Targeting the Lymph Nodes to Orchestrate Anti-tumor Immunity

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Koch Institute Symposia: Cancer Vaccines

June 23, 2023

Forward Looking Statement

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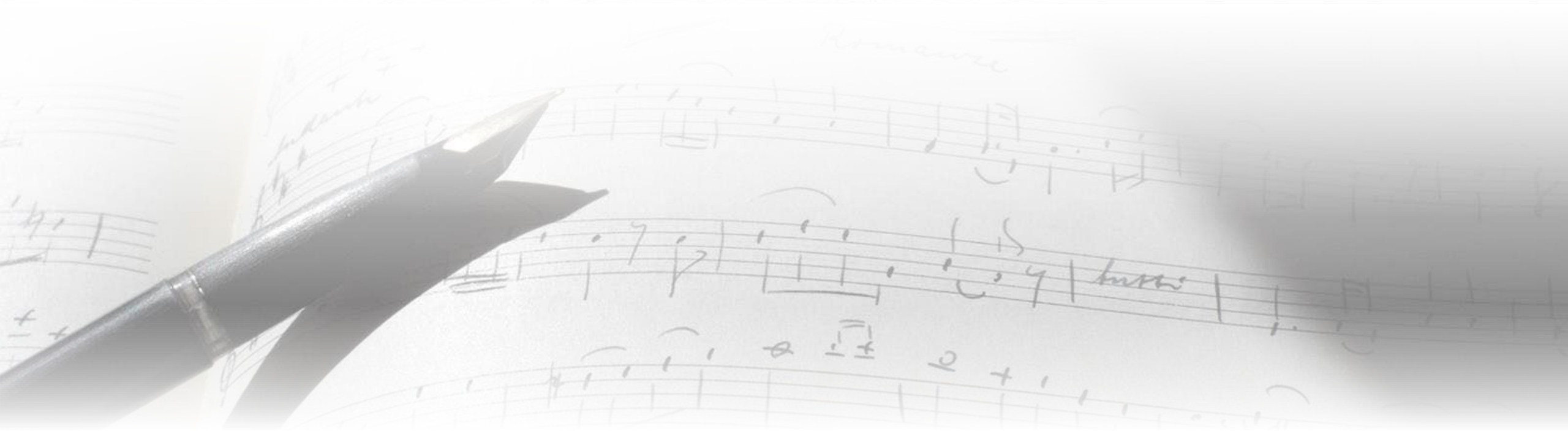
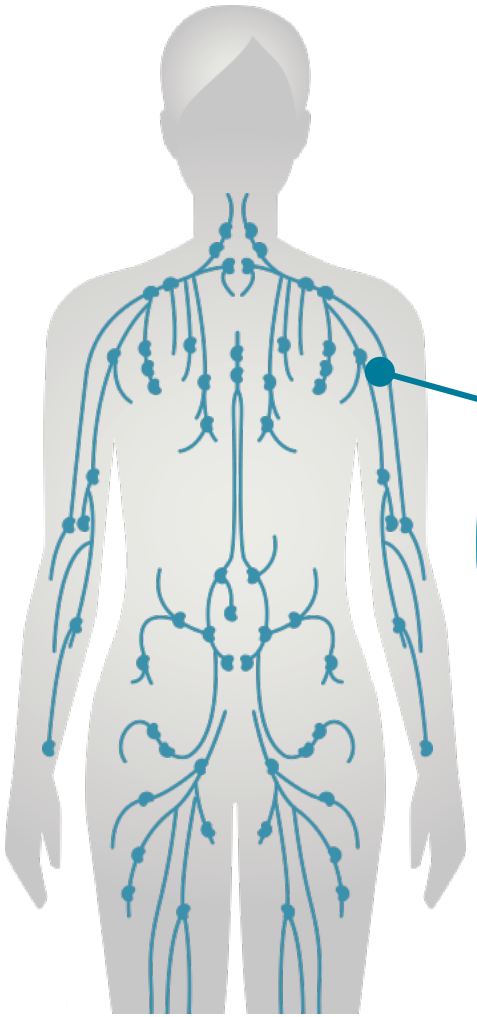
How can Lymph Node Targeting Orchestrate Therapeutic Anti-tumor Immunity?

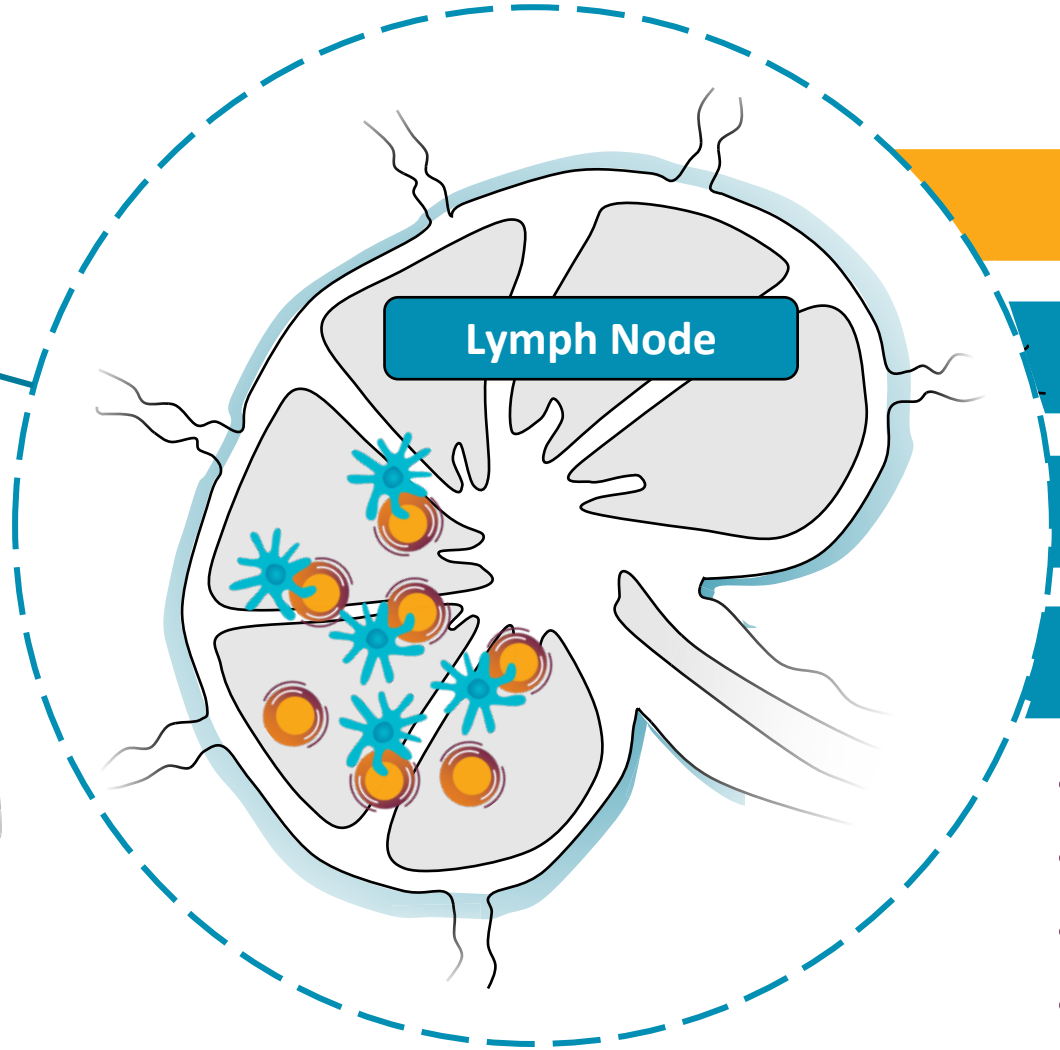


1) **The AMP Platform**: Designing a system to target immune agents to **lymph nodes**

2) **ELI-002:** Boosting **Endogenous Anti-tumor Immunity** against **mKRAS**

Immune Orchestration in the Lymph Nodes





The Immune "School House"

Numerous Immune Cells

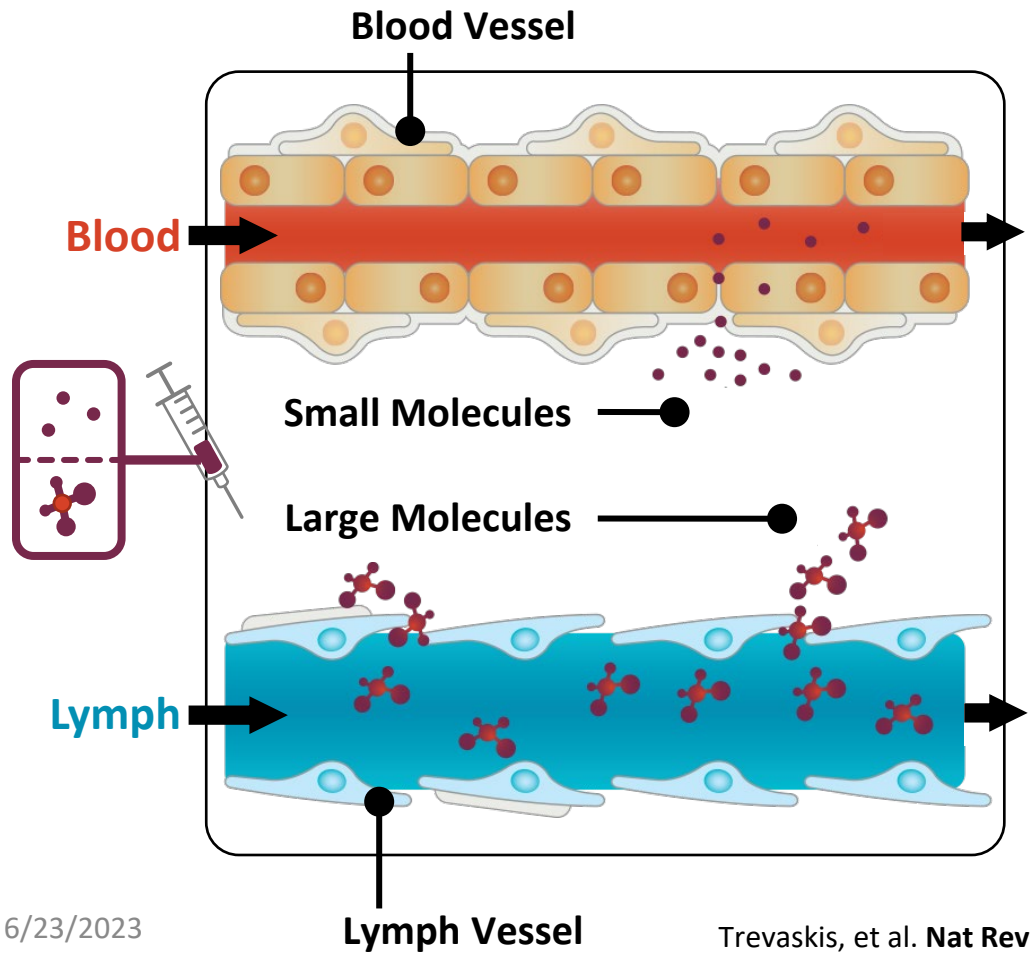
Response Coordination

APC : T Cell Interaction

- **Expansion**
- **Phenotype**
- **Effector Function**
- **Anti-tumor Activity**

