# Targeting the Lymph Nodes to Enhance Mutant KRAS-Specific Vaccine Responses

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RAS Targeted Drug Discovery Summit

September 15, 2020

# Why Immunotherapy?

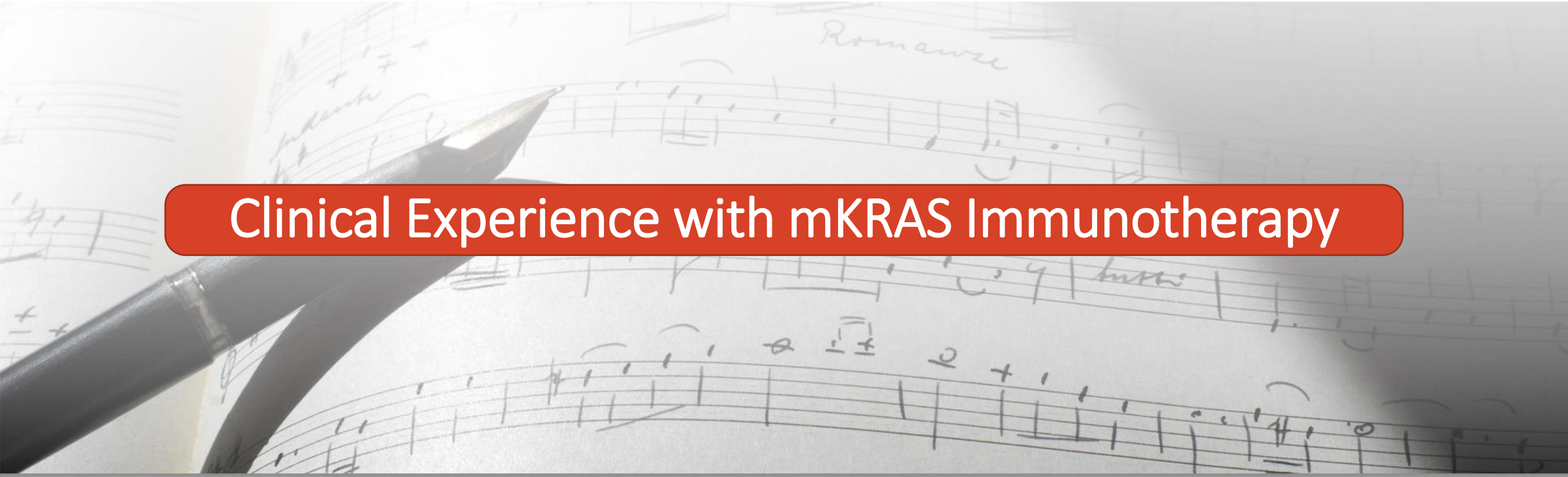
**Immunotherapy** (Vaccine, Adoptive Cell Therapy, Checkpoint inhibition)

## mKRAS is a Promising Target for Immunotherapy

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

## But Substantial Challenges Remain:

- Conventional vaccines have induced **low frequency T cell responses**
- ACT is effective but **difficult and expensive to manufacture**
- Historical studies have focused on advanced tumor patients with **bulky disease burden**
- Advanced tumors develop **suppressive microenvironment** (physical, immunological)



# Clinical Experience with mKRAS Immunotherapy

# Low Frequency mKRAS Immune Responses Deliver Measurable but Inadequate Clinical Benefit

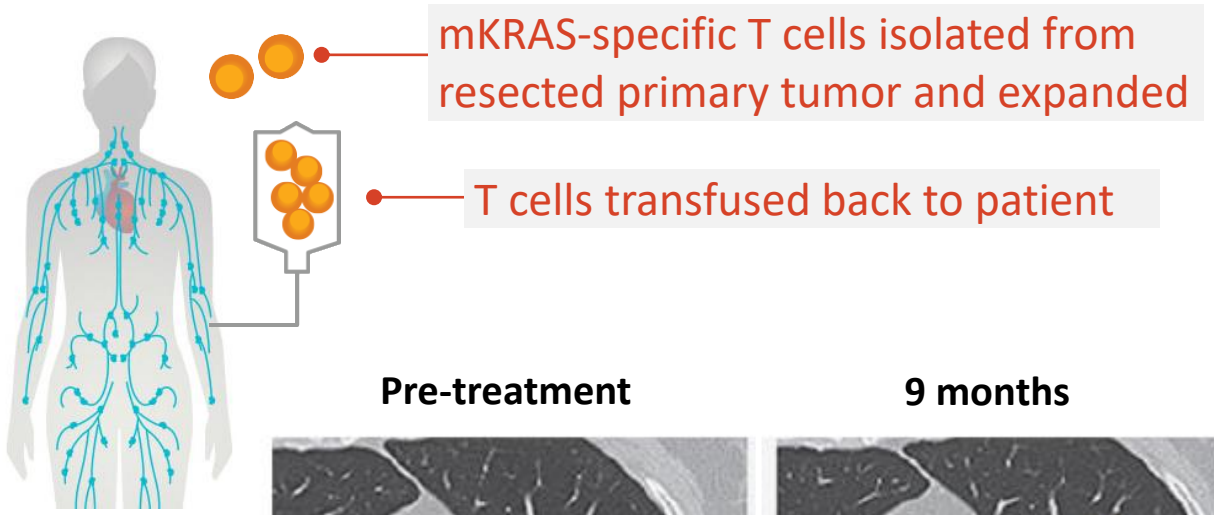
## Clinical Evidence of T Cell Efficacy Against mKRAS Tumors

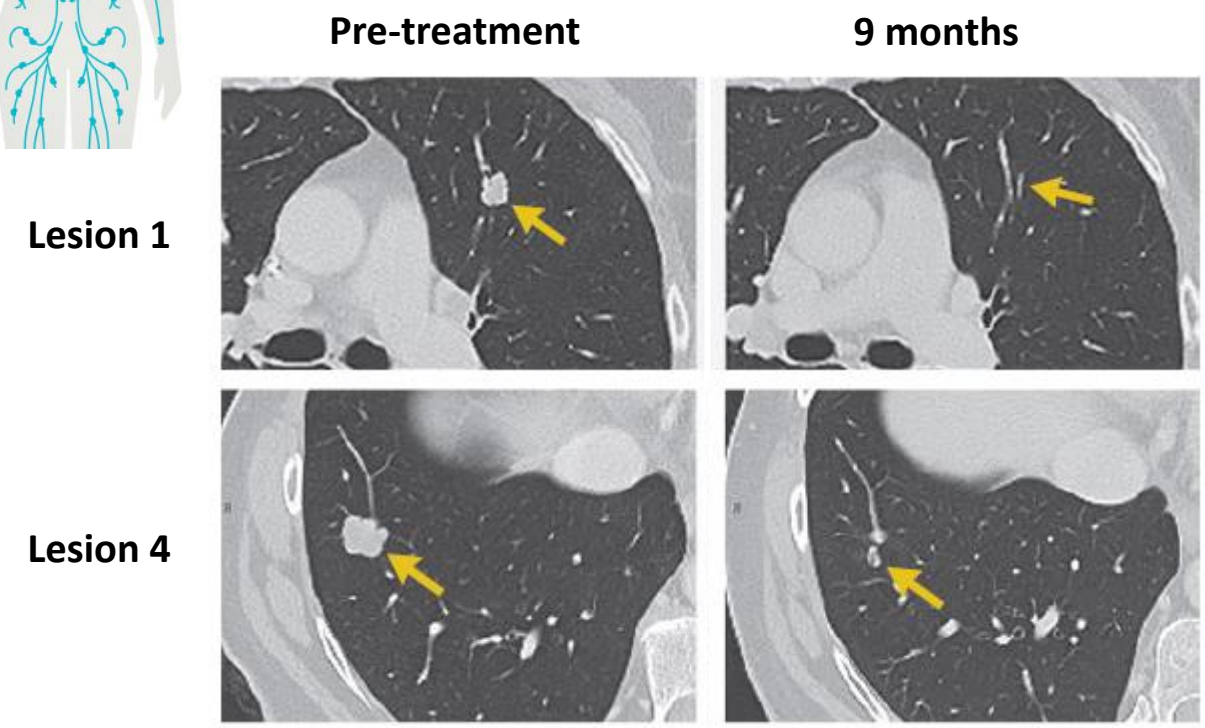
| mKRAS | Indication | Treatment | T Cell Assay | Citation |
|---|---|---|---|---|
| G12C | Colon, Lung, Pancreas Cx<br>Colon, Lung, Pancreas Cx<br>Pancreas Cx | Peptide vaccine<br>Autologous PBMC<br>Peptide vaccine | IFNg ELISPOT<br>IFNg ELISA<br>Proliferation | Rahma, 2014<br>Carbone, 2005<br>Gjertston, 2001 |
| G12D | Lung Cx<br>Colon, Lung, Pancreas Cx<br>Colon, Lung, Pancreas Cx<br>Pancreas Cx | Autologous T Cell<br>Peptide vaccine<br>Autologous PBMC<br>Peptide vaccine | ICS<br>IFNg ELISPOT<br>IFNg ELISA<br>Proliferation | Tran, 2016<br>Rahma, 2014<br>Carbone, 2005<br>Gjertsen, 2001 |
| G12R | Pancreas Cx | Peptide vaccine | Proliferation | Gjertsen, 2001 |
| G12S | Colon, Lung, Pancreas Cx | Autologous PBMC | IFNg ELISA | Carbone, 2005 |
| G12V | Colon, Lung, Pancreas Cx<br>Colon, Lung, Pancreas Cx<br>Pancreas Cx<br>Pancreas Cx | Peptide vaccine<br>Peptide vaccine<br>Peptide vaccine<br>Peptide vaccine | IFNg ELISPOT<br>IFNg ELISA<br>Proliferation<br>Tumor killing | Rahma, 2014<br>Carbone, 2005<br>Gjertsen, 2001<br>Gjertsen, 1997 |

