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Developing a Polymeric Nanoparticle Vaccine for Co-delivery of Synergistic Adjuvants and "Mix and Go" Cancer Neoantigens

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Background and Introduction

- Immune checkpoint blockade (ICB) has revolutionized cancer immunotherapy but is not effective in all patients.
- Patients with tumors that have minimal T cell infiltration often do not respond to ICB.
- Cancer vaccines can increase the number of cancer-specific T cells and make ICB work better.

There are 2 main components to a cancer vaccine:

Neoantigen: Tumor specific proteins that arise from tumor mutations. Not expressed on healthy cells.

Adjuvant: Activates an innate immune response to provide dendritic cell co-stimulation and cytokine secretion. We will be using cGAMP which activates the stimulator of interferon genes (STING) pathway.

These components need both need to delivered into the cytosol, using a pH responsive polymersome:

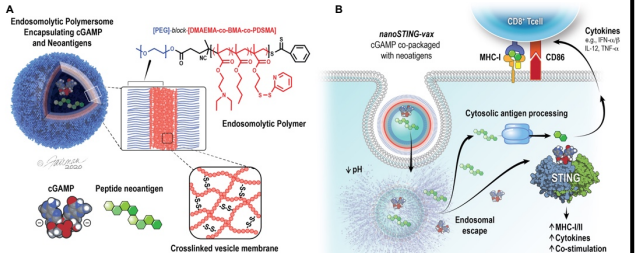


Figure 1. (A) cGAMP and tumor neoantigens are encapsulated in a pH-responsive polymeric nanoparticle, known as nanoSTING-vax. (B) NanoSTING-vax is endocytosed. In the low pH of the endosome the cGAMP and peptide are delivered to the cytosol where the cGAMP activates STING and the peptide is processed and presented on MHC class I molecules.

NanoSTING-vax Improves Lymph Node Accumulation

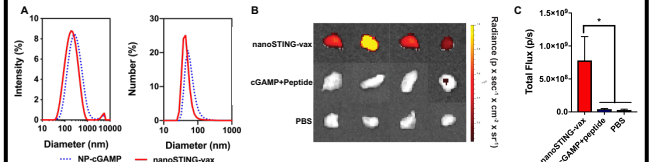


Figure 2. NanoSTING-vax size allows for increased lymph node accumulation. (A) Dynamic light scattering of nanoSTING-vax indicates the nanoparticles are ~100-200nm in diameter. (B) NanoSTING-vax increases the lymph node accumulation of peptide and cGAMP injected subcutaneously, as measured by IVIS. (C) Quantification of the IVIS images in B.

NanoSTING-vax Activates Dendritic Cells and T Cells

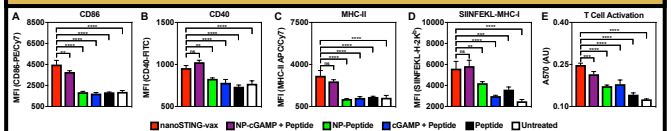


Figure 3. In vitro dendritic cell and T cell activation. Treatment with nanoSTING-vax enhances the expression of co-stimulatory markers CD86 (A) and CD40 (B), as well as MHC-II (C) on bone marrow derived dendritic cells (BMDCs). NanoSTING-vax also enhances the presentation of the antigen SIINFEKL on MHC-I (D) and the ability of BMDCs to activate T cells via a B3Z assay (E).

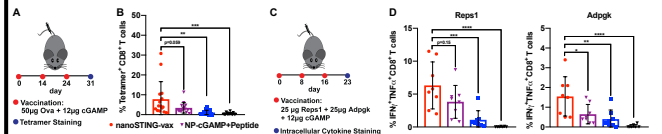


Figure 4. NanoSTING-vax increases the number of antigen-specific T cells *in vivo*. (A) Dosing scheme. (B) NanoSTING-vax increases the number of SIINFEKL-specific CD8+ T cells measured using tetramer staining. (C) Dosing Scheme. (D) NanoSTING-vax increases the number of Reps1 and Apgdk activated T cells measured using intracellular cytokine staining.

