hansonwade

STING & TLR-Targeted Therapies Summit 2022

Indaptus THERAPEUTICS

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Eradication of Established Tumors with Induction of Innate & Adaptive Immunological Memory in Multiple Preclinical Models with Systemically Administered Decoy Bacteria, a Multi-TLR Agonist Therapeutic Vaccine

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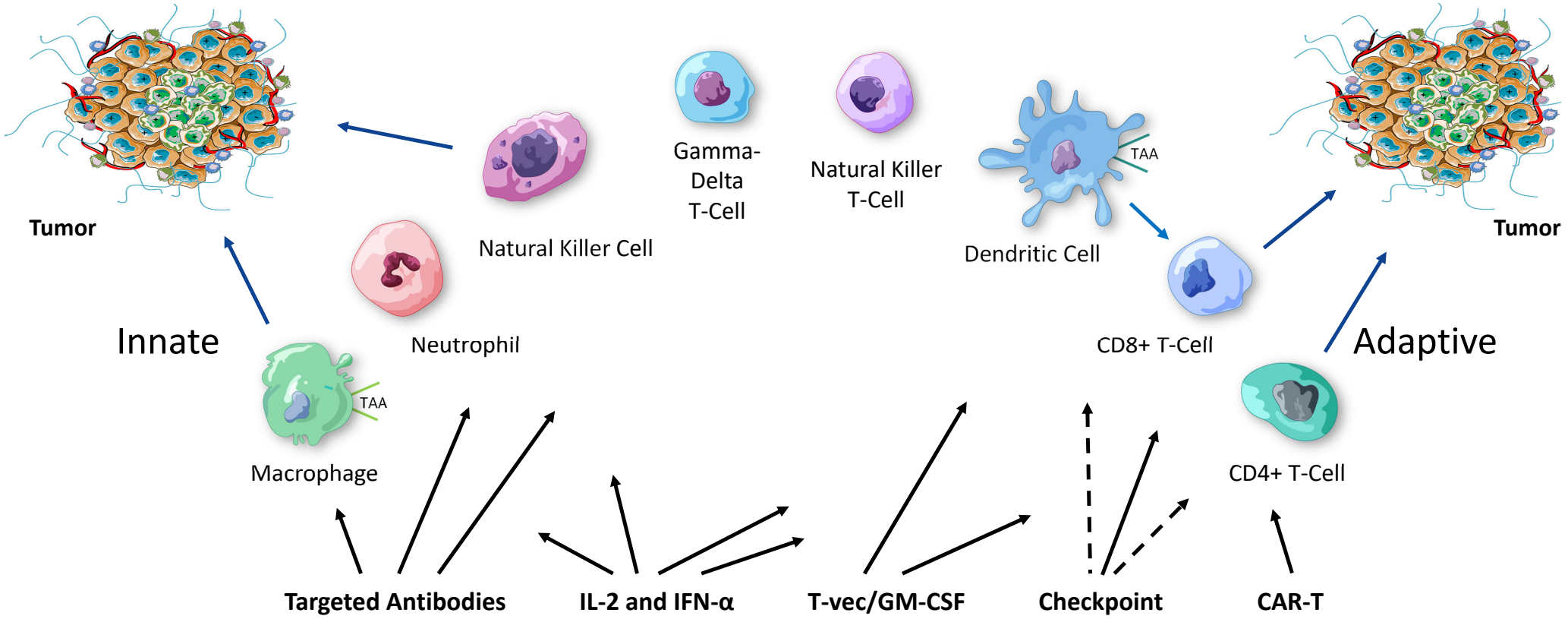
Michael J. Newman is an employee of Indaptus Therapeutics

Current Cancer Immunotherapies: Low Percentage Cures for Most Advanced Cancers

Current approaches activate only one or a few innate or adaptive immune cell types



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Improving Cancer Immunotherapy with TLR and STING Agonists
Indaptus Assumptions

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

- **We need innate and adaptive pathway activation in tumor and lymphoid organs**
  - Innate and adaptive pathways complement/cooperate to produce maximum efficiency
  - Most steps required for innate and adaptive immune responses take place outside of the tumor
  - Tumors negatively remodel entire systemic immune system and systemic immunity is required for successful anti-tumor immunity (Hiam-Galvez Nature Rev Cancer 2021)

- **Will require systemic administration and result in induction of many cytokines/chemokines**
  - How can this be done safely?
  - Continuous systemic exposure to multiple TLR agonists is toxic

Potential Source for a Multi-TLR Agonist (TLRa) Product: Historical Precedent – Coley's Toxins

- **Gram-negative bacteria contain multiple TLR agonists (+ NODa & STINGa)**

Maltose-binding protein, Outer membrane protein	TLR2a
Double stranded RNA	TLR3a
Lipopolysaccharide (LPS)-endotoxin	TLR4a
Flagellin	TLR5a
Single stranded RNA	TLR7/8a
Unmethylated CpG DNA	TLR9a

- **TLRs directly or 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

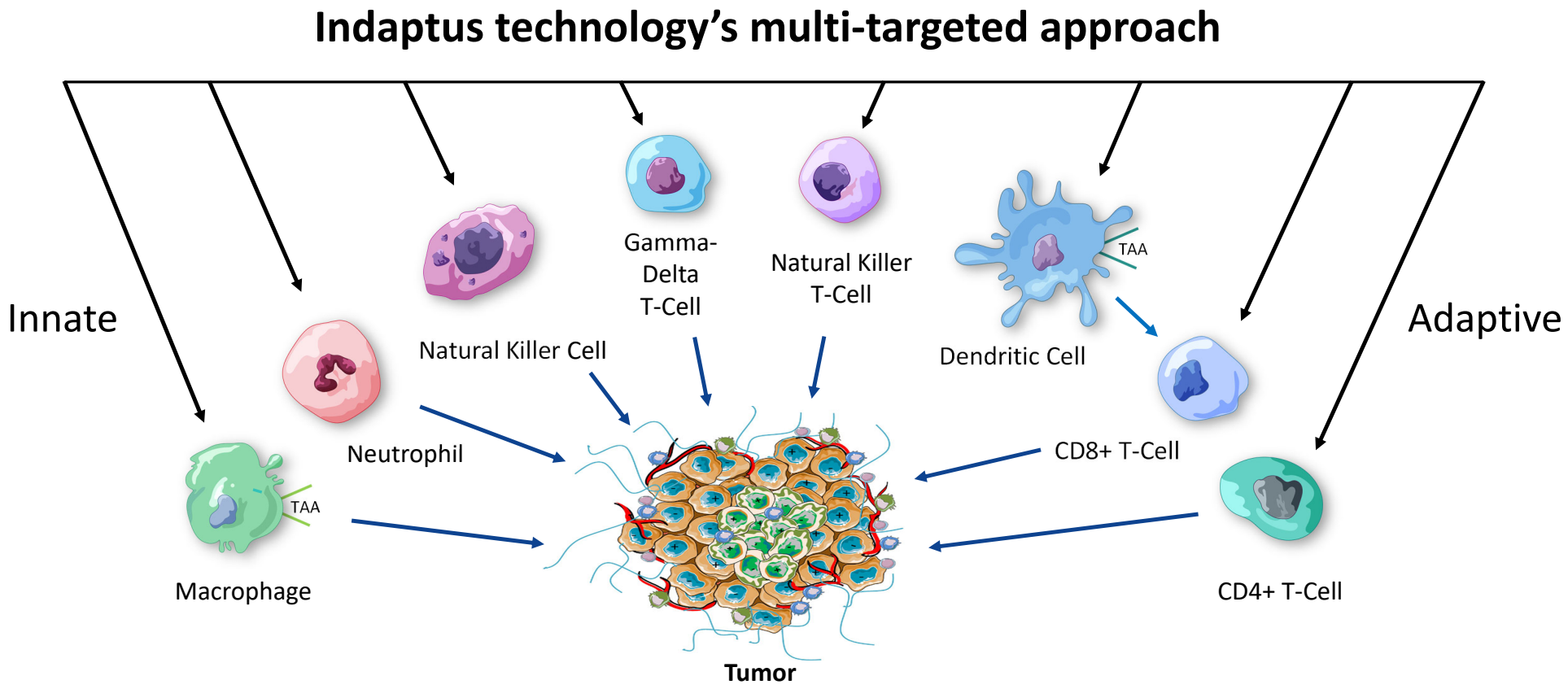
Problem – IV Administered Gram-Negative Bacteria are Toxic

- **TLR4a LPS-endotoxin constitutes ~75% of the Gram-negative outer cell membrane**
- **LPS is one of the most potent and broadly acting immune system danger signals**
- **Limits the number of bacteria (and other danger signals) that can be administered i.v.**
  - Can't provide optimal amount of other TLRa needed for activation of immune pathways
- **Two options – eliminate or reduce LPS**
  - Elimination of LPS was tried (Vion Pharmaceuticals) – no anti-tumor activity in Phase 1
  - TLR4 is required for dendritic cell activation (Fang et al Cell. Mol. Immunol. 11 150 2014)
    LPS stimulates NK cells, induces maturation of APC/Dendritic cells, primes and amplifies T and B-cell function and enhances T-helper Th1 immune responses (Arenas 2012)
  - Better bet – reduce LPS by ~90%
    Remaining 10% might be enough and allow i.v. administration of more of everything else

