Presented at the AACR Annual Meeting, 5-10 April 2024, San Diego, CA, USA, and online

Abstract 4099

AMP-peptide vaccination against multiple p53 mutant epitopes promotes lymph node delivery to generate potent, functional T cell immunity

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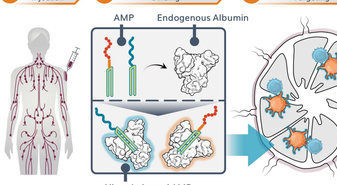
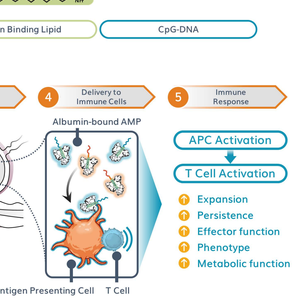
Why Target mp53 with Therapeutic Vaccination?

- **>30% of human tumors** have missense mutations in p53 [1,2]
  Annual incidence: 5.2M patients worldwide and 700K patients in the US
- An additional ~30% exhibit dysregulated p53 [3]
  such as copy number alterations, upstream deregulation and nuclear accumulation.
- Prevalent in nearly all tumor types. Sign of advanced disease.
- Poor clinical prognosis [4]



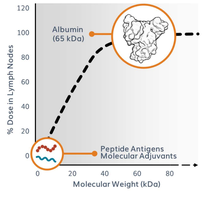


- **Truncal Driver Mutation**
  p53 mutations occur early in tumorigenesis and are therefore present among all cells within the tumor [5].
  Immune escape is unlikely as p53 signaling drives tumor survival, and its loss would stop tumor growth.
- **Public Neoantigen**
  Mutant p53 (mp53) peptides are not centrally tolerized; cognate TCRs are present in the naïve repertoire [6].
- **Proven Clinical MOA**
  Previously shown that mp53-specific T cells mediate anti-tumor efficacy [7].

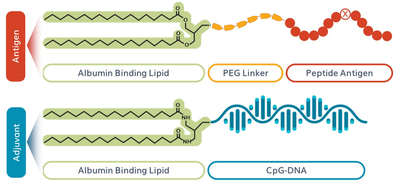
The AMP-Platform Delivers Directly to the Lymph Nodes

- **Smart trafficking to the lymph nodes** after subcutaneous dosing generates immune responses with increased magnitude, function, and durability [8,9].
- **Takes advantage of potent lymph node immune mechanisms**, including activation of innate and adaptive immune cells, antigen-spreading, and improved tumor T cell trafficking / infiltration.
- Mutant p53 peptides provide **validated antigens** for application of the Amphiphile (AMP) platform.
- Lymph node delivery of potent adjuvants **minimizes systemic exposure to improve safety.**

Lymph Node Biodistribution



AMP Platform Design



Clinical Experience with the AMP Technology [10,11]

- **ELI-002**, an AMP-vaccine targeting mKRAS, is currently being investigated in clinical trials for treatment of pancreatic and colorectal cancer (**AMPLIFY-201**: NCT04853017 and **AMPLIFY-7P**: NCT05726864).
- **ELI-002** has shown preliminary safety / tolerability, and significant increases in mKRAS T cell responses, associated with reduction / clearance of tumor biomarkers, and reduced risk of progression and death.
- Vaccine candidates targeting mutant p53 have been built from the AMP-platform, and utilize the ELI-002 adjuvant, AMP-CpG, providing the potential for favorable clinical tolerability and activity.

Off-the-Shelf Formulation

Composition

Adjuvant [TLR9 Agonist]
AMP-CpG 7909

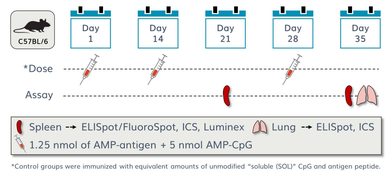
Antigen [30mer Peptides]
AMP-p53 Mutant Peptides
Potential candidates: 12 of the most frequently occurring p53 mutations [12].

	Mutant	% Patients
1	R248W	3.53%
2	R248Q	4.37%
3	R175H	5.60%
4	R273H	3.95%
5	R273C	3.31%
6	R282W	2.83%
7	G245S	2.11%
8	R249S	2.04%
9	Y220C	1.83%
10	C135Y	0.43%
11	R158H	0.52%
12	H214R	0.39%
		30.91% [12]

- Built from versatile AMP-platform.
- Formulation enables uncomplicated distribution and administration.

Repeat-Dose Immunization Strategy

Study Design

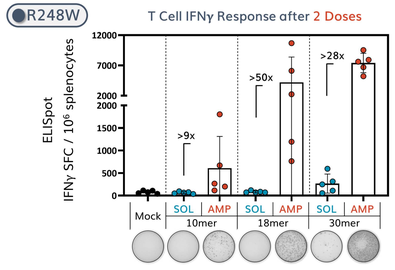


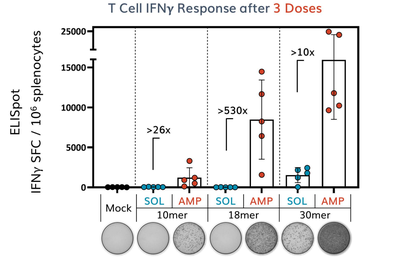
*Control groups were immunized with equivalent amounts of unmodified "soluble (SOL)" CpG and antigen peptide.

AMP Vaccination Yields Potent Response after Repeat Immunization in Mice

- T cell IFNγ response in splenocytes after **2 and 3 doses.**
- The 10mer, 18mer, and 30mer AMP-peptides are centered around the same R248W mutation.

