INGENIUM THERAPEUTICS

Memory Natural Killer Cells

Unlocking the potential of our innate immunity

OCT 2022

Disclaimer

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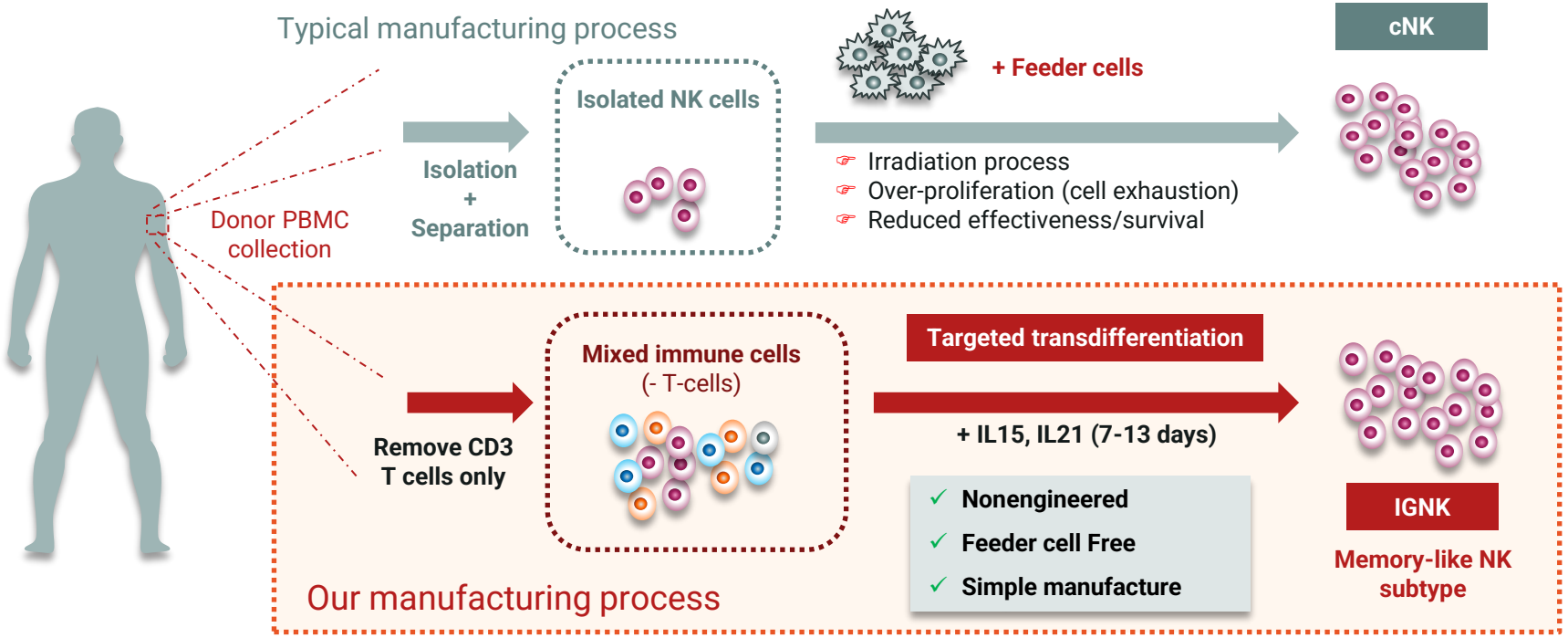
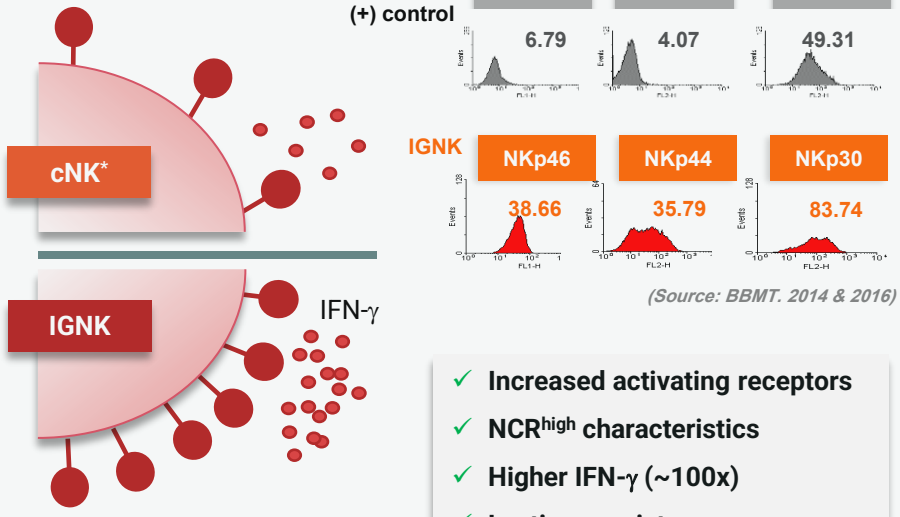
Patented cGMP manufacturing process



Memory-like NK cells in a fully cGMP process



(Source: BBMT. 2014 & 2016)

- ✓ **Increased activating receptors**
- ✓ **NCR^{high} characteristics**
- ✓ **Higher IFN-γ (~100x)**
- ✓ **Lasting persistence**

