



A Phase I/II Trial Of Carbonic Anhydrase IX Molecularly Targeted Kidney Cancer Vaccine Therapy

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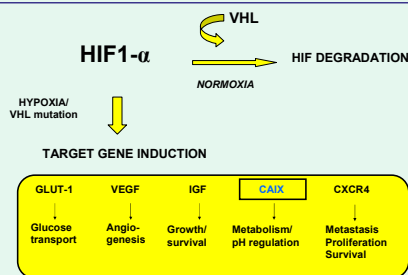
Introduction

The CAIX (MN/250) kidney cancer vaccine translational research protocol represents the culmination of ten years of investigator initiated, bench to bedside pre-clinical research, and will be the final forum for the clinical testing of a GMP-quality vector that was manufactured in collaboration with the National Cancer Institute (NCI) Rapid Access to Intervention Development (RAID) program. A single center clinical trial of a novel vaccine targeting a common tumor protein in patients with metastatic renal cell carcinoma (RCC) is proposed.

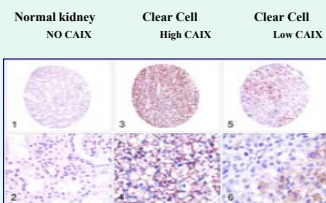
Approximately one third of RCC patients will have advanced disease at presentation, and one third of patients with localized disease will eventually progress to metastatic disease. Metastatic RCC poses a therapeutic challenge because of its resistance to conventional modes of therapy such as chemotherapy and radiation therapy. While it is clear that strides have been made in the struggle against metastatic RCC, the overall response rates of FDA approved therapies remain approximately 20% at best. Although, recent molecular targeted agents have recently been approved for RCC, these agents represent an incremental advance as disease progression is prolonged yet long term cures have not been achieved with these new therapies. Furthermore, these response rates are obtained at the cost of substantial toxicities to the patient. As a result, there remains an urgent need for the development of novel therapies to manage patients with metastatic or high risk, locally advanced RCC. One such concept would be to develop an immune based therapy that is also molecularly targeted. The objective of this clinical trial, therefore, is to test a novel tumor vaccine developed in our laboratory that is capable of inducing a specific immune response against RCC tumors in patients who have been carefully selected as those most likely to respond to the experimental therapy. We propose using patients' own immune cells that have been genetically engineered to express a protein consisting of carbonic anhydrase IX (CAIX), a novel RCC associated protein that is expressed in almost all RCC tumors and which is linked to GM-CSF, a potent immune stimulator which is capable of amplifying a CAIX-specific immune response. Based on our preliminary data we believe that the fusion protein, GM-CAIX, will provide added benefit and potency as compared to the use of either agent alone. The clinical protocol consists of a phase I/II clinical trial of a GM-CSF-CAIX based vaccine therapy. This study will utilize vaccine material produced with Current Good Manufacturing Practices (cGMP) in joint collaboration with the National Cancer Institute (NCI) Rapid Access to Intervention Development (RAID) program, and will introduce the concept of patient selection using CAIX-based "molecular eligibility criteria." As CAIX is expressed by other solid tumors in the context of tumoral hypoxia, an effective CAIX-based vaccine could have wider oncologic applications than RCC alone.

Background

VHL, Hypoxia, and RCC Tumorigenesis

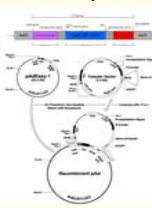


CAIX: A tumor specific tumor antigen present in >90% of clear cell RCC, but not in normal tissue

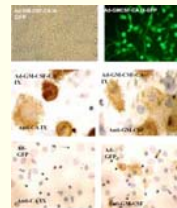


Pre-Clinical Vector

Generation of Adeno GMCSF-CAIX fusion using Adenovirus Expression System

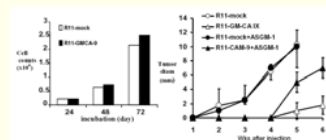


Expression of GMCSF-CAIX in Human DCs Transduced with Ad/hGMCSF-CAIX



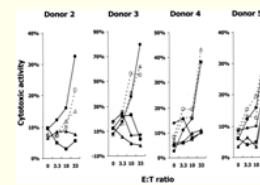
Hernandez et al., *Clin Cancer Res.* 2003

