CHEMICAL ENGINEERING
UNIVERSITY of WASHINGTON

# SEMINAR

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## Enhancing Immunity through the Rational Design of Vaccine Structure

1-2 pm PST Monday July 19th, 2021
Zoom link is provided via email, or
contact dyss@uw.edu

## Bio

Michelle Teplensky is an International Institute for Nanotechnology Postdoctoral Fellow at Northwestern University in Professor Chad Mirkin's laboratory. She is currently leading projects that work to develop nanotechnology as vaccine platforms against cancers and infectious diseases by understanding and manipulating structure-function relationships at the nanoscale. Prior to this position, she obtained her Ph.D. in Chemical Engineering from the University of Cambridge, UK under a Gates Cambridge Scholarship, and her B.S. in Chemical-Biological Engineering from MIT.

## Abstract

Immunotherapies, such as "cancer vaccines," potently activate the immune system against disease, stimulating targeted responses. Using both an adjuvant (immune system activator) and an antigen (immune system target), vaccines can drive the immune system to seek out and kill tumor cells. In prostate cancer (PCa), for example, clinically-used immunotherapeutics are tremendous proof-of-concept achievements against advanced disease, but are limited in scope and efficacy. They either do not significantly delay disease progression or only induce complete remission in a fraction of patients, likely due to "immunologically cold" tumor microenvironments (*i.e.* poor immune cell infiltration).[1,2] Immunotherapy vaccines that "turn tumors hot" (*i.e.* induce immune cell infiltration into tumors) are thus attractive for PCa because there are multiple well-established proteins upregulated on cancerous tissue compared to normal tissue that can be used as immune targets. Indeed, numerous immunogenic peptides that can be used as immune antigen targets have been identified for the protein, prostatespecific membrane antigen (PSMA). However, delivery of vaccine components has varied, and approaches have been logistically difficult, labor-intensive, and expensive to produce at scale, as many require handling of human cells. Moreover, it has been determined that the design of a vaccine and the *presentation* of the relevant components, and not *solely* the composition, is exceptionally important and can have profound impacts on the downstream immune response.[3]

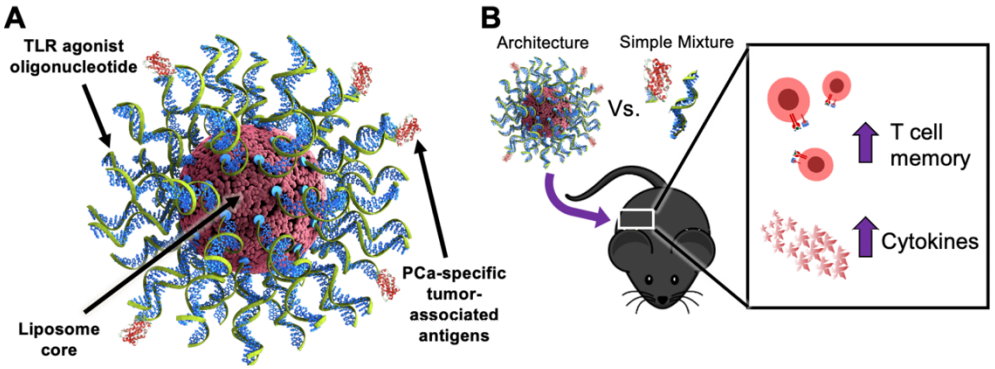


**Figure 1. A)** Spherical Nucleic Acid (SNA) vaccine, including adjuvant TLR agonist DNA as the dense radially-arranged shell, PCa peptide antigens, and a liposome core. **B)** SNA architecture elevates antigen immunogenicity and leads to enhanced T cell memory and cytokine secretion compared to a simple mixture of the same vaccine components.

Herein, I present our exploration of the effect of vaccine structure on function in PCa using the spherical nucleic acid (SNA) architecture, an emergent therapeutic platform which consists of a dense shell of oligonucleotides radially conjugated to a nanoparticle core (Fig. 1A). This arrangement imparts these structures with enhanced properties, including increased cellular uptake and higher resistance to nuclease degradation compared to linear counterparts, and gives them the potential to induce immune activation through toll-like receptors (TLRs).[4] Their modularity has allowed us to uncover key structure-activity relationships and design highly potent immunostimulatory SNA constructs. We have successfully developed an SNA vaccine against PCa incorporating human peptide antigens that failed out of clinical trials, by considering the importance of architecture and its effect on the kinetic relationships between antigen and adjuvant co-delivery. In a direct comparison of the SNA against a clinical formulation of PSMA peptides using humanized mice, which can recapitulate key human immune system components in an animal, we observe a significant increase in proinflammatory cytokine secretion and T cell memory

for the SNA architecture (Fig. 1B). Overall, this correlates to an improved ability of T cells raised from mice immunized with the SNA vaccine to robustly kill PCa target cells *ex vivo*. Importantly, these vaccines are capable of raising enhanced apoptotic responses from human peripheral blood mononuclear cells against PCa cells, which demonstrates the translational potential of SNAs.

Through this work, we have enhanced the potency of previously discovered PCa-specific tumor-associated antigens and demonstrated the power of leveraging vaccine architecture in improving an immune response. These results show that by *not* considering structure in previous vaccine formulations, the field has likely missed previously identified correct targets, writing them off when there was simply use of an incorrect structure and presentation to cells. With these findings, we have the opportunity to repurpose clinically-unsuccessful antigens by incorporating them into a potent vaccine architecture to enhance PCa therapy, thereby improving clinical outcomes through rational design at the nanoscale.

(1) Bilusic, M.; et al. Clin. Cancer Res. 2017, 23 (22), 6764–6770.
(2) Bonaventura, P.; et. al. Front. Immunol. 2019, 10 (168), 1–10.
(3) Wang, S.; et. al. Proc. Natl. Acad. Sci. 2019, 116 (21), 10473–10481.
(4) RadovicMoreno, A. F.; et. al. Proc. Natl. Acad. Sci. 2015, 112 (13), 3892–3897.