Lay Abstract
Breast cancer (BCa) is the second leading cause of cancer death for women in the United States, and metastatic BCa (mBCa) has only a <30% 5-year survival rate (SR). mBCa treatment has been improved by immunotherapy such as immune checkpoint blockade (ICB). Yet, a broadly and durably responsive BCa immunotherapy remains an unmet medical need. Our long-term goal is to develop efficacious and safe mBCa immunotherapy by synergistically combining ICB with subunit vaccines, which elicit broad, potent, and durable antitumor immunity and ameliorate tumor immunosuppression. We hypothesize that rational combination of ICB with therapeutic vaccines that prime a potent, durable, and broad spectrum of CD4+ and CD8+ T cell responses can be a powerful immunotherapy to enhance overall response rate and SR for mBCa. Cancer vaccines can supply adjuvants, tumor neoantigens or tumor-associated antigens (TAAs) to overcome immunosuppression, elicit or augment antitumor immune cells for ICB to target, and upregulate immune checkpoint levels, making vaccines synergistic with ICB for immunotherapy. Chemically-defined molecular vaccines are attractive due to typically good safety and ease of manufacture, transportation, and storage. The efficacy of peptide vaccines rely on potent adjuvants and adjuvant/antigen co-delivery to lymphoid tissues and cells. We recently showed that Toll-like receptor 7/8 (TLR7/8) agonist R848 and TLR9 agonist CpG is a potent combination adjuvants that potentiated neoantigen-specific immunity for cancer immunotherapy. Moreover, for efficient delivery of subunit vaccines, we developed albumin-binding vaccines (AlbiVax) based on a safe albumin-binding Evans blue derivative. AlbiVax enhanced immune delivery of individual adjuvants and antigens 100-fold and promoted antigen-specific T cell responses 14-fold, relative to a clinical benchmark Montanide or incomplete Freund’s adjuvant (IFA). Our objective in this application is to improve mBCa immunotherapy by rational combination of ICB with multi-epitope/di-adjuvant co-delivering AlbiVax (Medico-AlbiVax). Specifically, we aim to 1) develop mBCa Medico-AlbiVax to efficiently deliver vaccine molecules into immune tissues and cells, and elicit systemic, potent, long-lasting, and broad BCa immune responses, and 2) demonstrate the principle of rationally combining Medico-AlbiVax with ICB that targets the immune checkpoint(s) sensitized by Medico-AlbiVax for mBCa immunotherapy. This innovative application is supported by solid preliminary results. The ability of Medico-AlbiVax to bind to the host albumin protein carrier in a patient’s body not only leverages molecular vaccines’ ease in large-scale production, in vivo stability and long-term safety, but also leverages albumin/Medico-AlbiVax nanocomplexes for efficient delivery to immune tissues and cells. The unique chemical structure of Medico-AlbiVax ensures adjuvant/antigen co-delivery to elicit potent antitumor T cell responses. The potent di-adjuvant ensures to elicit potent and long-lasting immune responses with immune memory; and the multi-epitope vaccine broadens the spectra of antitumor immune responses, resulting in minimal escape of tumor cells from immune responses. We expect this pilot study to generate key evidence to support comprehensive preclinically and potential clinical testing for mBCa immunotherapy. The use of chemically-defined vaccines, FDA-approved or clinically investigated drugs, and a clinically safe albumin binder would facilitate their clinical translation and improve the clinical practice.