01 Use of mixed immune cells result in much higher cell numbers vs. known methods

02 Unprecedented numbers (~5x10^{10} cells) equivalent to 100+ doses(1) from single donor

03 Fully cGMP process with consistent cell production quality (150+ lots to date)

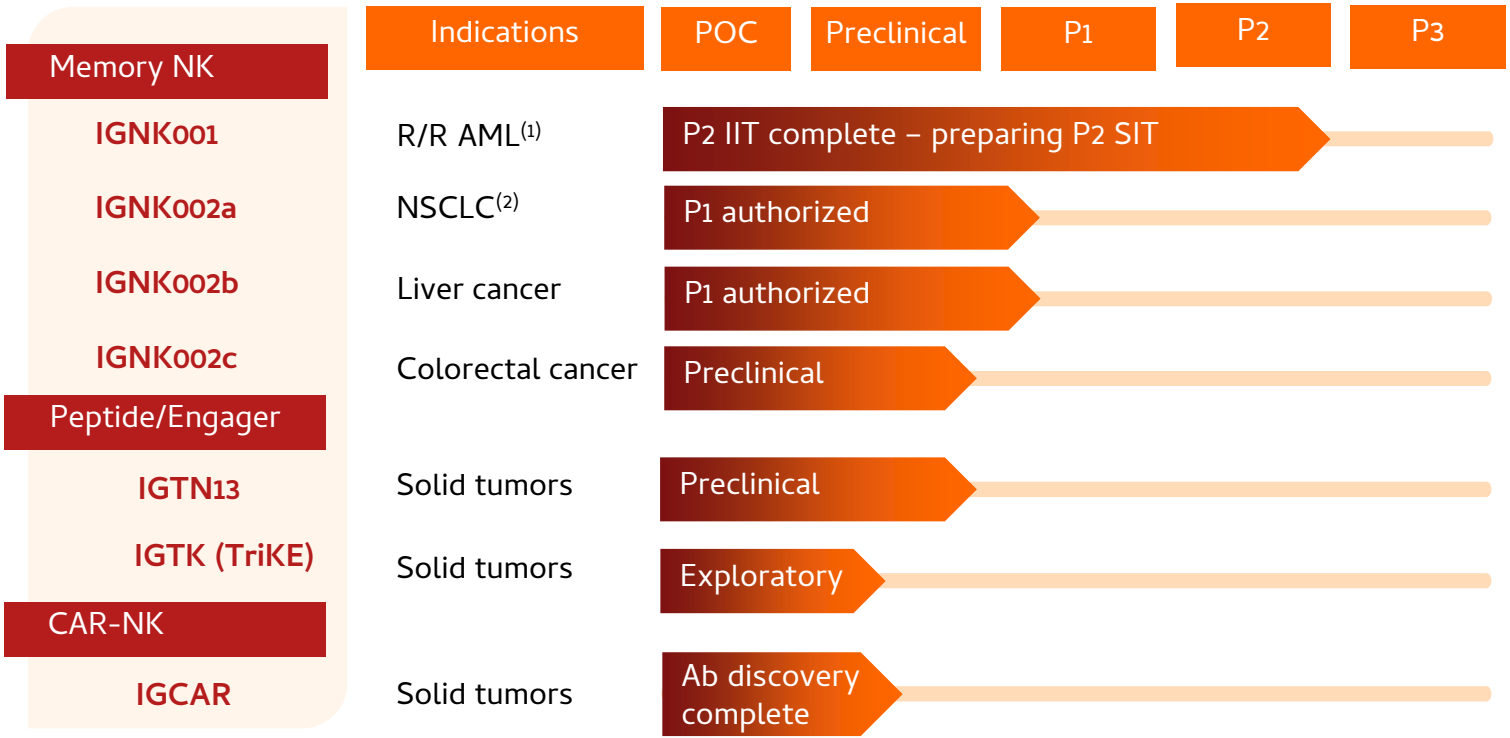
More receptors → Better tumor recognition/killing

Higher IFN-γ → Better adaptive/regulatory

** Conventional NK from PBMC*

(1) Based on expected dose for solid tumor indications

Pipeline



(1) R/R AML = relapsed/refractory acute myeloid leukemia
(2) NSCLC = non-small cell lung cancer

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IIT Phase 1/2 clinical study treatment scheme

Diverse genetic factors, high relapse rate and poor patient prognosis characterize R/R AML

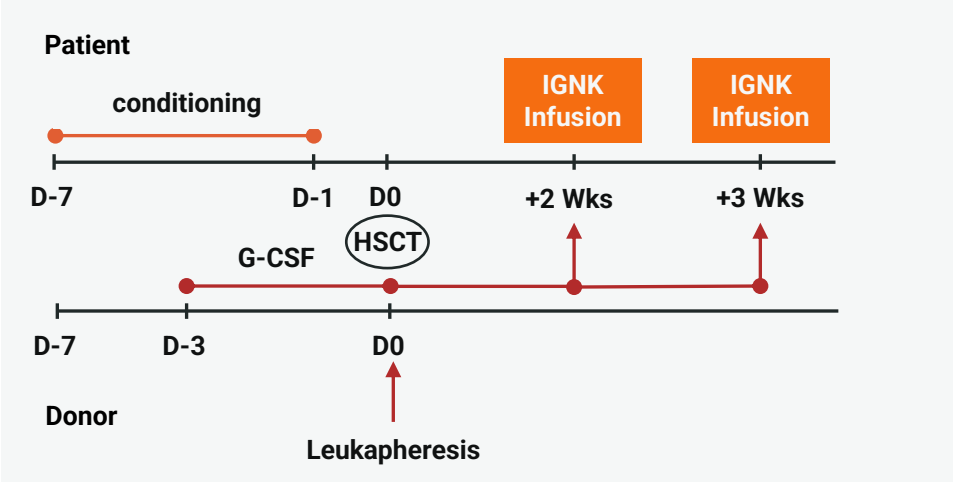
01 Total of 4 investigator trials completed (100+ patients infused) with demonstrated safety and efficacy

02 Dose escalation study (P1) and different treatment scheme (4x infusions vs. 2x infusions) attempted over 2 trials

→ *No added benefits from 4x infusions*

03 Current treatment scheme (2x infusions) developed and applied to 2 trials including a randomization study

* Reduced-intensity with busulfan, fludarabine, and antithymocyte globulin



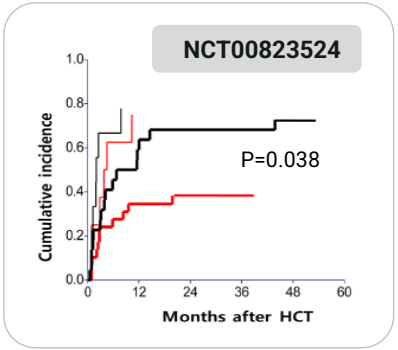
Note:
G-CSF = granulocyte colony stimulating factor; MNC = mononuclear cells; DNKI = donor NK cell infusion (IGNK); HSCT = hematopoietic stem cell transplant; HLA = human leukocyte antigen

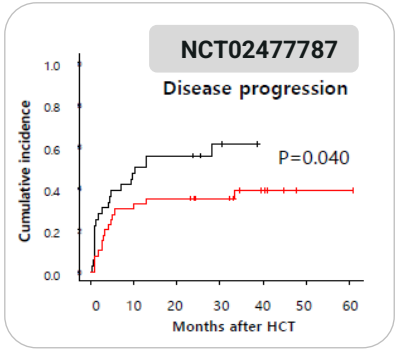
Pooled patient data from phase II trials

	DNKI (n=69)	Control (n=58)	P-value
CR after HCT	82.4% (56/68)	51.2% (21/41)	**.001**
PFS, median, 2/5-yr	5.7 (33.3/24.1%)	3.7 (15.5/11.0%)	**.028**
CIR, median, 2/5-yr	37.7/46.9%	58.6/63.1%	**.040**

* Combined data from NCT00823524 and NCT02477787 IIT

- ✓ **Over 100 patients and 5+ years follow-up**
- ✓ **Proven safety with minimal side effects**
- ✓ **Statistically significant treatment effects**
- ✓ **Patient survival increased by x3-fold**





