IDP-023 Has Superior Single Agent & Antibody-Dependent Cytotoxicity Against Solid Tumor Cell Lines Compared to Conventional NK Cells

Bigley, A.B., Spade, S., Collison-Pautz, M.R., Mandl-Cashman, S.

Indapta Therapeutics, 5000 Gulf Freeway, Houston, TX, 77023, USA

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Introduction

- IDP-023 is an investigational new drug product comprised of g-NK cells currently clinically explored for the treatment of advanced hematologic cancers (NCT06119685). g-NK lack FcεR1γ, resulting in elevated antibody-dependent cellular cytotoxicity (ADCC) through enhanced CD3ζ signaling downstream of CD16 engagement with the Fc portion of antibodies (see Fig. 1). g-NK cells are further characterized by high antibody-independent killing of HLA-E$^+$ tumor cells via elevated expression of HLA-E activating receptor NKG2C and low expression of HLA-E inhibitory receptor NKG2A. This is important because HLA-E overexpression is a common immune escape mechanism in cancer including breast and non-small cell lung cancer (NSCLC).
- Cetuximab is a monoclonal antibody (mAb) inhibiting the EGFR pathway showing promise in clinical trials for patients with high EGFR-expressing NSCLC. However, it has not been approved by FDA for NSCLC because its effect on overall survival was deemed modest relative to side effects. Combination with g-NK-cells could enhance efficacy of cetuximab without exacerbating side effects.
- The mAb trastuzumab targets HER2 and is approved in HER2+ breast and gastric cancers. However, trastuzumab alone or in combination with cytotoxic chemotherapy is ineffective for many patients, and most patients with metastatic breast cancer are incurable and develop resistance to trastuzumab. Thus, there is unmet need for adjuvants that could be administered to enhance efficacy of trastuzumab or rescue the therapy from resistance.

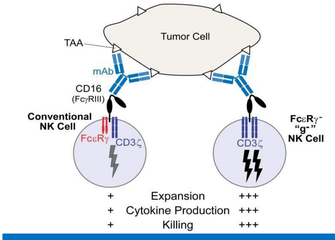

Fig. 1. Mechanism of Action. FcεR1γ deficient NK cells (g-NK cells), when stimulated by CD16, produce greater amounts of IFNγ and TNFα, and kill tumor targets better, compared to conventional NK cells from the same donor (1).

Methods

- We used flow cytometry to test the cytotoxicity and cytokine production of NK-cells from 7 unique donors expanded using either the IDP-023 method to expand g-NK cells or the Campana method (K562-mbIL15-41BBL + IL-2) to expand cNK cells **(1)**.
- We also analyzed single cell RNA sequencing data from the Obradovic dataset to measure g-NK cell frequency in the tumor microenvironment of patients with clear cell renal carcinoma **(2)**.
- We used the g-NK signature that we obtained from the Obradovic dataset to perform a meta-analysis of the FinHER and CALGB40601 datasets **(3-4)**.

IDP-023 has significantly superior cytotoxicity and cytokine responses (IFN-γ and TNF-α) against the A549 and SKBR3 cell lines relative to expanded donor-matched cNK cells

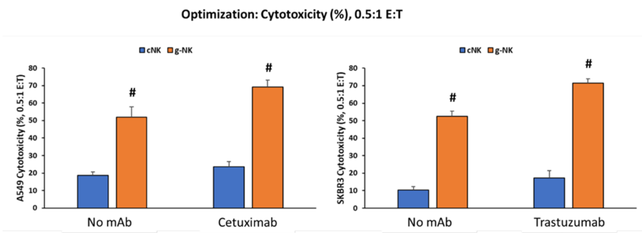

Figure 2: Cryopreserved IDP-023 g-NK cells have significantly superior cytotoxicity against the lung cancer cell line A549 (with and without cetuximab) and the breast cancer cell line SKBR3 (with and without trastuzumab) relative to cryopreserved cNK cells expanded using the Campana method. The anti-tumor cytotoxicity of IDP-023 g-NK cells is clearly enhanced by addition of mAb. Values are mean ± SE, N=7. #p<0.001 for differences between g-NK and cNK cells.

