Rational Vaccinology for Prostate Cancer Using Spherical Nucleic Acids

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Background: Immunotherapies, such as "cancer vaccines," potently activate the immune system against disease, stimulating targeted responses. Using an adjuvant (immune system activator) and an antigen (immune system target), these vaccines can drive the immune system to seek out and kill tumor cells. Previously, it was thought that the composition of the vaccine solely influenced the downstream response. However, recent work in our group has demonstrated that the *presentation* of the relevant components also plays a key role.

Methods: We are exploring this effect in the context of the spherical nucleic acid (SNA), an emergent therapeutic architecture which consists of a dense shell of oligonucleotides radially conjugated to a nanoparticle core. This arrangement imparts these structures with enhanced properties, including increased cellular uptake and higher resistance to nuclease degradation compared to the same sequence of linear oligonucleotides, and gives them the potential to induce immune activation through toll-like receptors (TLRs). We are able to chemically synthesize SNAs through post-liposome intercalation of immunostimulatory oligonucleotides by using hydrophobic anchors to our DNA.

Results: The modularity of the SNA has allowed us to uncover key structure-activity relationships and arrive at highly potent immunostimulatory constructs. We have successfully developed a prostate cancer vaccine based on what we have learned about the importance of architecture and its effect on kinetic relationships and antigen/adjuvant co-delivery. And, by modulating such parameters, we have created SNA vaccines with dramatically different downstream T cell activation, tumor cell killing, tumor burden, and animal survival.

Conclusions: By applying this work to prostate cancer-specific tumor-associated antigens, we are advancing the promise of a clinically translatable solution and showing how prostate cancer immunotherapy can be greatly improved through rational design at the nanoscale.

Conflict of Interest: C.A.M. owns stock in Exicure, which has licensed the SNA technology.

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