## Important Lessons:

- Peptide, autologous DC vaccines produce measurable T cell responses to mKRAS
- **T cell responses are low frequency**: 7 day ex vivo expansion is required to observe T cell responses
- **T cell responses are mKRAS-specific** with little cross-reactivity to WT KRAS
- Responses are both **CD4 and CD8**, restricted by various common **HLA**
- Numerous studies have show statistically significant **association of mKRAS immune response with DFS**

# Adoptively Transferred mKRAS-specific T Cell Proof of Principle – Elimination of Large Metastatic Tumors



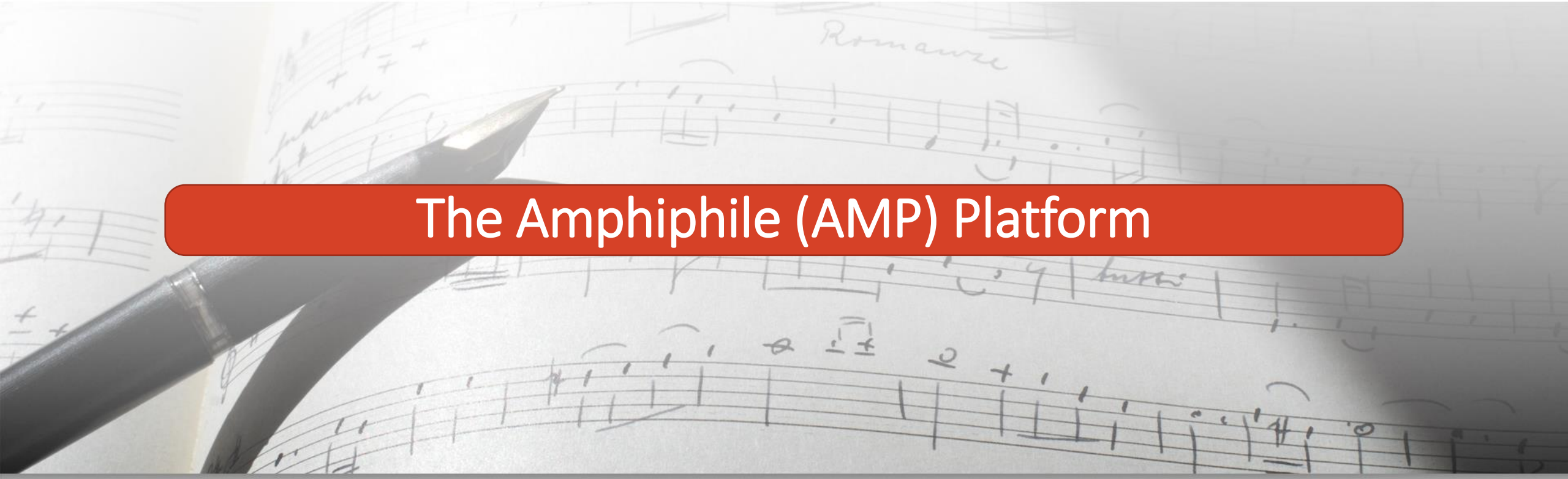

**Key Results:**

- Patient had 7 metastatic mKRAS lung lesions at the time of treatment
- All lesions showed objective regressions following therapy

**Important Lessons:**

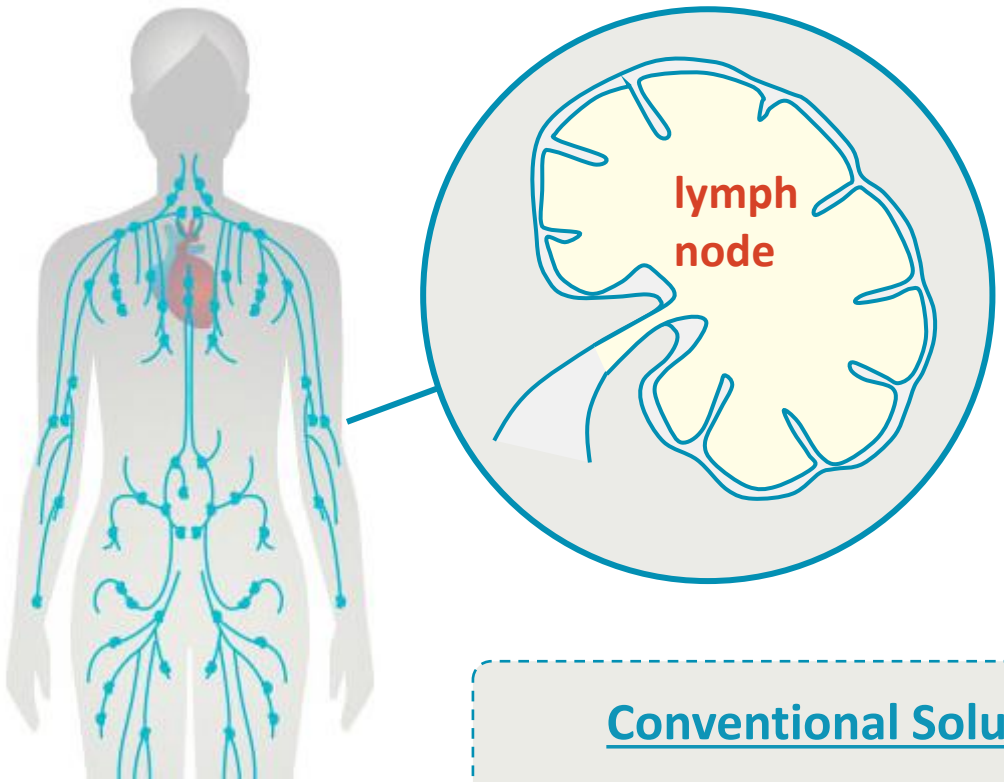
- Spontaneously arising T cells can detect and eliminate even large mKRAS tumors
- Naïve TCRs specific for mKRAS exist in native repertoire
- mKRAS is effectively presented by tumors
- Efficacy requires sufficient T cell expansion (~15% of peripheral T cells), functionality, and persistence

Tran, et al. **NEJM** 2016



# The Amphiphile (AMP) Platform

# Lymph Nodes are Where the Immune Response Against Cancer is Orchestrated



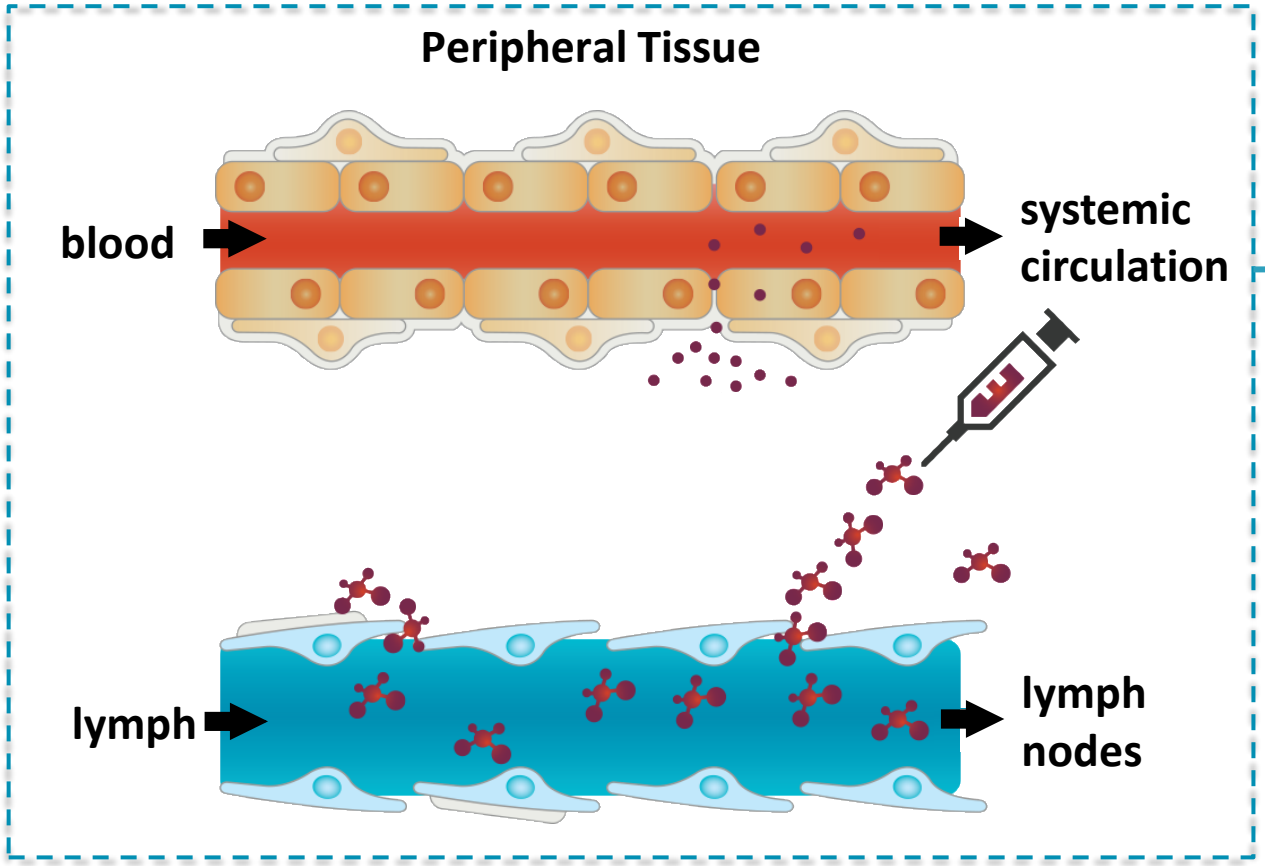

- **Natural Site for Immune Surveillance**
- **Site of Residence for Immune Cells**
- **The "School House" for T-Cells**
- **Potent Deterministic Immune Signaling**