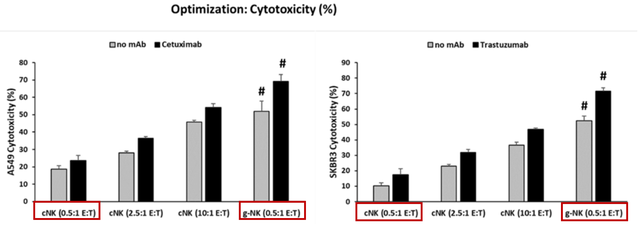

Figure 3: Cryopreserved IDP-023 g-NK cells have markedly superior cytotoxicity against the lung cancer cell line A549 (with and without cetuximab) and the breast cancer cell line SKBR3 (with and without trastuzumab) relative to cryopreserved cNK cells expanded using the Campana method. The anti-tumor cytotoxicity of IDP-023 g-NK cells is clearly enhanced by addition of mAb. The cytotoxicity of IDP-023 g-NK cells at a 0.5:1 E:T ratio is greater than the cytotoxicity of cNK cells at a 10:1 E:T ratio. Thus, it takes more than 20 cNK cells to achieve the same cytotoxicity against solid tumor cells as a single IDP-023 g-NK cell. Values are mean ± SE, N=7. #p<0.05 for differences between g-NK and cNK cells.

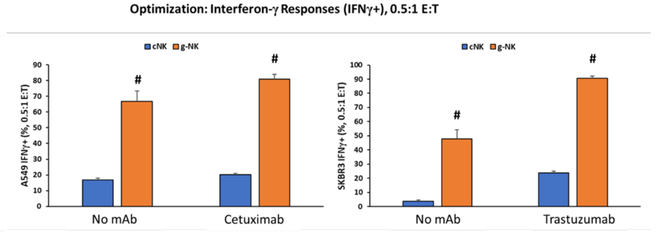

Figure 4: Cryopreserved IDP-023 g-NK cells have markedly superior Interferon-γ responses against the lung cancer cell line A549 (with and without cetuximab) and the breast cancer cell line SKBR3 (with and without trastuzumab) relative to cryopreserved cNK cells expanded using the Campana method. The anti-tumor Interferon-γ response of IDP-023 g-NK cells is clearly enhanced by addition of mAb. Values are mean ± SE, N=7. #p<0.001 for differences between g-NK and cNK cells.

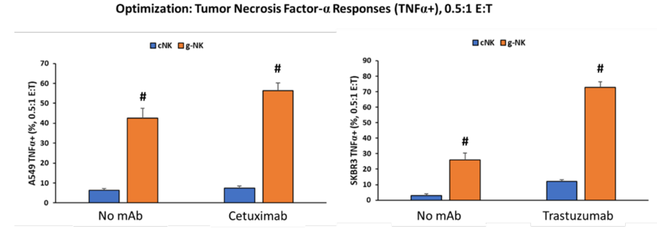

Figure 5: Cryopreserved IDP-023 g-NK cells have markedly superior TNF-α responses against the lung cancer cell line A549 (with and without cetuximab) and the breast cancer cell line SKBR3 (with and without trastuzumab) relative to cryopreserved cNK cells expanded using the Campana method. The anti-tumor TNF-α response of IDP-023 g-NK cells is clearly enhanced by addition of mAb. Values are mean ± SE, N=7. #p<0.001 for differences between g-NK and cNK cells.

g-NK cells have been identified in the tumor microenvironment of patients with clear cell renal carcinoma and are correlated with increased DDFS in trastuzumab-treated breast cancer patients