Indaptus Solution

- **Hypothesis to produce an i.v.-safe and effective product**
  - Use a single, pure strain of non-pathogenic, Gram-negative bacteria
  - Selectively reduce LPS-endotoxin activity by ~90%
  - Kill and stabilize the bacteria so that they don't fall apart prior to immune cell clearance
- **Potential advantages of approach**
  - IV-administered bacteria are passively targeted to the liver, spleen, leaky vasculature of tumors (lymph nodes?) and rapidly cleared from blood (within 15 minutes)
  - Innate and adaptive immune system priming or activation in lymphoid organs and tumor and passive targeting to tumors or metastasis in liver
  - Rapid clearance should reduce potential for systemic toxicities common with small molecule, protein and mammalian cell-based immunotherapies that depend on continuous exposure

Propose Use of "Decoy" Bacteria to Attract Immune Cells and Prime or Jump-Start Anti-Tumor Immune Responses



Patented Decoy Treatment Kills Bacteria, Significantly Reduces LPS-Endotoxin Activity and *In Vivo* Toxicity (Including *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 some live, attenuated bacterial products

Despite Reduced Toxicity, Decoy Treatment Does Not Significantly Compromise Induction of Cytokine Secretion by Human 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

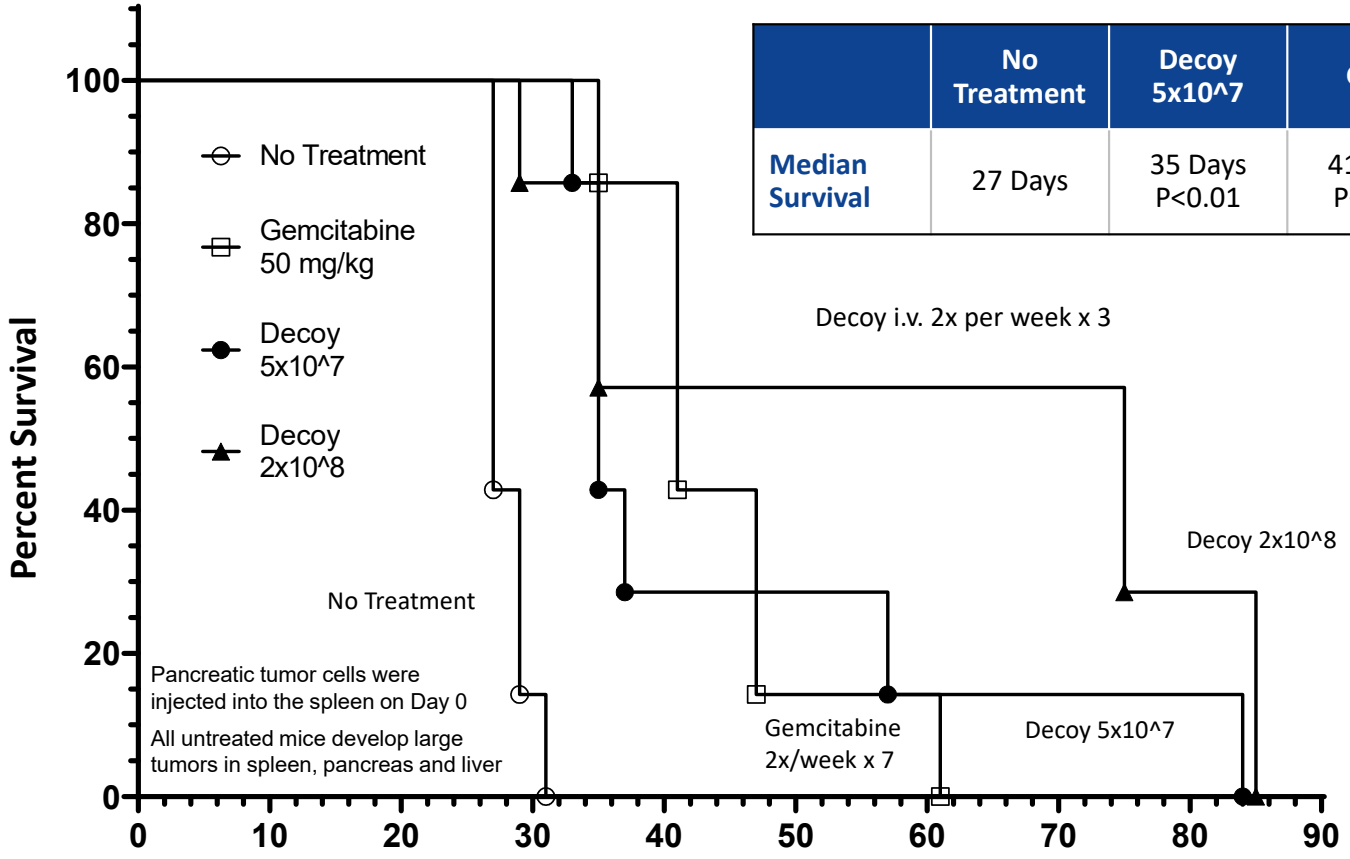
Multiple TLR Agonist Decoy Bacteria Induce Higher Levels of Anti-Tumor Cytokine/Chemokine Secretion by PBMCs than Mono-Specific TLR Agonists

Secretion by Human PBMCs *In Vitro*	CpG (TLR9)	Poly(I:C) (TLR3)	R848 (TLR7/8)	LPS (TLR4)	Decoy10 (Multi-TLR)
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

*One experiment

Single Agent *In Vivo* Decoy Anti-Tumor Activity
Metastatic Mouse 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



(Treatment started on Day 5 with 7 mice/group)

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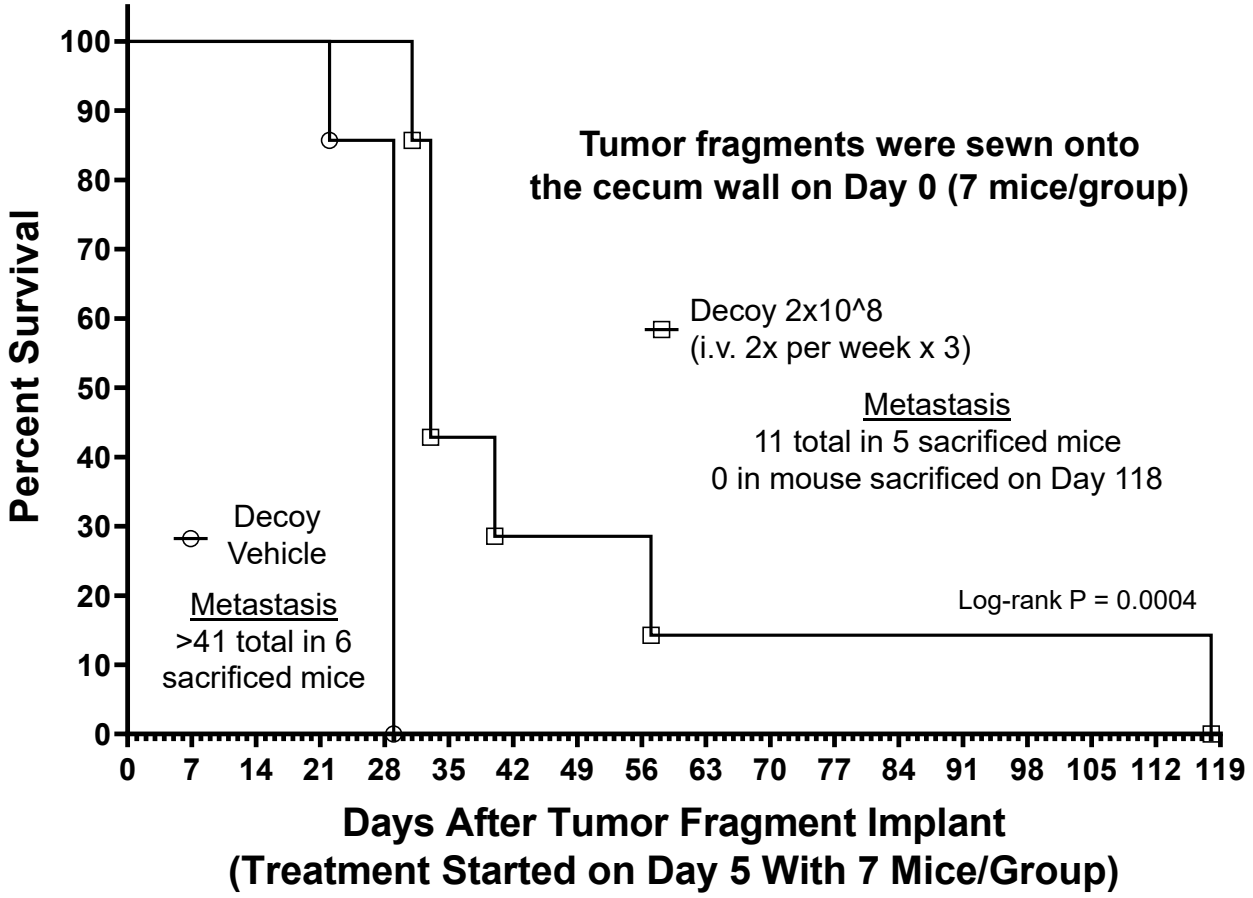
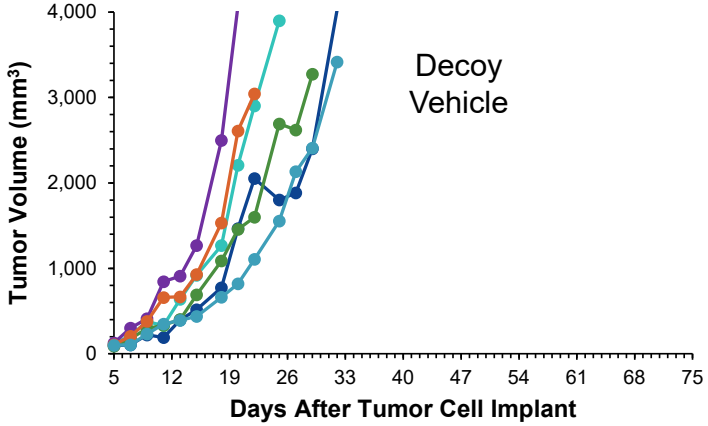
Single Agent *In Vivo* Decoy Anti-Tumor Activity
Orthotopic Mouse Colorectal Carcinoma

