Combination Systemic Therapy with a Multiple TLR Agonist Safely Eradicates Tumors with Induction of Innate and Adaptive Immunological Memory

Decoy Biosystems, Inc.

hansonwade STING & TLR-Targeting Therapies Summit
May 26, 2021

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Cancer – Problem and Solution

- 18 million new cases and 9.6 million deaths per year worldwide
- Mutations in 300 genes contribute to development of >100 different types of cancer and each tumor contains a unique combination of mutations
- Single target and two target combination-based anti-tumor or immune-stimulating approaches cannot address this degree of heterogeneity
- Higher efficiency cures will only be possible if we can safely activate both innate and adaptive cellular anti-tumor immune pathways

Improving Cancer Immunotherapy with TLRa and STING Decoy Assumptions

- **We need to activate more than just one TLR to cure advanced cancer**

- **We need innate and adaptive pathway activation in lymphoid organs (e.g. spleen)**
  - Tumors promote an immune-suppressive environment
  - Most steps required for innate and adaptive immune responses take place outside of the tumor
  - Tumors negatively remodel the entire systemic immune system: Hiam-Galvez Nature Rev Cancer 2021

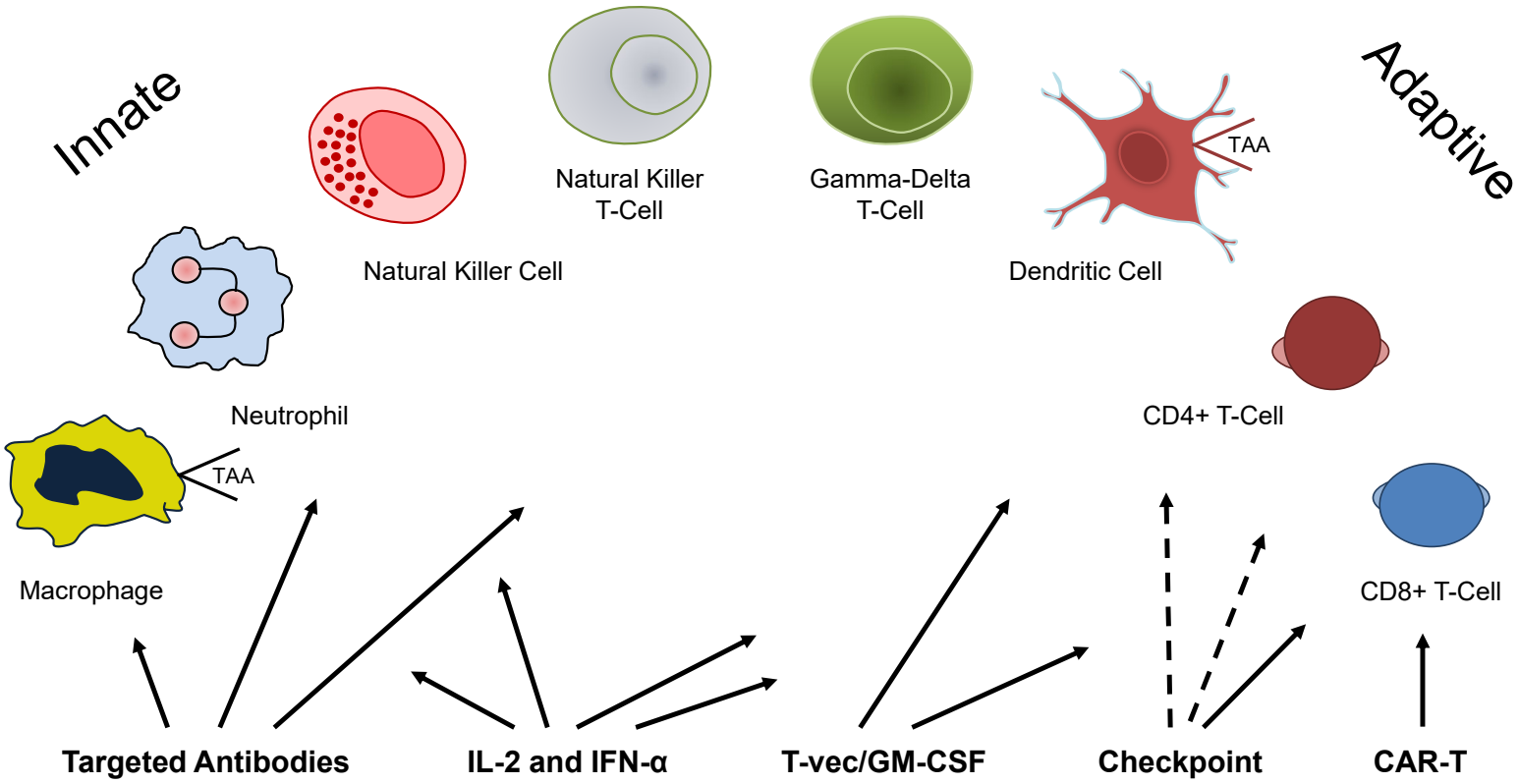
- **Induce many cytokines/chemokines; avoid toxicity by brief, passively targeted activation**
  - All Cytokines/Chemokines play a positive or essential role in immune responses
  - There are no intrinsically “bad” or “toxic” cytokines or chemokines

    “Bad” cytokines/chemokines are “good” ones that are present at too high a level for too long due to infection or genetic, epigenetic, metabolic or therapeutic mistakes

There are No Intrinsically "Good" or "Bad" Cytokines/Chemokines
Good or Bad Depends on Time, Place, Amount and How Long

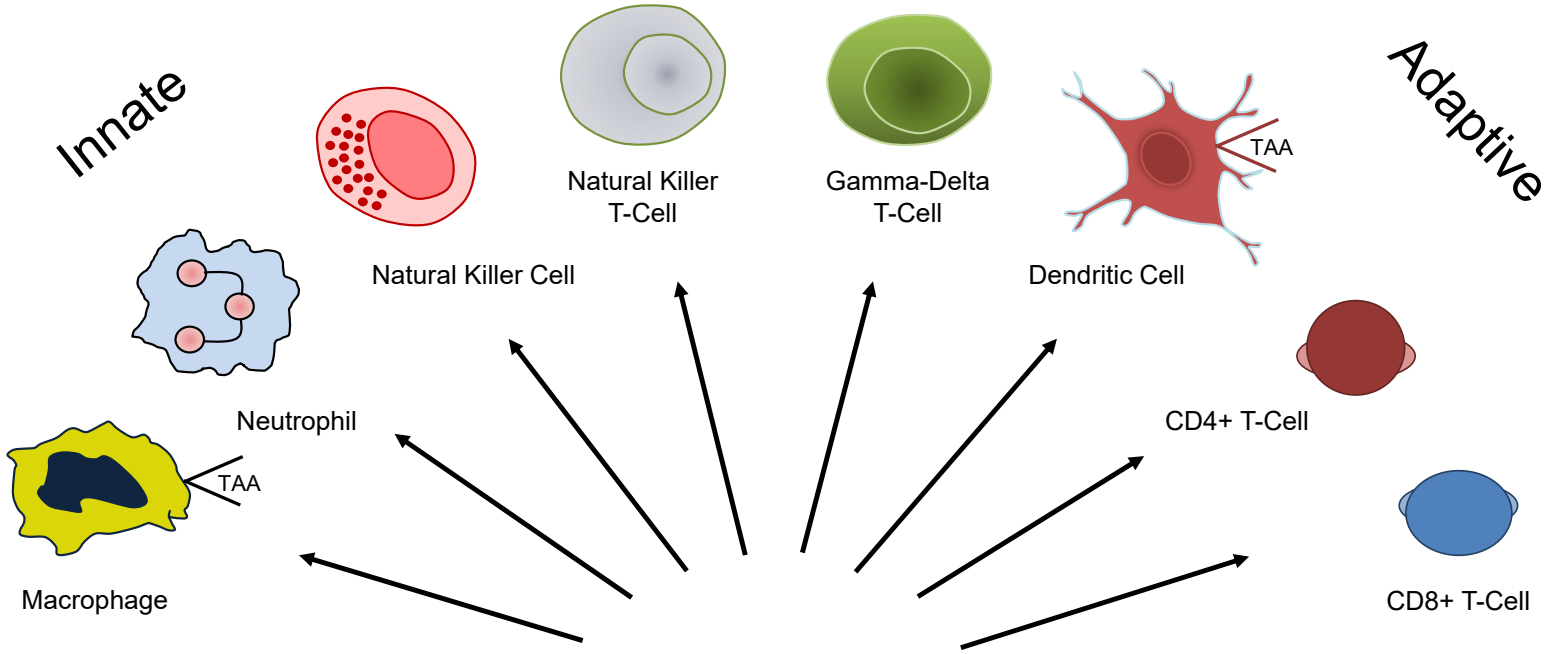
Cytokines and Chemokines Inducing Migration, Activation, Maturation and/or Proliferation	Responsive Immune Cell Type: All Participate in Anti-Tumor Immune Responses
GM-CSF, IL-1β, IL-4, IL-12, IL-15, IFN-γ	Dendritic Cells
IL-2, IL-12, IL-18, TNF-α	Gamma-Delta (γδ) T-Cells
IL-1β, IL-8, IFN-γ, MIP-1α, TNF-α	M1 Macrophage
IL-2, IL-10, IL-12, IL-15, IL-18, IL-21, IFN-γ	NK Cells
IL-12, IL-18, IL-21, IFN-γ	NKT Cells
GM-CSF, IFN-α, IL-4, IL-8, MIP-1α, TNF-α	Neutrophils
GM-CSF, IL-1β, IL-2, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-15, IL-17, IL-18, IL-21, IFN-γ, MIP-1α, TNF-α, TNF-β	T-Cells (Th1, Th17 or Th2 CD4+ or CD8+) Including CIK, CTL, LAK