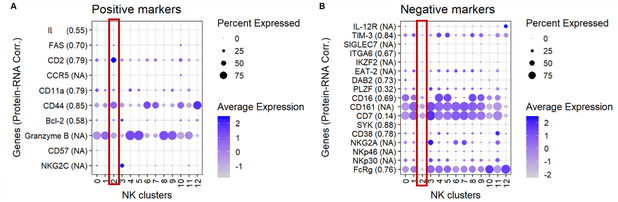

Figure 6: Single cell RNA sequencing data from the tumor microenvironment of patients with clear cell renal carcinoma revealed the presence of g-NK cells (cluster 2). This Obradovic dataset (2) was chosen due to the high number of NK-cells in the tumor microenvironment of this cancer. Once we identified the RNA profile of g-NK cells, we were able to look for correlations between the frequency of g-NK cells and disease prognosis in this and other data sets.

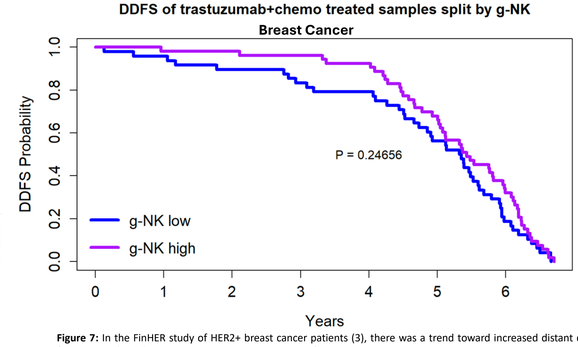

Figure 7: In the FinHER study of HER2+ breast cancer patients (3), there was a trend toward increased distant disease-free survival (DDFS) in patients with a high proportion of g-NK cells when treated with trastuzumab and chemotherapy.

g-NK cells are enriched in the tumor microenvironment of patients with low grade and early-stage clear cell renal carcinoma, and a high g-NK percentage is associated with a higher rate of pCR in HER2+ breast cancer patients treated with trastuzumab

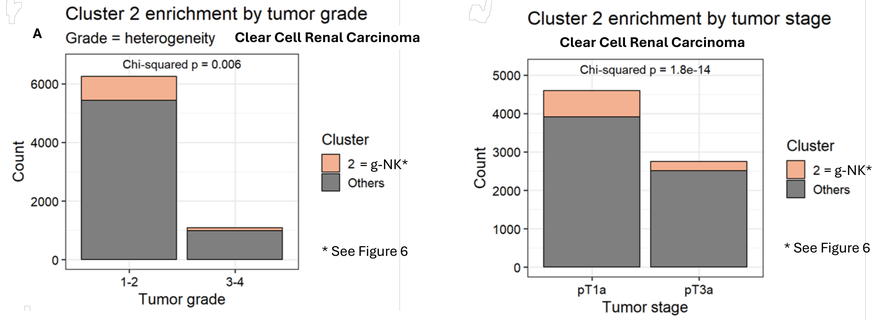

Figure 8: Cluster 2 (g-NK cells) is enriched in the tumor microenvironment of patients with low grade **(A)** and early stage **(B)** clear cell renal carcinoma (data obtained from the Obradovic dataset) (2). Conversely, the number of g-NK cells is decreased in high grade and late-stage samples. In a study of HER2+ breast cancer patients (CALGB 40601) (4), a higher percentage of g-NK cells was associated with a statistically significant increase in the pathologic complete response (pCR) rate of patients treated with trastuzumab **(C)**.

Conclusions

- Collectively, these data support the capacity of g-NK to mediate single agent activity against solid tumors and to combine with therapeutic mAb to potentially rescue treatment refractory breast or NSCLC patients. IDP-023 is currently being tested in a hematologic oncology Phase 1 clinical trial (NCT06119685).
- Endogenous g-NK cells can be identified in the tumor microenvironment of patients with various solid tumors.
- The presence of high proportions of g-NK cells in the tumor microenvironment is correlated with an increased probability of DDFS and pCR in HER2+ breast cancer patients treated with trastuzumab.

References

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