A Lymph Node Targeted Amphiphile Vaccine Induces Potent Cellular and Humoral Immunity to SARS-CoV-2

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Overview

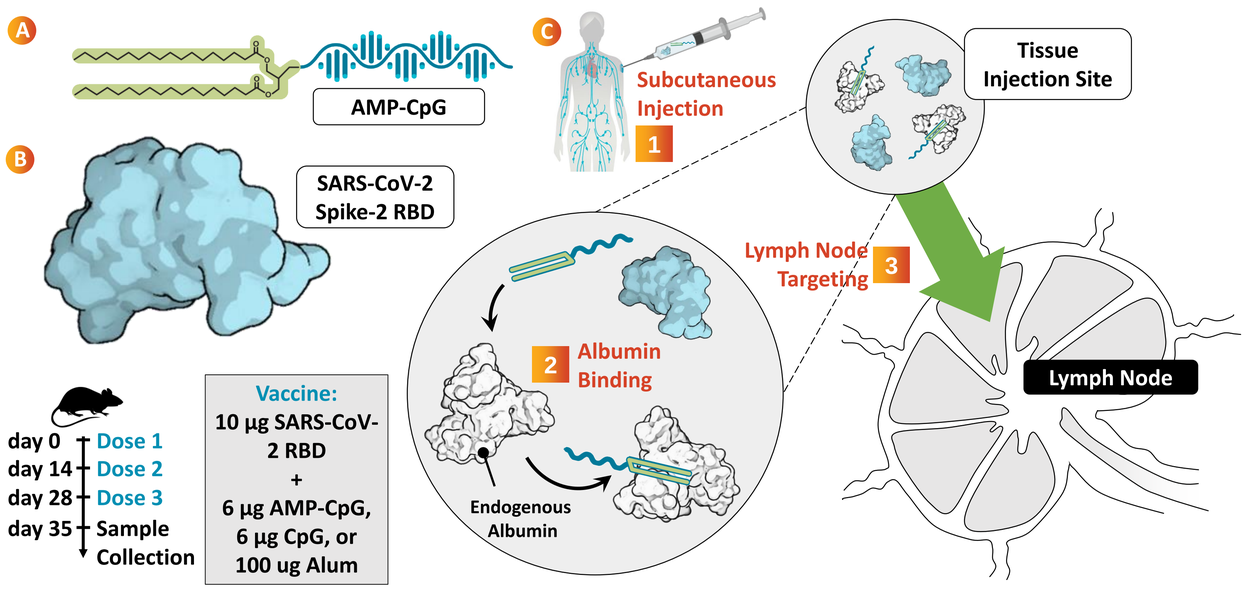
The SARS-CoV-2 pandemic's public health, economic, and social impacts mandate urgent development of effective vaccines to contain or eradicate infection. To that end, we evaluated a novel amphiphile (AMP) vaccine adjuvant, AMP-CpG, composed of diacyl lipid-modified CpG, admixed with the SARS-CoV-2 Spike-2 receptor binding domain (Spike RBD) protein for immunization (ELI 005). AMP immunogens are efficiently delivered to lymph nodes, where innate and adaptive immune responses are generated.

Female, 6 to 8-week-old C57BL/6J and BALB/c mice and 37-week-old C57BL/6J mice received two or more doses of benchmark (alum or CpG) or AMP-modified vaccines, comprised of Spike RBD protein and AMP-CpG adjuvant, subcutaneously injected into the tail base in two-week intervals. Antigen was dose spared to determine if AMP-CpG would maintain the immune response. Cellular immune responses were determined via ELISpot analysis of IFNγ production by splenocytes, intracellular cytokine staining of peripheral blood and lung-resident T-cells, and flowcytometric bead array analysis of Th1/2/17 cytokines. Humoral immune responses were determined via blood serum ELISAs to determine sera antibody binding titers, and pseudoviral neutralization assays for comparison to human convalescent serum.