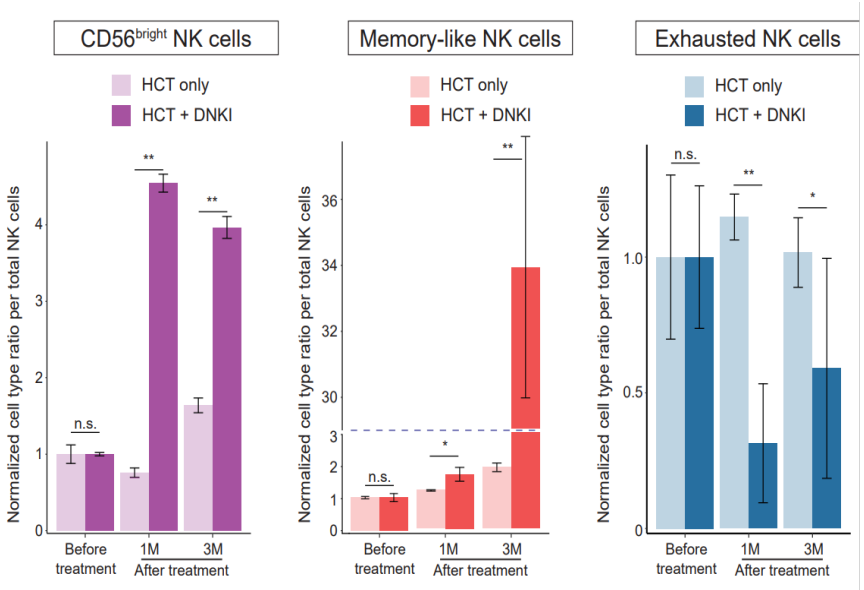
(1) NCT00823524: IGNK+HSCT (n=29) vs HSCT only (n=22) historical cohort (*BBMT 20 (2014) 696-702*)
(2) NCT02477787: IGNK+HSCT (n=40) vs HSCT only (n=36) randomization study (*manuscript under review*)
(3) CR=complete remission, PFS=progression-free survival, CIR=cumulative incidence of relapse, NRM=non-relapse mortality, GVHD=graft-vs-host disease

Memory-like NK cells with lasting persistence

01 Dramatic increase in CD56^{bright} NK cells with immunoregulatory functions

02 Up to 30-fold increase in memory-like NK cells

03 Improvement in NK cell condition as a result of reduced exhausted NK cells



Single treatment of IGNK001 results in NK cell recovery with persistence lasting months

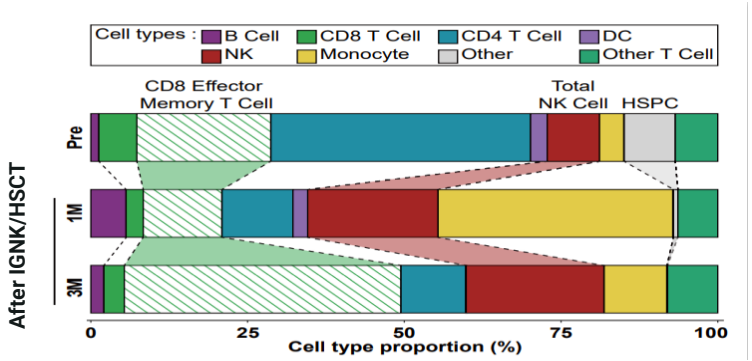
** Manuscript under review*

Lymphocyte population shift post treatment

01 Higher number of NK cells (~1.8 times) compared to pre-treatment

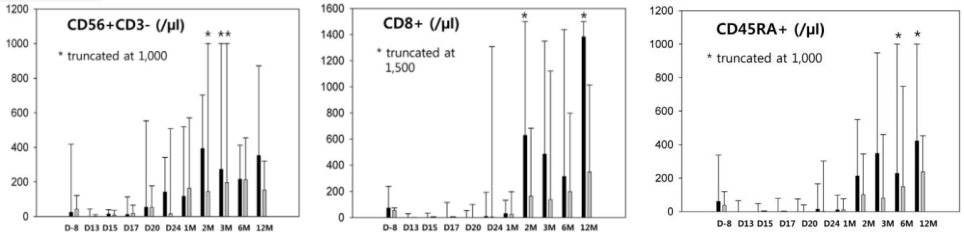
02 Significantly, CD8 effector memory T cells increased vs. pre-treatment

03 Immune reconstitution observed in patients' peripheral blood



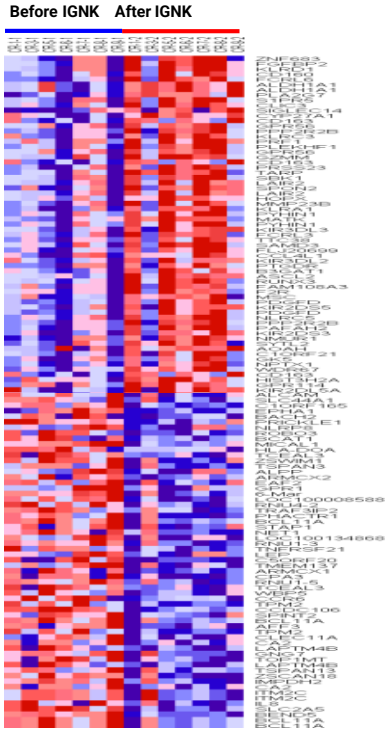
** Manuscript under review*

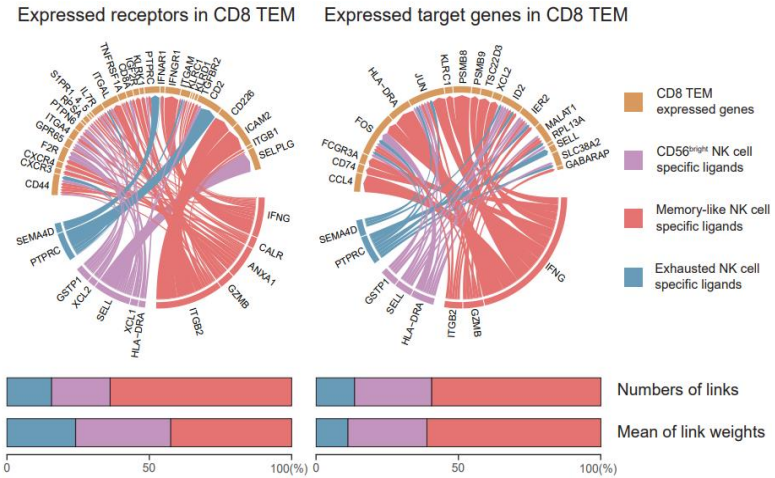
Lasting effects observed for at least 12 months post-treatment

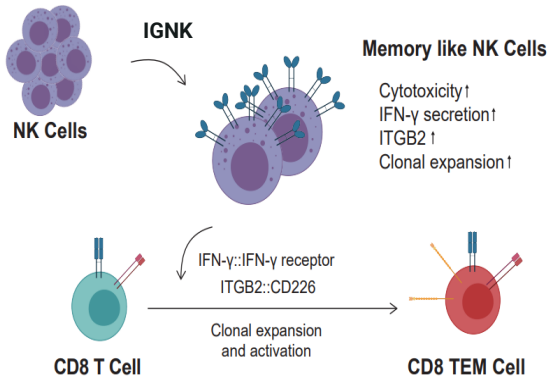


I. Choi et al. Biol Blood Marrow Transplant 20 (2014) 696-704

Donor-NK cell mediated T cell activation







** Manuscript under review*

Gene expression profiling results before and after IGNK treatment and scRNA-seq analysis at single cell level suggests immunoregulatory mechanism of IGNK001 that includes activation of CD8 T cells by IGN-γ to effector memory CD8 cells.

