

COVID-19 NC Collaboratory Projects

**Final Narrative
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A vaccine against COVID-19 that strongly induces three branches of immunity

PI: Jenny Ting, PhD

Co-Is: Kristy Ainslie, PhD , Eric Bachelder, PhD, Benjamin Vincent, MD,
Mark Heise, PhD, John Forsberg

COVID-19, a disease caused by SARS-CoV-2 infection represents an historic public health challenge in North Carolina. A primary strategy for the control of SARS-CoV-2 is a successful vaccination. Numerous vaccine strategies are being used on an emergency basis, however it is clear that variants of this virus as well as new coronavirus will continue to be a global problem and second generation vaccines including universal vaccines are needed.

An impactful solution for an anti-SARS-CoV-2 vaccine is one that causes a vigorous immune response activating all branches of the immune system: antibody response, T lymphocyte activation and innate immune promotion. Although many platforms of vaccines are being tested, subunit vaccines remain well-tested based on historic strategies. It is comprised of an antigen and an adjuvant that amplifies the immune response. A number of adjuvants have been used in vaccination, but most do not induce a strong T cell response. We tested an adjuvant that is formulated of polymeric microparticles encapsulating a cyclic-dinucleotide. The cyclic-nucleotide kick-starts an interferon response to augment T, B and innate immunity. This adjuvant has been tested by us previously in an influenza vaccine, and is retooled here for a SARS-CoV-2 vaccine. In the six months since we had the NC Collaboratoy grant, we were able to leverage the provide funding to:

1. Produce large quantities of stabilized SARS-CoV-2 S protein that we shared with others on campus;
2. Test these proteins for intact epitopes to make sure that they are folded properly;
3. Produce and test cGAMP microparticles delivered with the S protein in two strains of mice to show high levels of anti-S antibodies;
4. Compare cGAMP MP with other adjuvants, including Addavax, Quil A and alum in side by side comparisons;
5. Demonstrate that Addavax, QuilA and cGAMP MP all produced high (10^6) titer antibodies, but cGAMP MP is the only one that produced high TH1 dependent antibodies;
6. Show that cGAMP MP is the only one that produced a high T cell response;
7. Show that Addavax and cGAMP MP both provided 100% protection against SARS-CoV-2 infection.

Narrative Scientific Summary

Our data shows that SARS-CoV-2 vaccination against the stabilized spike (S2P) antigen adjuvanted with cGAMP microparticles (MPs) show robust antibody response, but more important it distinguished from a top adjuvant, Addavax, by generating a robust T cell response. S2P antigen delivered with the adjuvant, cGAMP MPs, led to similar anti-S2P specific IgG antibody responses as AddaVax (a MF59-like adjuvant). However, cGAMP MPs skewed the antibody response toward IgG2c, which is a Th1 associated antibody isotype and is beneficial for anti-viral responses. S2P vaccination with cGAMP MPs also led to comparable neutralizing antibody titers as AddaVax but achieved significantly higher IgG2c response. When comparing cGAMP MPs to a panel of other clinically relevant, FDA-approved adjuvants including QuilA, Addavax and Alum, cGAMP MPs lead to the most significant increase in antigen-specific antiviral T cell responses as read out by T cell cytokines. This indicates that cGAMP MP leads to improved T cell immune responses and stronger antigen-specific T cell responses compared to conventional clinical adjuvants. In a challenge experiment with SARS-CoV-2 mouse virus, the cGAMP MP and Addavax protected all of the animals. An important long term experiment is to determine if the heightened T cell response can provide better protection that are more durable after the initial vaccination than Addavax.

Two grants have been submitted to NIH. A publication describing the work will be submitted in April.

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