to better characterize the profile of those cells vulnerable to NK killing are ongoing.
3. Combination of NK with IL15 and mAb inducing ADCC could be a promising strategy for EC treatment