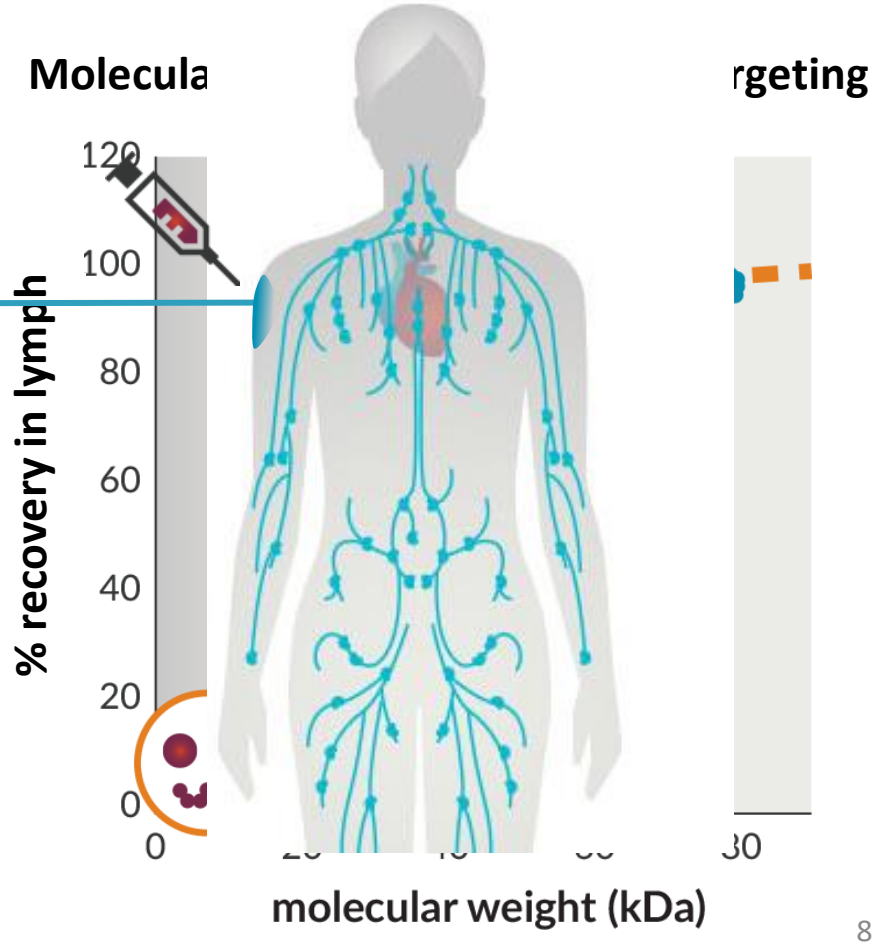
**Conventional Soluble Subunit Vaccines do not get to Lymph Nodes**

Poor exposure to target immune cells gives **Limited Efficacy**

# Albumin is the Ideal Carrier to Transport Immuno-therapies and Vaccines into Lymph Nodes

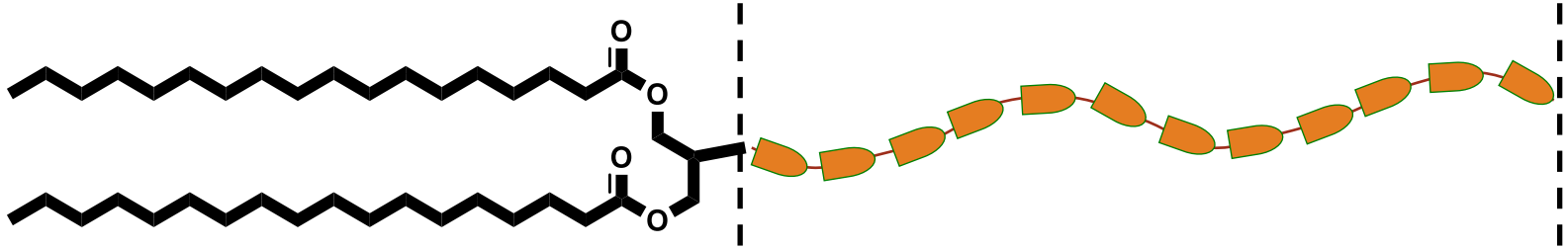
- Molecular size dictates trafficking fate of immuno-therapies and vaccines
- Albumin in the tissues is efficiently trafficked into lymphatics because of its large size

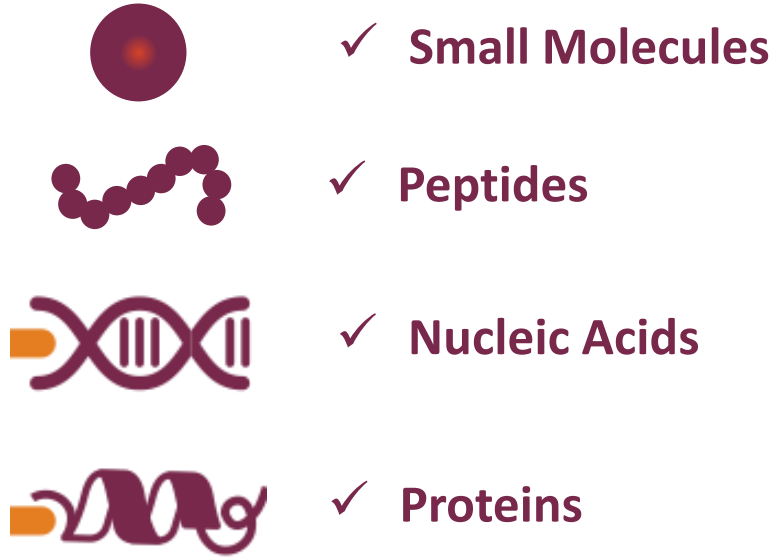


# Amphiphile (AMP) Platform Enables Lymph Node Delivery of Validated Therapeutics with Modular Application

## A Modular Conjugation Approach for Delivery of Immune Therapeutics to the Lymph Node





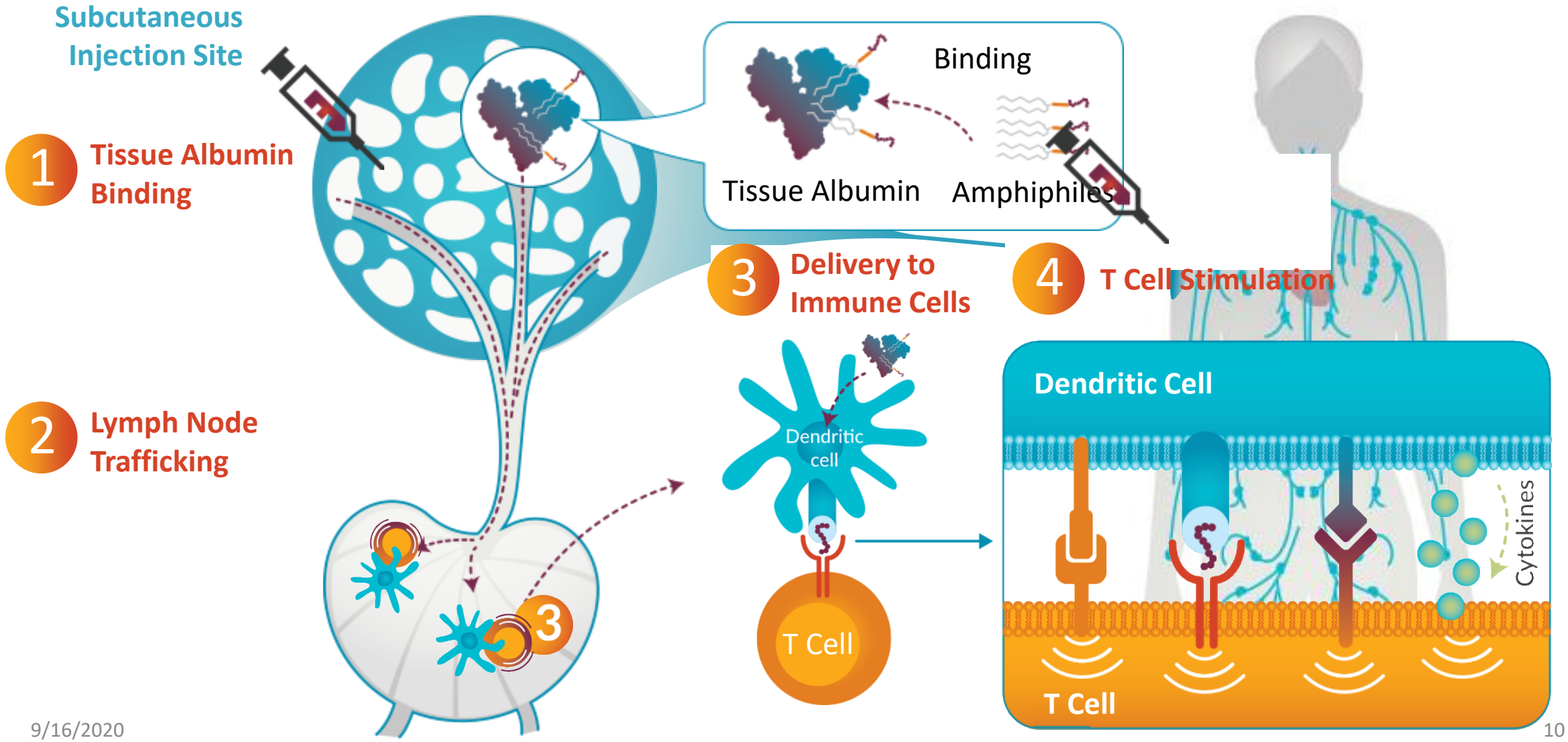
- ✓ Small Molecules
- ✓ Peptides
- ✓ Nucleic Acids
- ✓ Proteins

