Liminatus Pharma LLC

GCC Cancer Vaccine

Phase I Trial

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We have completed a Phase I Trial under the title of study of Ad5-GUCY2C-PADRE in stage I and II colon cancer patients in January 13, 2016.

Name of Sponsor: Department of Pharmacology and Experimental Therapeutics

Name of Investigational Product: Ad5-hGCC-PADRE

Title of Study: A phase I study of guanylyl cyclase C (GCC)-encoding replication-deficient human type 5 recombinant adenovirus vaccine (Ad5-hGCC-PADRE) in stage I and II colon cancer patients

Short Title: Phase I study of Ad5-hGCC-PADRE in colon cancer patients

Study Center(s): Thomas Jefferson University

Principal Investigator: Takami Sato, M.D., Ph.D.

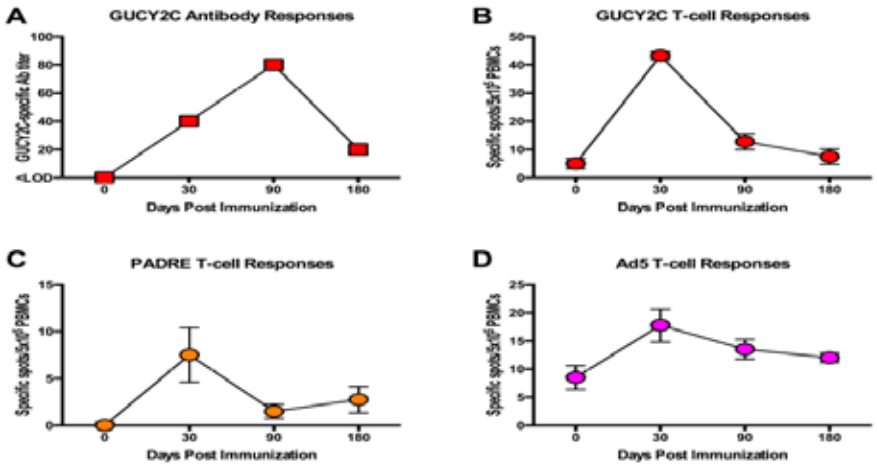
Co-Investigators: Scott A. Waldman, M.D., Ph.D., Adam E. Snook, Ph.D., Michael Mastrangelo, M.D., Nancy Lewis, M.D., Scott Goldstein, M.D., Walter Kraft, M.D., Yaa Oppong, M.D.

Studied Period (years): 2013.10 - 2016.1

Phase of Development: Phase 1

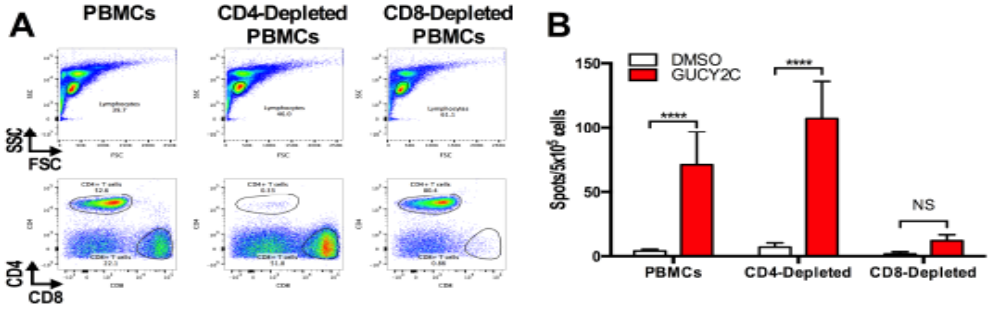
Objectives: The objectives of this study are to determine the safety, tolerability and toxicity of Ad5-hGCC-PADRE and to determine whether vaccine-induced immune responses are produced.

