Our laboratory develops synthetic materials as tools to dissect cellular immunology and as delivery agents for new immunotherapies and vaccines. In this talk, 2 distinct strategies for engineering the immune response will be described for enhanced vaccines and cellular immunotherapy. First, we have recently focused on the development of engineered synthetic amphiphiles designed to promote both the physical targeting of vaccines to lymph nodes and to enhance triggering of antigen-specific cells in these immune command centers. In cancer patients, visual identification of sentinel lymph nodes (LNs) is achieved by the injection of dyes that bind avidly to endogenous albumin, targeting these compounds to LNs where they are efficiently filtered by resident phagocytes. We translated this “albumin hitchhiking?” approach to molecular vaccines, via the synthesis of amphiphiles (amph-vaccines) comprised of an antigen or adjuvant cargo linked to a lipophilic albumin-binding tail by a solubility-promoting polar polymer chain. Structurally-optimized CpG-DNA/peptide amph-vaccines exhibited dramatic increases in LN accumulation and decreased systemic dissemination relative to their parent compounds in mice, leading to substantially enhanced efficacy of epitope-based vaccines while eliminating systemic toxicity from CpG. In parallel, we have discovered that multivalent amphiphiles that present nanoclustered antigens can dramatically enhance the engagement of antigen receptors on antigen-specific B-cells. Such antigen nanoclustering enhanced B-cell activation even when antigen was displayed in a highly multivalent manner on the surface of nanoparticles. Altogether, these engineered amph-vaccines provide a simple, broadly-applicable strategy to simultaneously increase the potency and safety of subunit vaccines.