“Albumin-hitchhiking” Reprograms Delivery of Vaccines and to Target Lymph Nodes

Tissue Injection Site: Anatomy / Physiology Dictates Distribution



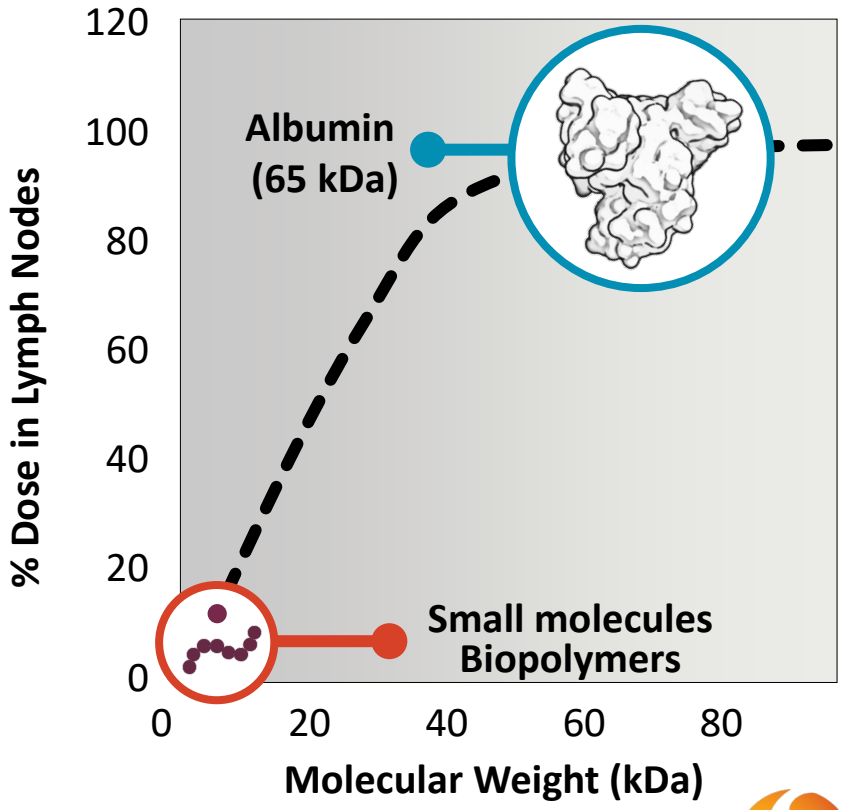
Systemic Circulation

- Poor Delivery
- Reduced Immunogenicity
- Toxicity

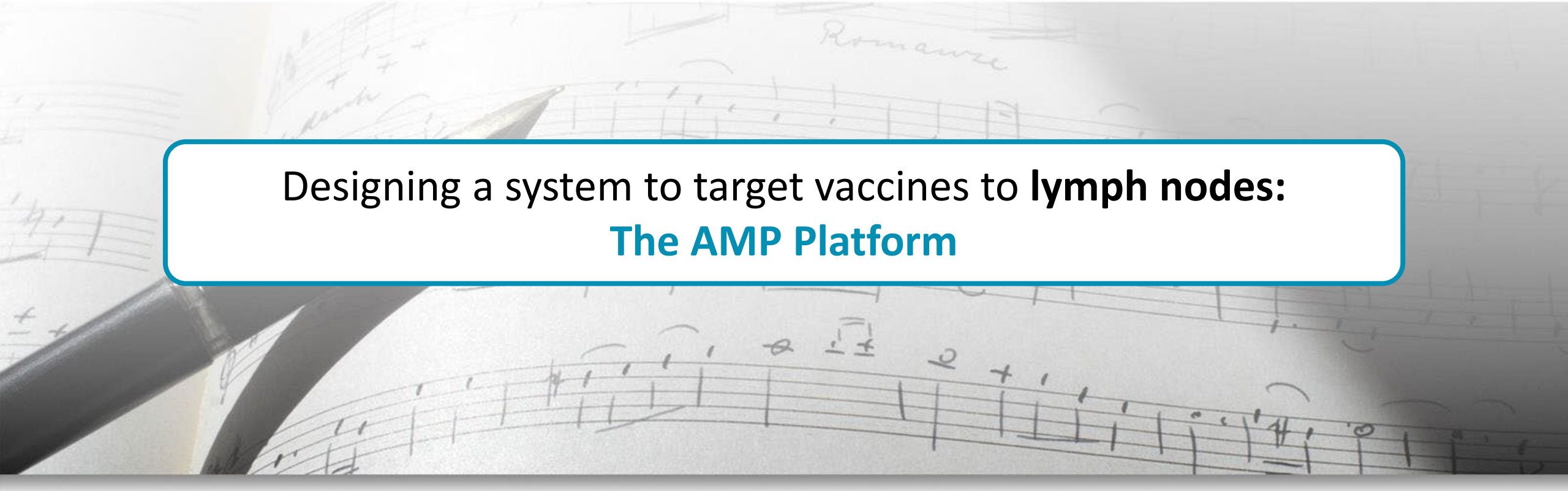
Lymph Nodes

- Immune Cell Delivery
- Enhanced Immunogenicity
- Safety

Molecular Size Drives Lymphatic Targeting



Trevaskis, et al. **Nat Rev Drug Discovery** 2015; Yousefpour, et al. **Nat Rev Bioengineering** 2023

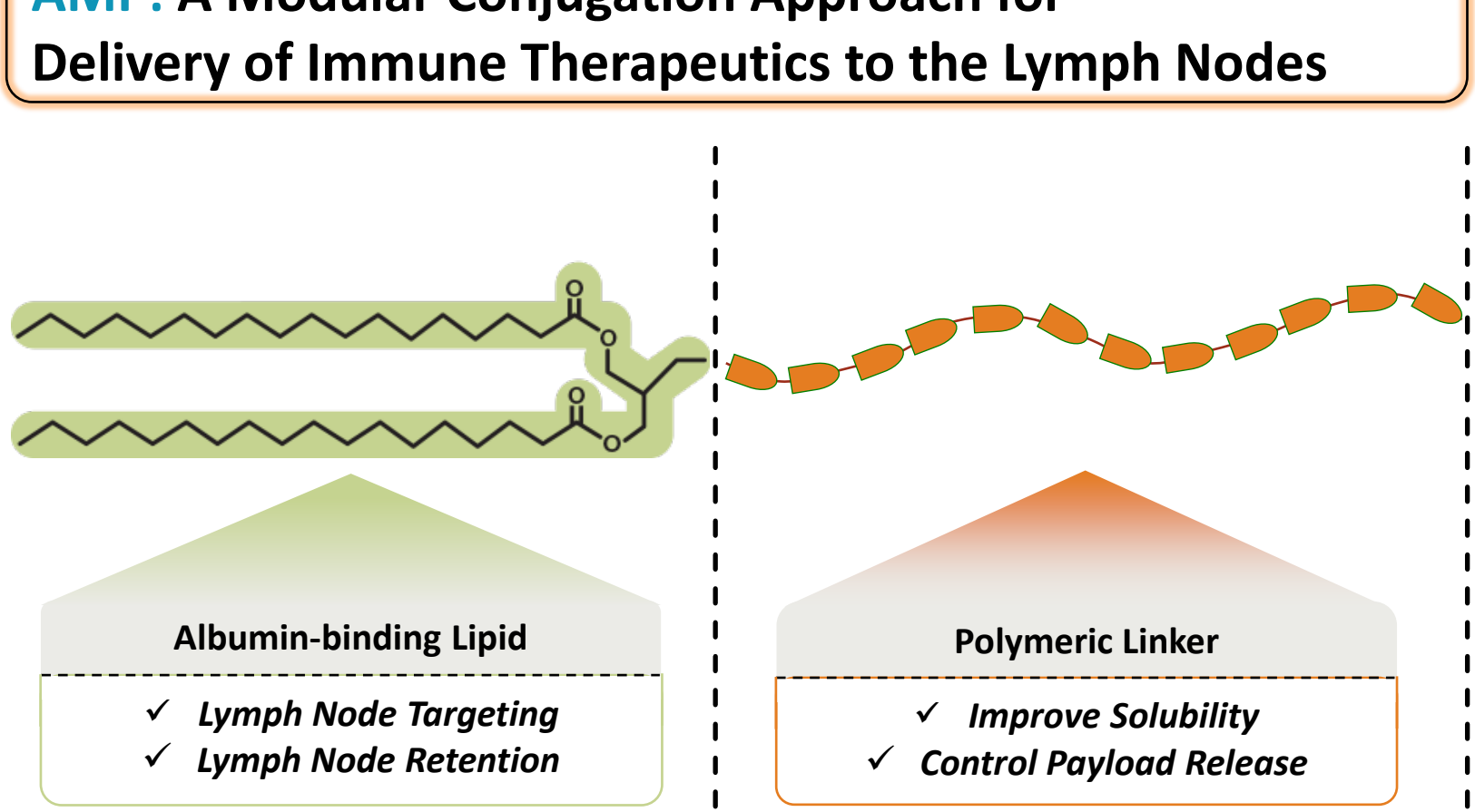


Designing a system to target vaccines to **lymph nodes:**

The AMP Platform

Amphiphile (AMP) Platform Enables Lymph Node Delivery of Vaccines with Modular Application

AMP: A Modular Conjugation Approach for Delivery of Immune Therapeutics to the Lymph Nodes