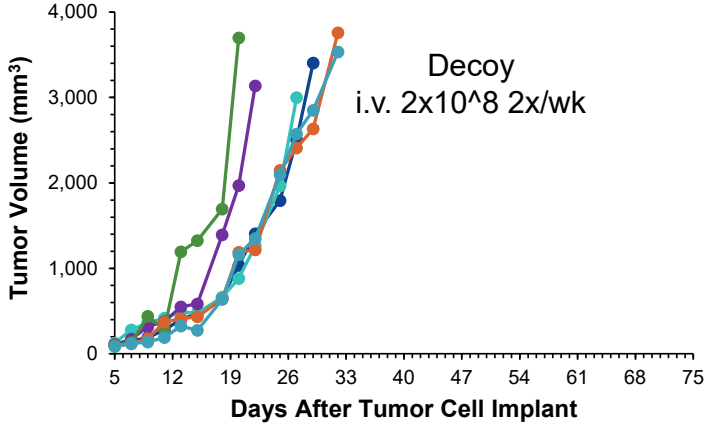


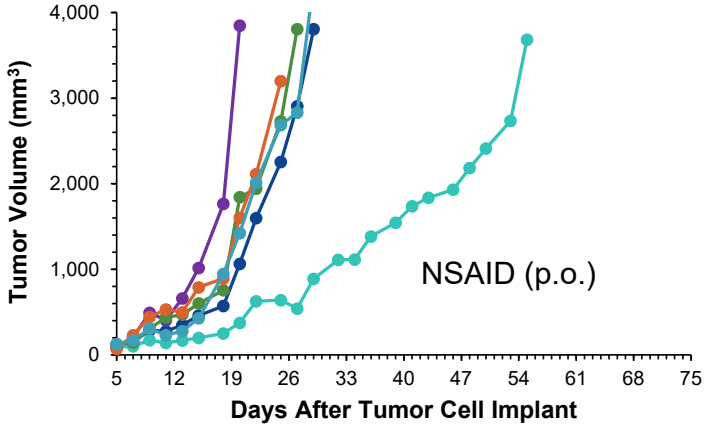
Decoy Synergizes With a Non-Steroidal Anti-Inflammatory Drug (NSAID) to Safely Eradicate Subcutaneous Mouse Hepatocellular Carcinomas (HCC)

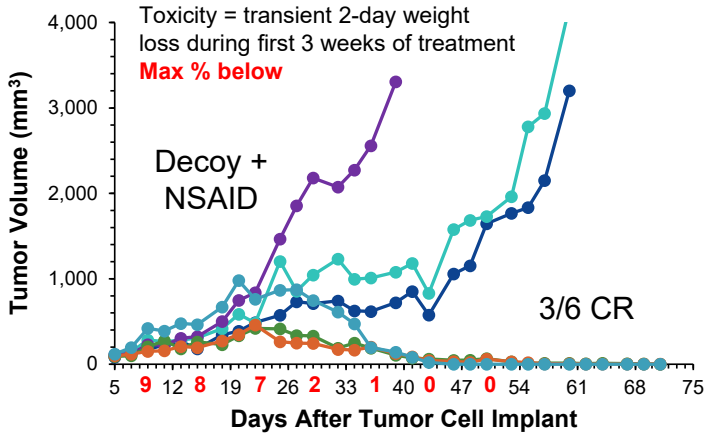
Treat 6 mice per group with Decoy 2x per week i.v. for 7 weeks / Start treatment at 103 mm^3