**1** **Albumin-binding**
✓ ***Lymph Node targeting***

**2** **Linker**
✓ ***Improve Solubility***

**3** **Therapeutic Payload**

# Amphiphiles Potently Stimulate T Cells in the Lymph Nodes



# AMP-Vaccines are Highly Optimized to Precisely Target Delivery to the Lymph Nodes

day 1 — Dose

day 2 — Analyze Lymph Node Uptake

**Vaccine**

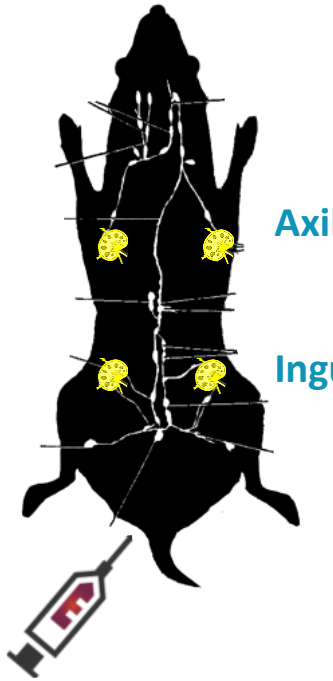
10 µg Peptide-FITC

30 µg CpG

Soluble Peptide-FITC + CpG

AMP Peptide-FITC + AMP-CpG

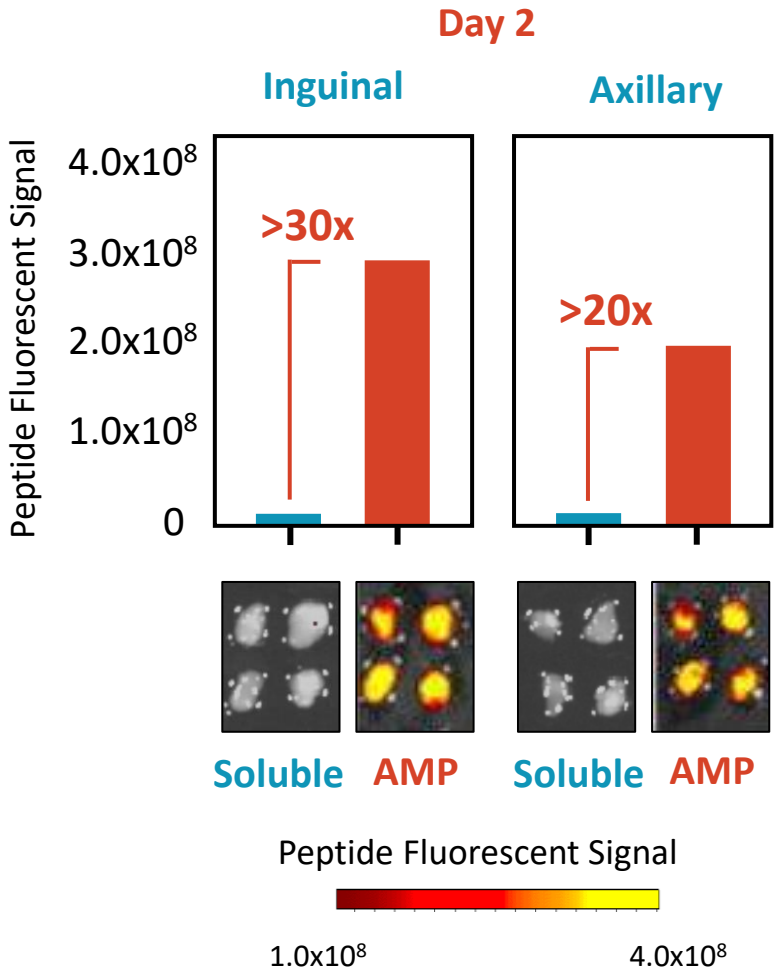
## 2 Lymph Node Analysis



Axillary Lymph Node

Inguinal Lymph Node

## 1 SC Injection



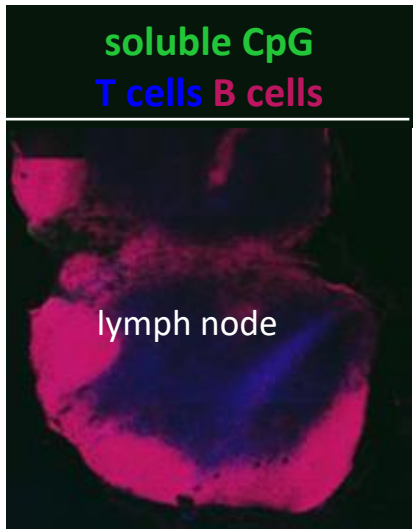

Liu, Irvine, et al. **Nature** 2014

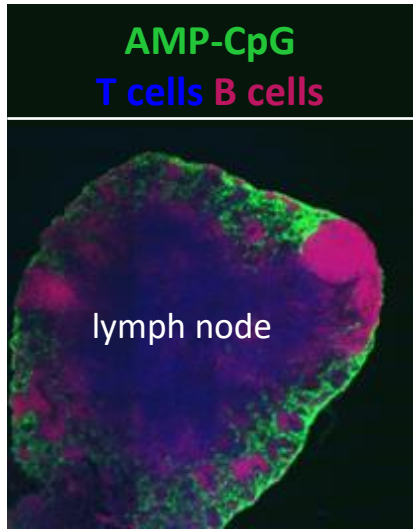
# AMP-Vaccines are Highly Optimized to Precisely Target Delivery to the Lymph Nodes