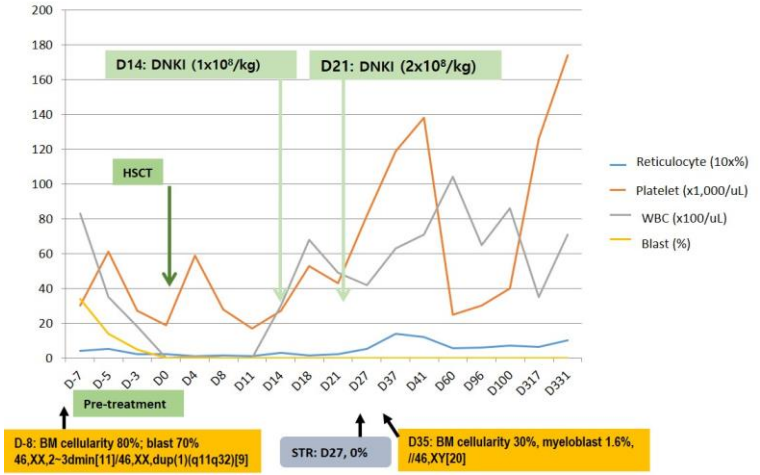
Case Study #1

Relapsed AML patient (66 years old, female)

- **Apr 2009:** Palpitation, WBC 4,800 with blast 33%
- **4 May 2009:** Bone marrow (BM) **showed AML** M2, 46, XX
- **7 May 2009: Achieved CR** after induction chemo (AD), followed by 3x consolidation
- **15 Sep 2010:** Blasts in PB, BM showed **AML recurrence** (blast 40%)
- **8 Oct 2010: Salvage chemo** (AD); persistent leukemia (BM blast 70%)
- **14 Dec 2010:** Received haplo-identical HSCT from donor (son) with **2x NK cell infusions**
- Currently **living healthily and disease-free** (**last follow-up: Sep 2022, 12 years post-treatment**)

(1) Schmid et al, Blood. 2006;108(3):1092-9.)
(2) Hiddemann et al, Leukemia. 1990;4(3):184-8
(3) Shallis et al, Blood Rev, Vol. 36, 2019

Data from investigator trial courtesy of Seoul Asan Medical Center, Korea



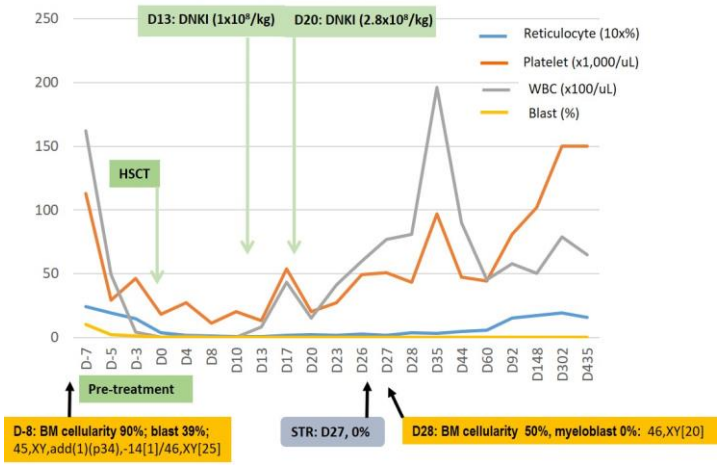
- ✓ 50-70% of AML patients relapse after CR(1),(2)
- ✓ 1-year survival for patients aged >65 less than 20%(3)
- ✓ Patient relapsed after chemo but was cured with a single treatment of IGNK001 alone following HSCT

Case Study #2

Refractory AML patient (66 years old, male)

- **Dec 2010:** Palpitation
- **9 Feb 2011:** Pancytopenia, BM **showed AML** with MDS related change
- **20 Feb 2011: Failed to achieve CR** after induction chemo (AI “7+3”)
- **5 Apr 2011: Failed to achieve CR** after re-induction chemo (AI “5+2”)
- **6 Jul 2011:** Received haplo-identical HSCT from donor (son) with **2x NK cell infusions**
- Currently **living healthily and disease-free** (**last follow-up: Sep 2022, 11 years post-treatment**)

Data from investigator trial courtesy of Seoul Asan Medical Center, Korea



- ✓ Patient failed to achieve CR after 2 rounds of chemo
- ✓ Now living disease free after only a single treatment of IGNK001 alone following HSCT
- ✓ Demonstrates lasting effect of IGNK001 treatment

Next step -
IGNK001 P2 sponsor trials
(IND submitted & processing)

Three major oncology institutions in Korea recruited for P2 study sites (clockwise)

- Seoul St. Mary's Hospital
- Seoul Asan Medical Center
- Samsung Medical Center

P2 sponsor trials for R/R AML

Single-arm, open-label, multicenter, pivotal study recruiting up to 45 patients

Follow-up

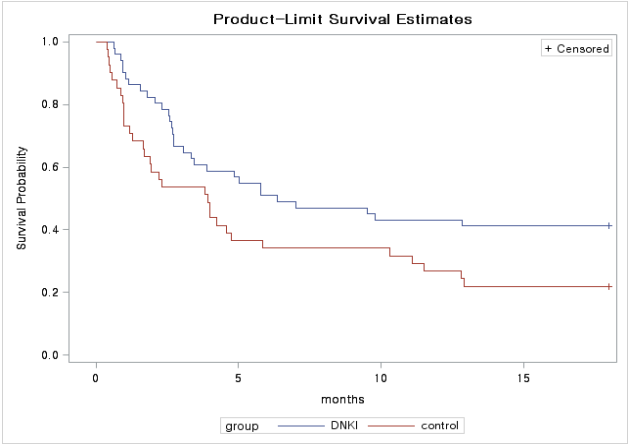
Trial to proceed with 18-months follow-up and expanded access program (EAP) available

Marketing authorization

Full commercialization upon completion of study by end-2024

Study designed to maximize trial success

- In depth statistical analysis were performed on pooled results IIT
- P-values and survival curves calculated for different follow-up (F/U) periods, PFS (%), median PFS (months) and patient subgroups
- Objective response rate (ORR) is the typical primary end-point for current cell therapy trials
- **IGNK001 achieved CR (ORR) of >82% vs. HSCT alone (p=0.001)**
- Statistical significance in **median PFS (months) with p=0.034** after excluding rel AND ref patients



18-months F/U Kaplan-Meier plot after excluding rel AND ref patients

- ✓ **90% of patients both relapsed and refractory did not survive**
  - ➡ *excluded in sponsor P2 trials but with access to EAP*
- ✓ **Median PFS (months) as primary endpoint to stay ahead of the curve**
  - ➡ More stringent than ORR with good probability of trial success
- ✓ **Minimum sample size for statistical significance is 20+ patients**
  - ➡ *Up to 45 patients recruited for P2 sponsor trials*