NanoSTING-vax Improves Response to ICB

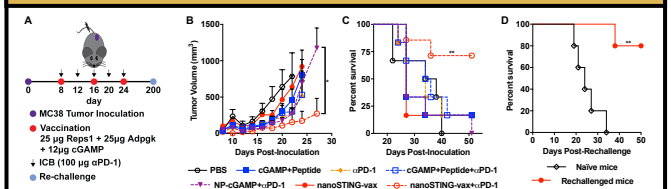


Figure 5. MC38 Tumor Challenge. (A) Dosing scheme of MC38 tumor challenge. (B) Tumor growth curve shows nanoSTING-vax + ICB (αPD-1) inhibits tumor growth the most. (C) Survival curve shows 5/7 complete responders with nanoSTING-vax + ICB. (D) Survival of mice re-challenged with MC38 tumors shows immunological memory.

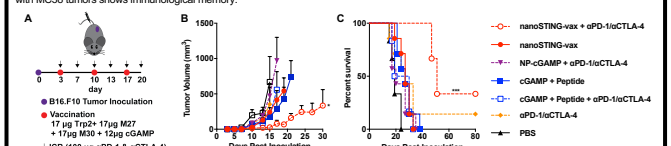


Figure 6. B16.F10 Tumor Challenge. (A) Dosing scheme of B16.F10 tumor challenge. (B) Tumor growth curve shows nanoSTING-vax + ICB (αPD-1/αCTLA-4) inhibits tumor growth the most. (C) Survival curve shows 2/6 complete responders with nanoSTING-vax + ICB.

"Mix and Go" Platform

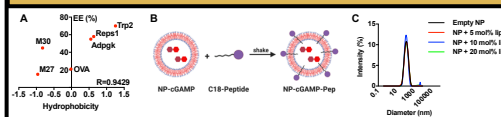


Figure 7. Lipidated peptides can insert into the nanoparticle. (A) Hydrophobic neoantigen peptides are encapsulated with higher efficiency into the nanoparticle, motivating the lipidation and insertion of all peptides. (B) Overview of lipid insertion. (C) Amount of peptide inserted does not affect nanoparticle size.

Using Adjuvant Combinations

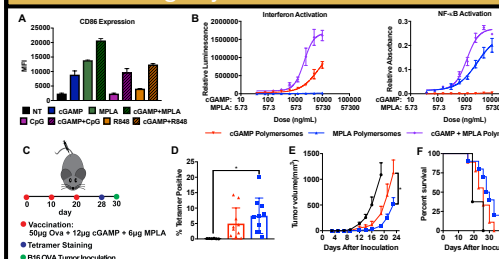
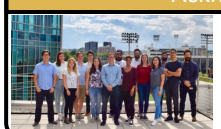


Figure 8. Multiple adjuvants enhance the immune response. (A) Using multiple adjuvants enhance CD86 expression on BMDCs. (B) Nanoparticles loaded with both cGAMP and MPLA have enhanced interferon and NF-κB activation. (C) Dosing scheme for mice vaccinated with nanoSTING-vax with or without MPLA. Mice vaccinated with nanoSTING-vax that also has MPLA loaded have more SIINFEKL-specific CD8+ T cells (D), delayed B16.OVA tumor growth (E), and improved survival (F).

Conclusions

- Dual delivery of cGAMP and neoantigen peptides generates CD8+ T cell responses that improves response to immune checkpoint blockade.
- Incorporating "mix and go" technologies and synergistic adjuvants will allow for a more effective and translatable personal cancer vaccine.

Acknowledgements



Kyle Becker, Carcia Carson, Jessalyn Baljon, Lihong Bishop, Moe Wehbe, Kyle Garland, Christian Palmer, Lucinda Pastora, Taylor Sheehy

Shae, D*; Baljon, JJ*; et al. Co-delivery of Peptide Neoantigens and Stimulator of Interferon Genes Agonists Enhances Response to Cancer Vaccines. *ACS Nano*, 2020, 14, 9904-9916.