

The evolution of poxvirus based cancer vaccines

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Poxvirus vectors were first described in 1981. The potential to use these vectors to develop recombinant vaccines was recognized immediately. Initially simple pox vectors employing various strains of vaccinia viruses were designed to express well characterized antigens from pathogens of interest including hepatitis viruses, herpes viruses, HIV and influenza. Surprisingly in more than two decades of research and development the few recombinant pox virus vectored vaccines that have reached the marketplace have been for veterinary use only, most notably rabies. Not a single recombinant pox vector has yet been approved for sale for the prevention or treatment of human disease.

In the late 1980's and early 1990's, several groups began using vaccinia virus vectors to express tumor associated antigens (TAAs) such as viral antigens associated with tumor formation (polyoma virus T-antigen), oncogenes (Her2/neu) and embryonic antigens (CEA) among others. Several of these vectors were successful in preventing tumor formation in mice but unfortunately most of these murine models employed immunogenic TAAs that were foreign to the mouse. Breaking tolerance to syngeneic TAAs in murine models or attempts to treat pre-existing tumors proved to be a much more difficult task.

In the last several years poxvirus based cancer vaccines have evolved significantly. New generations of poxvirus vectors have been developed including canarypox, fowlpox, MVA and others. These vectors are attenuated in humans but remain highly immunogenic. These new vectors along with novel vaccination strategies such as combining replicating and non-replicating vaccines in prime/boost protocols and using more aggressive route and dosing regimes resulted in significant early improvements in vaccine effectiveness. However as attempts were made to treat tumors in more challenging murine models we found it necessary to find ways to further enhance the quantity and quality of cellular immune responses. A greater understanding of human tumor immunology has afforded us an opportunity to increase the immune responses generated by recombinant vectors. The large genomic capacity of the poxvirus vectors provides for the ability to insert and express multiple co-stimulatory molecules, such as B7.1, LFA-3 and ICAM-1 among others, or to insert cytokines such as GM-CSF and IL-2. The large capacity the vector has also allows for the insertion of multiple TAAs to maximize the number and type of epitopes expressed. In addition the identification of tumor specific T-cell epitopes has led to the direct modification of these epitopes within the TAAs expressed by the vectors, increasing their immunogenicity without affecting their specificity.

Several of these sophisticated new pox vectors have been shown to be capable of treating substantial tumor burden in transgenic animals presumably through improvements in both the quantity and quality of the immune responses induced. Vaccines based

on these improved vectors have also been shown to be capable of inducing tumor specific T-cells in several phase I and II human clinical trials. These incremental advancements in vaccine design and subsequent encouraging clinical data have led us to begin the first randomized phase III clinical trial of a poxvirus based cancer vaccine. Preclinical and clinical data leading up to this trial will be presented.

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