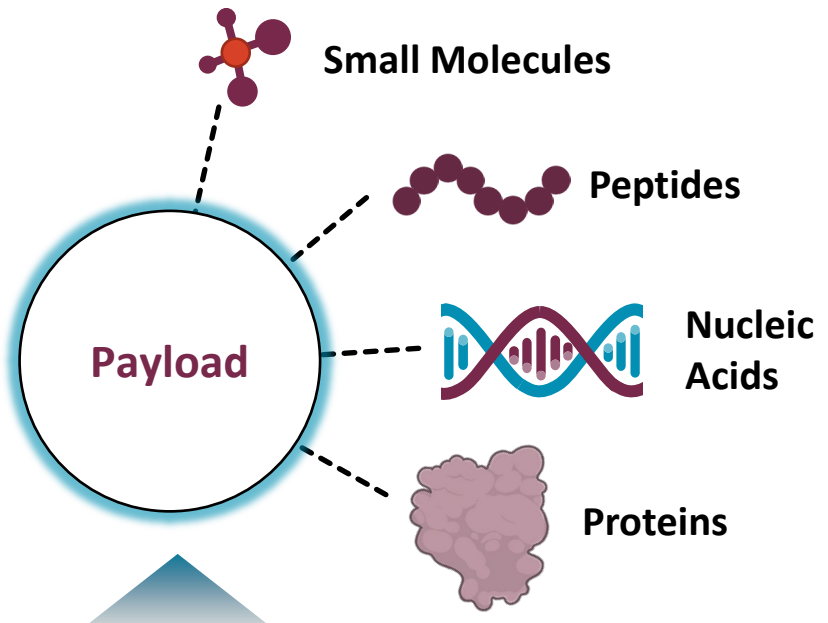


Albumin-binding Lipid

- ✓ *Lymph Node Targeting*
- ✓ *Lymph Node Retention*

Polymeric Linker

- ✓ *Improve Solubility*
- ✓ *Control Payload Release*

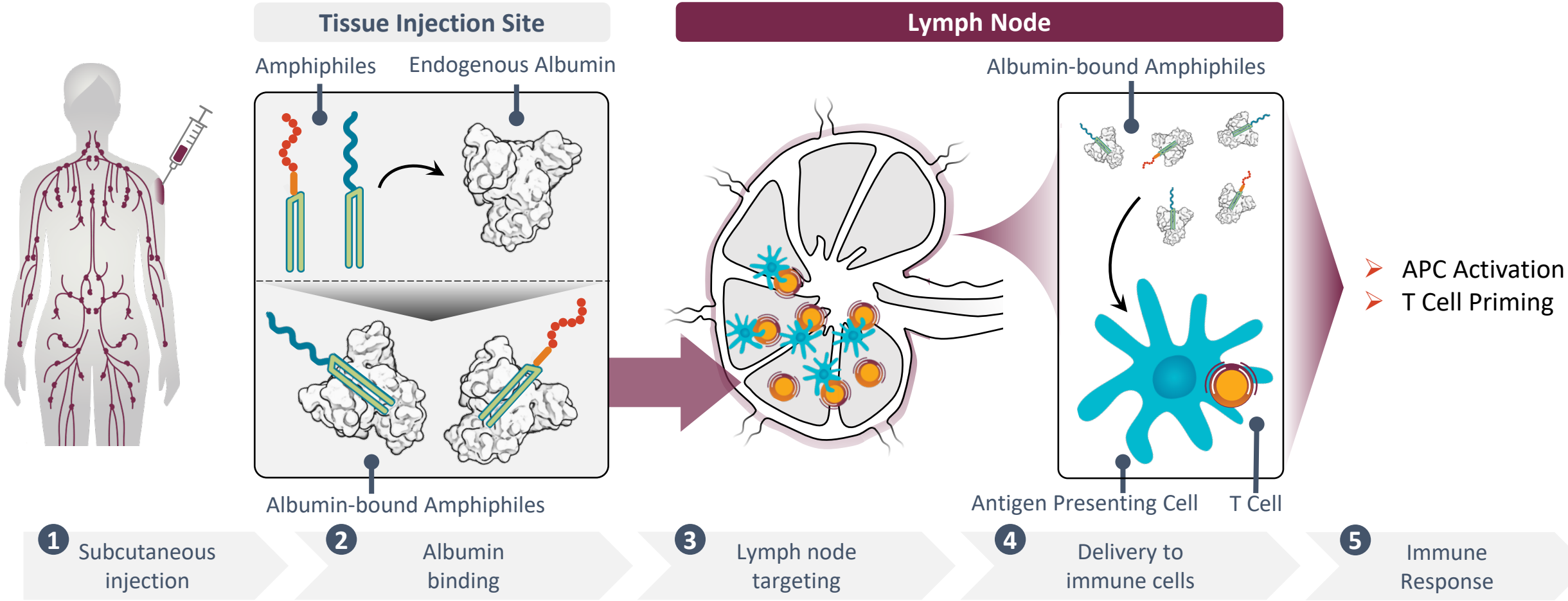


Payload

- ✓ *Antigens*
- ✓ *Adjuvants*

Liu, Irvine, et al. **Nature** 2014, Ma, Irvine, et al. **Science** 2019, Hartwell, Irvine, et al. **Sci Trans Med** 2022

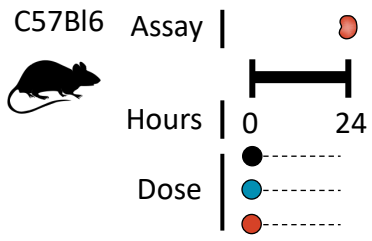
Targeting the Lymph Nodes with AMP to Orchestrate Immunity



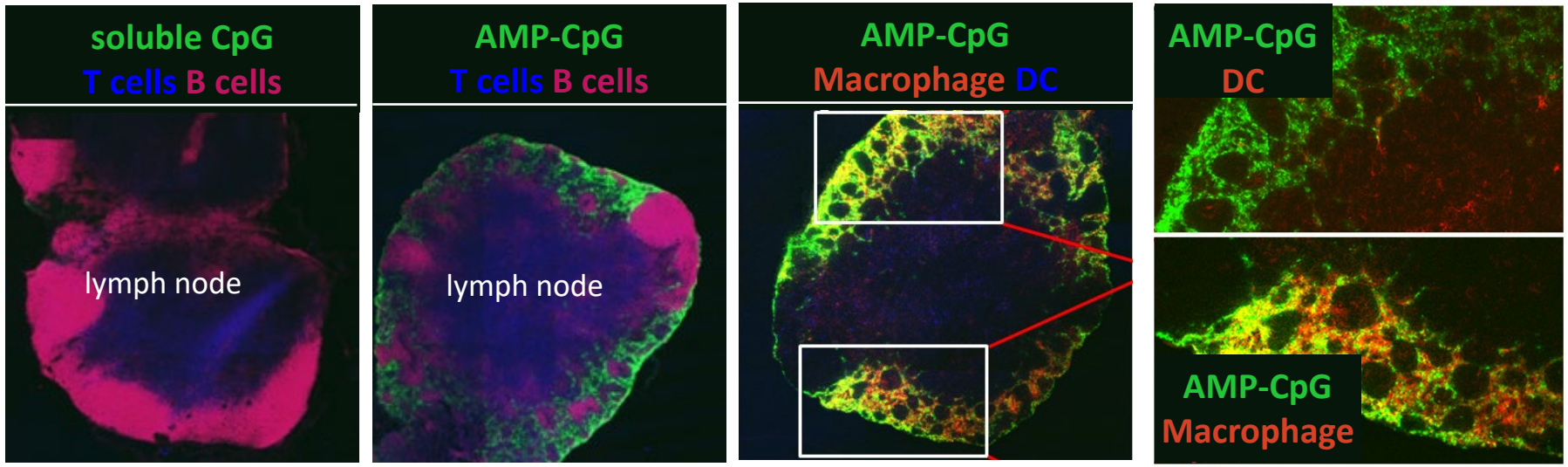
Liu, Irvine, et al. **Nature** 2014, Ma, Irvine, et al. **Science** 2019, Hartwell, Irvine, et al. **Sci Trans Med** 2022

Amphiphiles Target the Lymph Nodes for Efficient Uptake into Resident APCs

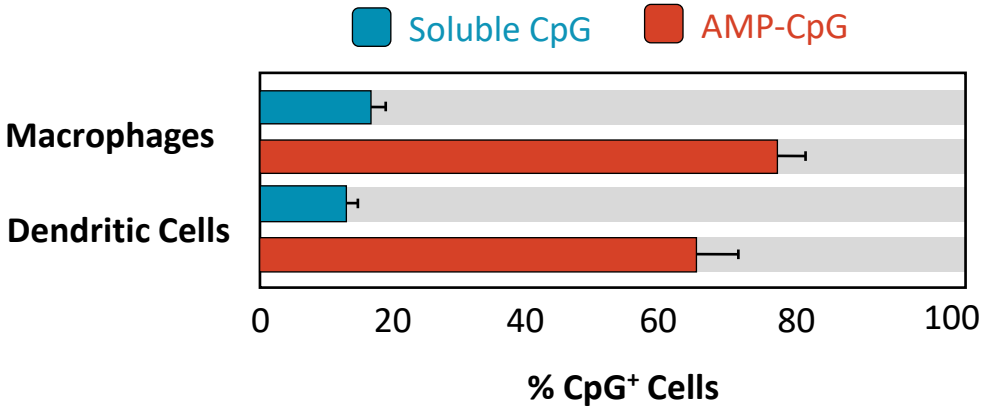
Experimental Schema:



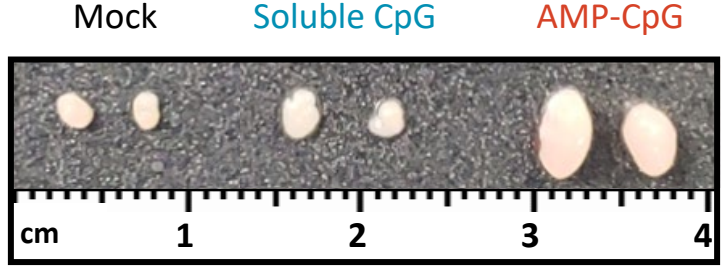
- Mock Dose
- Soluble CpG
- AMP-CpG
- LN Collection



CpG Uptake in Antigen Presenting Cells: Lymph Node



Lymph Node Enlargement: Lymph Node

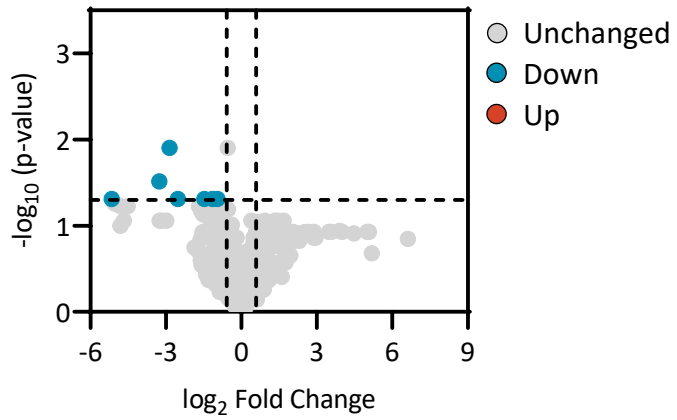


Liu, Irvine, et al. **Nature** 2014

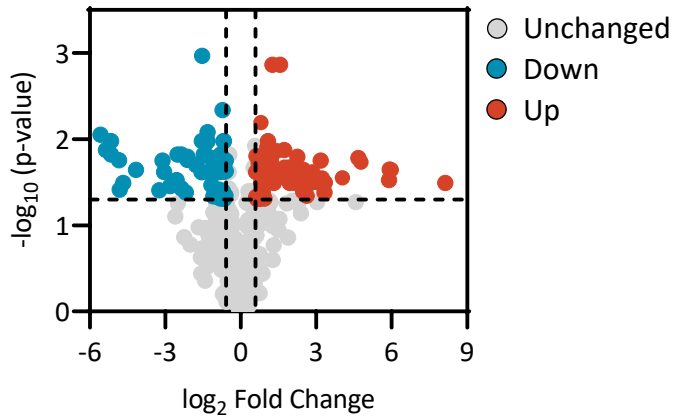
AMP-CpG Induces Potent Transcriptional Reprogramming of the Lymph Node Immune Response

