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Development and optimization of peptide-based nanoparticle NeoAg cancer vaccines

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Scientific Abstract:

Optimal T cell immunity to both pathogens and cancer requires the concerted action of CD8+ and CD4+ T cells. Leveraging this concept in therapeutic cancer vaccines has been inhibited by the absence of reliable methods for identifying tumor-specific neoantigen targets for each subset. We have developed a platform that combines bioinformatic prioritization of expressed variants identified through WES/RNAseq with functional recognition assays using autologous PBMC to efficiently validate patient-specific CD4+ and CD8+ neoantigens (NeoAg) in cancer patients across > 25 different histologies, and have begun clinical trials using peptide-based personalized cancer vaccines based on this approach. In parallel, our preclinical program has revealed that physical linkage between NeoAg recognized by CD4+ T cells and CD8+ T cells greatly increases the magnitude and efficacy of vaccine-induced responses, resulting in the eradication of large existing tumor burdens. The goal of this proposal is to develop and optimize a vaccine platform that can achieve the coordinated induction of NeoAg-specific CD4+ and CD8+ T cells in patients using self-assembling nanoparticles in which both types of target antigens are contained within a single 20-50nm particle composed of the same type of peptides used in our current vaccine that have been modified at their N-terminus for charge and their C-terminus for hydrophobicity. Specifically, we will test various modifications of flanking sequences to identify those optimal for presentation of target epitopes via class I versus class II MHC and will determine whether the vaccines can be targeted to dendritic cells via Clec9a receptor to increase presentation efficiency in the setting of vaccine mmunotherapy. Successful vaccine candidates will be directly advanced for clinical testing in cancer patients at MCC.

Lay Abstract:

Natural immune responses that protect us from viral and bacterial infections require the coordinated activity of two subsets of T lymphocytes known as CD4+ helper" T cells and CD8+ "killer" T cells. Through our ongoing translational research program at LJI and the UCSD Moores Cancer Center, we have found that this same concept applies to immune responses in cancer which are most effective when tumor antigen-specific CD4+ and CD8+ T cells are both engaged by a vaccine. We believe that integrating this concept into our personalized cancer vaccine clinical trial will be of significant benefit to our patients, and therefore the goal of this research is to develop vaccine platform that will enable both CD4+ and CD8+ T cells against a patient's tumor-specific target antigens to be generated in a manner that is safe, effective, reproducible, and consistent with the regulatory and manufacturing constraints which necessarily govern what can be administered to a patient. This work will involve testing various forms of a self-assembling peptide-based nanoparticle vaccine to identify the flanking sequences capable of insuring that a given vaccine peptide is presented to CD4+ and CD8+ T cells for recognition and the testing whether the vaccines can be targeted to the correct antigen-presenting cell to insure induction of potent therapeutic immunity. We will evaluate these in a preclinical animal model of cancer that mirrors key aspects of the human disease and, if successful, the findings from the research will be advanced for

clinical testing of the nanoparticle vaccine in patients at the UCSD Moores Cancer Center.