Limitations of Existing Immunotherapy



Current immunotherapies only cure a very small percentage of advanced cancer patients, because they activate only one or a few innate or adaptive immune cell types

No One Has Figured Out How to Do This Safely



History provides a clue about how to do this

World's First Immunotherapy

- **Coley's toxins (CT) – based on observation of regression of cancer in setting of infection**
  - Invented by Dr. William Coley at Memorial Sloan Kettering in NYC in 1894
  - Composed of heat-killed bacteria

- **Coley's toxins produced durable responses with several hundred advanced cancer patients**
  - Associated with induction of fever by killed, Gram-neg bacteria (Nauts Prog Clin Biol Res 107 687 1982)

https://www.cancerresearch.org/about-cri/cri-history

https://www.mskcc.org/blog/immunotherapy-revolutionizing-cancer-treatment-1891

- **Coley's toxins worked best i.v., but were too toxic, so given i.t. and s.c.**
  - i.t. and s.c. administration produced highly variable results

What Happened to Coley's Toxins?

- **FDA required to certify old and new drugs in 1962 and decided not to grandfather-in CT as an approved drug in 1963, despite cures, due to variability in clinical response**

- **Pharmaceutical industry abandoned the product – why?**
  - Mechanism of action wasn't known - could not determine source of variability and correct
  - Non-approval meant requirement to carry out expensive clinical trials
  - Very old drug - no patent coverage

Mechanism of Action of Coley's Toxins
Bacteria Contain Immune System Danger Signals

- **The most prominent danger signal family activates Toll-like receptors (TLR)**

Source	Danger Signal (TLR Ligand / Agonist)	Toll-Like Receptor
Bacteria	Lipoproteins, Peptidoglycans	TLR2 (1/2, 6/2)
Viruses (Bacteria?)	Double Stranded RNA	TLR3
Bacteria	Lipopolysaccharide (LPS / endotoxin)	TLR4
Bacteria	Flagellin	TLR5
Viruses (Bacteria?)	Single Stranded RNA	TLR7/8
Bacteria	Unmethylated CpG DNA	TLR9

- **TLRs directly and indirectly activate essentially all immune cells (innate + adaptive)**
  - Indirect activation occurs via induction of secretion of cytokines and chemokines

- **Cytokines and chemokines are principal inducers of anti-tumor immune responses**
  - Innate - cell recruitment, MΦ activation, NK cell activation, γδT-cell activation, ↓Treg
  - Adaptive - cell recruitment, APC/DC activation, T-cell activation ($CD4_H$/$CD8_{CTL}$), ↓Treg

Why Was Coley's Toxins Too Toxic When Administered I.V.?

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- **TLR4 agonist LPS-endotoxin is one of the most potent and broadly acting danger signals**
- **Constitutes about 75% of the Gram-negative outer cell membrane**
- **Limits the number of bacteria (and other danger signals) that can be administered i.v.**

  Can't provide optimal ratio for synergistic activation of innate and adaptive immune pathways

Decoy has Optimized and Re-Invented Coley's Toxins

- **Hypothesis to produce an i.v.-safe product**
  - Use a single pure strain of non-pathogenic, Gram-negative bacteria
  - Selectively reduce LPS-endotoxin activity by ~90% (10% should be "enough")
  - Kill and stabilize the bacteria so that they don't fall apart prior to immune cell clearance

- **Nano/micro-particles are passively targeted to lymphoid organs and tumors**
  - I.V.-administered "Decoy" bacteria should be passively targeted to the liver, spleen, leaky vasculature of tumors (lymph nodes?) and rapidly cleared by immune cells
  - Localized and pulsed innate and adaptive immune system priming or activation (a "jumpstart")

Patented Decoy Treatment Kills Bacteria and Significantly Reduces LPS-Endotoxin Activity and *In Vivo* Pyrogenicity

Treatment	Live Bacteria	LPS Endotoxin Activity (LAL Assay)	Pyrogenicity Threshold (Rabbit Assay)
No Treatment	100%	44.7 Units / 10^6 Bacteria	$3x10^4$ Bacteria
Decoy	0	3.6 Units / 10^6 Bacteria	$9x10^5$ Bacteria
Change induced by treatment	Killed all bacteria	92% reduction	97% reduction (requires more bacteria to increase rabbit temperature)

Decoy bacteria are also 100 to 2,500-fold less toxic in mice (LD_{50}) than live, attenuated bacterial products

Decoy Treatment Does Not Reduce (Most) Anti-Tumor Cytokine Secretion by Human Peripheral Blood Mononuclear Cells (PBMCs)

Secretion by Human PBMCs *In Vitro*	Untreated Bacteria	Decoy-Treated Bacteria (Decoy10)	Decoy-Treated Bacteria (Decoy20)
Anti-Tumor Cytokine	**pg/mL (mean of triplicate determinations ± %CV at same bacterial dose for each cytokine)**		
GM-CSF	1,094 ± 22	1,197 ± 2	1,695 ± 23
IFNγ	175,866 ± 7	47,488 ± 3*	55,321 ± 10*
IL-12p70	176 ± 14	528 ± 7	428 ± 37
TNFα	49,782 ± 11	77,919 ± 13	99,247 ± 16

*Similar IFNγ induction as untreated bacteria at higher Decoy10 or Decoy20 doses
Results suggest that we have (partly) dissociated toxicity from anti-tumor cytokine induction

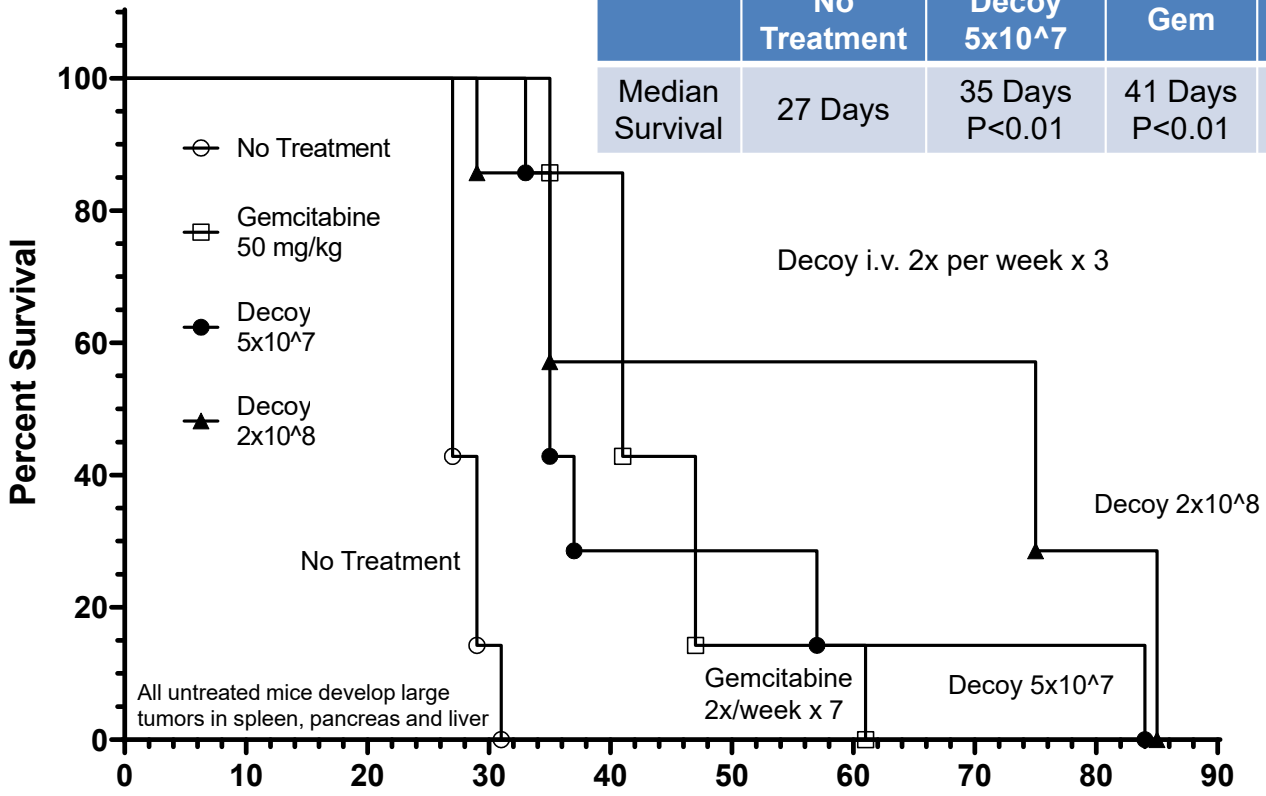
Multiple TLR Agonist Decoy Bacteria Induce Higher Levels of Anti-Tumor Cytokine/Chemokine Secretion by Human PBMCs than Mono-Specific TLR Agonists