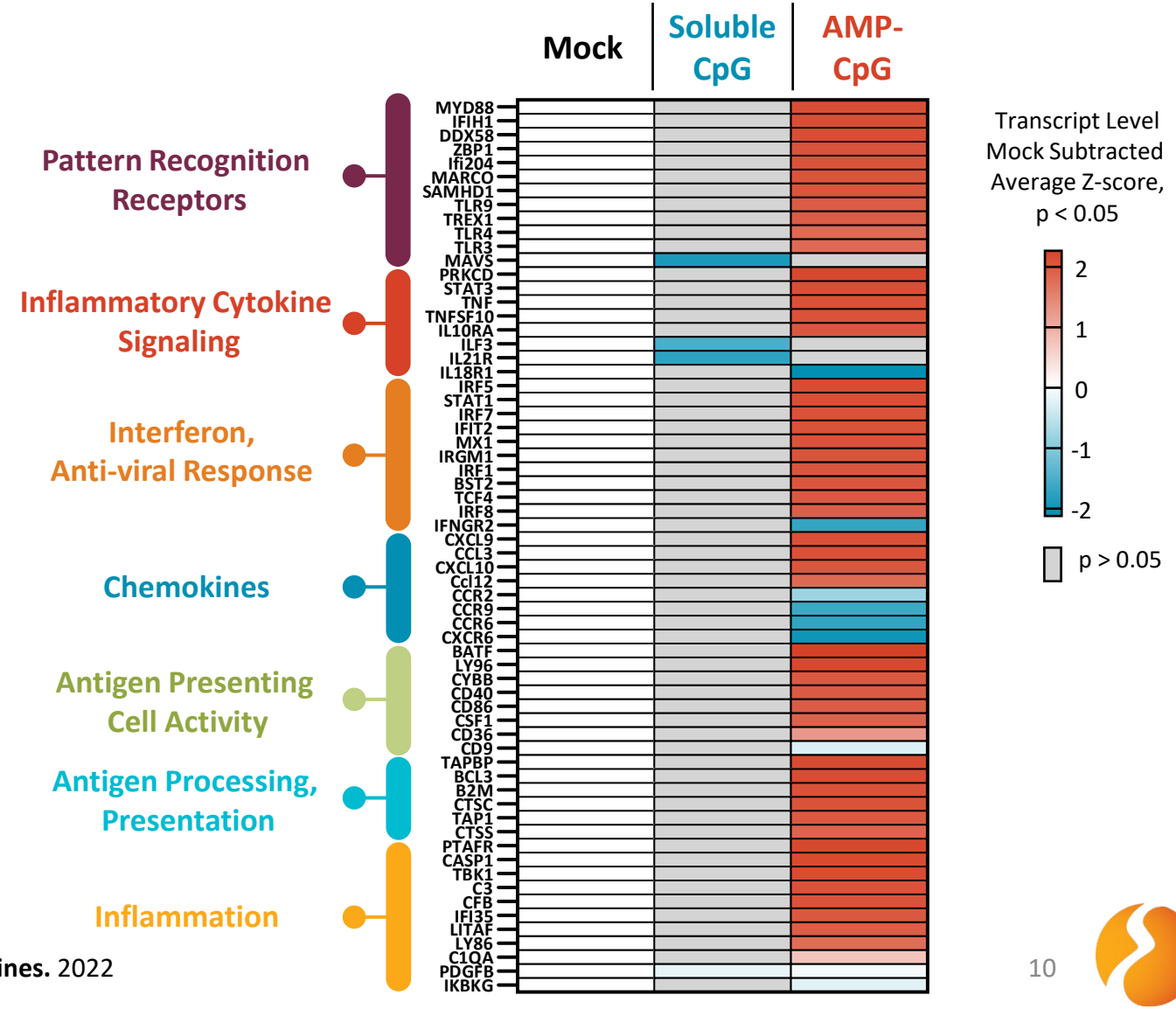
Lymph Node **Transcriptomics: 24 hours**

Soluble CpG: 24 hours



AMP-CpG: 24 hours

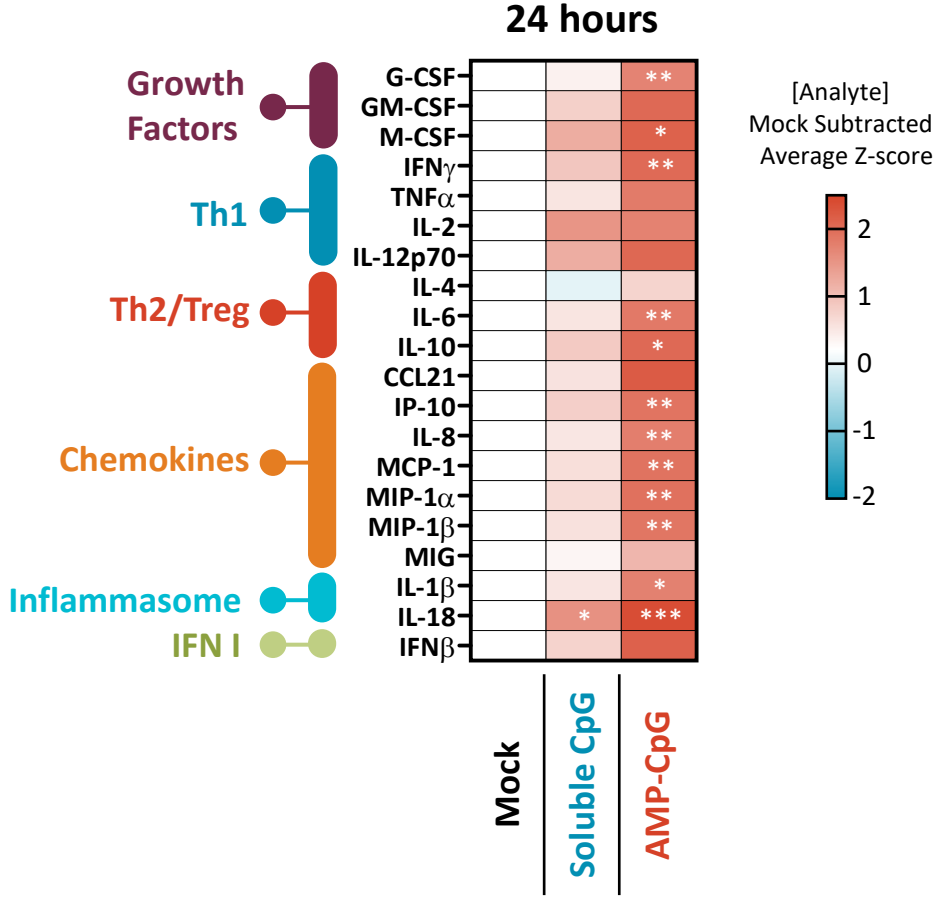




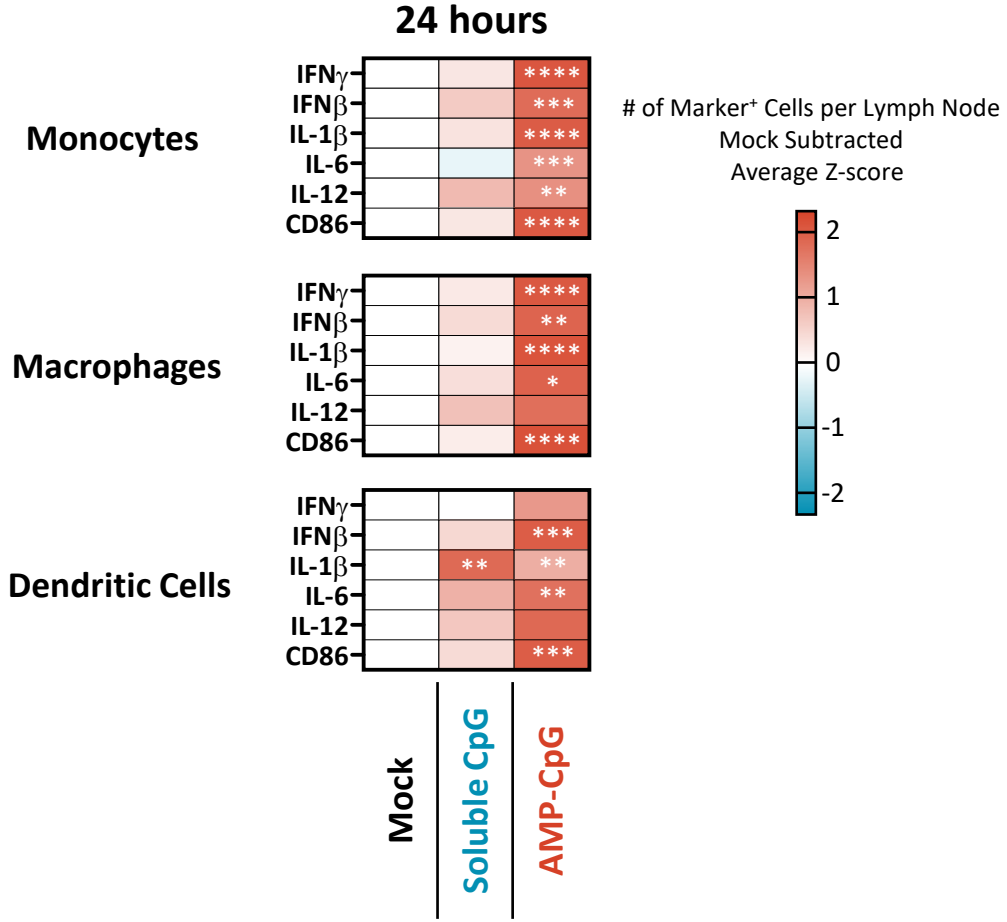
Steinbuck, et al. **Science Advances**. 2021; Seenappa, et al. **NJP Vaccines.** 2022