The Ad5-GUCY2C-PADRE vaccine was well-tolerated, producing only mild adverse events (AEs). GUCY2C-specific antibody and T-cell responses were observed in a subset of subjects. Consistent with preclinical mouse data, T-cell responses were composed of CD8+, but not CD4+, T cells. Analysis of 10 subjects receiving Ad5-GUCY2C-PADRE demonstrates proof-of-concept that GUCY2C is immunogenic in humans and that GUCY2C-directed vaccination is safe. Moreover, the presence of GUCY2C-specific antibody and CD8+ T-cell, but not CD4+ T-cell, responses is consistent with selective CD4+ T-cell tolerance observed in mouse models. These data establish GUCY2C as a safe and immunogenic target for immunotherapy in cancer patients.



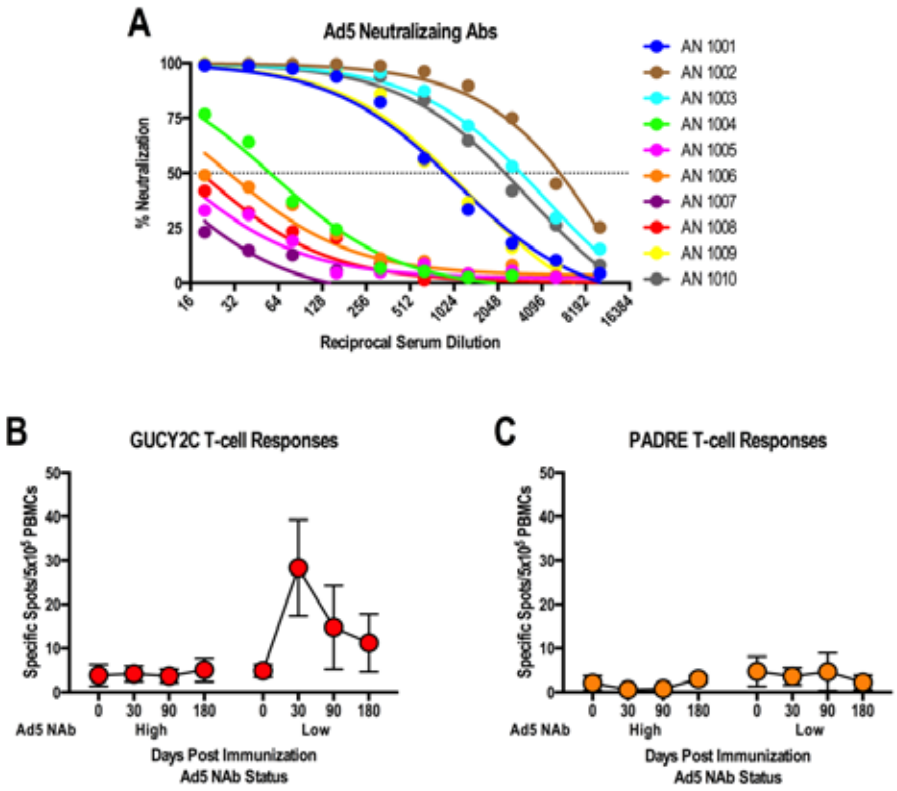
GUCY2C-Specific T-Cell and B-Cell Responses in Subject 1007

GUCY2C-specific antibody (A) and T-cell responses (B) were produced in subject 1007 following immunization. Similarly, modest PADRE-specific T-cell responses (C) were produced and Ad5-specific T-cell responses (D) were increased in subject 1007 by Ad5-GUCY2C-PADRE vaccination. T-cell responses were quantified by IFN-γ ELISpot (J Immunother Cancer. 2015; 3(Suppl 2): P450).



CD8+, but not CD4+, T-cell Responses to GUCY2C

Peripheral blood mononuclear cells (PBMCs) isolated from subject 1007 were unfractionated or depleted of CD4+ T cells or CD8+ T cells, confirmed by FACS analysis (A). Unfractionated, CD4+ T-cell depleted, or CD8+ Tcell depleted PBMCs were then analyzed by IFN-γ ELISpot, revealing CD8+ T-cell, but not CD4+ T-cell, responses to GUCY2C (B) (J Immunother Cancer. 2015; 3(Suppl 2): P450).