NSAIDS reduce myeloid-derived immune-suppressive cells

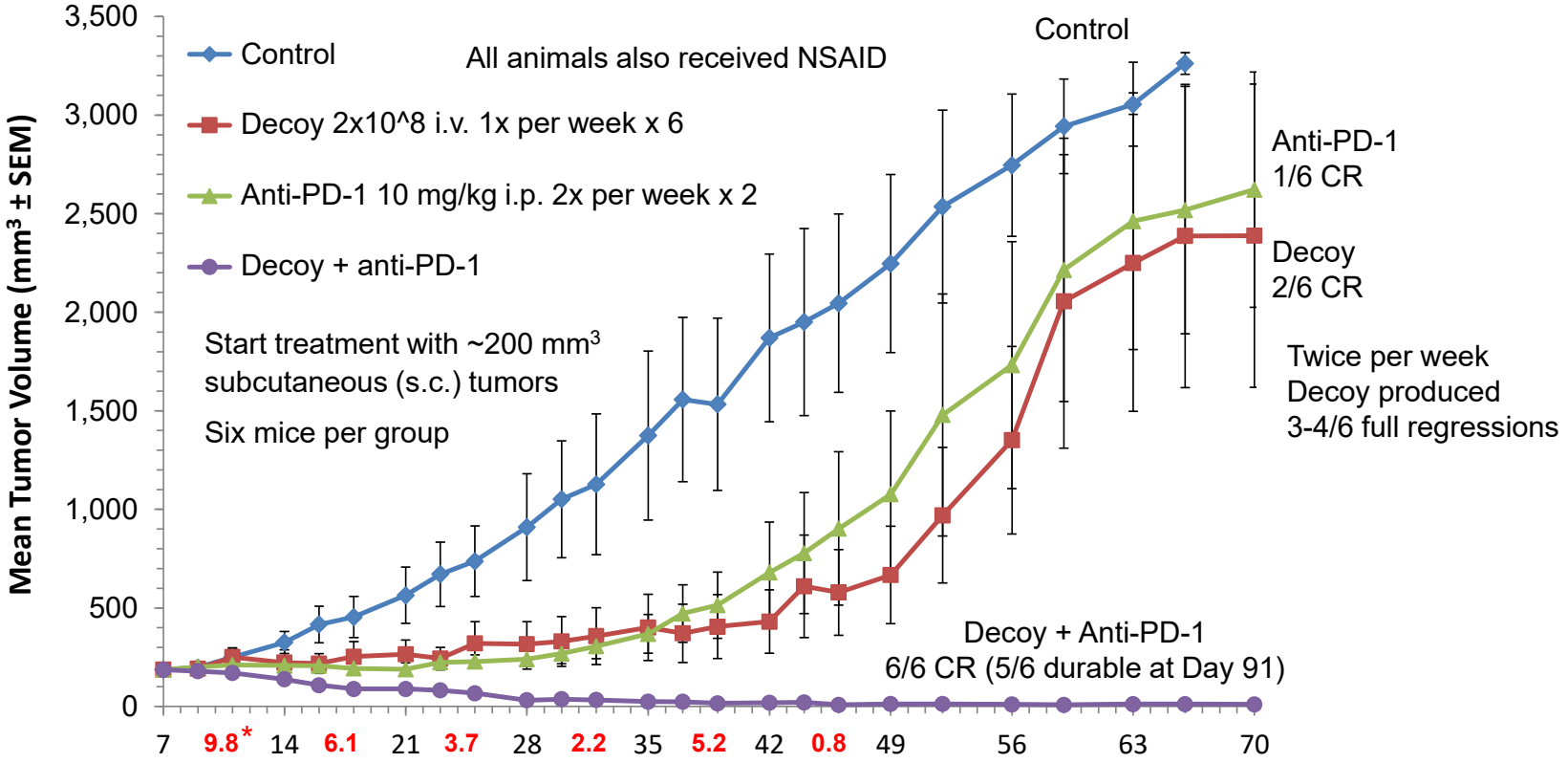








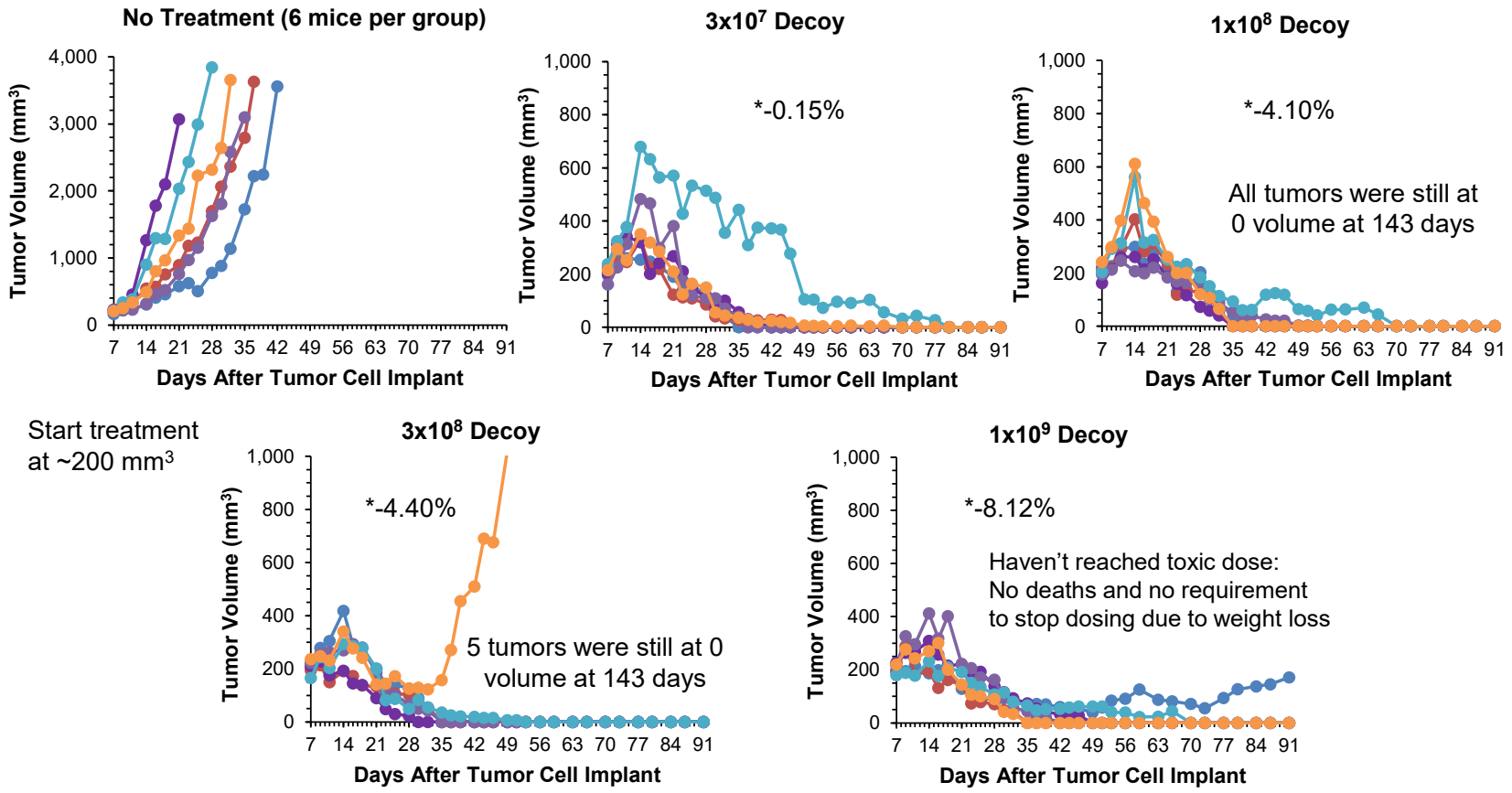
Combination With Anti-PD-1 Checkpoint Therapy Produces 100% Complete Responses With Hepatocellular Carcinoma



* Max % transient weight loss each week for combo treatment
No increase in toxicity with triple combo

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

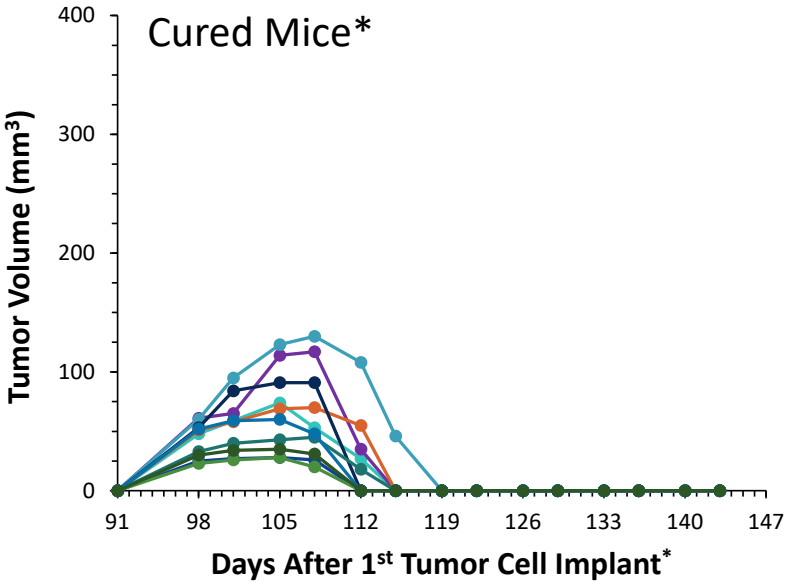
All treated animals also received a non-steroidal anti-inflammatory drug (NSAID) + Anti-PD-1



*Maximum transient body weight loss relative to start of treatment

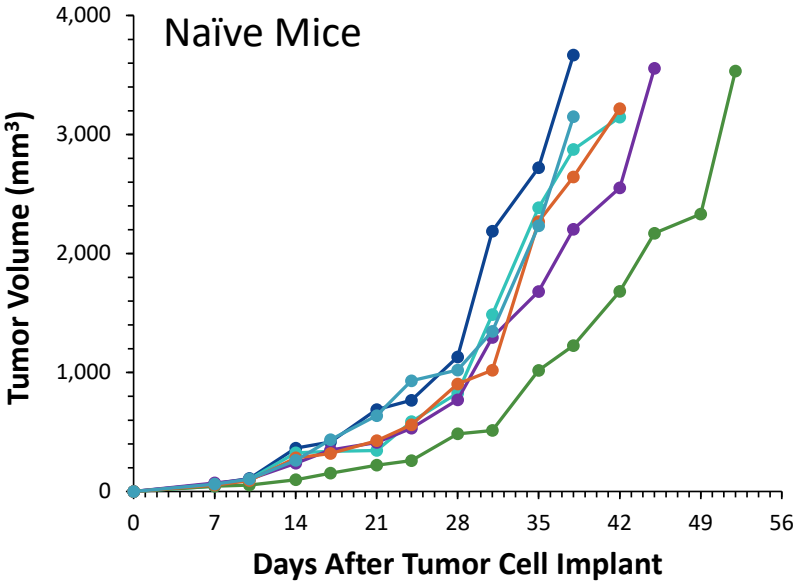
Mice Cured by Decoy + NSAID + Anti-PD-1 and Re-Challenged with Fresh HCC Tumor Cells Reject the Tumors (Immunological Memory)

Eleven Cured Mice were Re-Challenged with Fresh HCC Tumor Cells on Day 91 on the Opposite Flank from the First Challenge



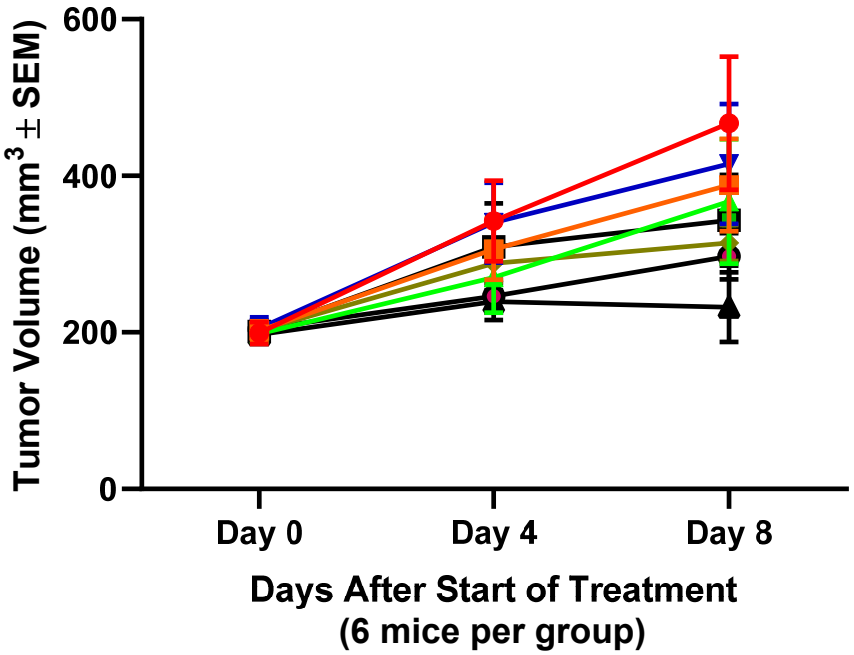
*All 1st challenge tumor sites remained tumor-free