Secretion by Human PBMCs *In Vitro*	CpG (TLR9)	Poly(I:C) (TLR3)	R848 (TLR7/8)	LPS (TLR4)	Decoy10 (TLR2,4,5,9)
Anti-Tumor Cytokine	pg/mL (triplicate full titration peak average from two exp)				
GM-CSF	0	2	136	276	1,246
IFNγ	7	248	61,914	33,293	171,284
IL-12p70	4	15	205	84	375
TNFα	65	334	36,663	24,944	73,069
MIP-1α*	0	272	17,866	19,278	29,942

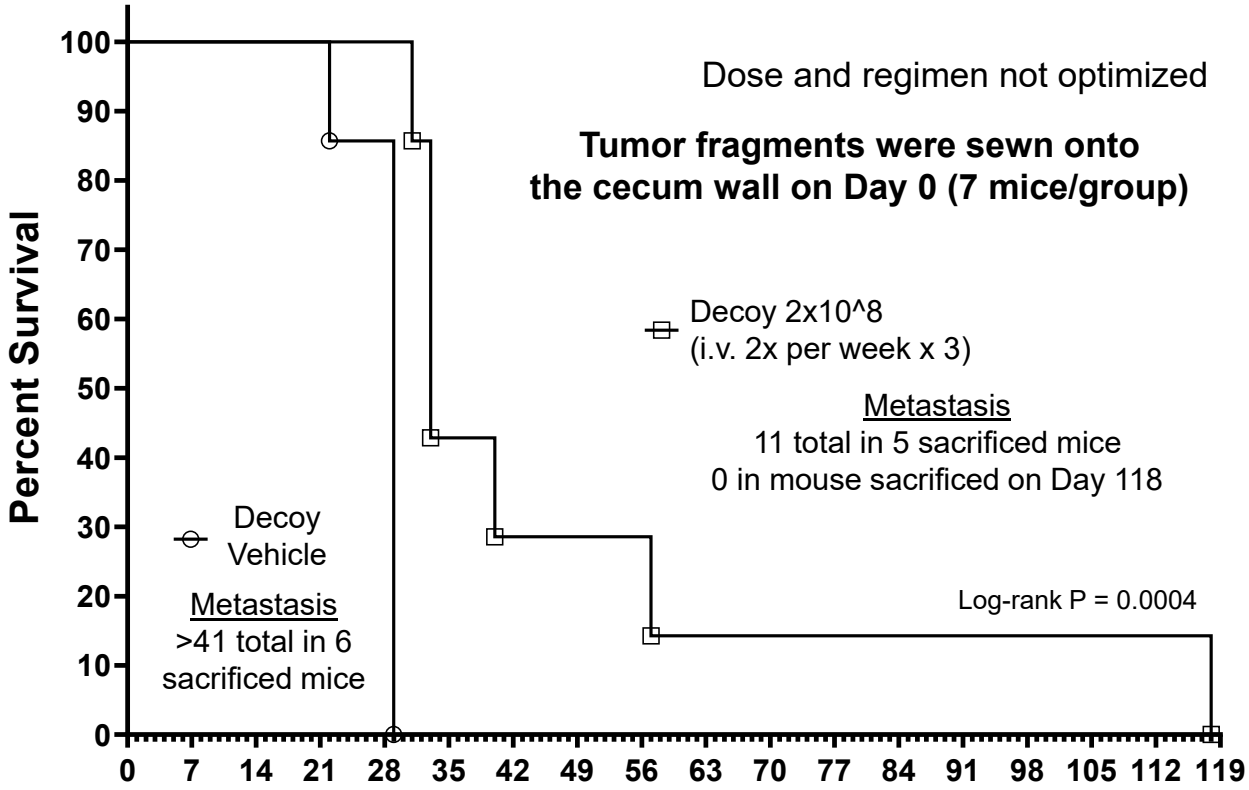
*From one experiment

Single Agent Decoy Extends Survival of Mice with Metastatic Mouse PAN02 Pancreatic Carcinoma

	No Treatment	Decoy 5x10^7	Gem	Decoy 2x10^8
Median Survival	27 Days	35 Days P<0.01	41 Days P<0.01	75 Days P<0.01

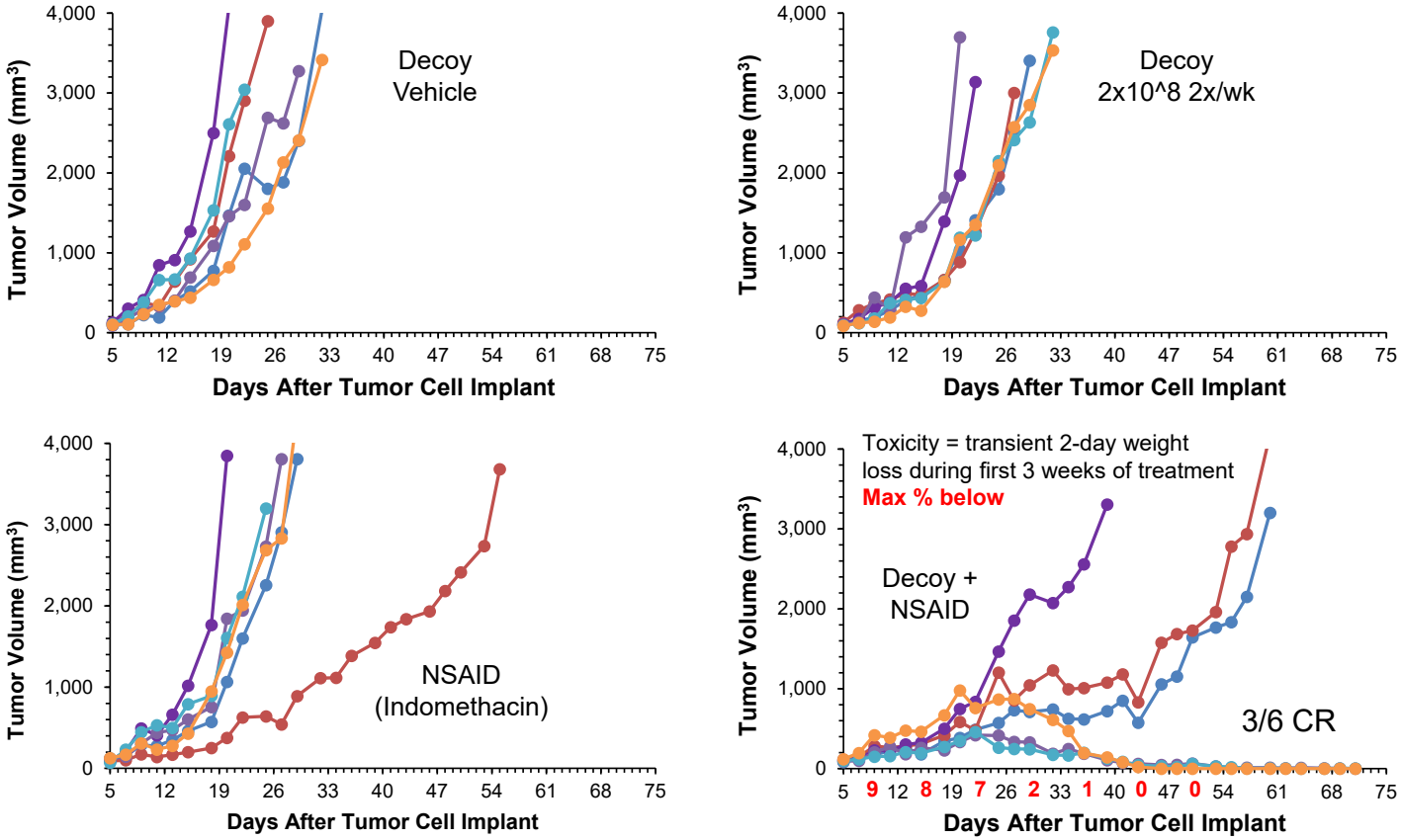


Single Agent Decoy Inhibits Metastasis and Extends Survival of Mice with Orthotopic Mouse CT26 Colorectal Carcinoma