➡ High probability of trial success

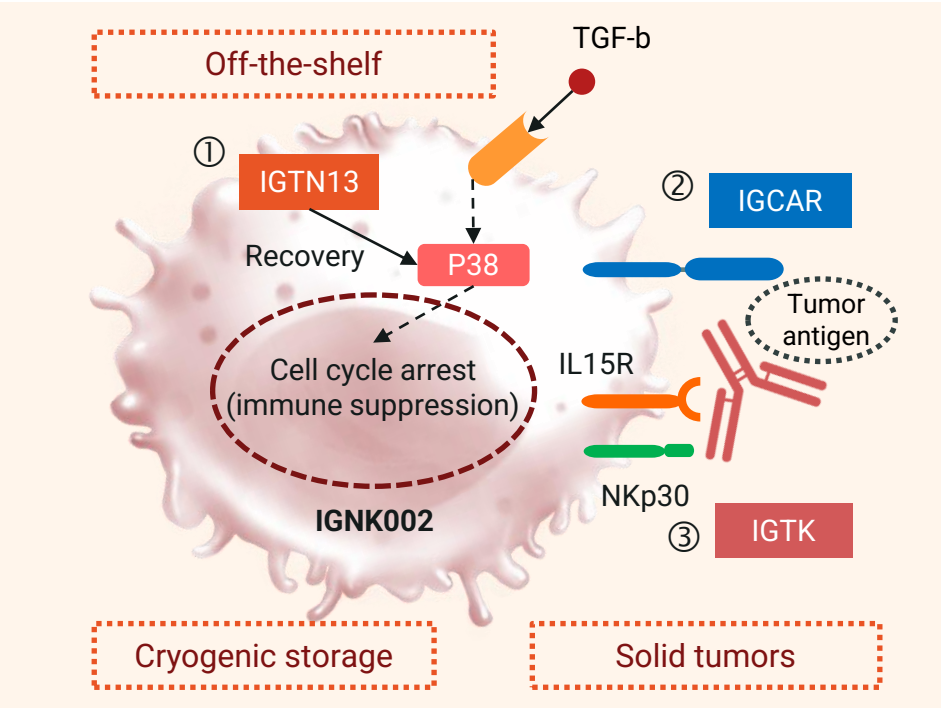
CAR-T vs IGNK001

	YESCARTA	KYMRIAH	IGNK001*
First approved indication	R/R DLBCL	ALL	R/R AML (IIT)
Primary Endpoint	ORR(1)	ORR(1)	TBD(2)
ORR	83%	83%	82% (CR)(3),(4)
CR	54%	64%	**82%(4)**
Median F/U period	7.9 months	4.8 months	**68.9 months(4)**
Side effects(5)	CRS 94% neurotoxicity 87% TRM 4%	CRS 79% neurotoxicity 65% TRM 3%	**No effect on CRS, neurotoxicity, GVHD**
Manufacture duration	Median 17 days (Range: 14-51 days)(6)	22 days (Target turnaround time)(6)	7-13 days
Price per treatment	$373,000(6)	$475,000(6)	**~$150,000 (est.)**

Note:
(1) FDA approval on the basis of ORR improvement compared to standard treatment
(2) To be decided following consultation with the Ministry of Food & Drug Safety (Korea)
(3) ORR not measured during investigator trials but will be included in P2 sponsor trials
(4) Pooled results from 2 investigator trials
(5) Percentage of total patients treated with symptoms
(6) According to manufacturer
CRS=cytokine release syndrome, TRM=treatment related mortality

IGNK001 already fulfils FDA approval criteria

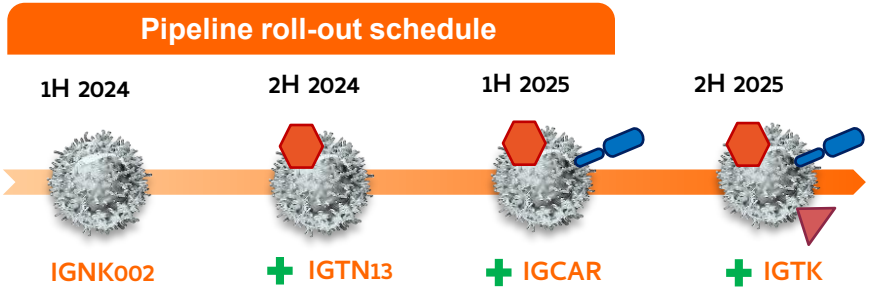
Optimization of IGNK platform



01 TXNIP-derived patented TN13 peptide inhibits p38 kinase and restores TGF-β-mediated NK cell suppression in TME

02 Ingenium CAR-NK delivered via mRNA for enhanced tumor cell targeting

03 Ingenium IL15/NKp30 TriKE NK engager for increased NK cell-mediated killing

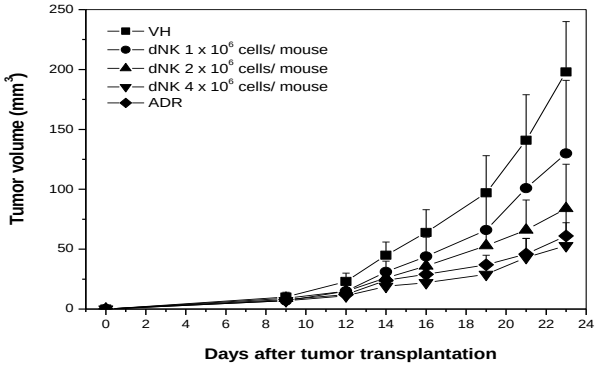


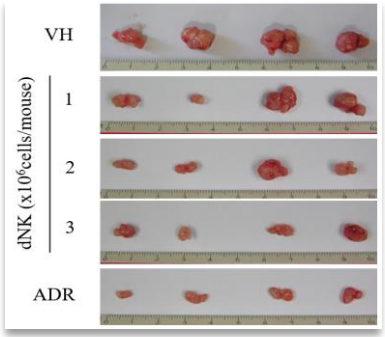
Promising preclinical anti-tumor effects

01 Increasing IGNK001 dosage resulted in greater tumor suppression against various cancers including lung, liver and colon (Right image depicts liver cancer mouse model)

02 Higher IGNK001 dosage approached similar tumor suppression effects to positive control (doxorubin/ADR)

03 Infusing patients with sufficient numbers of NK cells is critical to ensuring treatment success





Comparison of tumor volume in nude mice (=4) implanted with SNU-354 human hepatoma cells followed by IGNK treatment at different doses between 1-4x10^6 cells/mouse.

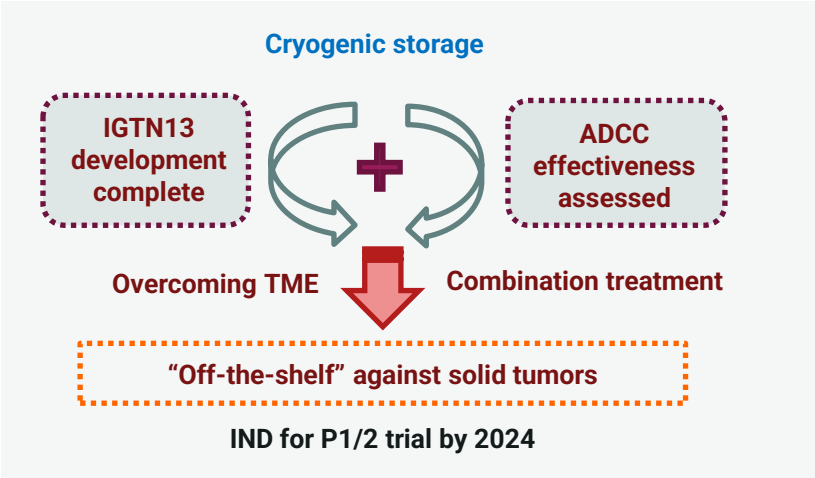
IGNK001 preclinical studies

Off-the-shelf memory-like NK against NSCLC

01 **Cryogenic formulation:** No change in cytotoxicity or viability after 16 weeks of cryogenic storage (as of July 2022, test to continue for up to 2 yrs)