Six Naïve Mice were Challenged with the Same Tumor Cells as the Cured Mice on the Same Day



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

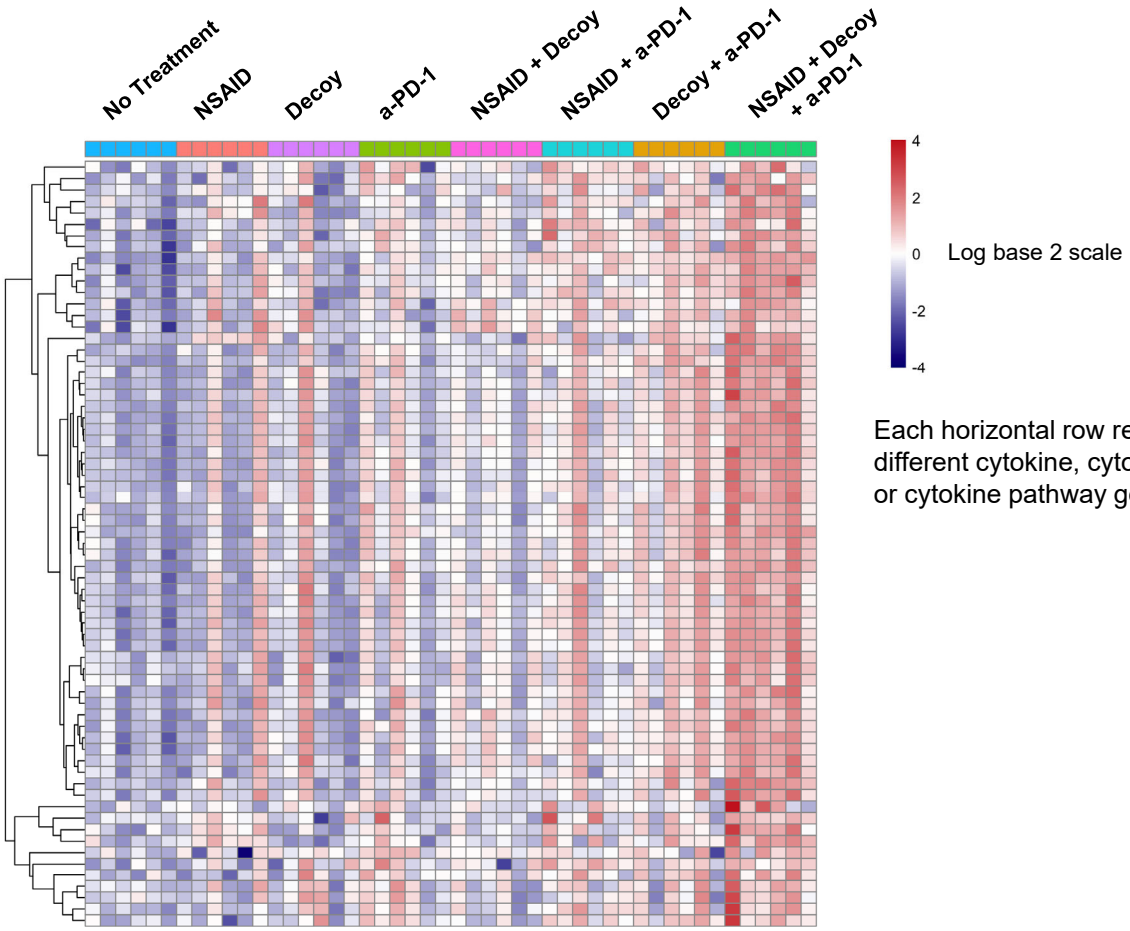
NT		0 / 6
NSAID	1.68	0 / 6
Decoy	1.61	0 / 6
a-PD-1	2.30	0 / 6
N + D	2.21	2 / 6
N + P	2.92	1 to 2 / 6
D + P	3.60	2 / 6
N + D + P	5.89	5 to 6 / 6

Number of long-term regressions per group

Systemic Administration of Decoy Bacteria (1 IV Dose), 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 mm^3 tumors were treated for 1 week



Each horizontal row represents a different cytokine, cytokine receptor or cytokine pathway gene

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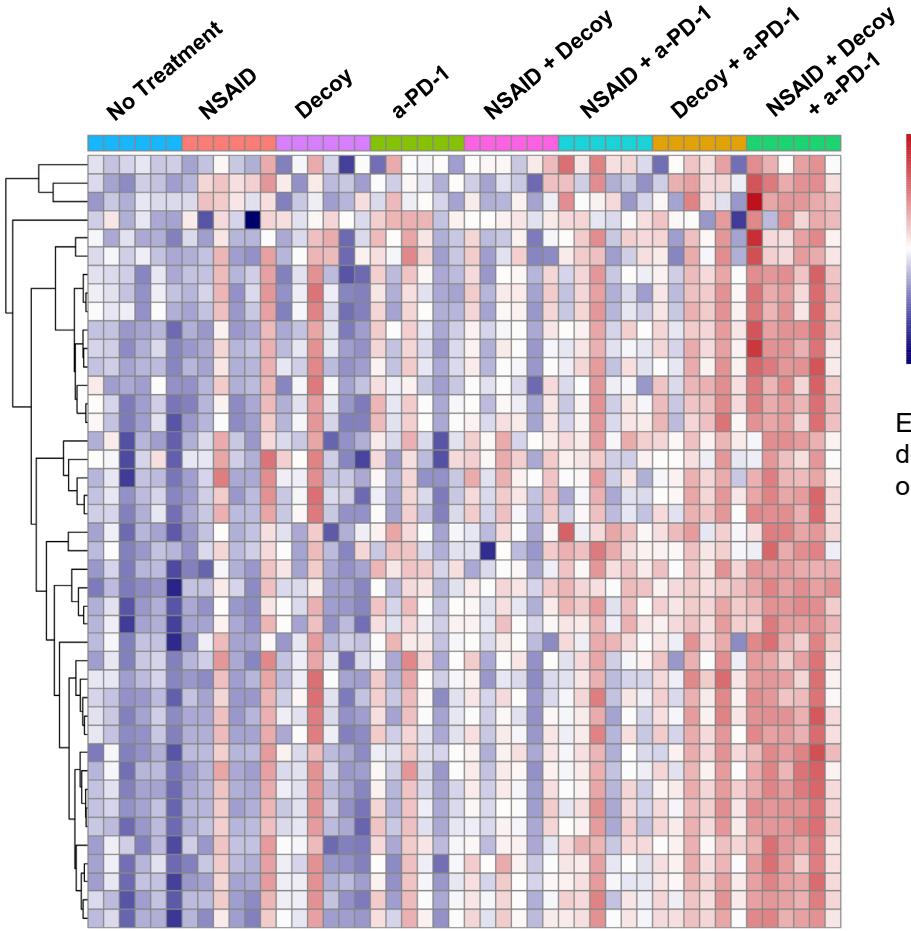
Systemic Administration of Decoy Bacteria (1 IV Dose), NSAID and Anti-PD-1 Induces Chemokine Immune Pathways in HCC Tumors

NanoString 770 gene expression analysis: Chemokines and Receptors in tumor

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

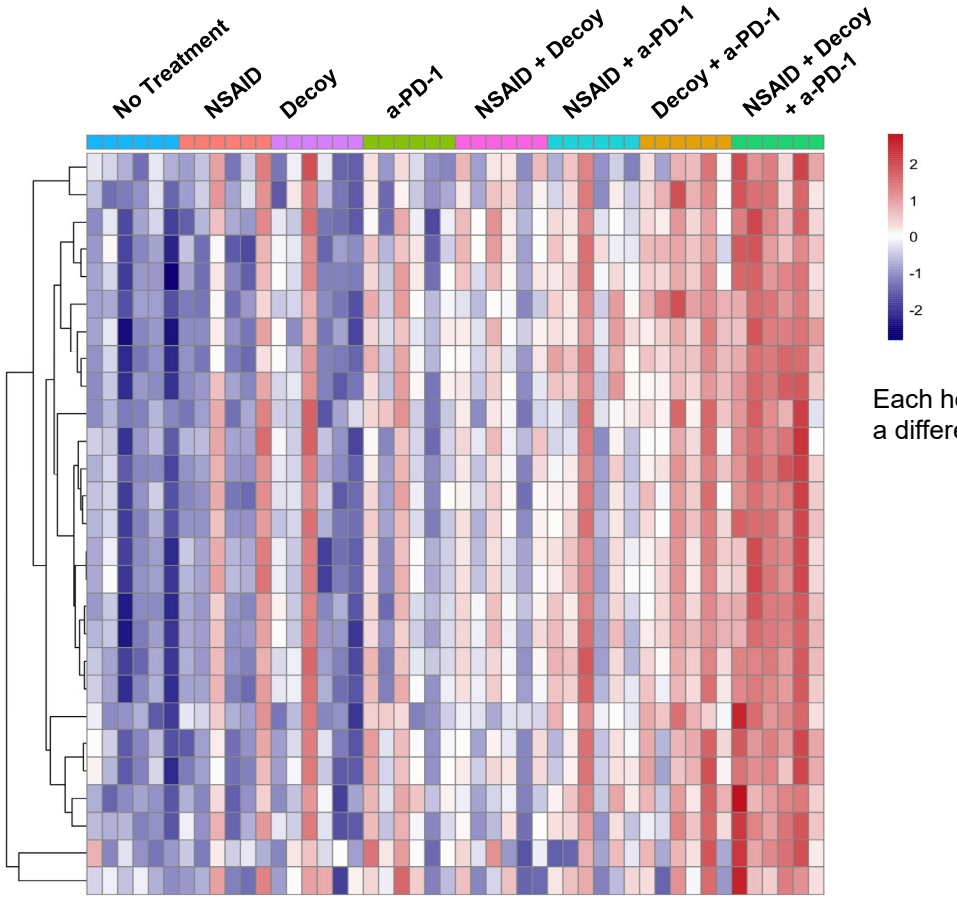


Each horizontal row represents a different chemokine, chemokine receptor or chemokine pathway gene