R248W

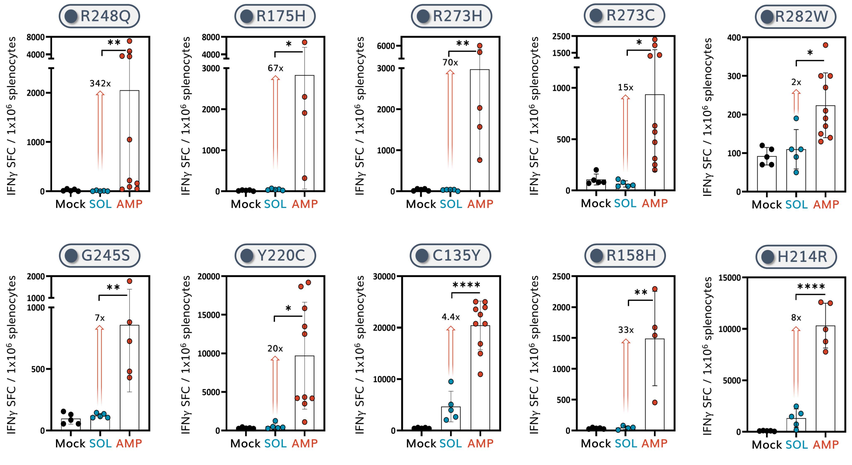




- Longer antigen peptides contain greater numbers of potential epitopes, increasing the probability of a strong immune response in various human HLA haplotypes.
- Potent T cell responses are observed after only two doses with AMP-mp53 R248W, which are further improved after a third bi-weekly dose.

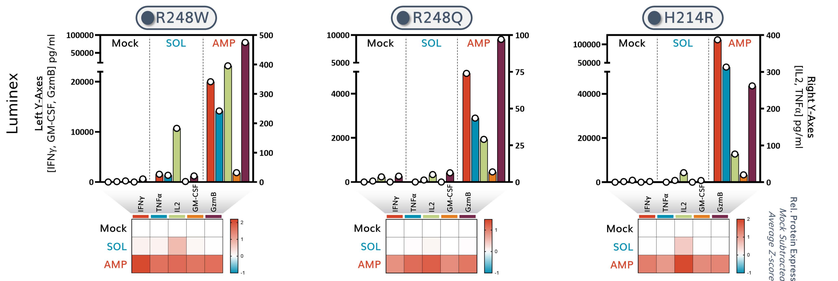
ELI-008 Could Potentially Cover 30% of Human p53-Mutated Cancers

- The **most common p53 mutants** in human cancers were targeted with individual AMP-peptide vaccines.
- ELI-008 vaccine candidates elicit **significant IFNγ responses in T cells** after 3 doses.



mp53 AMP-peptides elicit strong T cell responses upon immunization, demonstrating the potency of the AMP-platform as well as the versatility and ease of application.

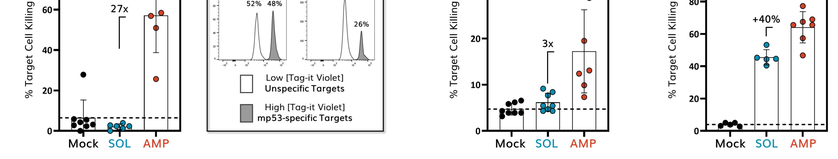
AMP-mp53 Vaccination Elicit Comprehensive Polyfunctional Responses



- Polyfunctional T cells in spleen produce high levels of IFNγ, TNFα, GM-CSF, IL2 and GzmB after 3 doses

AMP-mp53 Vaccination Generates Cytotoxic T Cells

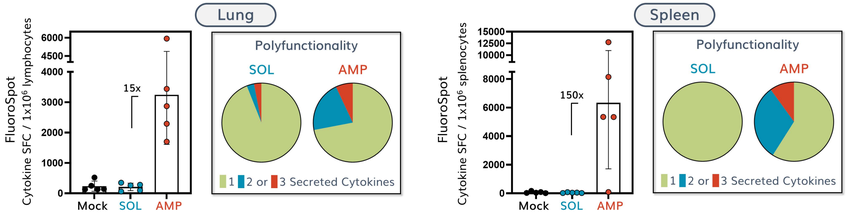
- AMP-mp53 immunized mice were intravenously challenged with mp53-peptide pulsed target cells



- AMP-mp53 vaccinated mice were able to recognize and eliminate peptide-pulsed target cells *in vivo*.

mp53-specific T cells Patrol Potential Metastatic Sites in Peripheral Organs

- FluoroSpot analysis of IFNγ, TNFα and IL2 in **lung-resident lymphocytes** and **splenocytes** after 3 doses. R248W



- Polyfunctional T cells reside not only in secondary lymphoid tissues like spleen, but in peripheral organs such as the lung, which is one of the predominant sites for metastatic spread in many cancers.

TAKE HOME MESSAGES

- AMP enhances vaccine potency via targeted lymph node delivery.
- ELI-008 substantially improved T cell responses over soluble comparator vaccines:
  - Polyfunctional T cells that produce T_H1-associated cytokines: IFNγ / TNFα / IL2 / GM-CSF
  - Secretion of Granzyme B, potent cytolytic function
- AMP-vaccines have the potential to address a high, unmet medical need for millions of patients with p53 mutations.
- The AMP-platform technology is simple, rapid and scalable for broad clinical application.

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Funded by:

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