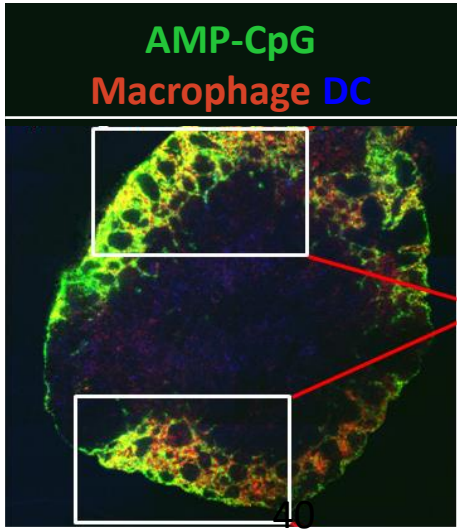
day 1 — Dose

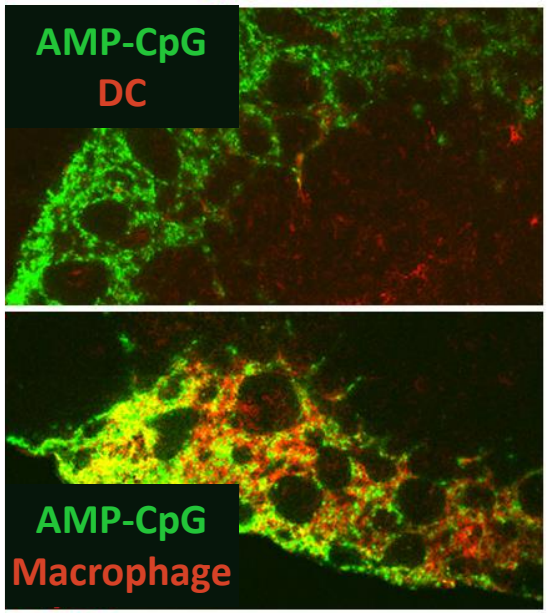
day 2 — Analyze Lymph Node Uptake

**Vaccine**
10 µg CpG-FAM



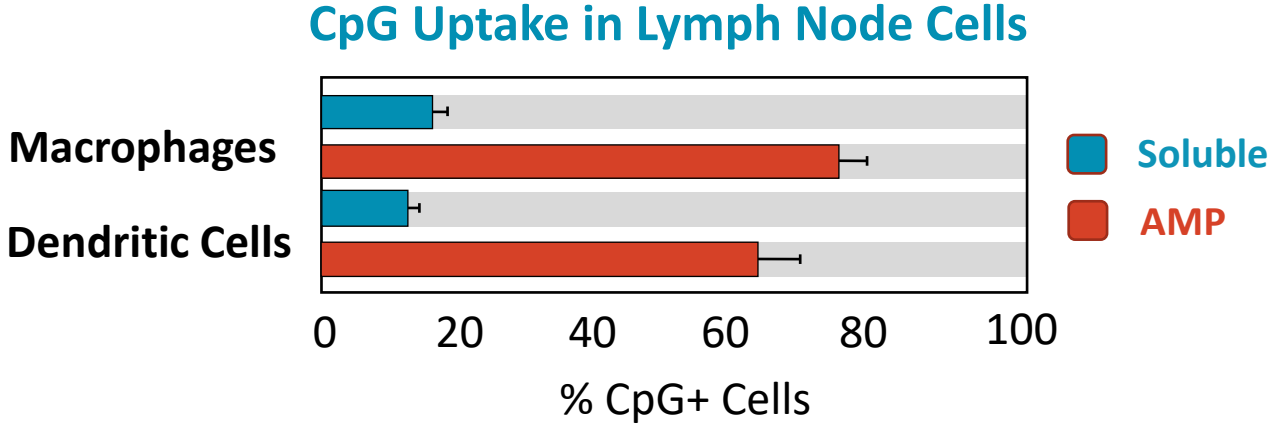



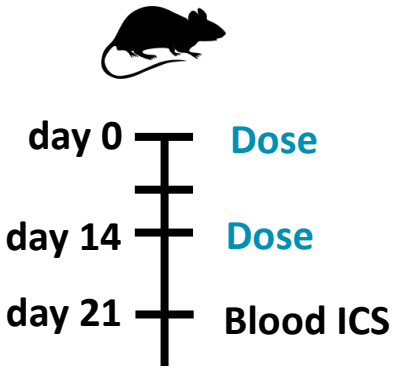

**Soluble CpG-FAM**

**AMP-CpG-FAM**

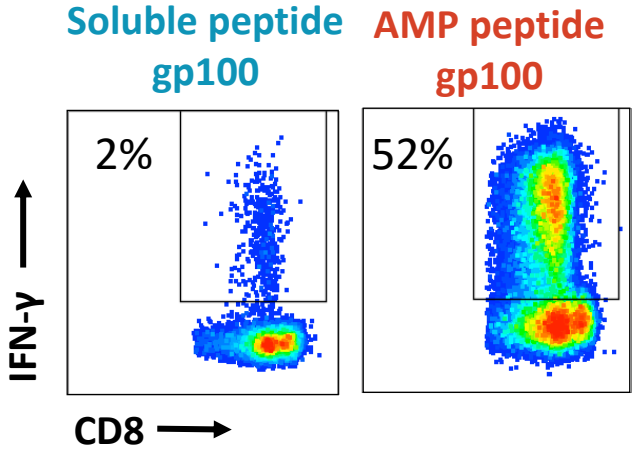



Liu, Irvine, et al. **Nature** 2014

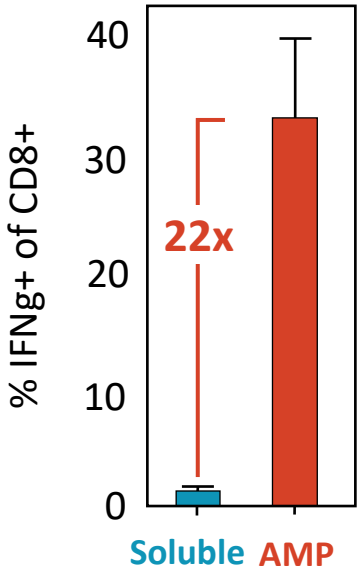
# Lymph Node Targeted AMP-Vaccines Potently Enhance Functional CD8 T Cell Responses




**Vaccine**
**10 µg antigen**
**8 ug equivalent CpG**




**IFNg+ CD8+ T cell Response**



# Lymph Node Targeting Drives Unprecedented Immune Responses

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

Moynihan et al., **Nature Medicine**, March 2016

Moynihan et al., **Cancer Immunology Research**, June 2018

Ma, et al., **Science**, July 2019

- **>10-fold** improved lymph node delivery over conventional soluble vaccines in mice and primates
- **>50-fold** enhanced delivery of vaccines to immune cells in mice and primates
- **>30-1000-fold** increase in functional immune responses relative to conventional soluble vaccines
- **Eradication** and **durable cures** of large aggressive tumors in multiple models (lung, melanoma, breast, colorectal, head and neck, glioma)
- **Broad** application across many therapeutic classes and indications
  - Boosting natural immune responses
  - Enhancing Adoptive Cell Therapies (CAR-T, TIL)

# ELI-002 Preclinical Studies: mKRAS Vaccine

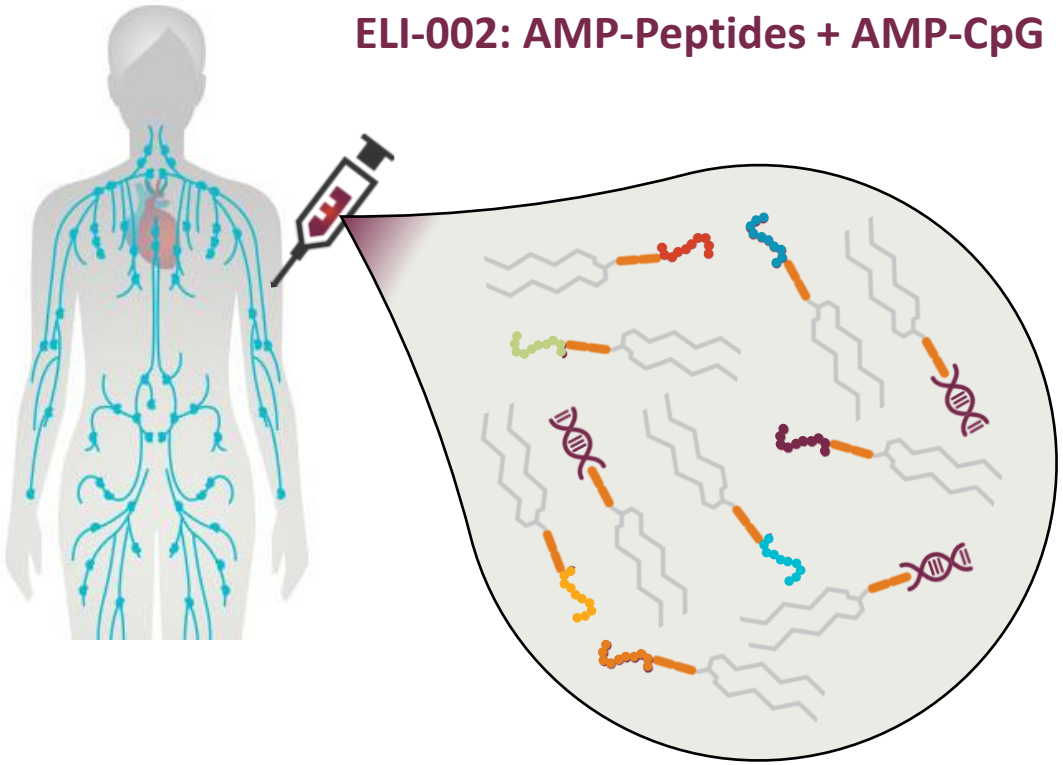
# AMP Vaccination Against mKRAS Drives Powerful Functional Immunity

- **>400-fold** increase in functional T cell responses relative to conventional soluble vaccines in mice
  - **Polyvalent** responses simultaneously target all 7 mKRAS sequences
  - **CD4 and CD8** T cell induction
  - **>5000-fold** increase in **polyfunctional cytokine** effector profile relative to conventional therapies
  - **>100-fold** increase in **cytolytic effector** functionality relative to conventional therapies
- **Potent** in vivo **killing** of mKRAS-presenting cells

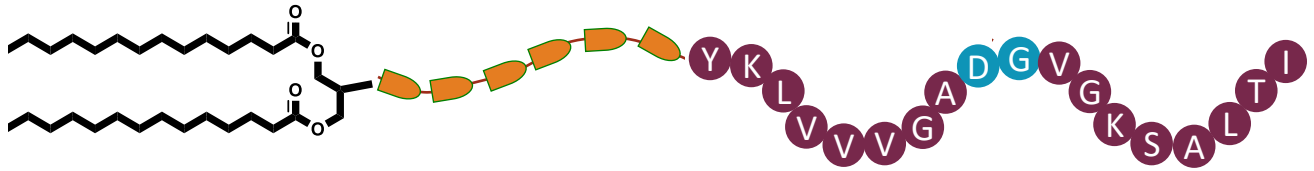
# ELI-002: Lymph Node Targeting Polyvalent mKRAS Vaccine Immunotherapy