02 **Overcoming TME: "IGNK Shield"** (IGNK002 + IGTN13 peptide) at preclinical stage

03 **ADCC:** Combination possibility with current targeted therapies (pembrolizumab combination study in progress)



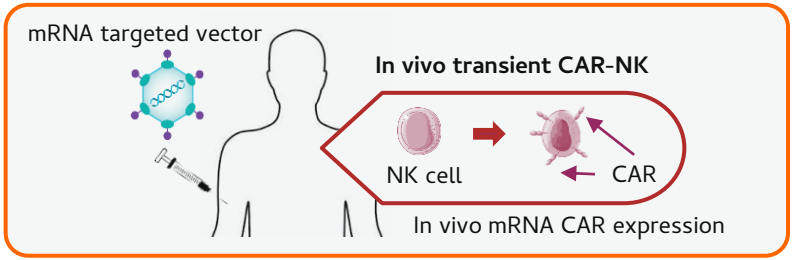
PBMC (healthy donors) → cGMP manufacture → Cryogenic storage + biobanking → Cold storage distribution to hospitals → Patient infusion when needed

Next generation cancer therapy

01 Transient CAR NK from IGNK002 through targeted CAR mRNA expression

02 Using the latest scientific breakthroughs from COVID-19 vaccine

03 End goal of to use mAb-conjugated mRNA LNPs to target patient's NK cells *in vivo* to become transient CAR-NK cells



A. Transient CAR for enhanced tumor targeting
B. IFN-g induced immune activation
C. Memory-like NK cells with innate non-specific tumor recognition for immunosurveillance and to avoid antigen-specific tumor escape

TME infiltrator: patented IGTN13 peptide

01 TXNIP k/o shows defective NK differentiation
[Lee & Choi. Immunity 2005]

02 TXNIP as a functional switch for p53 activity
[Jung & Choi. Cell Metabolism 2013]

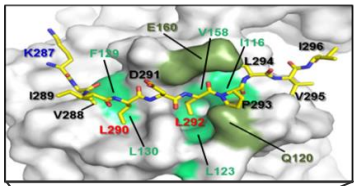
03 TXNIP-derived IGTN13 peptide binds and inhibits p38 kinase
[Jung & Choi, Nature Communications 2016]

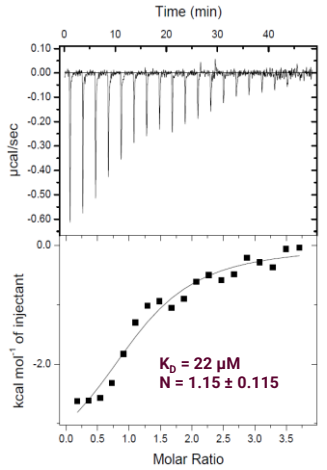
➡ IGTN13 restores both TGF-β-mediated NK cell suppression and fratricide and simultaneously lowers TGF-β secretion in cancer cells
[* Preclinical studies]

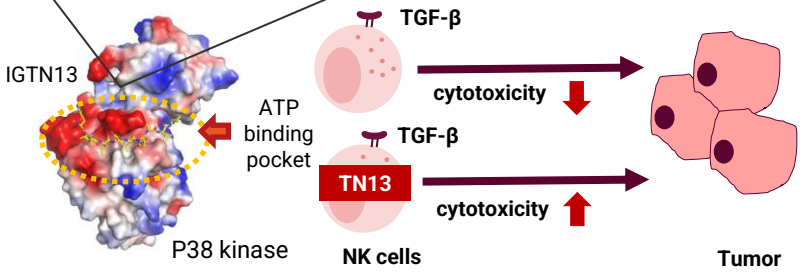
Preclinical efficacy study with IGNK002 against lung cancer underway (completion by Nov 2022)

Peptide Clones	TXNIP amino acid sequence
	Basic Φ_A-X-Φ_B
PLV-GFP-5xlinker-TN15	^{284}GSKKVILDLPLVIGS^{298}
PLV-GFP-5xlinker-TN14	^{284}GSKKVILDLPLVIG^{297}
PLV-GFP-5xlinker-TN13	^{284}GSKKVILDLPLVI^{296}
PLV-GFP-5xlinker-TN12	^{284}GSKKVILDLPLV^{295}

Docking protein	Docking sequence
	Basic residue Φ_A-X-Φ_B
MKK6	SKGKKRNPGLKIPKEA
MKK3b	GKSKRKKD----LRISCNS
MEF2A	RKPDLR------VVIPPSS
TXNIP(TN13)	^{284}GSKKVI----LDLPLVI^{296}







IGTN13 preclinical

Figure 1: Restoration of NK cell cytotoxicity by IGTN13 against lung cancer cell line (right) after being suppressed by TGF-β (middle)

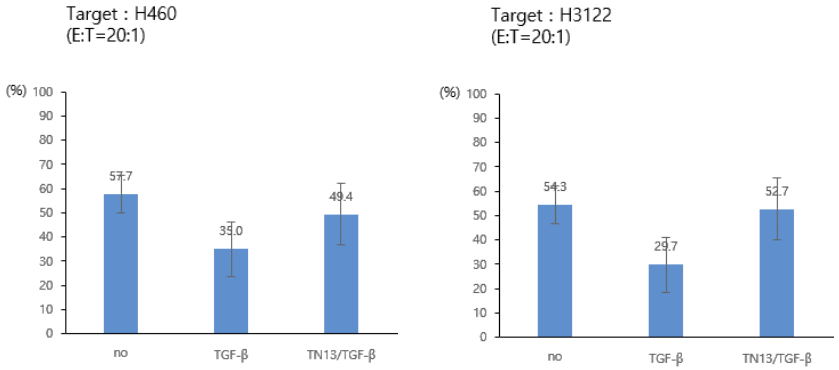


Figure 2: IGTN13 action reduces TGF-β expression in H460 tumor cells dose-dependently (left) and can also reduce TGF-β–mediated NK cell fratricide (right)

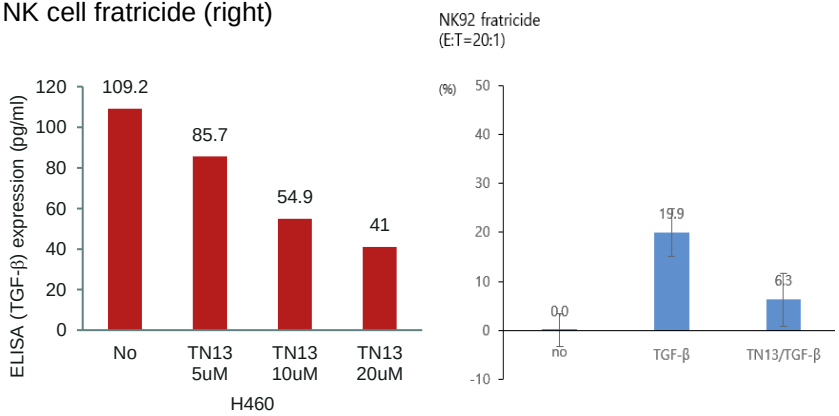
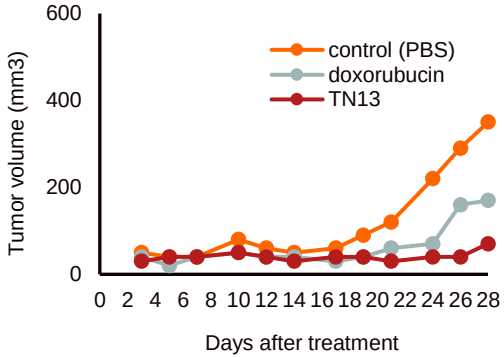