AMP-CpG Induces Coordinated Immune Activation in Draining Lymph Nodes

Lymph Node **Proteomics:**



Lymph Node **Innate Cell Recruitment and Activation:**

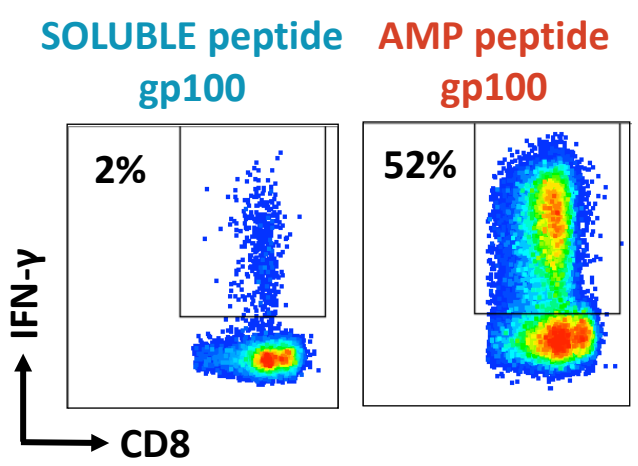


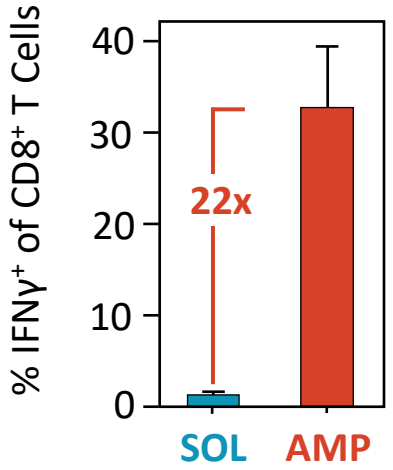
Steinbuck, et al. **Science Advances**. 2021; Seenappa, et al. **NJP Vaccines.** 2022

The AMP Platform Efficiently Targets the Lymph Nodes

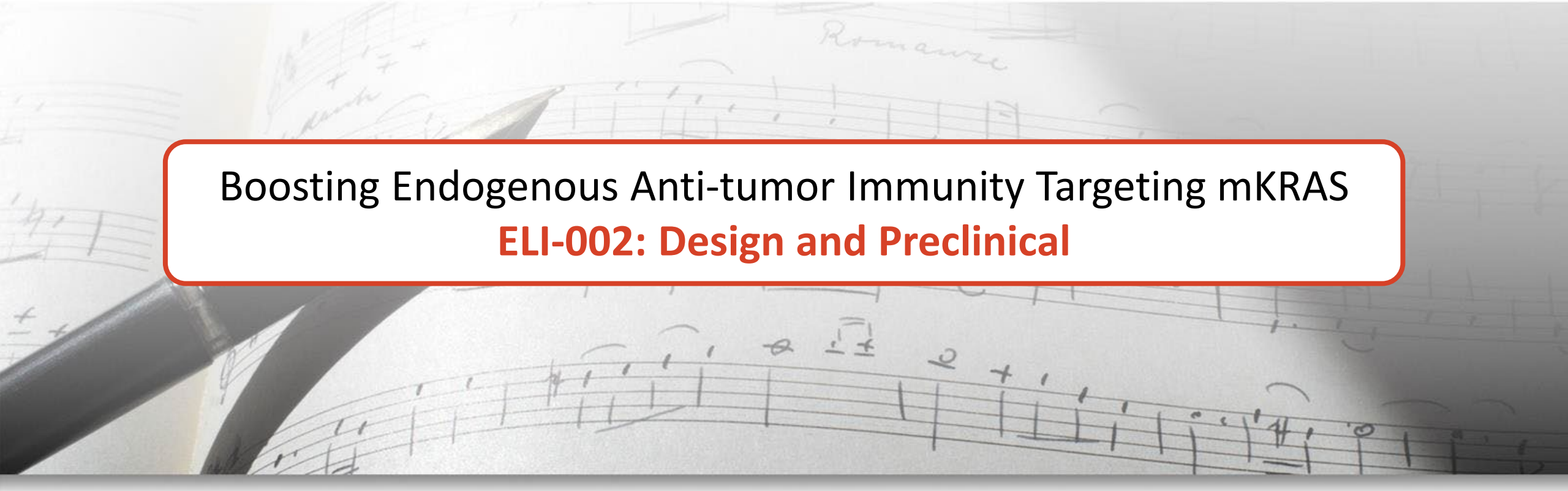
- Enhanced Lymph Node Delivery and Retention
- Increased Uptake into APCs
- Potent APC Activation
- Inflammatory Transcriptional Programming
- Robust Cytokine/Chemokine Milieu

Enhanced Anti-tumor T cell Responses





Liu, Irvine, et al. **Nature** 2014; Moynihan, Irvine, et al. **Nature Medicine** 2016



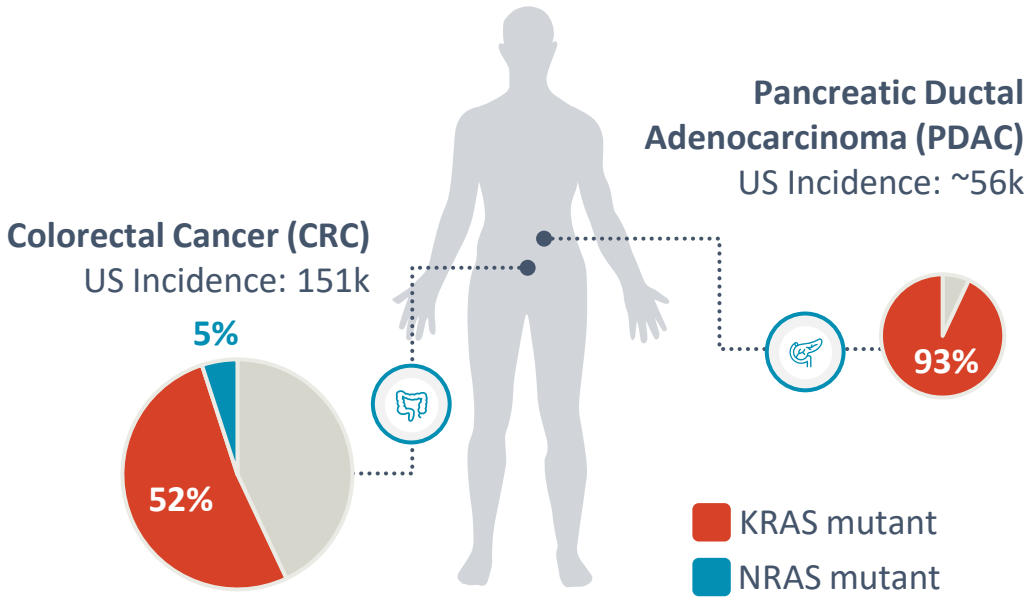
Boosting Endogenous Anti-tumor Immunity Targeting mKRAS

ELI-002: Design and Preclinical

Why Immunotherapy to Target mutant KRAS?

1 Mutant KRAS Drives 25% of Solid Human Cancers

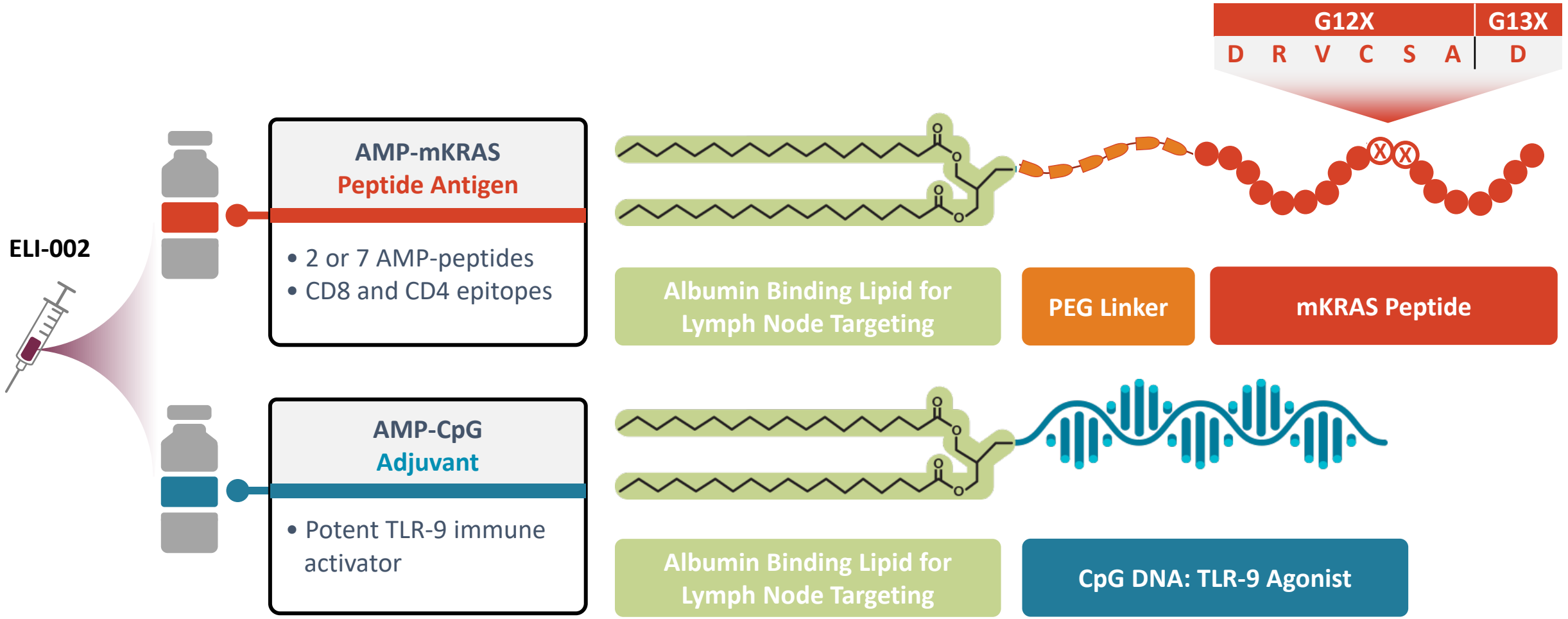
- **Prevalent** among numerous tumor types
- Overall **poor clinical prognosis**
- **Limited therapeutic options**



2 Mutant KRAS is a Promising Tumor Antigen

- **Truncal**: mutations occur early, expressed uniformly in tumor cells
- **Driver**: mKRAS signaling is required for tumor growth and survival
- **Highly prevalent**: involved in ~25% of solid tumors
- **Public neoantigen**: not centrally tolerized, cognate TCRs present in naïve repertoire
- **Broad HLA presentation**: potential off-the-shelf use in diverse patient population
- **Proven Clinical MOA**: mKRAS-specific T cells known to mediate anti-tumor efficacy
- **Multi-targeting potential**: broad recognition of mKRAS variants to prevent escape