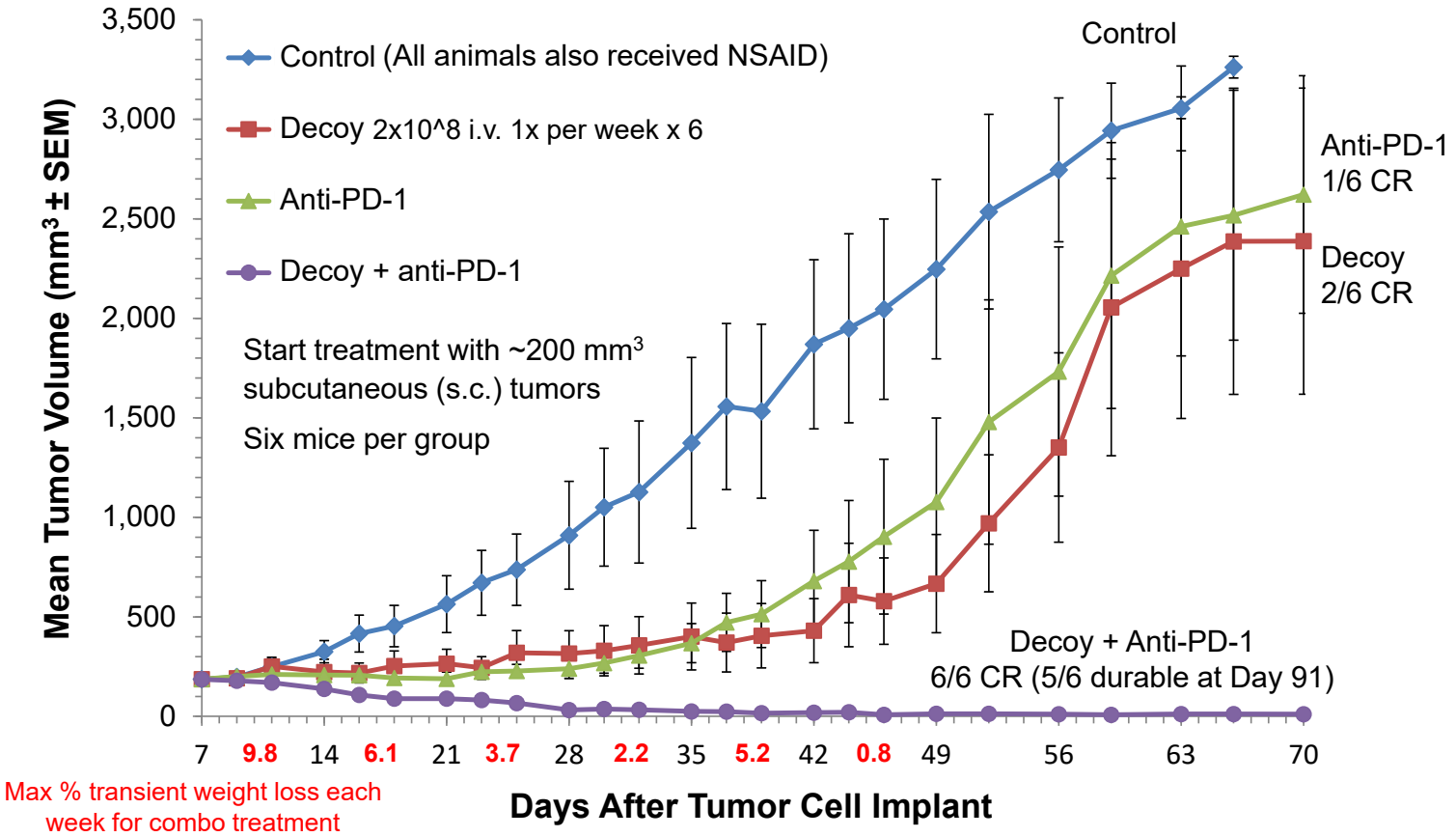


Decoy Synergizes with a Low-Dose, Oral NSAID to Eradicate Established Mouse Subcutaneous H22 Hepatocellular Carcinoma (HCC)

Treat 6 mice per group with Decoy 2x per week i.v. for 7 weeks / Start treatment at 103 mm^3

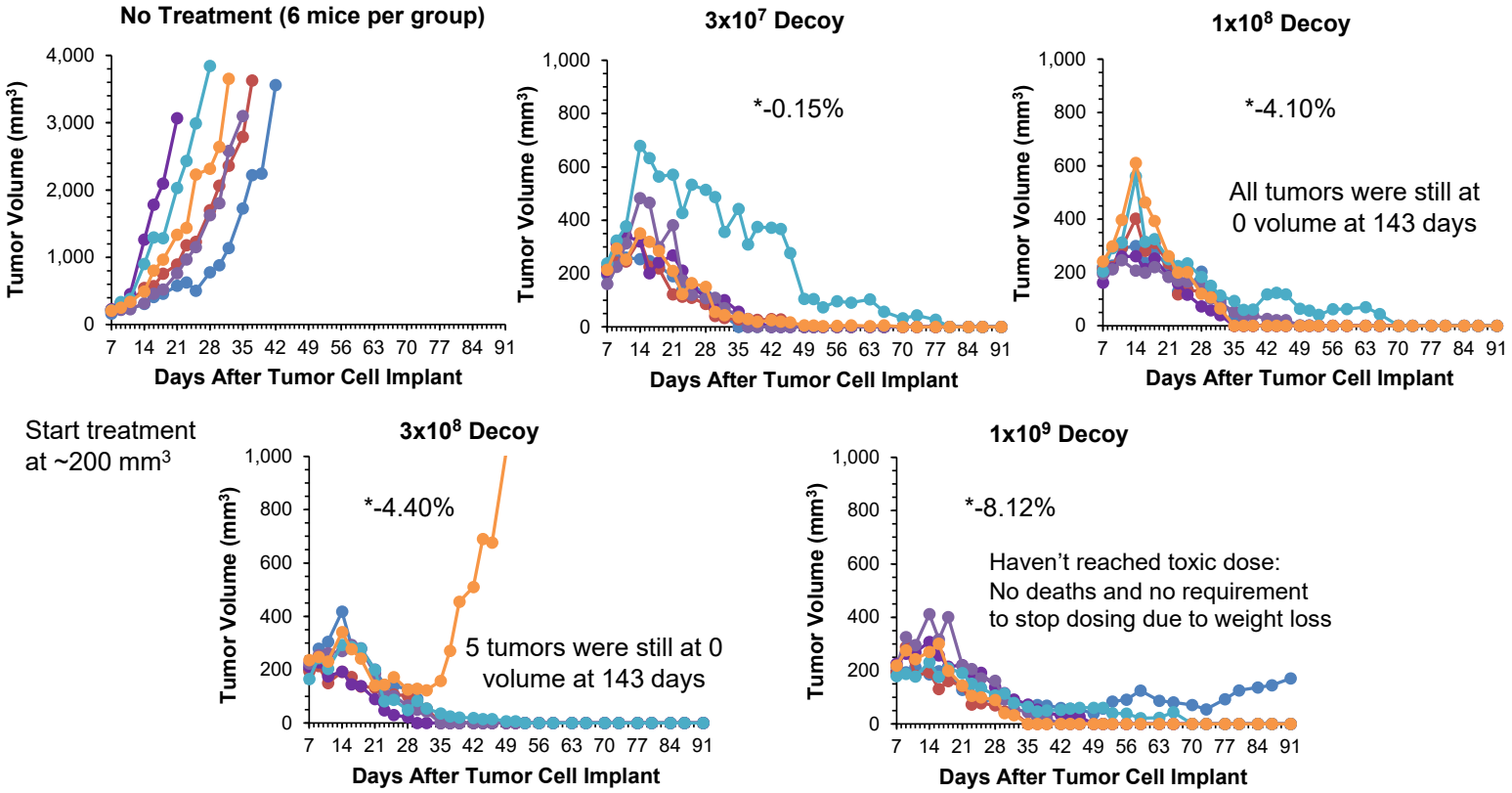


Decoy is as Good or Better Than Anti-PD-1 Checkpoint Therapy and Synergizes to Safely Eradicate Established Mouse Hepatocellular Carcinoma (HCC)



Synergistic Eradication of Murine HCC by Decoy Combination Exhibits a Very Wide Therapeutic Index (>33-fold)

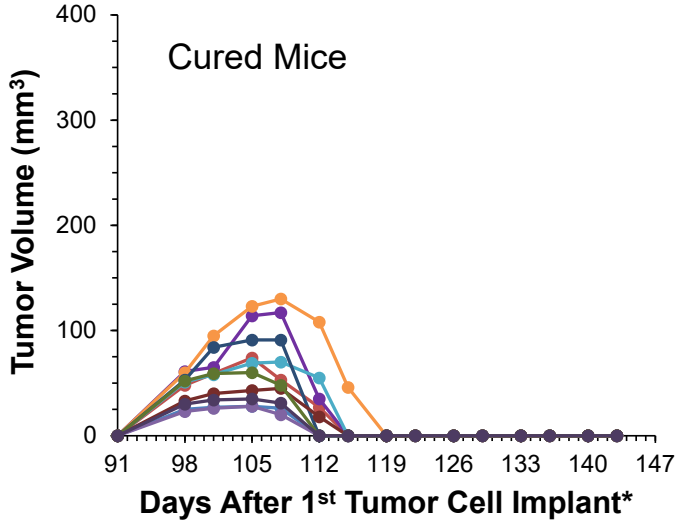
All Decoy-treated groups also received the same standard regimen of NSAID + anti-PD-1