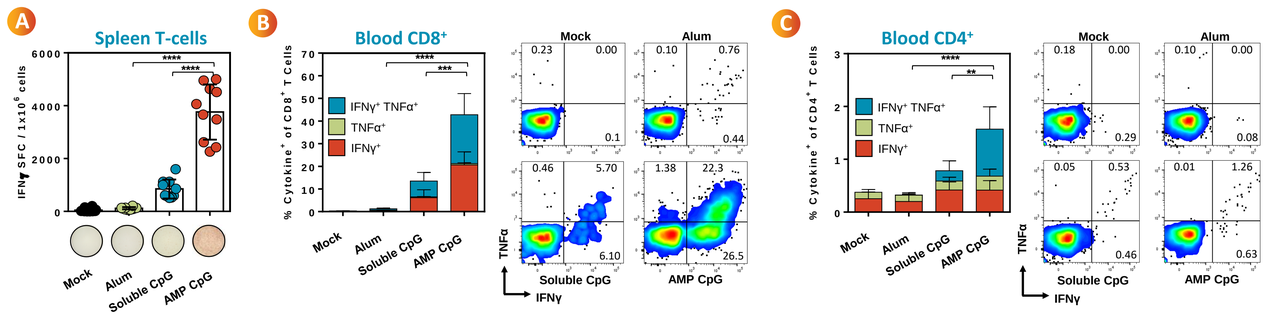
Compared to alum, AMP immunization induced 29-fold higher antigen-specific T cells which produced multiple Th1 cytokines and trafficked into lung parenchyma. Antibody responses favored Th1 isotypes (IgG2bc, IgG3) and potently neutralized Spike-2-ACE2 receptor binding, with titers >100-fold higher than the natural immune response from convalescent COVID-19 patients; responses were maintained despite 10-fold dose-reduction in Spike antigen. Both cellular and humoral immune responses were preserved in aged mice.

ELI-005 exhibits the qualities of an optimal SARS-CoV-2 vaccine, which should (1) induce robust and durable CD8+ and CD4+ T cell responses, (2) elicit high magnitude neutralizing antibodies, (3) produce Th1 bias in the elicited antibody and T cell responses, (4) potentially expand pre-existing cross-reactive T cells, (5) enable dose-sparing of required immunogens to improve the speed and cost of broad vaccination campaigns, and (6) be efficacious in elderly populations. These advantages merit clinical translation to SARS-CoV-2 and other protein subunit vaccines.

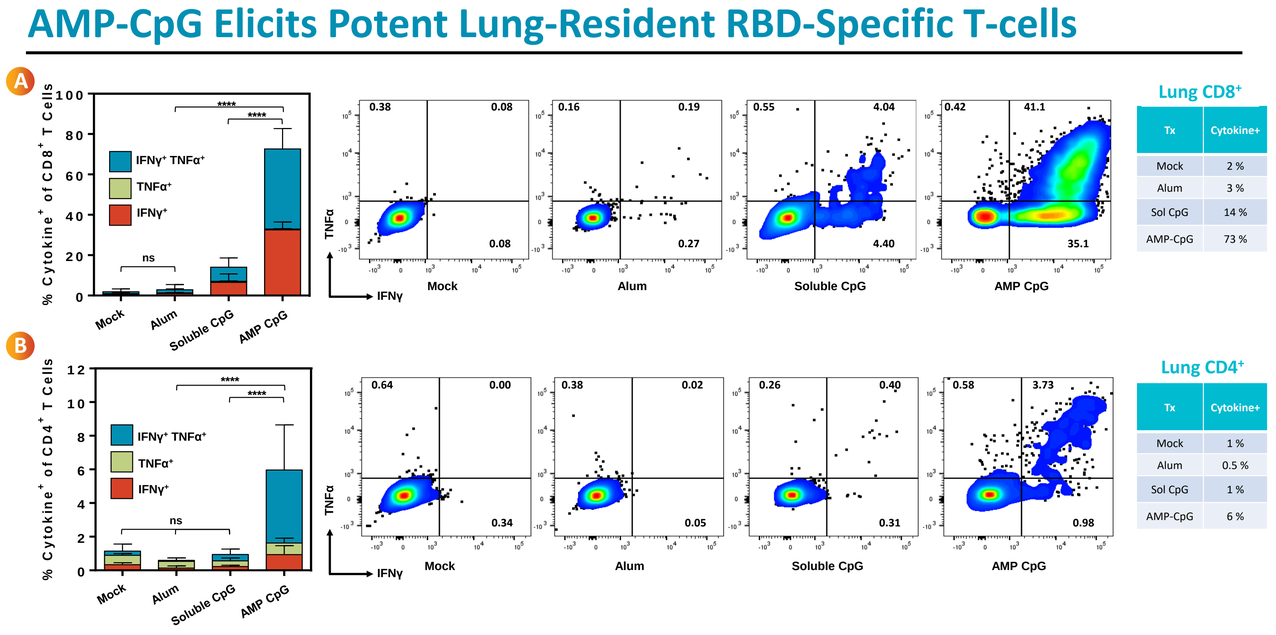
A Lymph Node Targeted SARS-CoV-2 Subunit Vaccine