Figure 3: Tumor volume reduction by IGTN13 in BALB/C SPF nude mice transfected with H460



01 Promising *in vitro* preclinical results against lung cancer

02 Restores NK cell activity within high TGF-β setting

03 Significant anti-tumor effects with no observed safety issues

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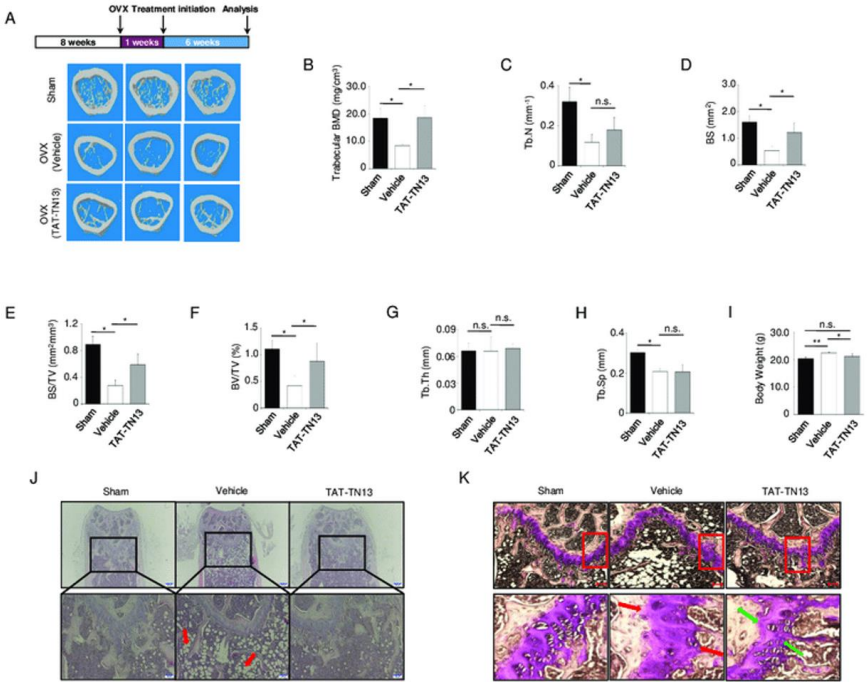
IGTN13: Potential applications

TAT-IGTN13 effectively prevents OVX-induced bone loss in vivo and inhibits RANKL-induced osteoclast formation



Journal of Clinical Medicine

MDPI

Article

Inhibition of Osteoclastogenesis by Thioredoxin-Interacting Protein-Derived Peptide (TN13)

Mi Jeong Kim [1,†], Won Sam Kim [1,†], Jae-Eun Byun [1,2], Jung Ha Choi [1], Suk Ran Yoon [1,3,*], Inpyo Choi [1,3,*] and Haiyoung Jung [1,*]

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ELSEVIER

Thioredoxin-interacting protein-derived peptide (TN13) inhibits LPS-induced inflammation by inhibiting p38 MAPK signaling

Dong Oh Kim [a], Jae-Eun Byun [a, b], Hyun-A. Seong [b], Suk Ran Yoon [a, c, ***], Inpyo Choi [a, c, **], Haiyoung Jung [a, *]

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Alzheimer's Disease treatment candidate

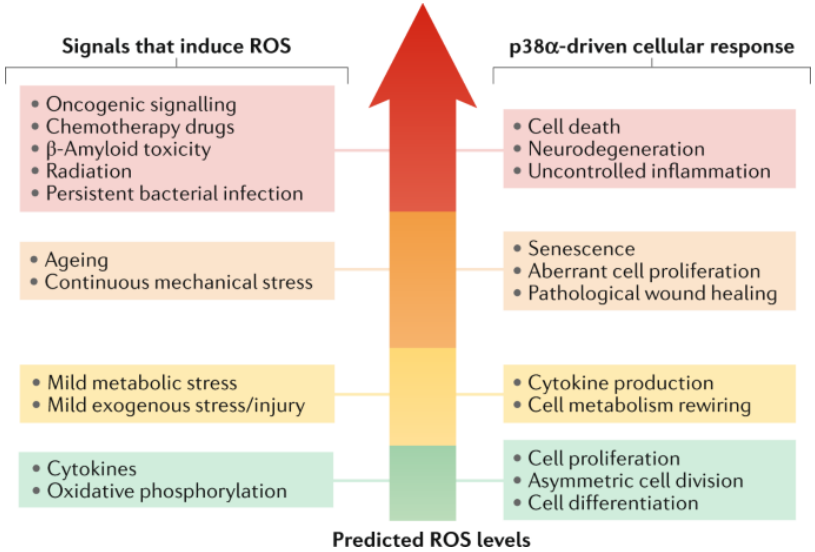
01 P38 MAPK inhibition is a crucial target for chronic inflammatory diseases including Alzheimer's Disease (AD)
[Lee & Kim. Molecules 2017 Aug 2;22(8):1287]

02 A selective p38 MAPK inhibitor alleviates neuropathology and cognitive impairment in AD mouse model 5XFAD
[Lee et al. Alzheimer's Research & Therapy 12: 45 (2020)]

03 Numerous studies underway using selective p38 MAPK inhibitors for the treatment of AD

IGTN13 specifically inhibits p38a MAPK and is a potential candidate for AD treatment

Interplay between ROS and p38α signalling.



Nature Review Molecular Cell Biology 22, 346-366 (2021)

First-in-class peptide P38 MAPK inhibitor

- P38 MAPK inhibitors failed at clinical trials despite promising preclinical results due to selectivity and/or toxicity issues
  - ➡ *None have reached commercialization so far*
- Peptides offer higher potency and selectivity with low toxicity
- Options include IGNK002 pretreatment with IGTN13, IV infusion with IGNK002 treatment or targeted LNP payload delivery

Peptides vs small molecules

- ✓ High potency
- ✓ High selectivity
- ✓ Low toxicity
- ✓ Low tissue accumulation

Only peptide P38 MAPK inhibitor under development

No observed side effects from in vivo studies to date

Careful approach in treatment applications and strategy

Notable P38 MAPK inhibitors:

Doramapimod (Boehringer Ingelheim) and **VX-745** (Vertex) discontinued due to adverse effects

ARRY-371797 (Pfizer) for treatment of dilated cardiomyopathy due to a Lamin A/C gene mutation discontinued in Aug 2022

Losmapimod (Fulcrum/GSK) under P3 and granted FDA fast track/orphan drug status - Fulcrum obtained full rights from GSK who discontinued development