Ad/GMCSF-CAIX Inhibits Tumor Growth in SCID Mice



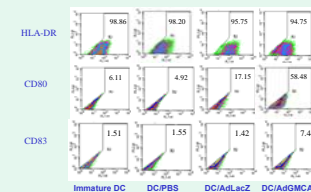
Hernandez et al., *Clin Cancer Res.* 2003

Ad/CAIX Transduced Human DCs Generates CAIX-specific MHC-restricted CTLs

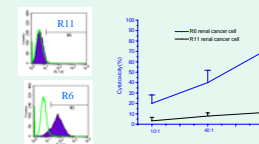


Makuyama, et al., *Clin Cancer Res.* 2004

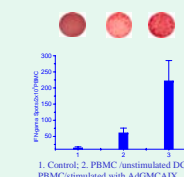
RAID GMP AdGM-CA9 Vector



Up-regulation of co-stimulatory signals and maturation markers of human DCs infected by clinical grade GMP produced Ad-GMCSF-CAIX



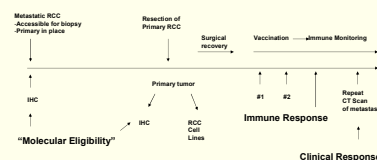
Enhanced cytotoxicity of RCC cell lines expressing CAIX by CTL stimulated by cGMP AdGMCAIX



Enhanced IFN- γ release from PBMC stimulated by cGMP AdGMCAIX

Proposed Clinical Study

Phase I/II Study of Ad-GMCAIX DC Vaccination in mRCC



Primary end-points of the phase I portion of the study are: Safety, Toxicity (NCI CTC), DLT, MTD

Primary endpoints on the phase II portion of the study are: to assess the clinical response rate (RECIST), immunological response, and to correlate the biologic/immunologic effects with clinical response

	Pre-Vaccine	D 0	D 14	D 28	D 55	D 70
Informed Consent	X					
Nephrectomy	X					
IHC for CAIX	X					
Lympho-biopsy	X					
Blood for Serum	X	X	X	X	X	X
Blood for Immunological Tests	X	X	X	X	X	X
Blood for CBC	X	X	X	X	X	X
Blood for Cytin Panel	X	X	X	X	X	X
Blood for ANA and RF	X	X	X	X	X	X
Vital and Physical	X	X	X	X	X	X
AdVCAIX/DC Vaccine	X	X	X	X	X	X
Immune Tests (CT)	X	X	X	X	X	X

Biologic/Immunologic testing will be conducted on day-21 (day of nephrectomy), day 28 (wk4), and day 70 (wk 10) and will include:

- PBL Phenotype and Cytokine Release
- Delayed type hypersensitivity (DTH) testing
- ELISPOT Assays for immune monitoring
- CA IX targeted cytotoxicity assay
- Determination of TCR Va-Vb repertoire and CDR3
- Tumor-infiltrating lymphocytes

Summary

Taken together, our results demonstrate that human PBMC-derived dendritic cells transduced with adenovirus vector encoding GMCSF-CAIX fusion gene can induce RCC antigen specific immune responses, providing an exciting potential of CAIX to serve as an effective treatment modality for advanced RCC patients. These pre-clinical studies form the foundation for a planned clinical trial using autologous dendritic cells pulsed with GMP manufactured Adeno-GMCAIX in patients with advanced kidney cancer. The RAID produced GMP vector demonstrates excellent in-vitro activity with upregulation of immune pathways, enhanced CAIX directed cytotoxicity and cytokine release.