BIOMATERIALS THAT ENGINEER INFECTION IMMUNITY

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Gene-based nucleic acid vaccines are capable of eliciting protective immunity in humans to persistent pathogens, e.g., HIV, malaria, and tuberculosis, for which conventional protein/peptide vaccines have failed. Recent identification and characterization of genes coding for tumor antigens has stimulated the development of nucleic acid-based cancer vaccines. With increasing life expectancy in high-income countries and newly emerging infections in low-income countries, new technologies are required to address changing vaccine needs. Nucleic acid vaccines have the potential to address these needs, but despite decades of research there is still no commercial product for human use. Nucleic acid vaccines (pDNA, mRNA) have certain advantages over protein antigen vaccines: (a) they lack the MHC haplotype restrictions of peptide/protein antigens and (b) nucleic acid vaccines are not subject to neutralization by the host immune response, thus allowing repeat boosting. Messenger RNA (mRNA) is a promising alternative to plasmid DNA (pDNA) since (a) mRNA does not require nuclear entry for activity, (b) mRNA does not integrate into the host genome, and (c) mRNA does not require cancer derived promoters (e.g., CMV). However, to be commercially competitive as a platform technology, mRNAbased vaccines must match the potency of viral vectors at doses of RNA that are not cost prohibitive. Our work seeks to maximize mRNA vaccine efficacy by (a) enhancing vaccine delivery route, (b) developing an autocatalytic, self-replicating mRNA (SRmRNA) vector, and (c) magnifying dendritic cell (DC) antigen uptake and activation using chemokine therapy. We could carry out this entire immunization study using the classic model antigen, ovalbumin (OVA) (as the protein or its gene). However, the strong CD8+T cell responses elicited against the highly immunogenic OVA peptide may not be indicative of responses to more native epitopes from pathogens or tumor antigens. Consequently, here we will focus on preventing bacterial infections of implanted medical devices. This project has developed a scaffold-based vaccine technology, superior to mucosal or systemic delivery. Implants release mRNA vaccines (or pDNA for comparison) that transfect arriving antigen-presenting cells (specifically dendritic cells - DCs) to produce T- and B-cell memory and antibody expression against the select pathogen, and potentially stimulate direct native killer T-cell responses (ideal for intracellular infecting bacteria).

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