Systemic Administration of Decoy Bacteria (1 IV Dose), 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

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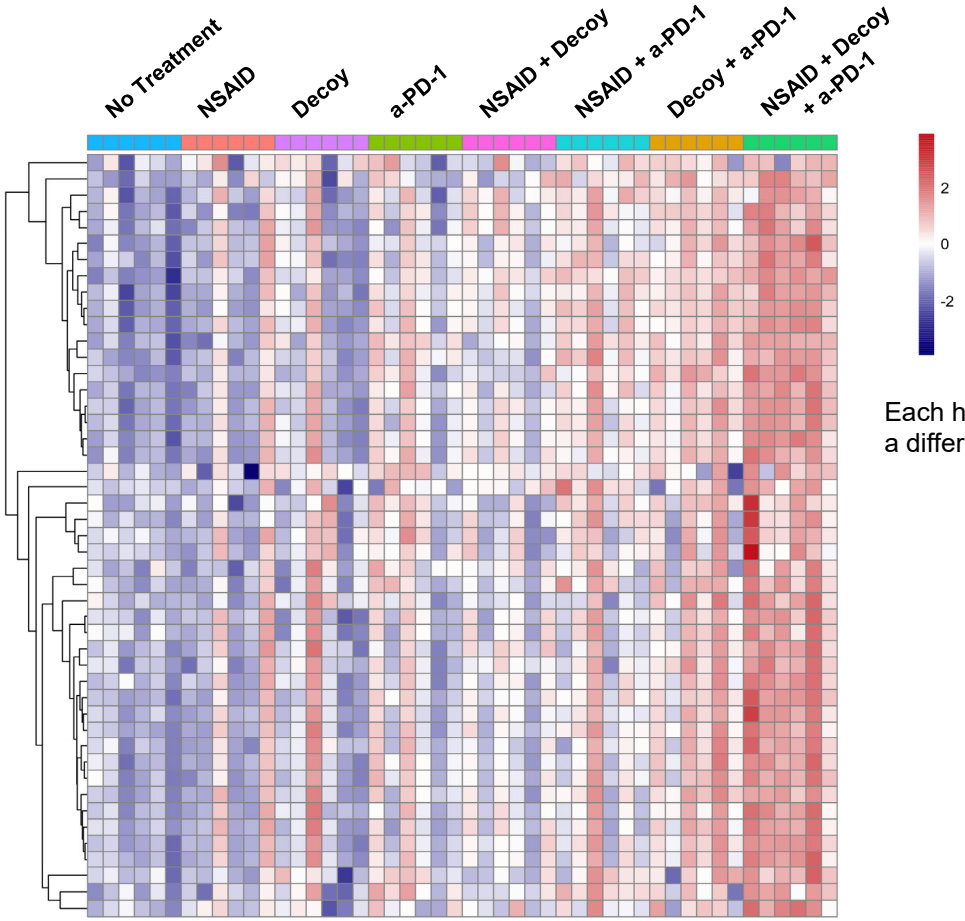
Systemic Administration of Decoy Bacteria (1 IV Dose), NSAID and Anti-PD-1 Induces Adaptive Immune Pathways in HCC Tumors

NanoString 770 gene expression analysis: Adaptive Immune response in tumor

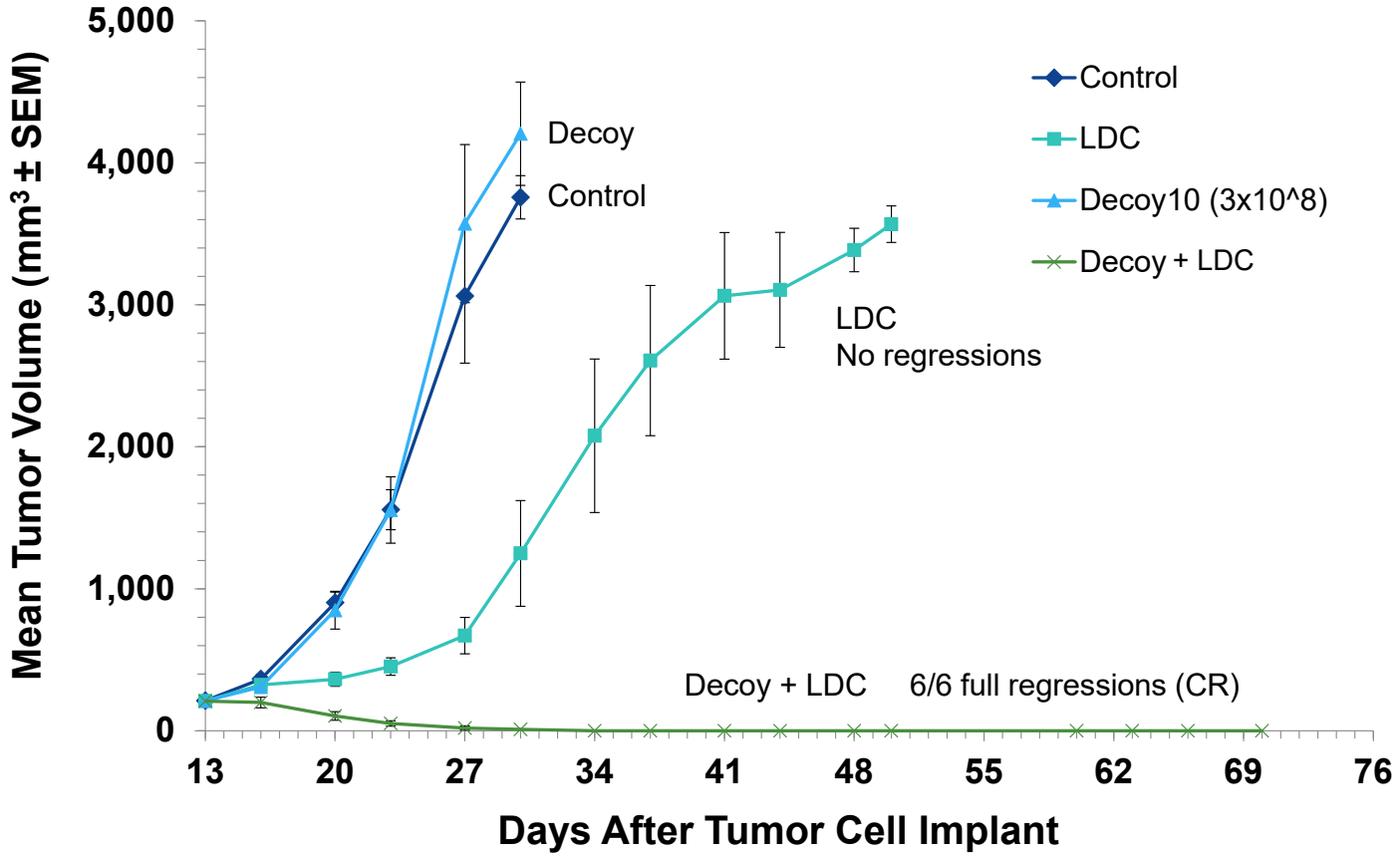
Mice with 200 mm^3 tumors were treated for 1 week



Each horizontal row represents a different adaptive pathway gene

Decoy Bacteria Synergize with Low-Dose Chemotherapy (LDC) to Safely Eradicate s.c. Mouse 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



