GDA-201 – An “Off the Shelf” NAM-Expanded Natural Killer (NK) Cell Therapy

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GDA-201 Highlights

- GDA-201 is an allogeneic, non-engineered, NK cell therapy, capable of targeting multiple tumor types by combining with antibodies to treat cancer.
- It has shown impressive clinical activity in combination with Rituxan in relapsed / refractory NHL1.
- Broad potential to combine with other modalities (bi-specifics, Fc engagers) to address unmet need in hematologic malignancies and solid tumors.
- Our proprietary nicotinamide (NAM)-based cell expansion platform, achieves clinically-relevant doses of donor NK cells with enhanced function.

1ClinicalTrials.gov Identifier: NCT03019666
GDA-201

- Product Profile
  - Preclinical Proof of Principle
  - Genomics
  - Summary
GDA-201 Is an Enhanced NK Cell Immunotherapy

- GDA-201 infusion is a promising immune therapy for cancer
  - No HLA-matching required
  - Lower risk of GvHD and CRS
  - Ability to synergize with multiple antibodies for targeted tumor killing

- Available from allogeneic donors, scalable manufacturing, and cryopreservation for off-the-shelf treatment

- Proprietary NAM platform preserves cellular functionality during expansion and thaw

**NAM Expansion of Natural Killer Cells**

**GDA-201 + Tumor-Specific Antibodies**
GDA-201 Manufacturing

NAM allows for NK cell phenotype preservation during expansion and cryopreservation

Allogenic NK cells collected by apheresis

Seed CD3- cells from apheresis material

DAY 0

Highly functional NK cells:
~50-100 billion NK cells with purity >99%

DAY 14

Proprietary expansion with NAM +IL-15

Proprietary cryopreservation and infusion ready

NORMAL DONOR

A single donor can produce multiple clinical doses
GDA-201

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Preclinical Data Demonstrate Enhanced NK Cell Function

Ex Vivo expansion of GDA-201 with NAM leads to:

- Maintenance of CD16 expression, the high affinity Fc receptor which allows for use with multiple antibodies to target tumors for ADCC
- Increased CD62L expression which leads to \textit{in vivo} cell homing and retention to lymphoid tissues
- Increased cytotoxicity for more efficient tumor cell killing
- Increased secretion of inflammatory cytokines for activation of host adaptive immune cells

\*Oral presentation ASH 1017
NAM-Expanded NK Cells Show ADCC Synergy in Combo with Rituximab Against Lymphoma Cells
NAM Increases CD62L (L-selectin) Expression Which Allows for NK cell Trafficking to Lymphoid Organs

**CD62L (L-Selectin)**

![Graph showing CD62L expression levels with NAM concentrations.](image)

- **Before expansion**
- **-NAM**
- **+NAM**

* = p<0.05
** = p<0.01
NAM Expansion Led to Longer NK Persistence in hNSG Mice

IL-2 injected every other day following NK infusion

350 cGy NK infusion Sacrifice

Day -1 0 1 2 3 4 5 6 7 8 9

Bone Marrow

* = p<0.05

Spleen

** = p<0.01

% NK cells

- NAM
+ NAM

* = p<0.05
** = p<0.01
Cryopreserved GDA-201 Decreases Lymphoma Burden in the Spleen of NSG Mice

*The mice were sacrificed 7 days post NK infusion n = 10 mice/group

In vivo retention in the spleen

Tumor burden in the spleen

*The mice were sacrificed 7 days post NK infusion n = 10 mice/group
NK Cells Have Ability to Prime Adaptive Immune Response and Kill Tumor Cells

Advantages of GDA-201:
- NAM increases expression of death receptors (FasL) on surface of NK cells
- NAM increases secretion of inflammatory cytokines (IFN-γ and TNF-α) by NK which can activate host adaptive immune cells (T cells and dendritic cells (DC))
Expansion with NAM Increases Function of GDA-201

NAM increases secretion of pro-inflammatory cytokines

NAM increases expression of Fas-L

*Data generated in collaboration with (Dr. Richard Childs) at NHLBI
NAM Increases Cytotoxic Potential of GDA-201

In Vitro Lysis of Tumor Cell Lines by GDA-201

K562 – CML

Colo205 – Colon Cancer

H1299 – NSCL Carcinoma

H460 – LCLC carcinoma

NK cells: Target cells ratios
Cyropreserved-GDA-201 Retains Killing and ADCC Activity Against DLBCL (SUDHL-6) Cells

Proprietary cryopreservation preserves GDA-201 activity
Cyropreserved-GDA-201 Has Potential to Kill Solid Tumors

GDA-201 acts in synergy with Herceptin against a resistant (SKOV3) ovarian cancer line

![Graph showing the lysis of SKOV3 + Herceptin and GDA-201 cells over time with different concentrations of GDA-201 and Herceptin.](image-url)
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**Objective:** To identify pathways leading to the preservation of NK cell function after *ex-vivo* expansion with NAM compared to control NK cells grown in the absence of NAM.

**Methods:**
- RNA samples were collected from magnetically purified CD56+ NK cells cultured with and without 5mM NAM and hIL-15 at days 3 and 14 post expansion.
- The RNA samples were collected from 4 replicated experiments.
- Cel-Seq libraries were analyzed using Next Generation Sequencing by Illumina.
- For statistical analysis and increased sensitivity the data was divided to three datasets, but only dataset from Day 14 is presented. Differentially expressed genes (DE-genes) were defined based on pairwise comparison.
Greater that 150 Differentially Expressed Genes +/- NAM

- 150 DE-genes divided into 2 clusters
- Cluster 1 – 96 downregulated DE-genes
- Cluster 2 – 54 upregulated DE-genes
Pathways of Overlapping DE Genes in NK cells expanded +/- NAM at 14 Days

A. Dataset C, day 14 NAM +/- 5mM NAM pairwise comparison yielded >150 DE-genes that were defined by p-value=0.05

B. GO Biological Process Enrichment Overlapping analysis of DE-genes

C. Biological Pathways that were enriched from overlapping clustered DE-genes. Red= up-regulated pathways. Blue= down-regulated pathways
Ingenuity Pathway Analysis Predicts Telomerase Pathway is Up-regulated by NAM

Ingenuity Pathway Analysis of DE-genes predicts significant upregulation of Telomerase elongation and Telomerase maintenance pathways
GDA-201 Summary

• NAM enhances CD62L expression and maintains CD16 expression

• NAM enhances cytotoxicity and ADCC activity against a variety of lymphoma and solid tumor cell lines

• GDA-201 shows enhanced \textit{in vivo} tumor killing

• Ingenuity pathway analysis shows that NAM up-regulates genes in telomerase pathway to avoid NK cell senescence during \textit{ex vivo} expansion

• Proprietary cryopreservation formulation maintains viability and function post-thaw