AMP-CpG Elicits Potent RBD-Specific T-cells in Blood and Spleen



AMP-CpG Elicits Potent Lung-Resident RBD-Specific T-cells



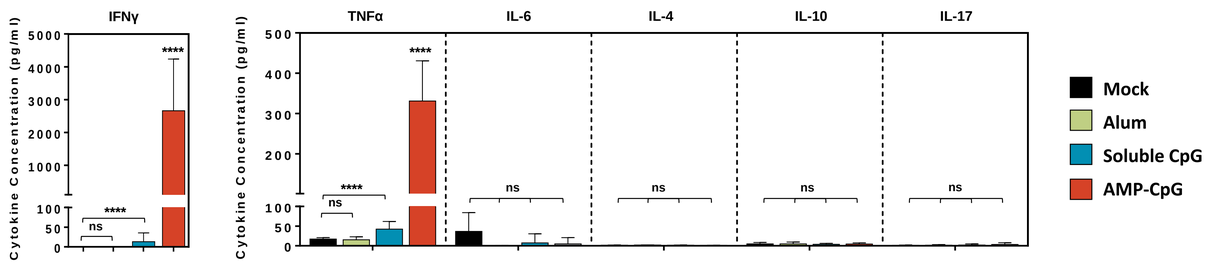
Lung CD8+

Tx	Cytokine+
Mock	2 %
Alum	3 %
Sol CpG	14 %