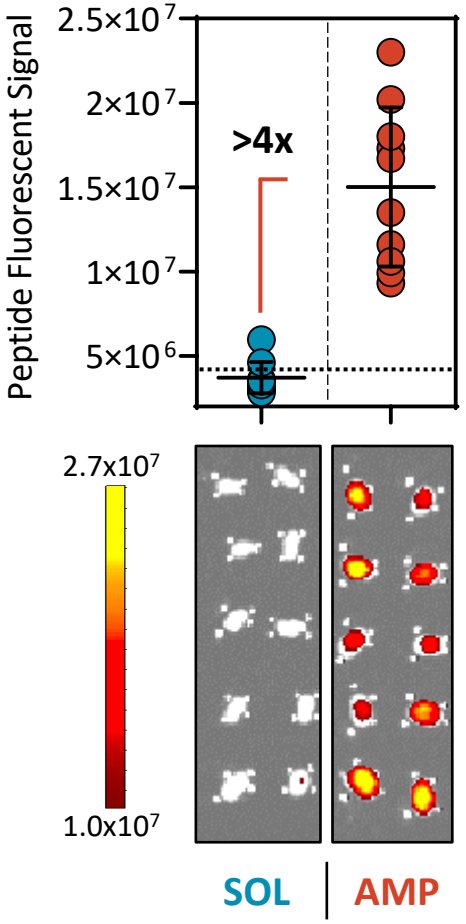
ELI-002: a Lymph Node Targeted Therapeutic Vaccine for mKRAS-driven Solid Cancers



ELI-002 Efficiently Targets the Lymph Nodes to Induce Potent Functional mKRAS-specific T cell Responses

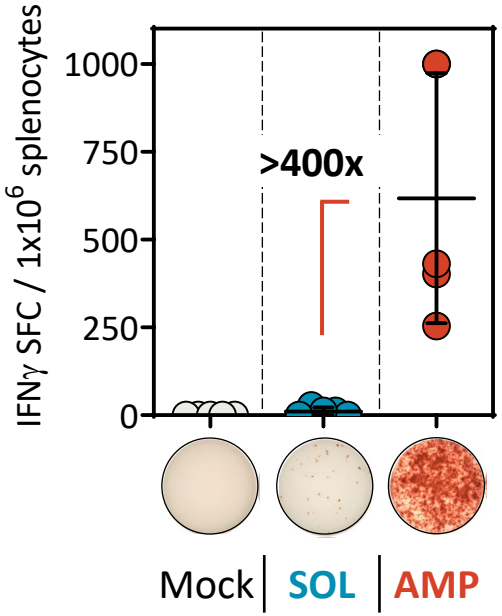
Peptide Targeting: 24h

Lymph Node



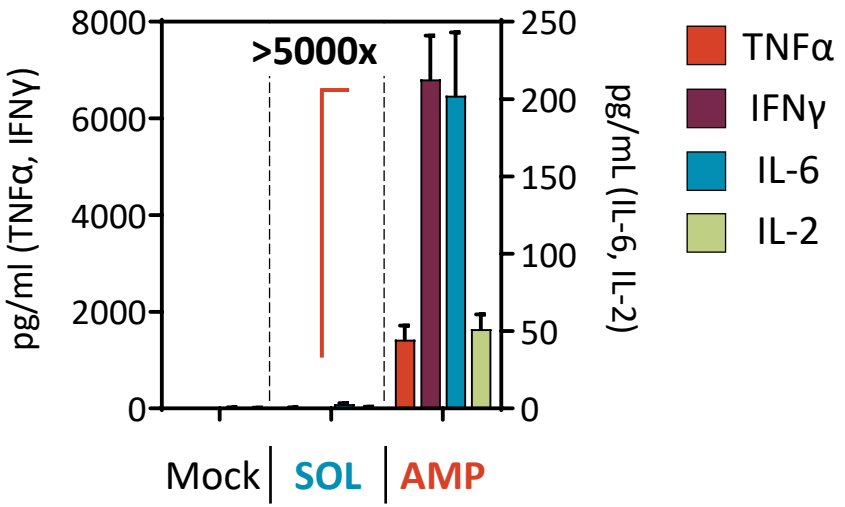
T Cell Response: G12D

Spleen

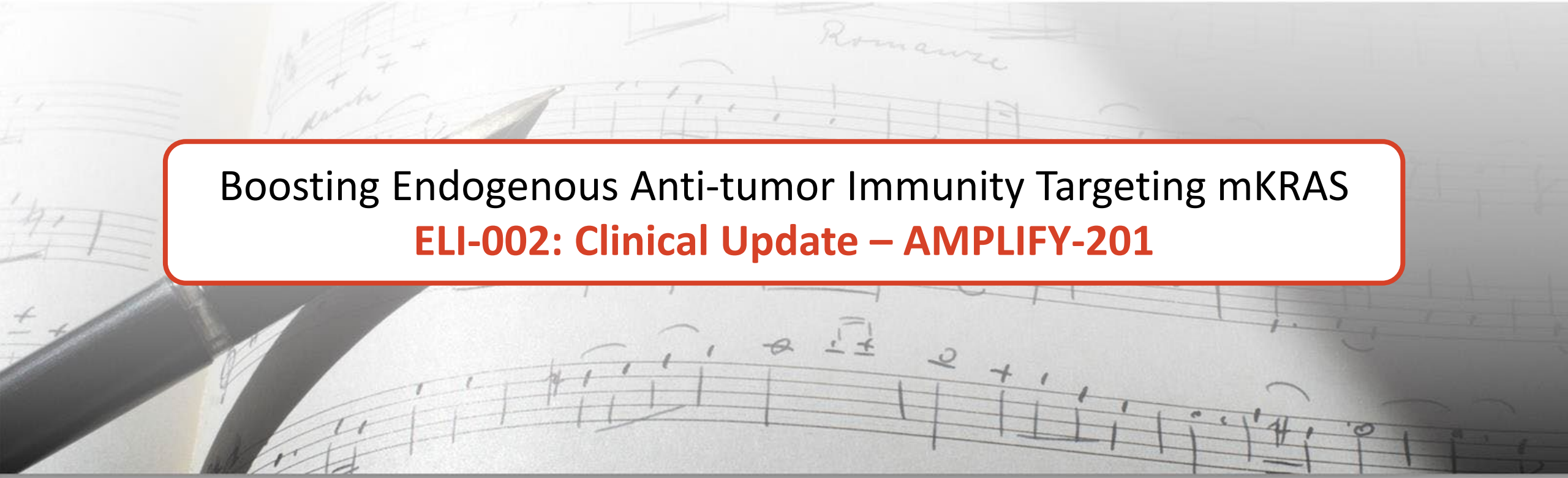


T Cell Response: G12D

Spleen



Drakes, DeMuth, et al. **BioRxIV** 2022



Boosting Endogenous Anti-tumor Immunity Targeting mKRAS

ELI-002: Clinical Update – AMPLIFY-201

AMPLIFY-201 Strategy

Technological and Clinical Innovation in Product Development

1 Technological Innovation: AMP Lymph Node Targeting

- **Smart trafficking to the lymph nodes** to generate enhanced immune responses
- Mutant KRAS peptides provide a **validated antigen** for application of the AMP platform
- Lymph node delivery of potent adjuvants **prevents systemic exposure to improve safety**

2 Clinical Innovation: Adjuvant Treatment of High Relapse-Risk

- Targeting surgically debulked tumors **enables T cells to address Minimal Residual Disease (MRD) to potentially eliminate** remaining tumor cells and protect against recurrence
- Activating the immune system **before loss of HLA expression** in the tumor microenvironment in a chemotherapy-free window of opportunity
- Treatment prior to advanced disease setting, **before onset of tumor immune resistance**
- **Tumor biomarkers (ctDNA, serum tumor antigen) are early predictors of disease control or recurrence**

AMPLIFY-201 Study Overview

Phase 1 dose-ranging study to assess safety and efficacy of ELI-002 2P adjuvant therapy

CLINICAL PROGRAM OVERVIEW: NCT04853017

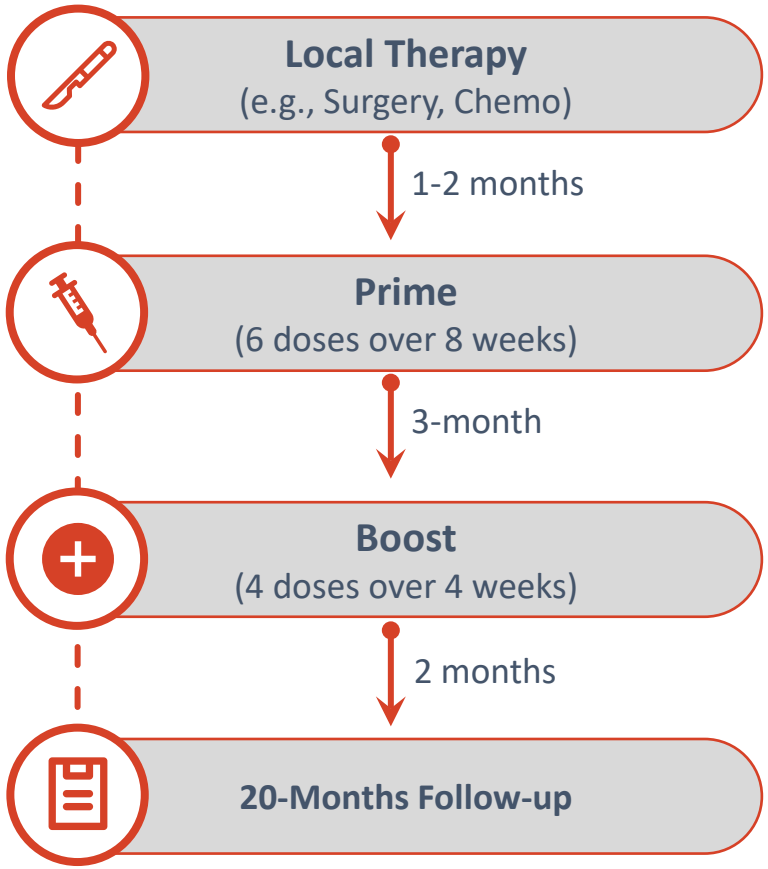
Key Criteria

- ✓ mKRAS G12D / R – aligned to 2 peptide formulation
- ✓ No metastatic disease after locoregional treatment
- ✓ No radiographic evidence of disease (NED)
- ✓ High risk of relapse (MRD+ ctDNA/serum biomarkers)

Baseline Characteristics

25 patients enrolled across 5 dose cohorts,
23 evaluable at database cutoff (4/25/2023)

- **Advanced:** 68% had stage III or oligometastatic resected stage IV disease
- **Pre-treated:** All received prior chemo and surgery, 28% had prior radiation



Basket Trial Enrollment

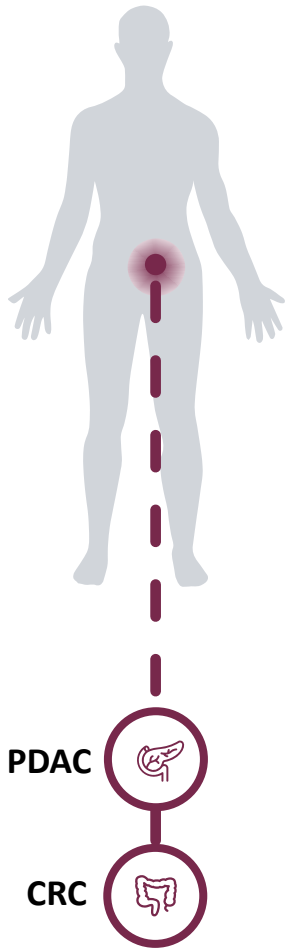
Pancreatic Ductal Adenocarcinoma (PDAC)	n=20
Colorectal Cancer (CRC)	n=5