**A Lymph Node Targeted Polyvalent mKRAS Peptide + TLR-9 Agonist CpG Vaccine Therapy**

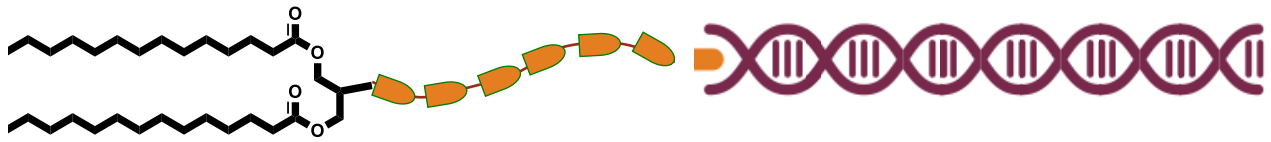
**ELI-002: AMP-Peptides + AMP-CpG**



**AMP-Peptides: 7 mKRAS Peptides: G12D, R, V, S, A, C, G13D**




**AMP-CpG: CpG TLR-9 Immunostimulatory DNA**



| Lymph Node Targeting | Linker | Vaccine Payload |
|---|---|---|

# AMP-Vaccines Accumulate in Lymph Nodes to Enhance Uptake in Resident Immune Cells

day 0 — Dose

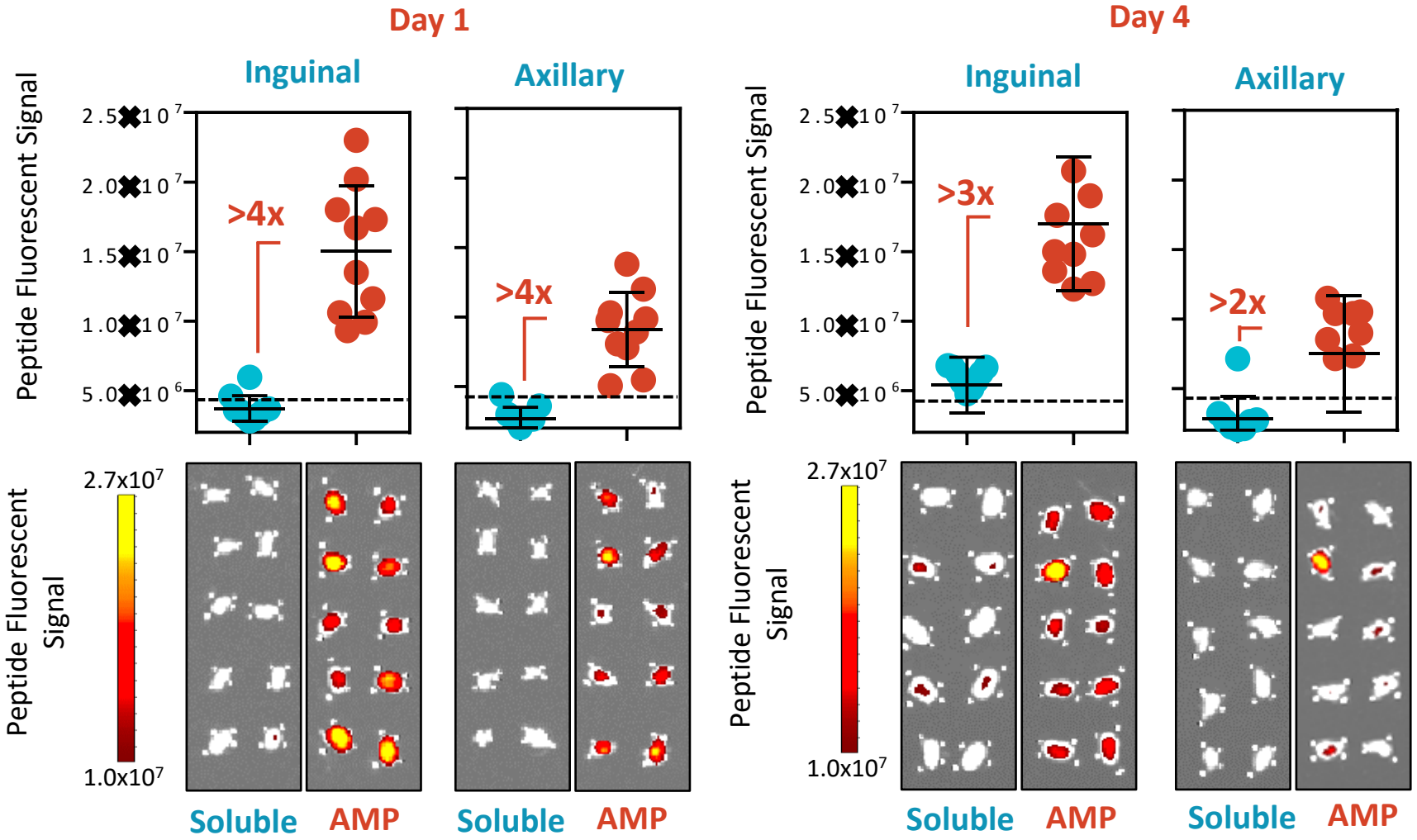
day 1

day 4 — Analyze Lymph Node Uptake

**Vaccine**

**20 µg mKRAS-G12D FITC peptide**
**30 µg CpG**

- **Soluble KRAS G12D-FITC + CpG**
- **AMP-KRAS G12D-FITC + AMP-CpG**



# AMP-Vaccines Enable Potent T Cell Responses to mKRAS

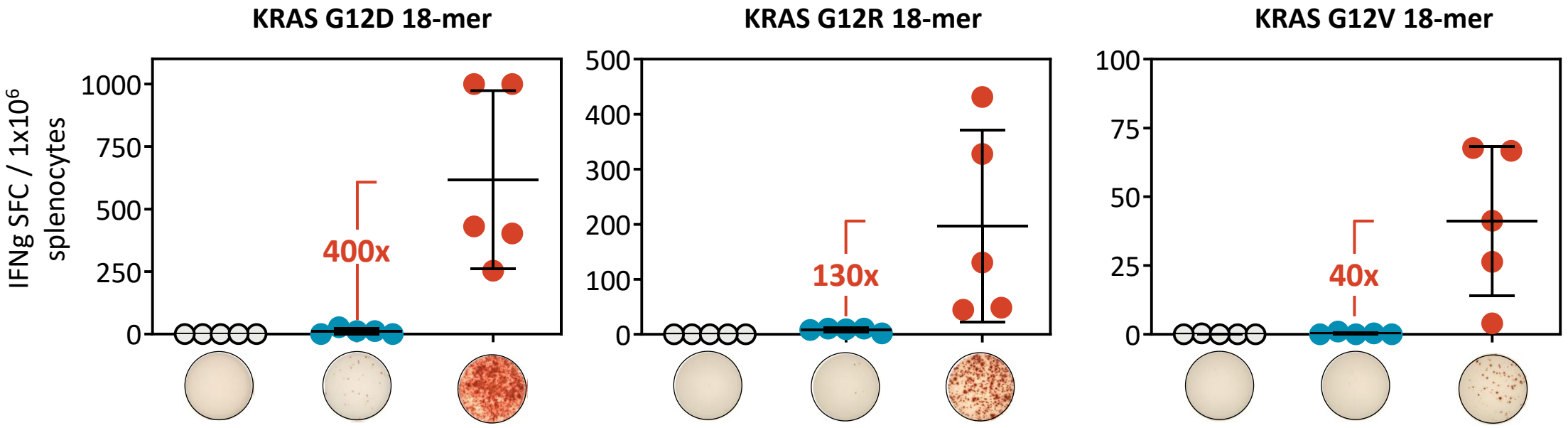
day 0 — Dose 1
day 14 — Dose 2
day 21 — ELISPOT

**Vaccine**
20 µg mKRAS peptide
30 µg CpG

- untreated
- Soluble KRAS G12X + CpG
- AMP-KRAS G12X + AMP-CpG

## T Cell Cytokine Response

**Splenocyte Restimulation with:**



# AMP-Vaccines Prime and Boost Polyfunctional Cytokine Secreting T cell Responses to mKRAS

day 0 — Dose 1

day 14 — Dose 2

day 21 — Cytokine CBA

day 28 — Dose 3

day 34 — Cytokine CBA

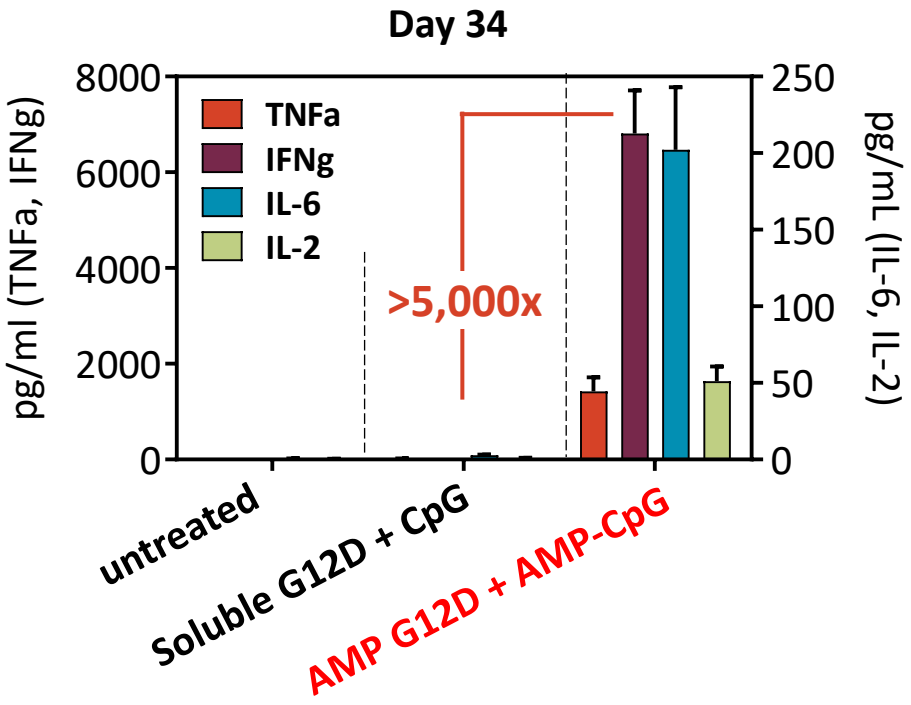
day 42 — Dose 4

day 50 — In Vivo Killing

**Vaccine**

**20 µg mKRAS peptide**
**30 µg CpG**
**or**
**50 µg polyI:C**

**T Cell Cytokine Response: Splenocyte Restimulation with G12D 18-mer**



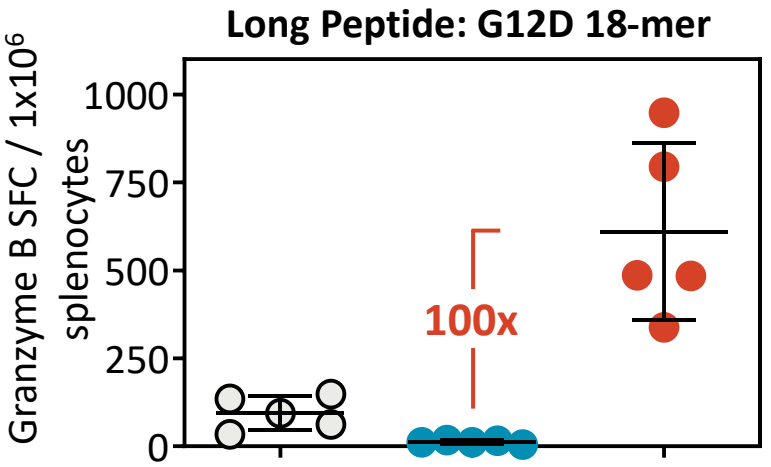
# AMP-Vaccination Induces Cytotoxic mKRAS-specific T Cells