AMP-CpG	73 %

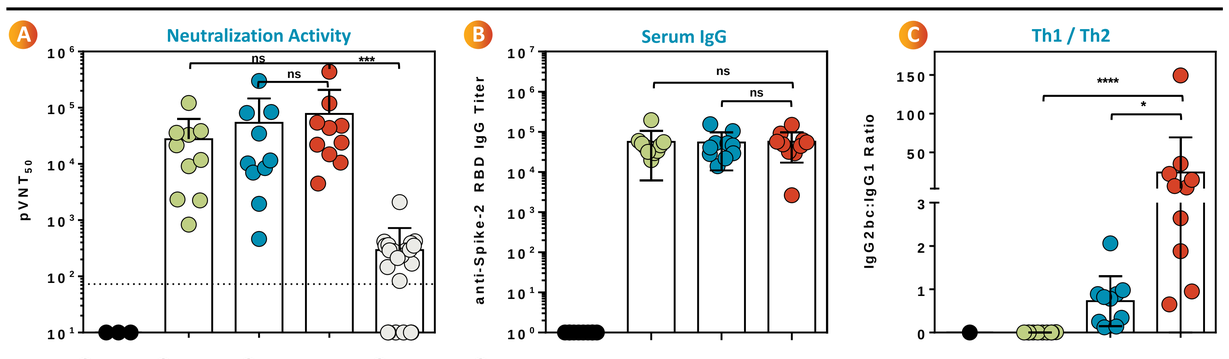
Lung CD4+

Tx	Cytokine+
Mock	1 %
Alum	0.5 %
Sol CpG	1 %
AMP-CpG	6 %

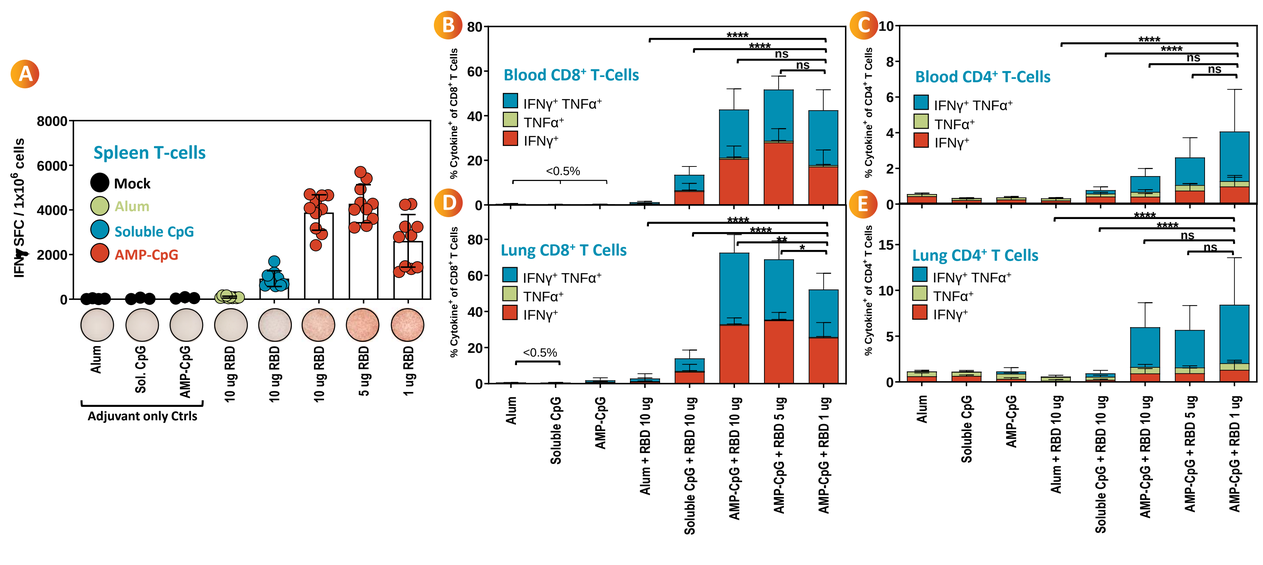
Lung Resident T-Cells Produce Th1 Cytokines, no Th2/Th17 Cytokines