Endpoints

- **Safety**
- **Maximum Tolerated Dose (MTD) or RP2D**
- ctDNA/serum biomarker change from baseline
- Immunological Responses
- Relapse Free Survival (RFS)

AMPLIFY-201 Study Design

Adjuvant treatment of patients with evident molecular disease following standard therapy



Prior Therapy

Locoregional Therapy:

- Surgery
- \+
- Neoadjuvant / Adjuvant Chemotherapy

Screening Period

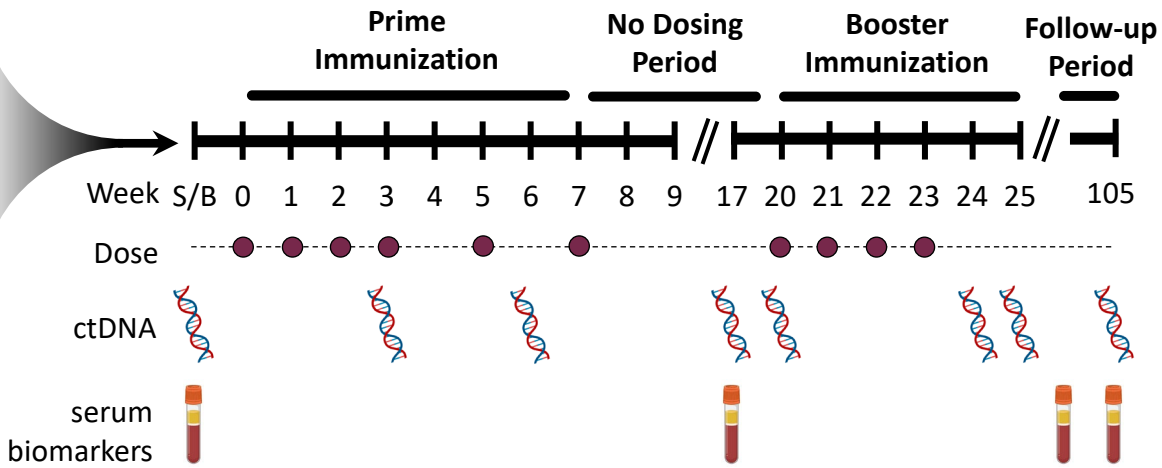
- **mKRAS+**: G12R+ or G12D+
- **No Evidence of Disease**: Imaging Negative
- **Minimal Residual Disease+**: ctDNA+ or serum biomarker+

SOC: Observation

PDAC: ctDNA+ RFS ~5 mo.

CRC: ctDNA+ RFS ~12 mo.

Amph-Peptides 2P 1.4 mg + 0.1, 0.5, 2.5, 5 or 10 mg Amph-CpG-7909



Cohort	Fixed Dose Amph-Peptides 2P	Ascending Dose Amph-CpG-7909
1	1.4 mg	0.1 mg
2	1.4 mg	0.5 mg
3	1.4 mg	2.5 mg
4	1.4 mg	5.0 mg
5	1.4 mg	10.0 mg

Groot, et al. **Clin Cancer Res** 2019; Lee, et al. **Annals Oncol** 2019; Kotani, et al. **Nature Med** 2023

20/25 pancreatic, 5/25 colorectal enrolled at database cutoff (4/25/2023)

AMPLIFY-201 Safety & Tolerability

ELI-002 was well tolerated at all dose levels, with no DLTs or SAEs

Safety and Tolerability

Very well Tolerated

No DLTs
No CRS
No Grade 3-4 related adverse events (AEs)

11/25 (44%) experienced Grade 1/2 AEs

3/25 (12%) experienced injection site reactions

No increase in adverse events was seen as Amph-CpG-7909 was dose escalated

	Cohort 1 (0.1 mg) n=3	Cohort 2 (0.5 mg) n=6	Cohort 3 (2.5 mg) n=5	Cohort 4 (5.0 mg) n=5	Cohort 5 (10.0 mg) n=6	Overall n=25
Adverse Event Term [a]						
Patients with Any Related TEAE, n (%)	1 (33.3)	3 (50.0)	2 (40.0)	3 (60.0)	2 (33.3)	11 (44.0)
Injection site reaction	0	1 (16.7)	1 (20.0)	1 (20.0)	0	3 (12.0)
Fatigue	0	1 (16.7)	2 (40.0)	0	1 (16.7)	4 (16.0)
Headache	1 (33.3)	1 (16.7)	0	0	1 (16.7)	4 (16.0)
Asthma	0	0	0	0	1 (16.7)	1 (4.0)
Dyspnea	0	0	0	0	1 (16.7)	1 (4.0)
Nausea	1 (33.3)	0	0	1 (20.0)	0	2 (8.0)
Diarrhea	0	0	0	0	1 (16.7)	1 (4.0)
Anemia	1 (33.3)	0	0	0	0	1 (4.0)
Contusion	1 (33.3)	0	0	0	0	1 (4.0)
Dry skin	0	1 (16.7)	0	0	0	1 (4.0)
Herpes simplex reactivation	0	1 (16.7)	0	0	0	1 (4.0)
Hot flush	0	1 (16.7)	0	0	1 (16.7)	2 (8.0)
Myalgia	0	0	0	1 (20.0)	0	1 (4.0)
Nasal congestion	0	1 (16.7)	0	1 (20.0)	0	2 (8.0)
Lymphadenopathy	0	0	0	0	1 (16.7)	1 (4.0)
Pruritus	0	0	0	1 (20.0)	0	1 (4.0)
Patient Summary						
KRAS Mutation	DDD	DDDDDD	DRDDD	DDRDD	RRDDRD	
Dose Limiting Toxicity	0	0	0	0	0	0
Biomarker Reduction / Clearance	2 (67)	5 (83)	3 (60)	4 (80)	3 (100) [b]	17 (77) [c]
T cell Response	2 (67)	5 (83)	4 (80)	5 (100)	4 (100) [d]	20 (87) [e]

TEAE: Treatment Emergent Adverse Event; a Preferred terms per the Medical Dictionary for Regulatory Activities, version 25.0; b Measured among 3 evaluable patients; c Measured among 22 evaluable patients; d Measured among 4 evaluable patients; e Measured among 23 evaluable patients

AMPLIFY-201 Tumor Biomarker Responses

Robust responses observed across tumor types and KRAS mutations with ELI-002 monotherapy

Tumor Biomarker Responses

Complete Biomarker Clearance

32%, 7/22

Biomarker Reduction

77%, 17/22

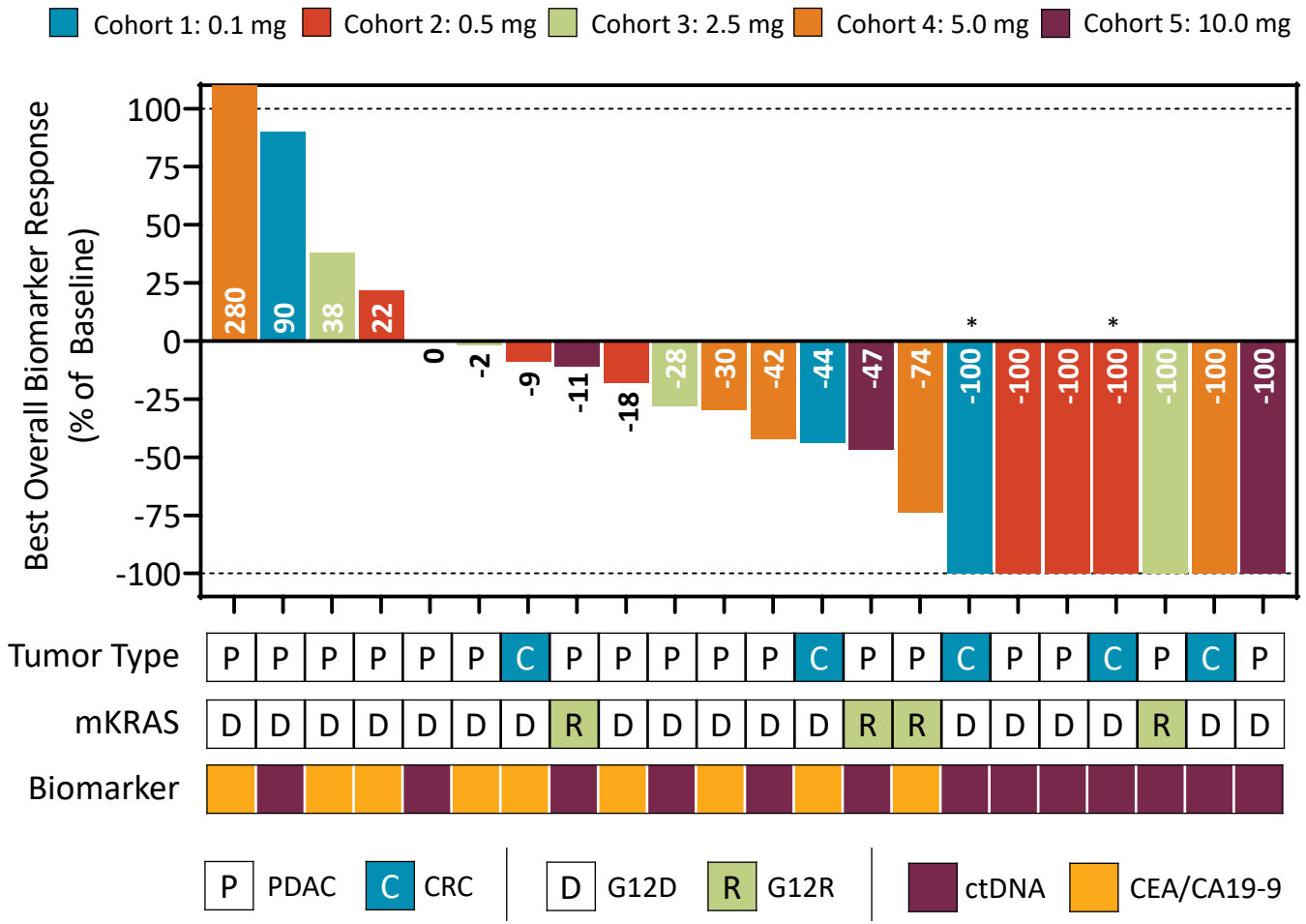
Breadth of Responses

PDAC & CRC

G12D & G12R

Diversity of HLA Background

AMPLIFY-201 Waterfall Plot: Biomarker Reduction/Clearance



* Patients biopsied, both exhibited T cell infiltration and continued study treatment