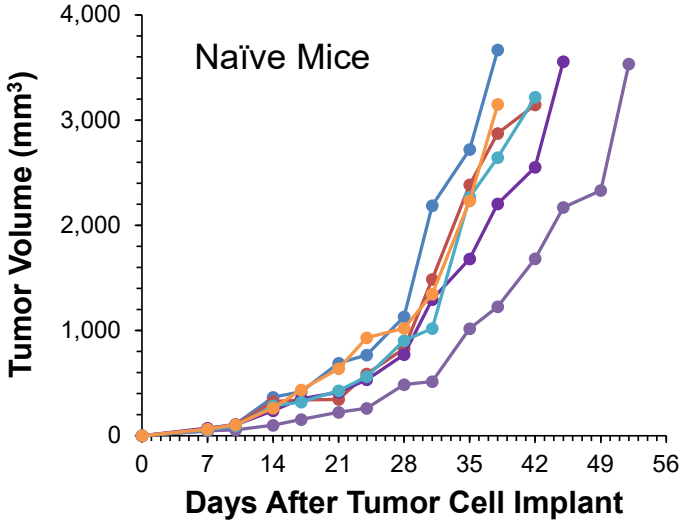
*Maximum transient body weight loss relative to start of treatment

Mice Cured by Decoy Combination and Re-Challenged with Fresh HCC Tumor Cells Reject the Tumors (Immunological Memory)

Eleven cured mice were re-challenged with fresh HCC tumor cells on Day 91 on the opposite flank from the first challenge



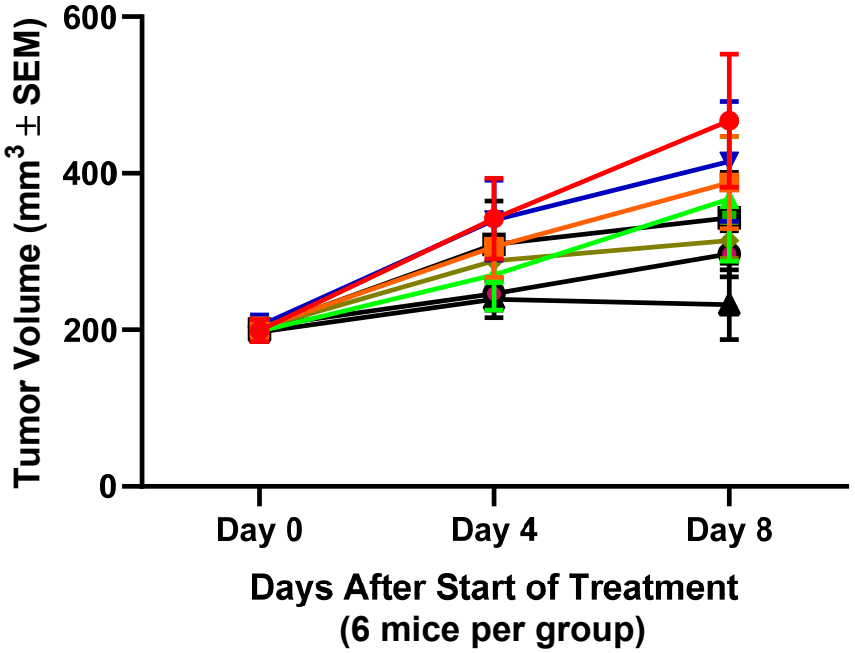
Six naïve mice were challenged with the same tumor cells as the cured mice on the same day



All 1st challenge tumor sites remained tumor-free

Tumor-Eradicating Combinations Transform “Cold” HCC Tumors to “Hot”

Treatment Effects on Tumor Volume
(RNA prepared on Day 8 for NanoString Analysis)



Fold increase in
Tumor Inflammation Signature Score (TIS)
“Cold” vs. “Hot” Tumor

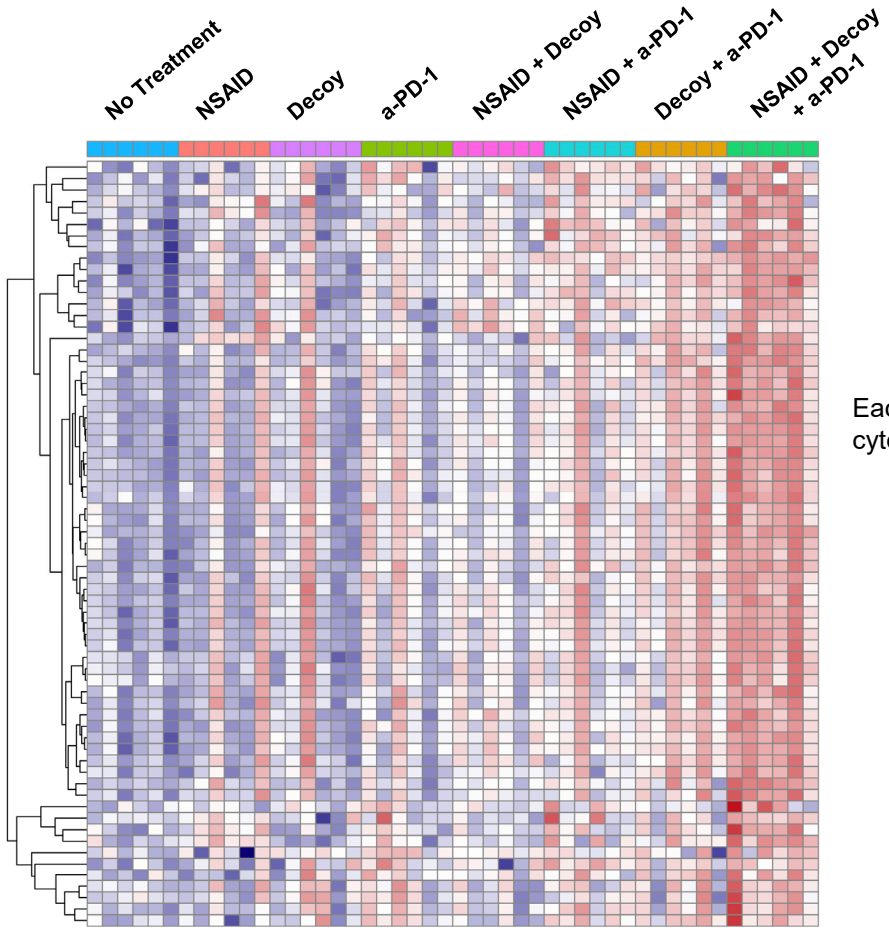
NT		0 / 6
NSAID	1.68	0 / 6
Decoy	1.61	0 / 6
a-PD-1	2.30	0 / 6
N + D	2.21	2 / 6
N + P	2.92	1 to 2 / 6
D + P	3.60	2 / 6
N + D + P	5.89	5 to 6 / 6

Number of long-term regressions per group

Systemic Administration of Decoy Bacteria, NSAID and Anti-PD-1 Induces Cytokine Immune Pathways in HCC Tumors

NanoString 770 gene expression analysis: Cytokines and Receptors in tumor

Mice with 200 mm3 tumors were treated for 1 week

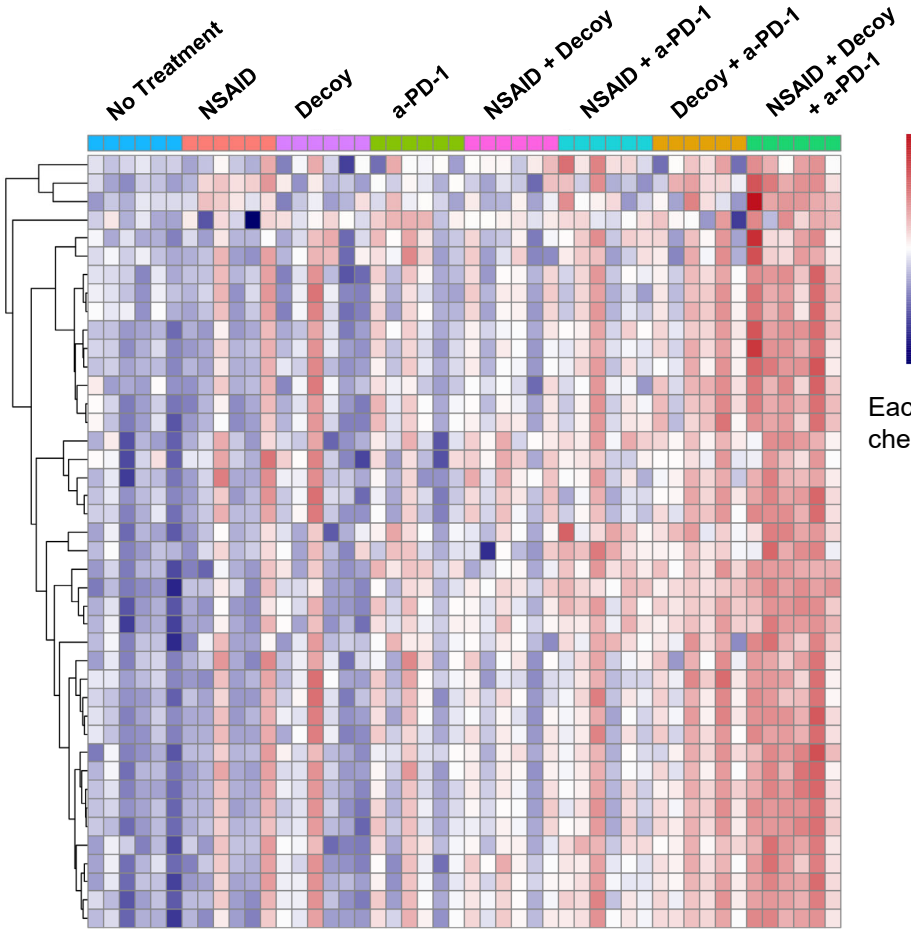


Each horizontal row represents a different cytokine or cytokine receptor gene

Systemic Administration of Decoy Bacteria, NSAID and Anti-PD-1 Induces Chemokine Immune Pathways in HCC Tumors