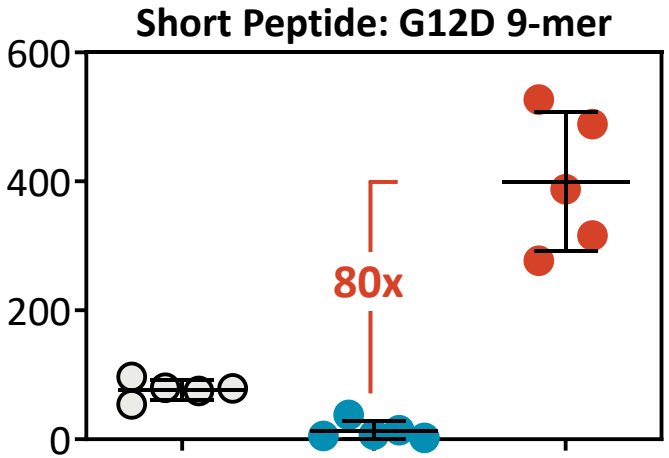
day 0 — Dose 1
day 14 — Dose 2
day 27 — Dose 3
day 41 — Dose 4
day 55 — Dose 5
day 66 — Dose 6
day 74 — ELISPOT, In Vivo Killing

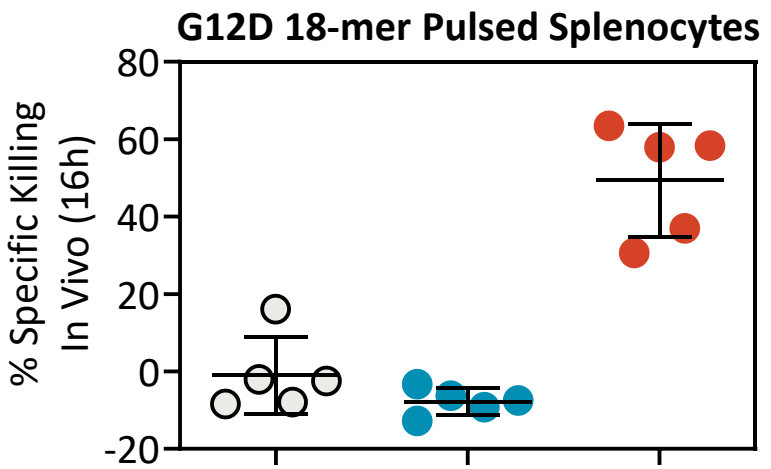
**Vaccine**
20 µg mKRAS peptide
30 µg CpG
or
50 µg polyI:C

untreated
Soluble KRAS G12D + CpG
AMP-KRAS G12D + AMP-CpG

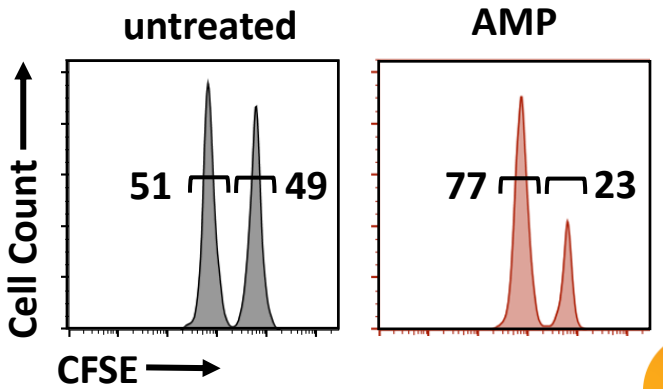
## T Cell Cytolytic Response




CFSE high: KRAS G12D 18-mer
CFSE low: no peptide



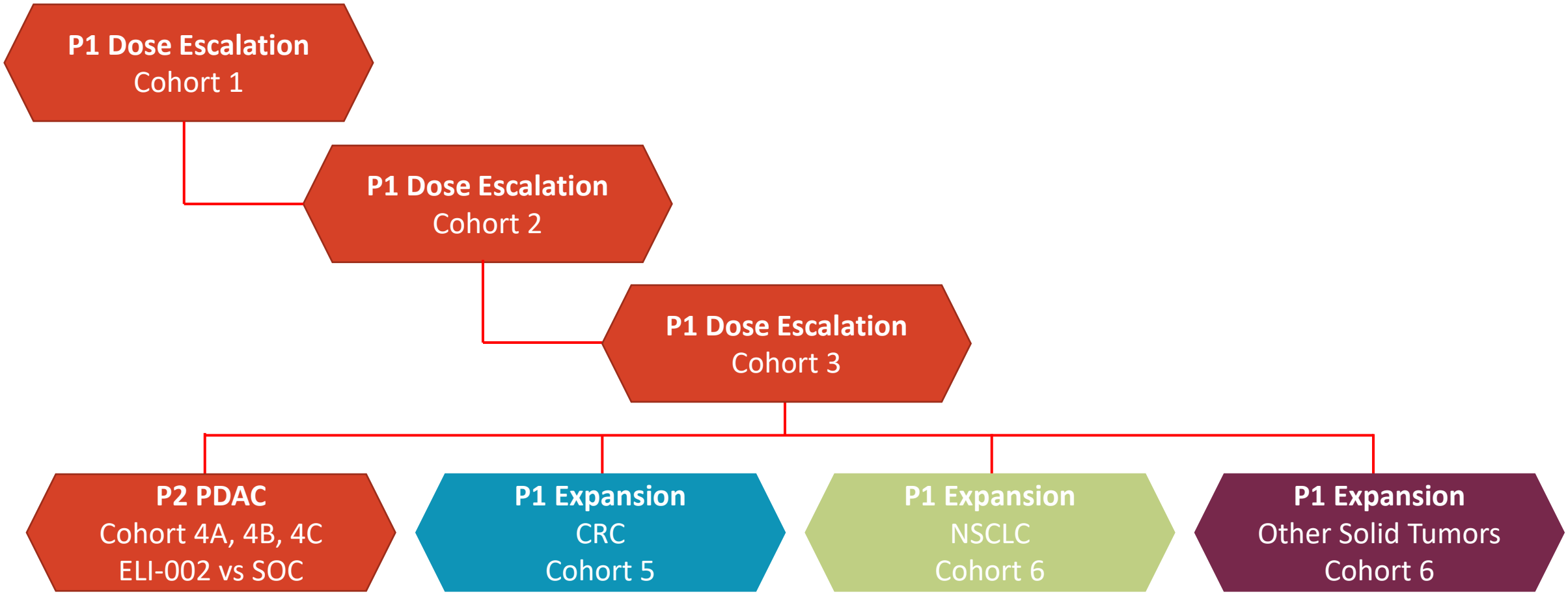
# ELI-002 Clinical Development

# AMP 7-Peptide Vaccine with AMP-CpG Addresses 99% of Mutations Driving 25% of All Solid Tumors

- 57,000 pancreatic, 56,000 colorectal, and 58,000 lung mKRAS cancers annually in US
- Trial designs target minimal residual disease patients (MRD) post pancreatectomy / colectomy → 80% of PDAC patients will relapse within one year
    - Microscopic tumor burden – maximize immune effector : tumor target ratio – minimal immune suppression from tumor environment
- Trial design includes cross-over for progressing patients not originally randomized to treatment group to test ELI-002 for RECIST radiographic response
- Cell free DNA (ctDNA) marker can identify those patients who will relapse for study and measure vaccine impact on MRD