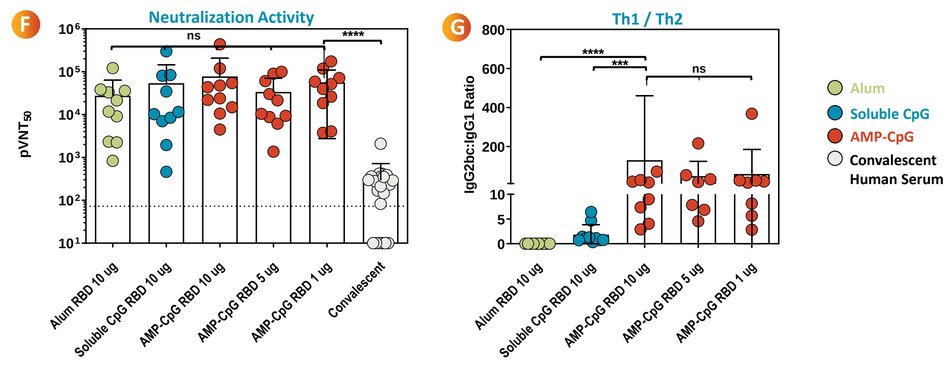


Potent Neutralizing Antibodies with Th1 Dominant Isotype Profile

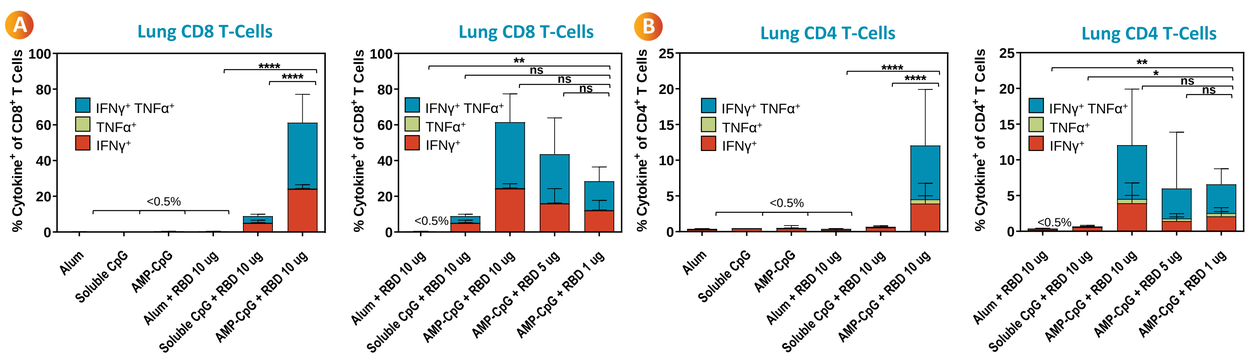


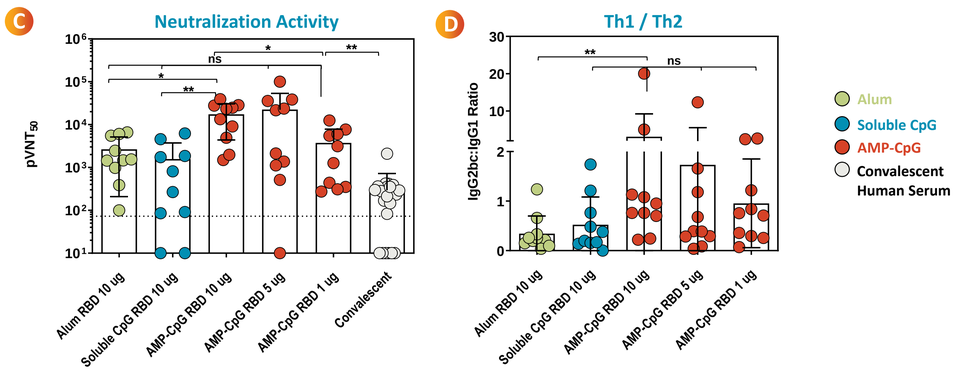
AMP-CpG Enables 10x Dose Sparing of RBD Protein





In Aged Mice AMP-CpG Enables 10x Dose Sparing of RBD Protein





Summary

1) Potent peripheral blood CD8+ (43% cytokine+) and CD4+ (1.5% cytokine+) T-cell responses

- **Polyfunctional Th1** cytokine secretion
- Responses maintained at **10-fold lower Spike RBD** protein dose
- Potent responses induced in both **young and aged mice**

2) Lung resident CD8+ (73% cytokine+) and CD4+ (6% cytokine+) T-cell responses

- **Polyfunctional Th1** cytokine secretion
- Responses maintained at **10-fold lower Spike RBD** protein dose
- Potent responses induced in both **young and aged mice**

3) Strong neutralizing antibody titers

- **High titer** responses exceed human convalescent levels
- Optimal **Th1 dominant** isotype profile
- Responses maintained at **10-fold lower Spike RBD** protein dose
- Potent responses induced in both **young and aged mice**