NanoString 770 gene expression analysis: Chemokines and Receptors in tumor

Mice with 200 mm3 tumors were treated for 1 week

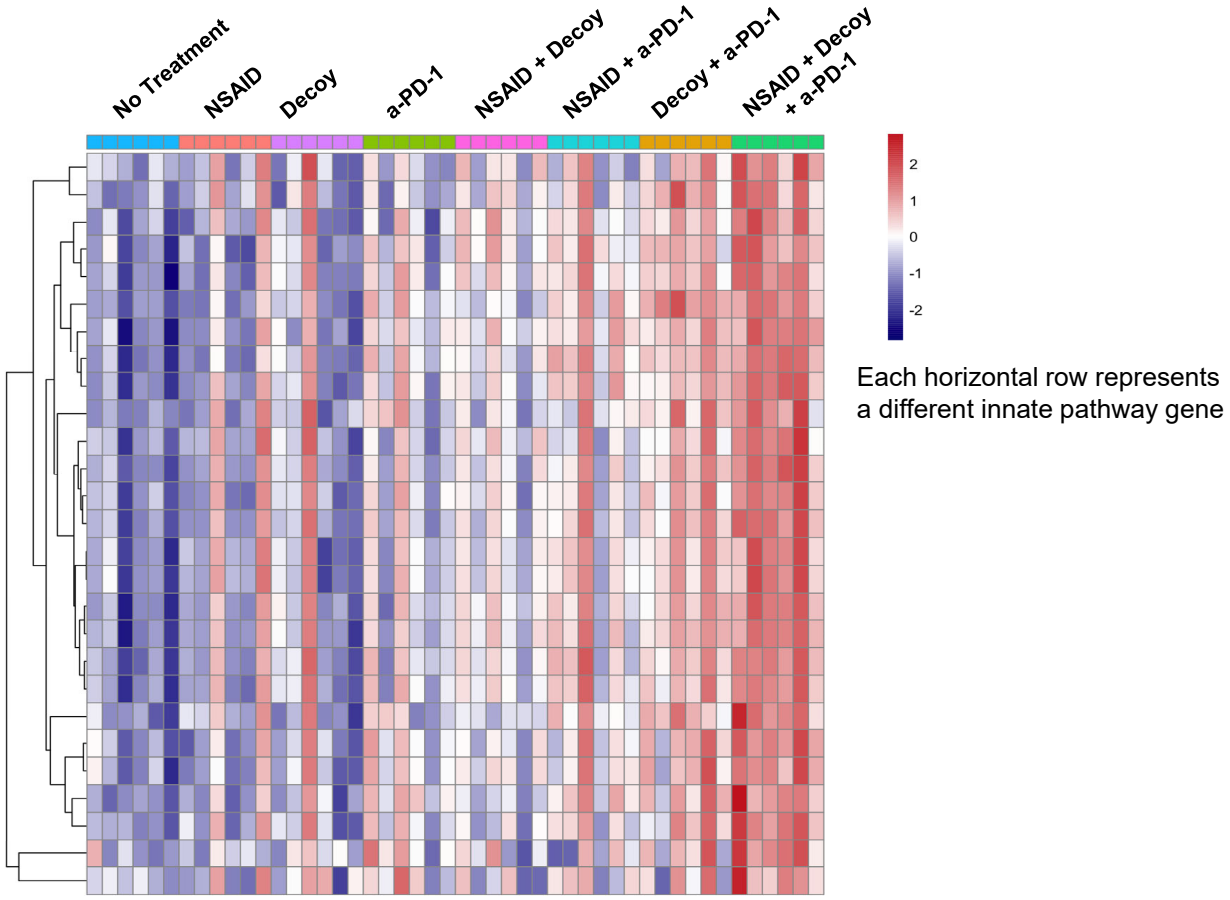


Each horizontal row represents a different chemokine or chemokine receptor gene

Systemic Administration of Decoy Bacteria, NSAID and Anti-PD-1 Induces Innate Immune Pathways in HCC Tumors

NanoString 770 gene expression analysis: Innate Immune response in tumor

Mice with 200 mm^3 tumors were treated for 1 week

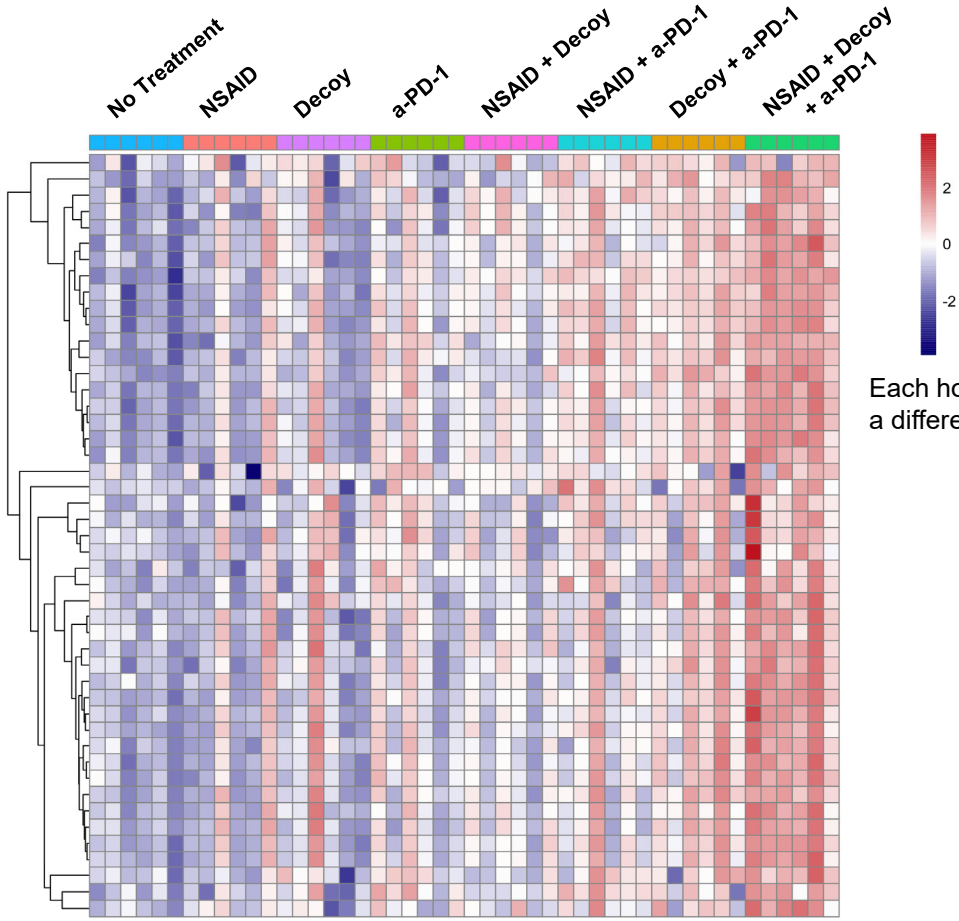


Each horizontal row represents a different innate pathway gene

Systemic Administration of Decoy Bacteria, NSAID and Anti-PD-1 Induces Adaptive Immune Pathways in HCC Tumors