# mKRAS+ Expansion Cohorts Will Rapidly Assess PDAC, CRC, NSCLC, and Other Solid Tumors (Endometrial/Ovarian/Bile Duct)

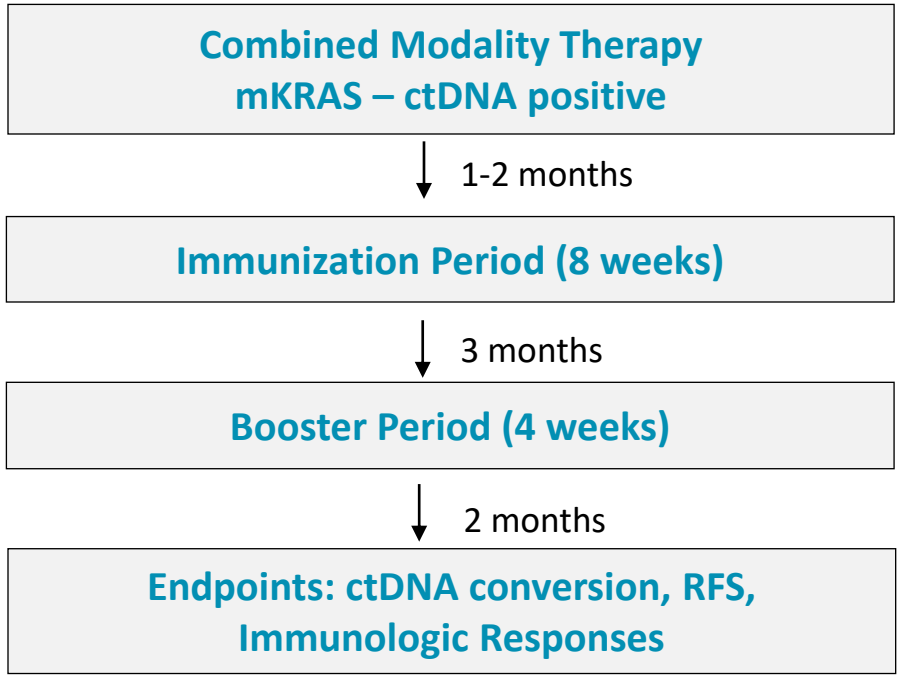
## ELI-002 Study Cohort Schematic




4A – ELI-002; 4B – observation; 4C – observation crossover to ELI-002 at time of radiographic relapse

# ELI-002 (KRAS)
# Operable Pancreatic Cancer Phase 1/2 Clinical Trial

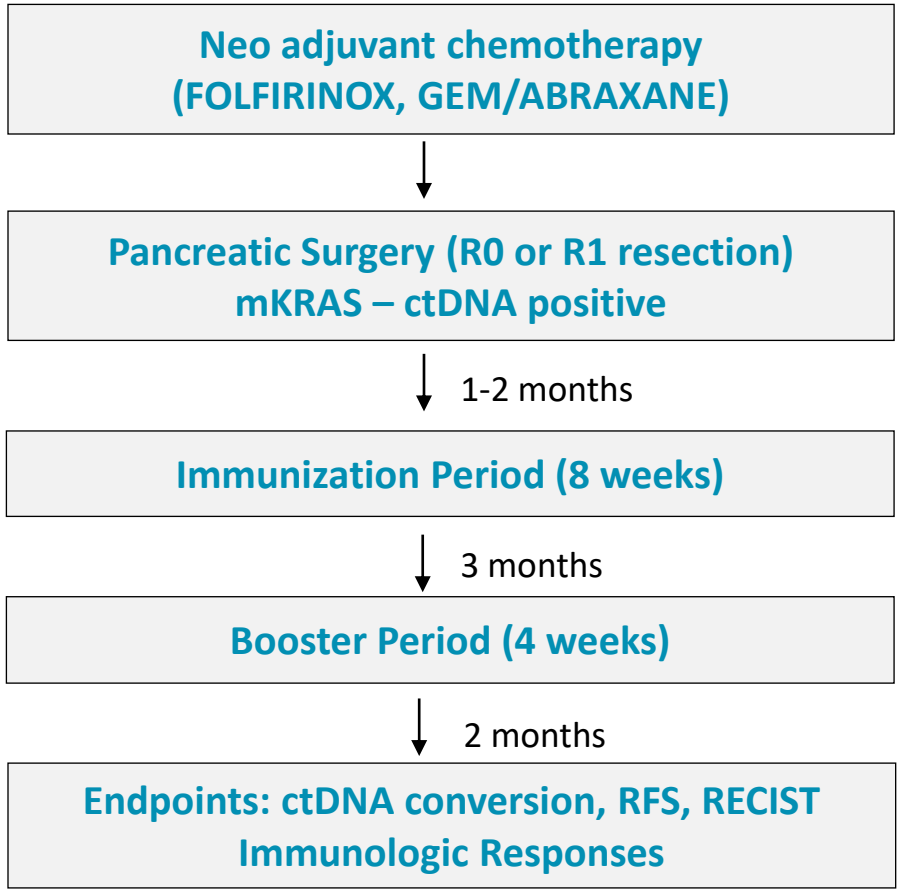
## Multi-center Phase 1 3+3 Dose Escalation




| | |
|---|---|
| **Objectives** | • Safety and tolerability<br>• Immunologic POC<br>• Recommended P2 dose |
| **Enrollment** | • 9-18 MRD+ patients<br>• MRD+ by mKRAS ctDNA |
| **Treatment** | • 3 progressive dose level cohorts<br>• Prime, boost ELI-002 |
| **Endpoints** | • Safety<br>• ctDNA conversion<br>• LN enlargement, cytokines, immune response |

# ELI-002: Pancreatic/Other mKRAS+ Tumor Subjects who are MRD+ Despite Chemo and Surgery

## Multicenter Phase 2 2:1 vs standard treatment (observation) with crossover at relapse




| | |
|---|---|
| **Objectives** | • Safety and tolerability<br>• Immunologic POC |
| **Enrollment** | • 90 PDAC patients<br>• MRD+ by mKRAS ctDNA |
| **Treatment** | • Established RP2D<br>• Prime, boost ELI-002 |
| **Endpoints** | • Relapse free survival<br>• ctDNA conversion<br>• iRECIST response rate after crossover<br>• LN enlargement, cytokines, immune response |

## mKRAS-targeted immunotherapy offers

- Attractive immunogen profile
- Historical CPOC signal in CRC, PDAC, NSCLC
- Broad multi-targeted G12/13 potential activity

## ELI-002 shows promising immune response profile

- Precise lymph node targeting
- **High frequency** T cell responses
- **Polyvalent** mKRAS-specificity
- **Polyfunctional** effector profile
- Potent **cytotoxic** functionality

## ELI-002 Clinical Development

- **FIH P1 in MRD+, P2 single arm CRC, NSCLC, OST, and P2 randomize PDAC**
- **Cross-over** in randomized PDAC cohort from observation to ELI-002 at time of relapse: iRECIST
- **ctDNA** enabled patient selection and molecular disease monitoring
- Comprehensive **immunological** profiling
- **Designed for robust CPOC** across multiple indications

# AMP-Vaccination to Discover and Develop mKRAS-specific TCR-T Cell Therapy

NIH NATIONAL CANCER INSTITUTE

**HLA-transgenic Mice (human immune response)**

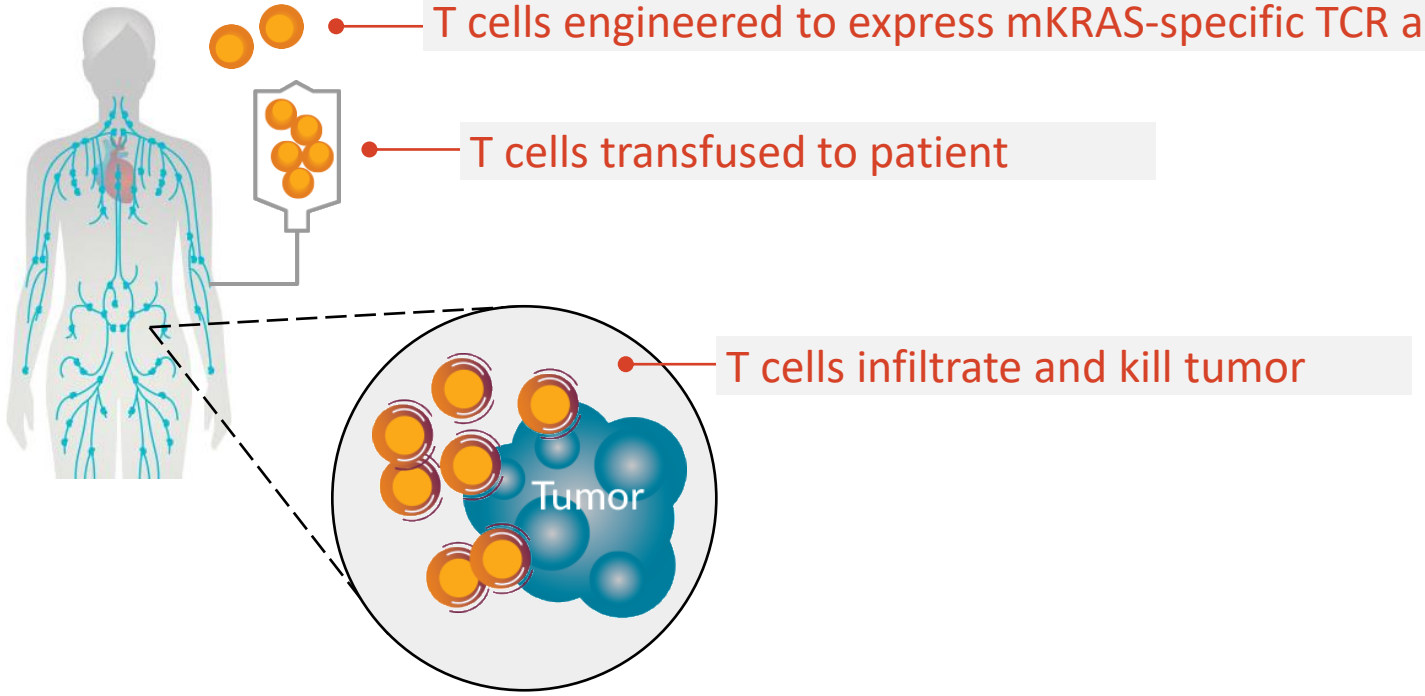
**AMP-KRAS + AMP-CpG**

**Dose 1**

**Dose 2**

**mKRAS-specific TCRs compatible with human tumor recognition**

elicio THERAPEUTICS




Tran, et al. **NEJM** 2016

elicio THERAPEUTICS

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