Ad5 Neutralizing Abs (Nabs) Limit GUCY2C Responses in Humans

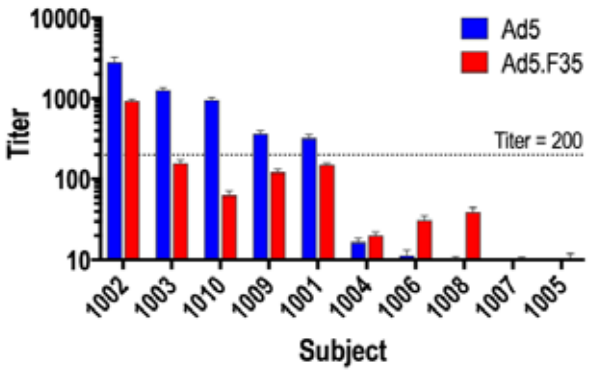
Quantification of Ad5 NAbs in pre-vaccination blood samples revealed Ad5 NAb titers of <1/100 in 50% of subjects (Ad5 NAb Low) and >1/1000 in the remaining subjects (A). Quantification of GUCY2C-specific (B) and PADRE-specific (C) T-cell responses in subjects separated by Ad5 NAb titer revealed Ad5 NAbs as a barrier to Ad5-GUCY2C-PADRE vaccination in colorectal cancer patients. T-cell responses were quantified by IFN-γ ELISpot (J Immunother Cancer. 2015; 3(Suppl 2): P450).

The responses are consistent with selective CD4+ T-cell tolerance observed in mouse models. Overall, such data establish GUCY2C as a safe and immunogenic target for immunotherapy in cancer patients and GUCY2C-directed vaccination is safe in colorectal cancer patients.

Rationale for GCC Cancer Vaccine Modification from Ad5 to Ad5.F35 Vector

Ad5 is a natural human pathogen, producing mild infections in nearly the entire human population. These natural exposures induce Ad5-specific neutralizing antibodies (NAbs) that prevent reinfection, or Ad5-based vaccination, by preventing infection of host cells, a necessary step in target antigen expression and induction of immune responses.

Ad5 NAbs are common in most human populations, including ~40% in the US, reducing the immunogenicity of Ad5-based vaccines. Importantly, most naturally-occurring Ad5 NAbs target the fiber molecule on the surface of Ad5. In contrast to Ad5, the seroprevalence of Ad35-specific antibodies in most countries is low (<10%). Together, these observations suggest that replacement of the fiber molecule in Ad5 with the fiber molecule from Ad35 will produce a chimeric Ad5 viral vector (known as Ad5.F35) that is not affected by naturally-occurring Ad5 immunity. Indeed, in a cohort of 102 patients with preexisting Ad5 NAbs, serum from 8 patients (67%), was incapable of neutralizing chimeric Ad5.F35 in vitro. Moreover, while 50% of subjects in the Phase 1 study possessed high Ad5 NAbs (titer > 200), only 1/10 subjects possess high Ad5.F35 NAbs (Figure). Thus, Ad5.F35 is advantageous, compared to Ad5, because of the reduced seroprevalence of Ad5.F35 NAbs to <25%, without additional safety risk.



In that context, we have modified the first-generation GCC Cancer Vaccine by replacing the Ad5 fiber molecule with the Ad35 fiber molecule, producing a chimeric viral vector, known as Ad5.F35. In contrast to Ad5, the seroprevalence of Ad35-specific antibodies in most countries is very low (<10%) and replacement of the fiber molecule in Ad5 with the fiber molecule from Ad35 will produce a chimeric Ad5.F35 viral vector that is resistant to most naturally-occurring Ad5 immunity, while preserving its safety and efficacy profile.

Animal study before Phase II Trial (GCC Cancer Vaccine modification to Ad5.F35 vector)

GMP Lot #1 of the Ad5.F35-hGCC-PADRE vaccine has undergone GMP-grade manufacturing and passed functionality testing. This represents 50% of the GMP-grade vaccine required for Phase II clinical studies. This batch produces GUCY2C upon infection of cells, and it is replication-incompetent (RCA-negative). The remaining lot of the GMP vaccine is currently being manufactured. Lot#1 has been used to complete the in-life portion and immune assays for the critical non-clinical studies required for the FDA IND for the phase II trial. No toxicities were observed and the lot produced GUCY2C immune responses that were comparable to the original Ad5-hGCC-PADRE vector.