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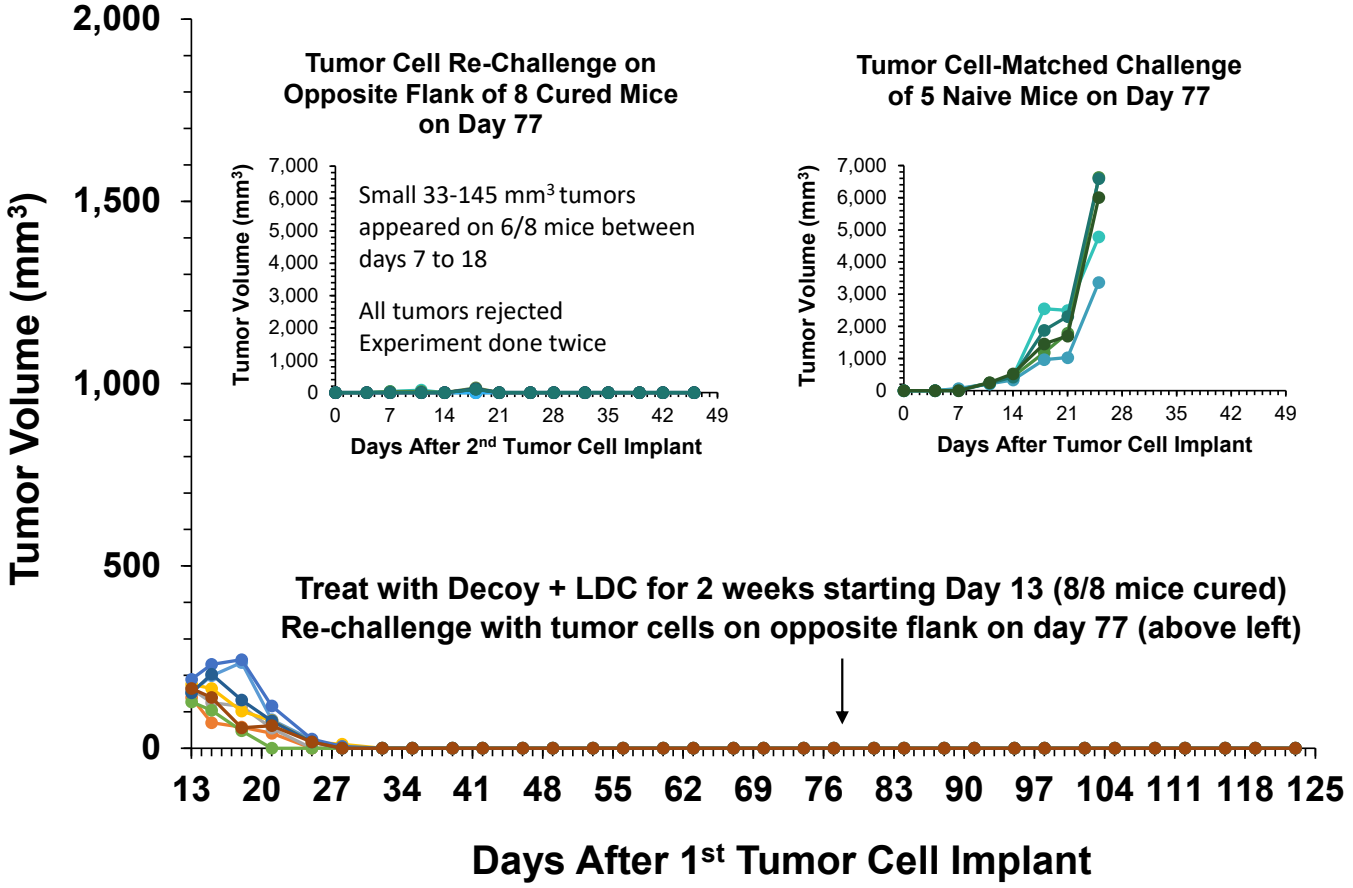
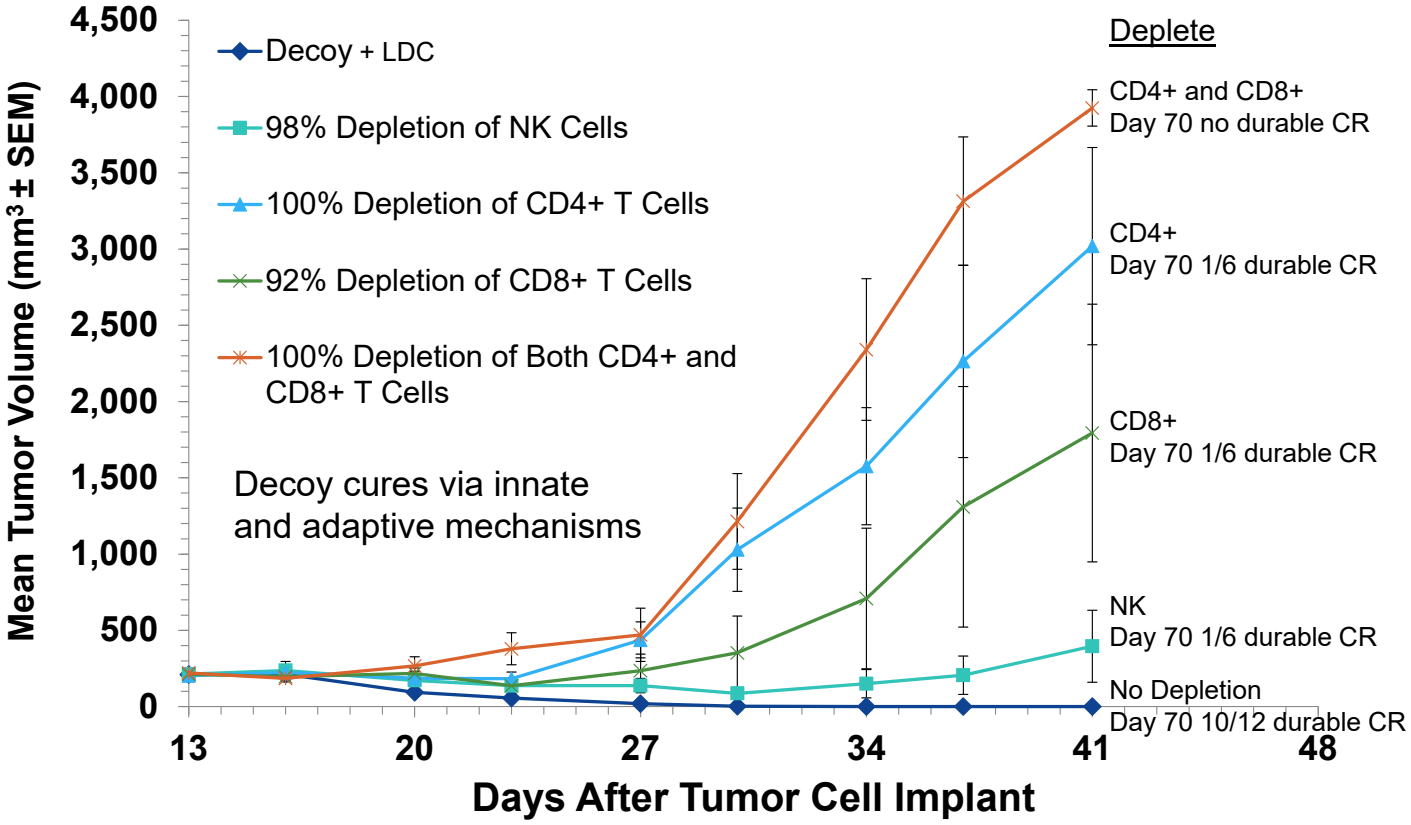
Synergistic Eradication of NHL Tumors by Decoy Technology is Reproducible, Durable and Induces Immunological Memory



High Percentage Eradication of s.c. NHL by Decoy + LDC Involves NK Cells, CD4+ and CD8+ T Cells (Innate and Adaptive)