AMPLIFY-201 T Cell Responses

Vast majority of patients had robust T cell response across dose cohorts

mKRAS-specific T cell Response

87% of Patients with T cell Responses

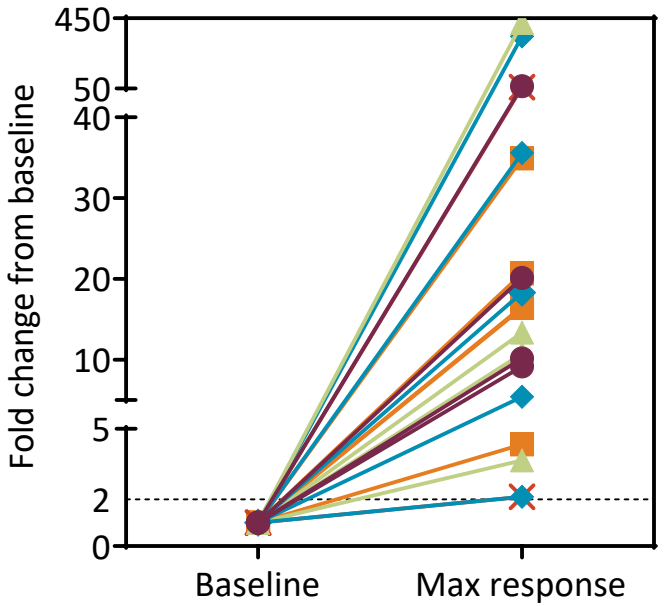
Responses measured directly *ex vivo* without *in vitro* expansion

Detected by ex vivo PBMC Fluorospot (IFNγ GrB) and ICS (IFNγ , TNFα, IL2)

56x Average Fold Increase over Baseline

100% Response in High-dose Cohorts

Direct Ex Vivo T Cell Response



Response per Dose Level

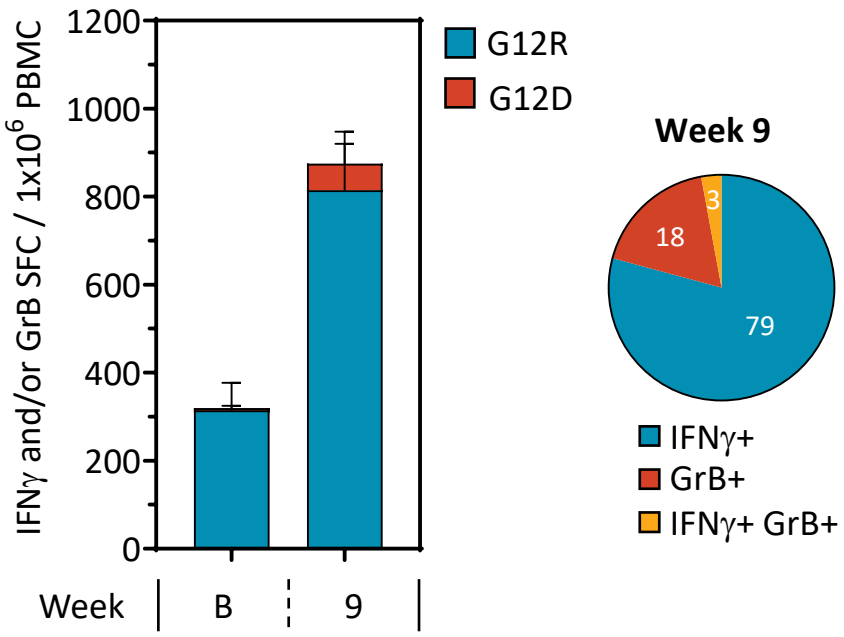
AMP-CpG Dose Level	*ex vivo* T cell response (n, %)	Average fold-change
0.1 mg	2/3 (67%)	30
0.5 mg	5/6 (83%)	82
2.5 mg	4/5 (80%)	113
5.0 mg	5/5 (100%)	19
10.0 mg	4/4 (100%)	26
Total	20/23 (87%)	56

Responses shown are best overall responses vs baseline for each patient at any timepoint during the assessment period

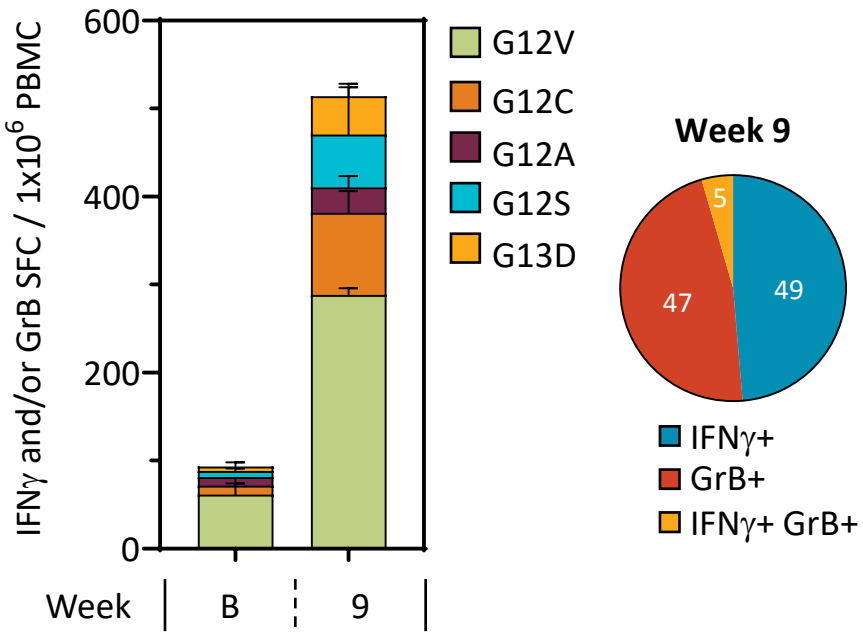
AMPLIFY-201 T Cell Responses

Direct Ex Vivo Assessment of Functional mKRAS-specific T Cell Responses in Patient 17

G12D / R Responses



G12V / C / A / S / G13D Responses



AMPLIFY-201 T Cell Tumor Infiltration

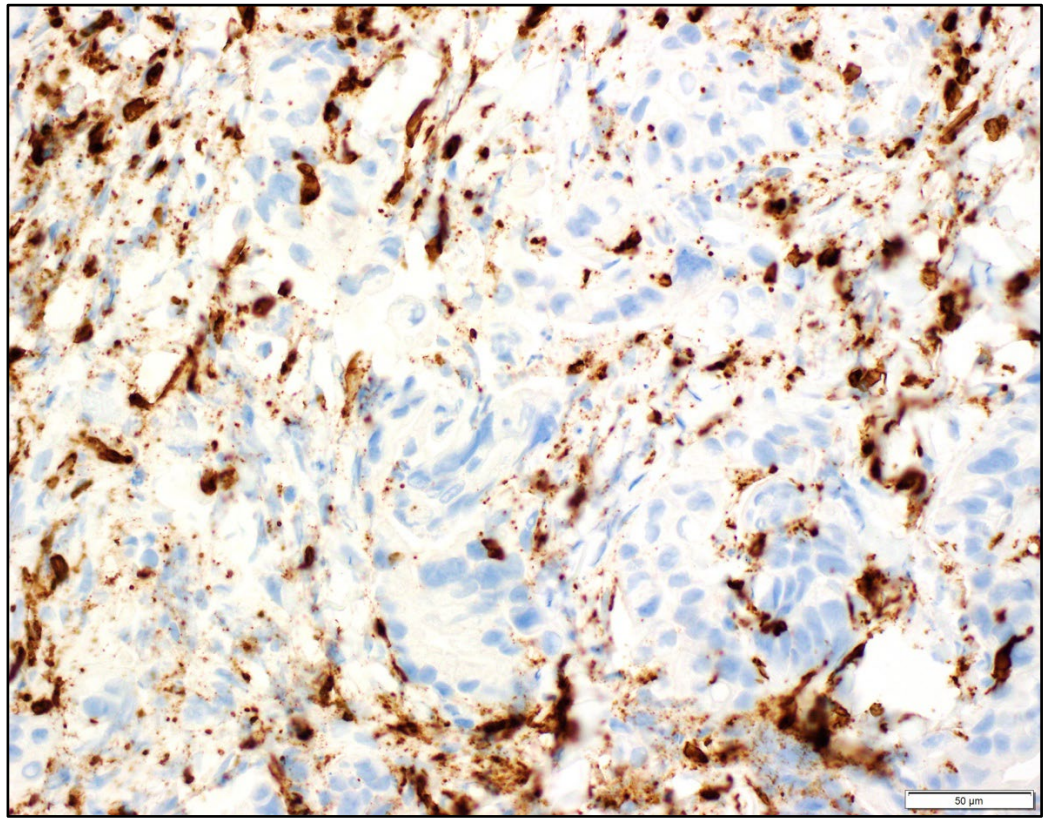
Preliminary clinical evidence shows dense T cell tumor infiltration following ELI-002 therapy

Tumor Infiltrating T cell Response

76 T cells / hpf
Subset of patients had tumor biopsy following observation of radiographic lesion on treatment
2-3 T cells / hpf expected in PDAC (↑ 29x increased)
Associated with ctDNA clearance in this patient
Subsequent CPI therapy led to clinical response

Tumor Biopsy CD3 Immunohistochemistry:

Pancreatic tumor, 2.5 mg dose level



Hpf: High-powered field; Ademmer, *et al.* **Clin Exp Immunol.** 1988; Ino, Y. *et al.* **Br J Cancer**. 2013

Lymph node-Targeted Therapeutic mKRAS-specific Cancer Vaccine ELI-002:

Safe and Well-tolerated

- Amphiphile Lymph Node Targeting can improve vaccine safety
- Unlike soluble TLR9 agonist CpG-7909, Amph-CpG-7909 showed no dose limiting toxicity
- RP2D determined at 10 mg Amph-CpG-7909: Favorable safety, tumor biomarker response, and T cell response

Novel adjuvant trial design using ctDNA / serum tumor biomarkers was feasible

- Goal: Minimize HLA loss, tumor-acquired immunosuppressive mechanisms; Maximize T cell : Tumor cell ratio
- Tumor biomarker data (ctDNA and serum tumor antigen) can provide early efficacy signal

A high proportion of ELI-002 2P patients had tumor biomarker reduction (77%), a subset achieved clearance (32%)

- Notable mKRAS-specific T cell responses induced, average 56-fold [range 2-423-fold] increase directly ex vivo
- T cell infiltration was 10 to 29-fold higher than literature in pancreatic tumors

ELI-002 7P trial NCT05726864 activated for KRAS G12D, G12V, G12R, G12C, G12A, G12S, G13D in PDAC, CRC, NSCLC

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AMPLIFY-201

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Patients and their families

Liu, Irvine, et al. **Nature** 2014; Steinbuck, DeMuth, et al. **Science Advances** 2021; Moynihan, Irvine, et al. **Nature Medicine** 2016; Seenappa, DeMuth, et al. **NPJ Vaccines** 2022; Drakes, DeMuth, et al. **BioRxIV** 2022; O'Reilly, Pant, et al. **ASCO Annual Meeting** 2023