Milestones

IGNK001
R/R AML, high risk MDS

IGNK001 + rituximab
ALL, DLBCL

IGNK002 + anti-PD1 (pembrolizumab)
NSCLC, solid tumors

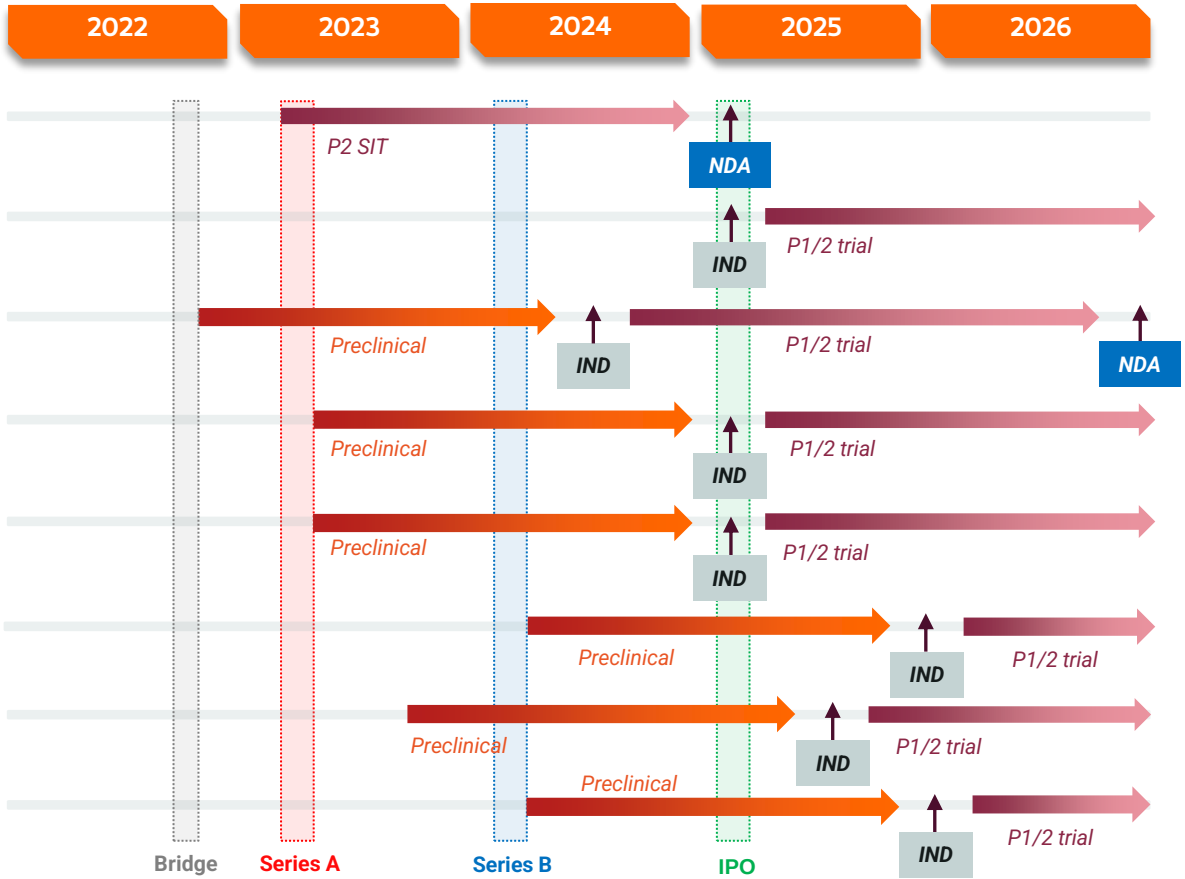
IGNK002 + anti-CTLA4 (ipilimumab)
NSCLC, solid tumors

IGTN13 (+ IGNK002)
solid tumors (liver, spleen, colorectal)

IGTN13
Alzheimer's, osteoporosis, arthritis

IGCAR (Ingenium CAR-NK)
solid tumors (liver, spleen, colorectal)

IGTK Engager (TriKE)
solid tumors (liver, spleen, colorectal)



INGENIUM THERAPEUTICS

Publications

Selected research by Dr. Inpyo Choi, CSO, Ingenium Therapeutics Inc.

SARS-CoV-2 peptides bind to NKG2D and increase NK cell activity *Cell Immunol. 2022 Jan;371:104454.*

TXNIP Regulates Natural Killer Cell-Mediated Innate Immunity by Inhibiting IFN-γ Production during Bacterial Infection *Int J Mol Sci. 2020 Dec14;21(24):9499*

Toll-Like Receptors in Natural Killer Cells and Their Application for Immunotherapy *J Immunol Res. 2020 Jan 4;2020:2045860.*

Thioredoxin-interacting protein-derived peptide (TN13) inhibits LPS-induced inflammation by inhibiting p38 MAPK signaling *Biochem Biophys Res Commun. 2018 Dec 9;507(1-4):489-495.*

Suppressor of Cytokine Signaling 2 Negatively Regulates NK Cell Differentiation by Inhibiting JAK2 Activity *Sci Rep. 2017 Apr 6;7:46153*

Thioredoxin-interacting protein regulates haematopoietic stem cell ageing and rejuvenation by inhibiting p38 kinase activity *Nat Commun. 2016 Dec 8;7:13674*

Donor-Derived Natural Killer Cell Infusion after Human Leukocyte Antigen-Haploidentical Hematopoietic Cell Transplantation in Patients with Refractory Acute Leukemia *Biol Blood Marrow Transplant. 2016 Nov;22(11):2065-2076**

MicroRNA-150 regulates the cytotoxicity of natural killers by targeting perforin-1 *J Allergy Clin Immunol. 2014 Jul;134(1):195-203.*

Donor-derived natural killer cells infused after human leukocyte antigen-haploidentical hematopoietic cell transplantation: a dose-escalation study *Biol Blood Marrow Transplant. 2014 May;20(5):696-704**

TXNIP maintains the hematopoietic cell pool by switching the function of p53 under oxidative stress *Cell Metab. 2013 Jul 2;18(1):75-85.*

Human microRNA-27a* targets Prf1 and GzmB expression to regulate NK-cell cytotoxicity *Blood. 2011 Nov 17;118(20):5476-86*

Generation of donor natural killer cells from CD34(+) progenitor cells and subsequent infusion after HLA-mismatched allogeneic hematopoietic cell transplantation: a feasibility study *Bone Marrow Transplant. 2010 Jun;45(6):1038-46**

Thioredoxin-interacting protein links oxidative stress to inflammasome activation *Nat Immunol. 2010 Feb;11(2):136-40.*

Suppressor of cytokine signaling 2 regulates IL-15-primed human NK cell function via control of phosphorylated Pyk2 *J Immunol. 2010 Jul 15;185(2):917-28.*

Osteopontin promotes the development of natural killer cells from hematopoietic stem cells *Stem Cells. 2008 Aug;26(8):2114-23.*

The regulation of NK cell function and development *Front Biosci. 2008 May 1;13:6432-42.*

VDUP1 is required for the development of natural killer cells *Immunity. 2005 Feb;22(2):195-208*

(Clinical trials of NK cell therapy for AML)*

Thank You

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