NanoString 770 gene expression analysis: Adaptive Immune response in tumor

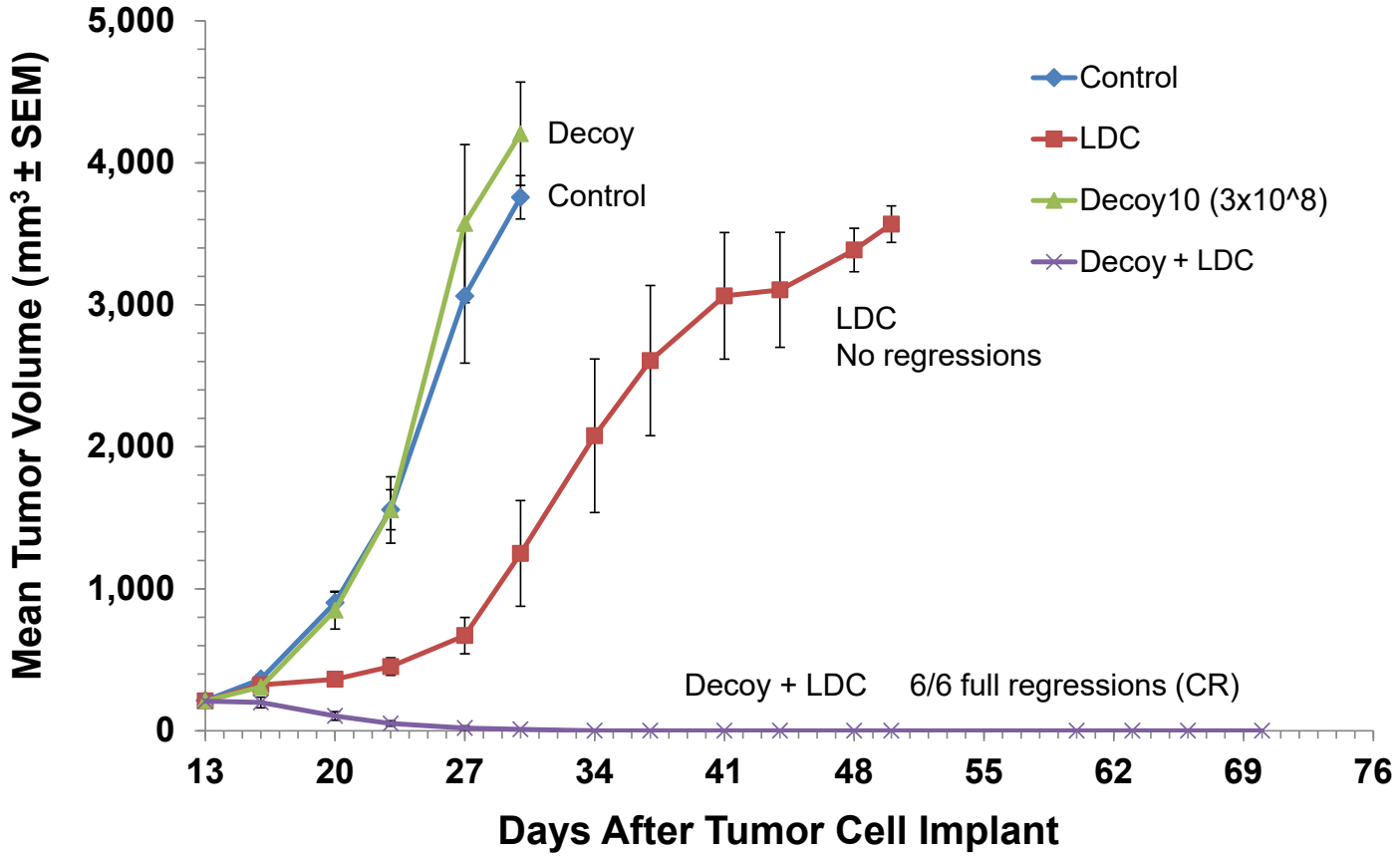
Mice with 200 mm^3 tumors were treated for 1 week



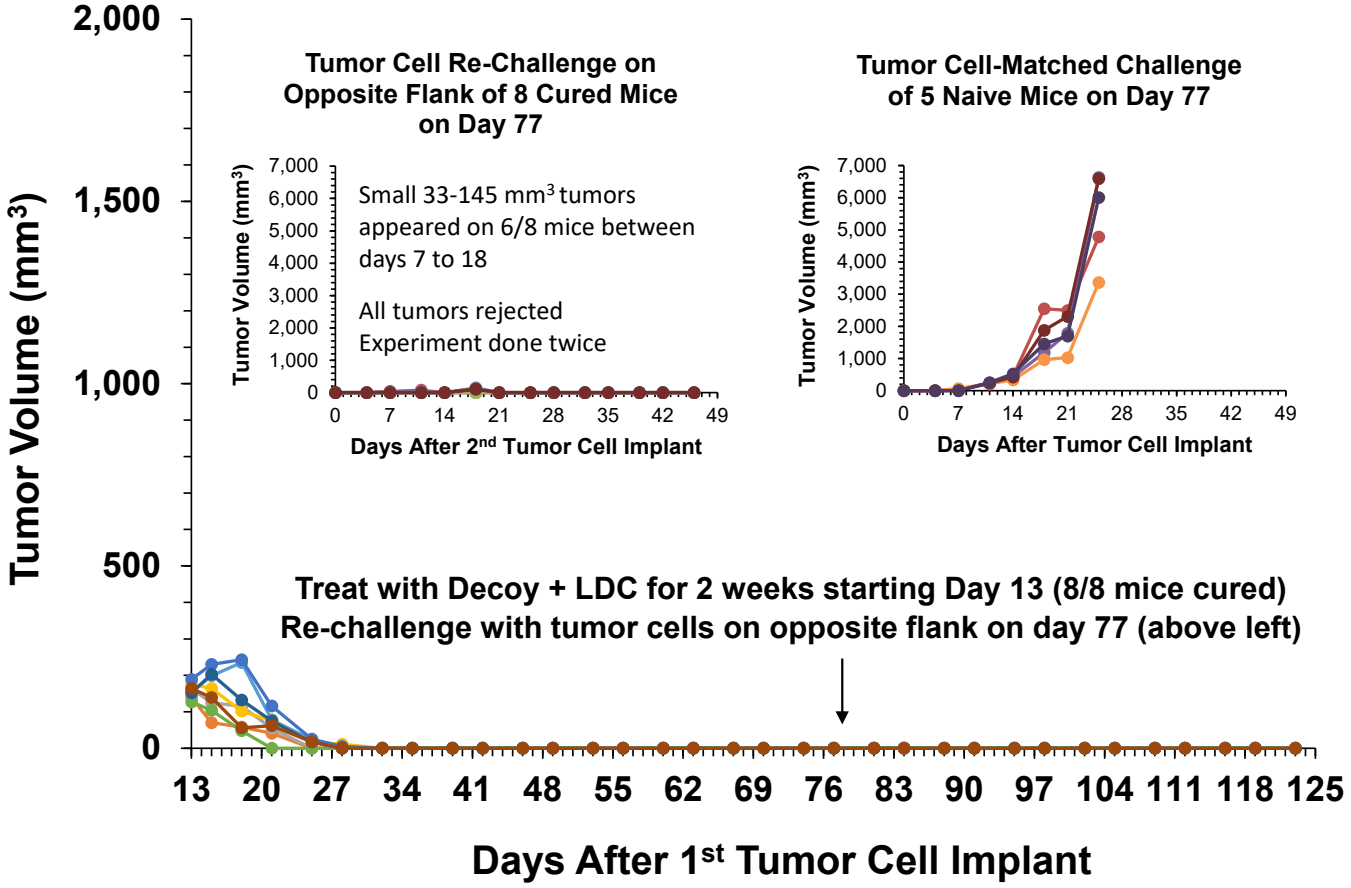
Each horizontal row represents a different adaptive pathway gene

Decoy Bacteria Synergize with Low-Dose Cyclophosphamide (LDC) to Safely Eradicate s.c. Mouse A20 Non-Hodgkin's Lymphoma (NHL)

Treat 6 mice per group with i.v. Decoy 2x per week for 2 weeks / Start treatment at ~200 mm^3

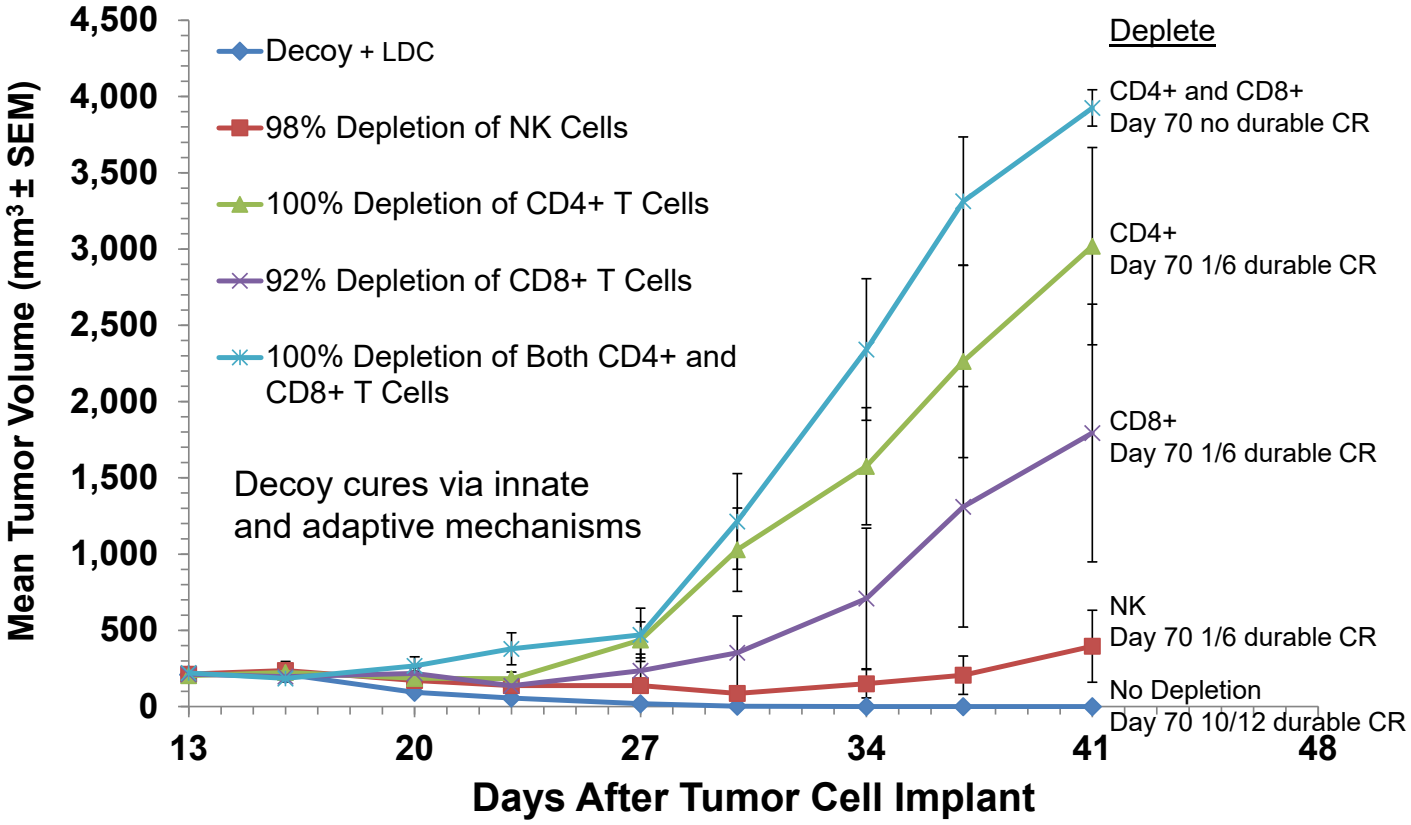


Synergistic Eradication of NHL Tumors by Decoy Technology is Reproducible, Durable and Induces Immunological Memory