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



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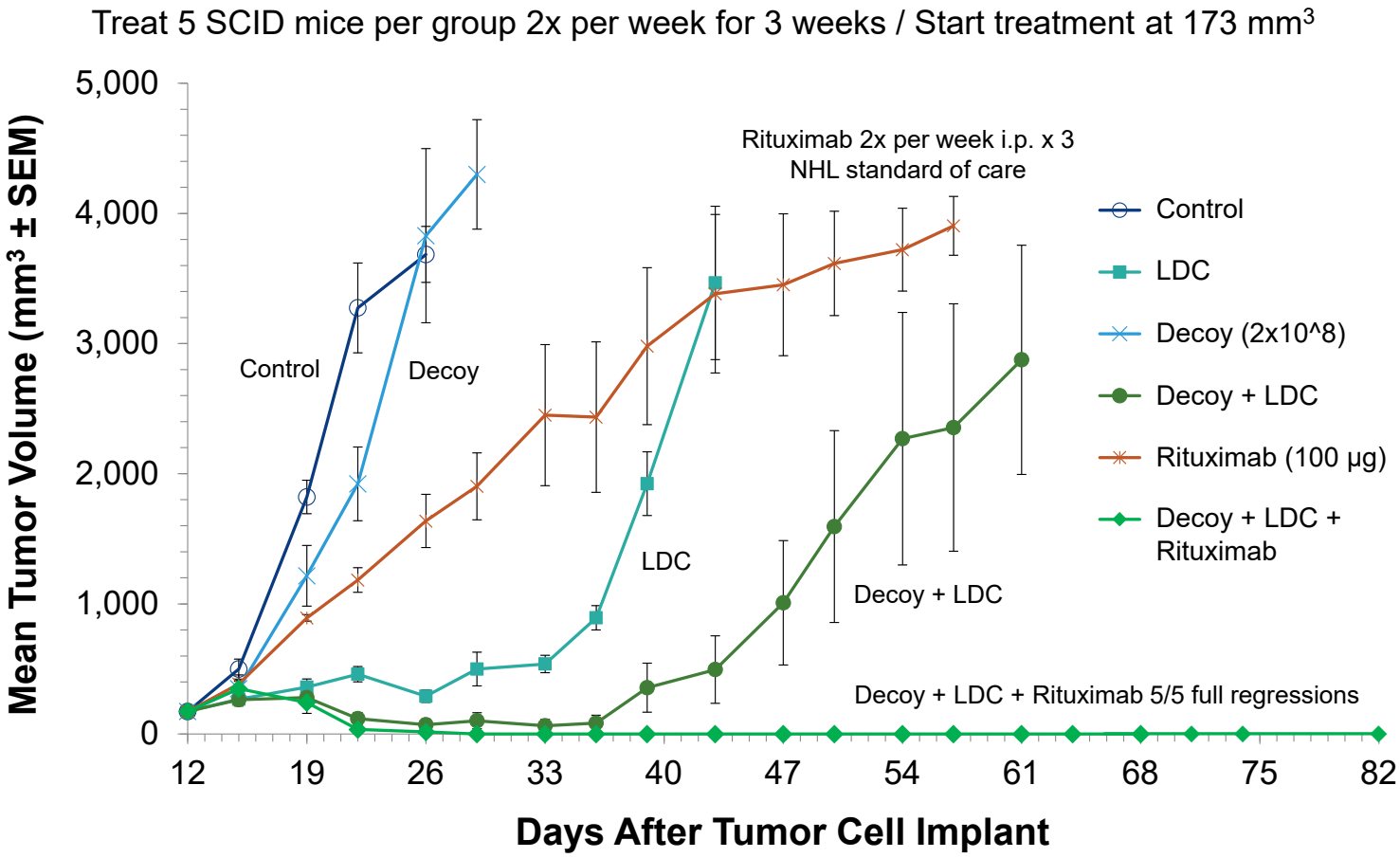
Decoy Technology Synergizes with Rituximab to Induce Eradications of s.c. Human NHL Xenografts via Innate Immunity



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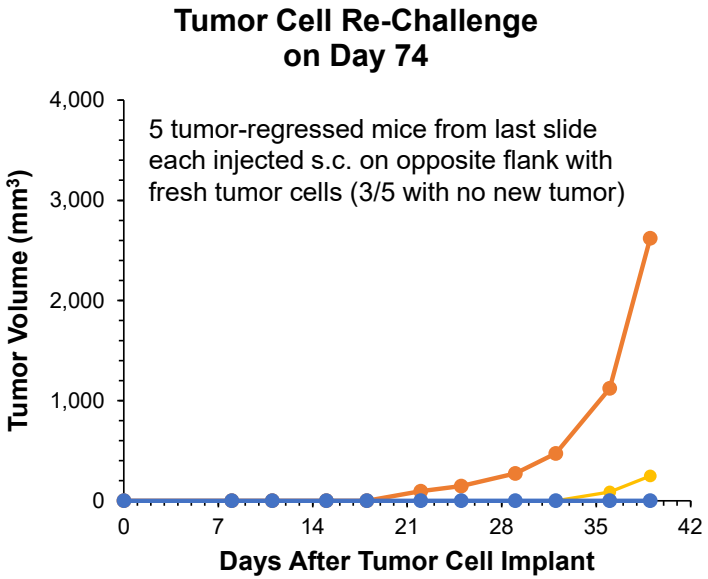
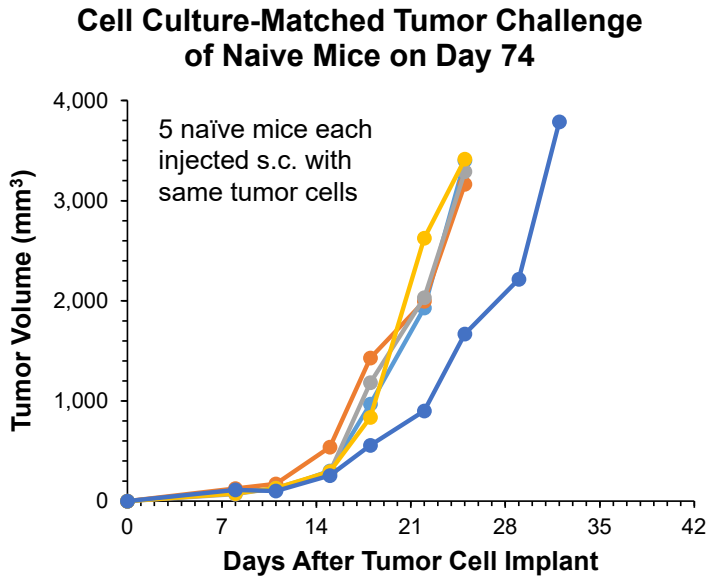
Decoy Technology can Synergize with Rituximab to Induce Immunological Memory Via the Innate Immune System

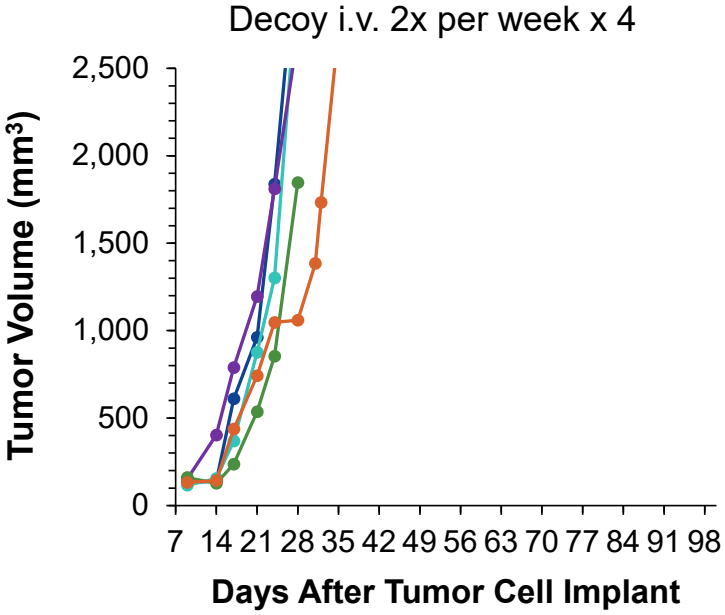




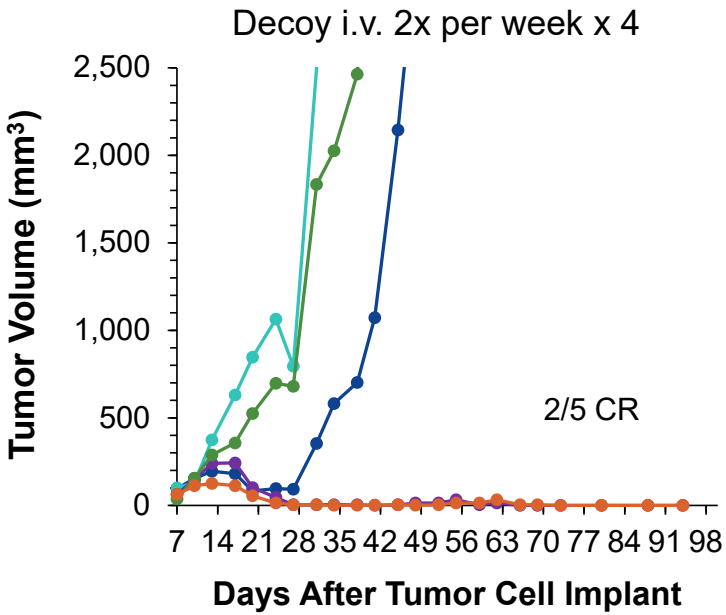
- Tumor rejection by immunological memory via the innate immune system alone is very rare, but consistent with a multiple danger signal mechanism
- Results suggest that Decoy technology may synergize with other marketed ADCC mechanism-based, targeted antibody therapeutics (~12 on market)

Preliminary Studies Suggest: Introduction of a Foreign Antigen Sensitizes Mouse Tumors to Eradication by Single Agent IV Decoy Bacteria

s.c. mouse tumor not responsive to Decoy



s.c. mouse tumor expressing a foreign antigen



All treatments started Day 10-12 with ~170 mm^3 tumors

Repeat with immune profiling for single agent mechanism of action

Indaptus Summary

- Decoy technology safely primes or activates innate & adaptive immune pathways, leading to single agent anti-tumor activity and combination-mediated eradication of established tumors in pre-clinical models
- Decoy technology induces both innate and adaptive anti-tumor immunological memory
- Decoy technology does not require targeting with or to a specific tumor antigen, but has the potential for improvement via tumor antigen provision or targeting
- Phase 1 initiation planned in 2022
- Acknowledgements:
  - AntiCancer, Crown Bioscience, HD Biosciences, Molecular Diagnostic Services, Pacific BioLabs, Southern Research Institute, WuXi AppTec