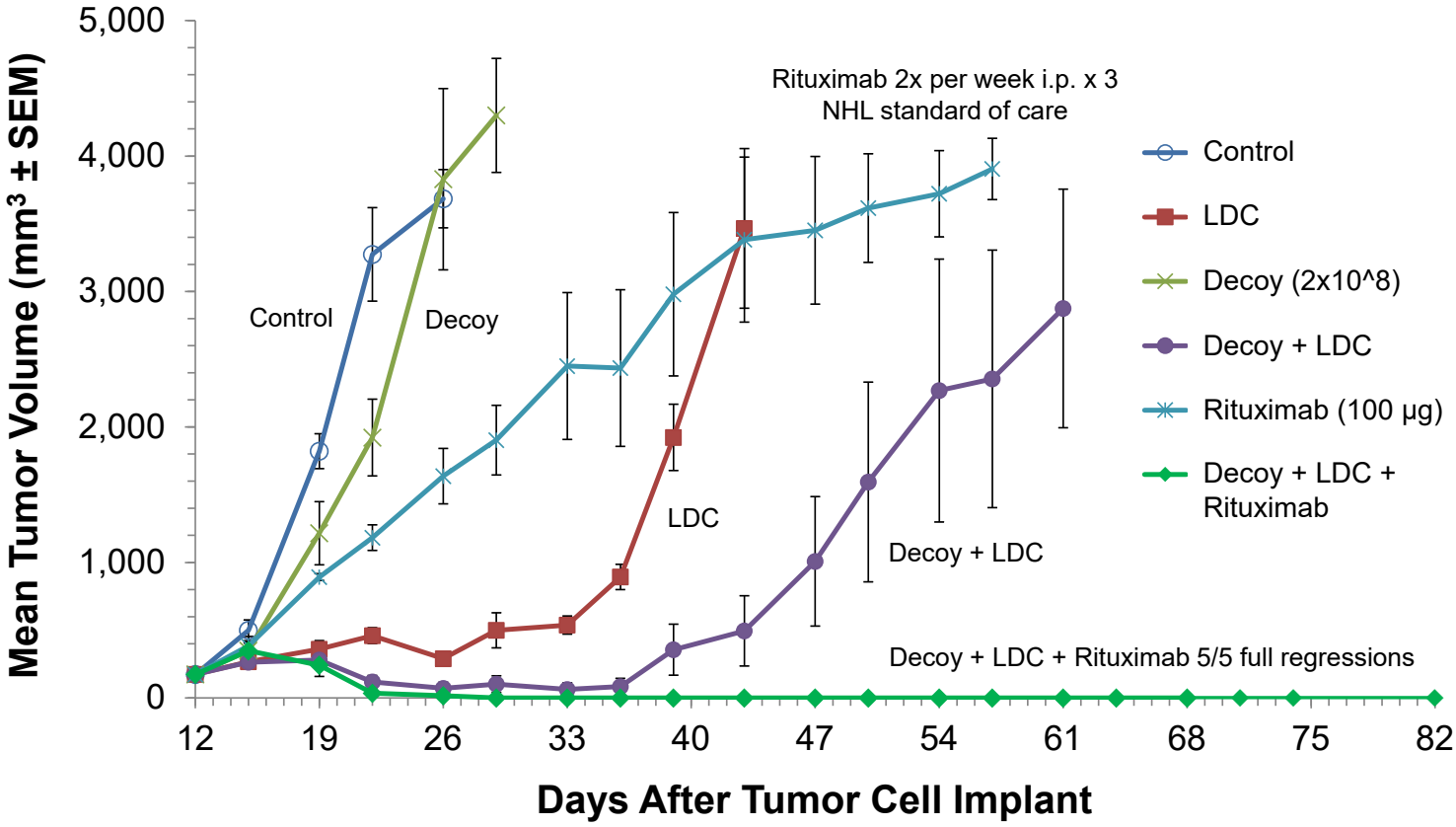
High Percentage Eradication of s.c. NHL by Decoy + LDC Requires NK Cells and CD4+ and CD8+ T Cells

Treat all groups (6 mice per group) with i.v. Decoy + LDC for 2 weeks / Start treatment at ~200 mm^3

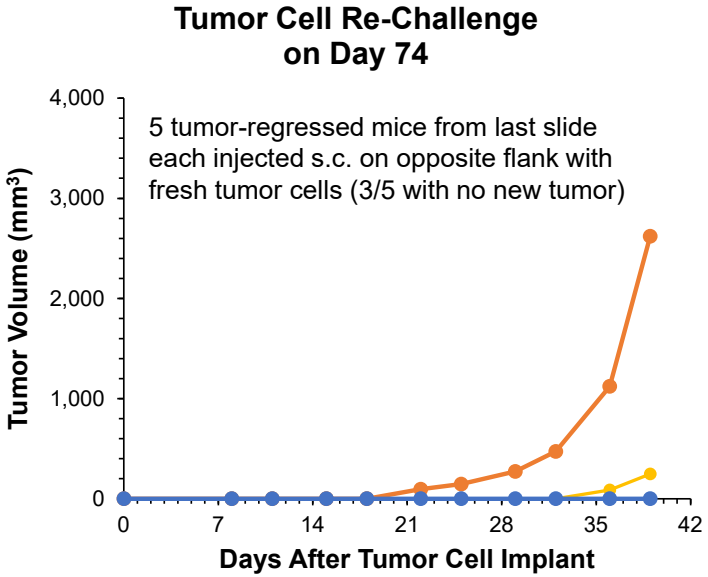


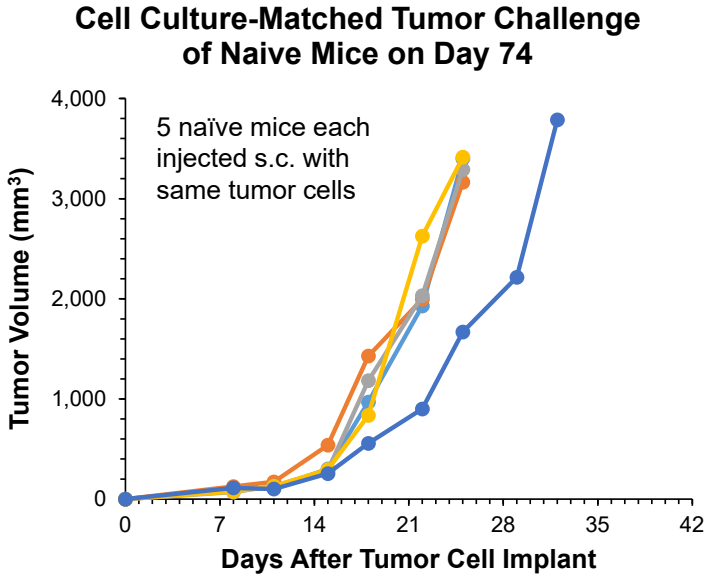
Decoy Technology Synergizes with Rituximab to Induce Eradications of s.c. Human Ramos NHL via Innate Immunity

Treat 5 SCID mice per group 2x per week for 3 weeks / Start treatment at 173 mm^3



Decoy Technology can Synergize with Rituximab to Induce Immunological Memory Via the Innate Immune System





- Tumor regression with immunological memory via the innate immune system alone is very rare, but consistent with a multiple danger signal mechanism
- Results suggest that Decoy technology may synergize with other marketed ADCC mechanism-based, targeted antibody therapeutics (~12 on market)

Decoy Summary

- Passive targeting with attenuated and killed bacteria safely activates innate and adaptive immune pathways, leading to combination-mediated eradication of multiple tumor types
- Does not require targeting with or to a specific tumor antigen
- Induces both innate and adaptive anti-tumor immunological memory
- Exhibits significant single agent activity against chronic HBV and HIV in pre-clinical models
- Late pre-clinical development stage
- Oncology Phase 1 in 1st half of 2022
- Acknowledgements:
  - AntiCancer, Crown Bioscience, HD Biosciences, Molecular Diagnostic Services, Pacific BioLabs, Southern Research Institute, WuXi AppTec