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Abstract

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Grant Number:	1P01AI041580-010002
PI Name:	TISCH, ROLAND MICHAEL.
PI Email:	rmtisch@med.unc.edu
PI Title:	ASSOCIATE PROFESSOR
Project Title:	ANTIGEN SPECIFIC IMMUNE DEVIATION TO PROTECT ISLET GRAFTS

Abstract: Description (adapted from applicant's abstract): A critical factor in early pancreas and islet graft failure in individuals suffering from insulin-dependent diabetes mellitus (IDDM) is recurrent autoimmune- mediated destruction of the insulin producing beta cells. One approach to establish host tolerance to the grafts is to promote beta cell antigen-specific immune deviation. In this way, antigen-specific regulatory Th2 cells are induced to suppress the activity of autoreactive Th1 cells. The investigators and others have shown that this approach is indeed effective in preventing diabetes in the NOD mouse, a murine model for spontaneous IDDM. Furthermore, the applicants have recent evidence demonstrating that an ongoing diabetogenic response can be suppressed in NOD mice treated with the beta cell autoantigen glutamic acid decarboxylase (GAD65). The current challenge, however, is to establish strategies of immune deviation which induce effective, long-term protection in a safe manner. With this in mind, the applicants have developed four specific aims. First, the applicants will determine the phenotype and peptide specificity of GAD65- specific regulatory T cells capable of suppressing ongoing IDDM in NOD mice. Furthermore, the investigators will examine the relative contribution of CD4+ Th2 cells in disease suppression, and the precise mechanism by which this protection is mediated. Second, the applicants will determine whether GAD65- and insulin chain-specific peptide immunotherapy can effectively induce regulatory T cells and suppress ongoing IDDM in NOD mice. Third, the investigators will assess the feasibility of genetic vaccines as a delivery system to induce beta cell antigen-specific regulatory T cells and in turn, prevent and suppress the diabetogenic response. Fourth, the investigators will determine whether beta cell autoantigen-specific induced immune deviation can lead to permanent protection for syngeneic islets grafted in overtly diabetic NOD mice. In addition, the applicants will assess the applicability of antigen-specific immune deviation to suppress an islet allograft response.

Thesaurus Terms:
diabetes mellitus therapy, insulin dependent diabetes mellitus, pancreatic islet transplantation, vector vaccine

T lymphocyte, antigen presentation, cytokine, glutamate decarboxylase, nonhuman therapy evaluation, transplant rejection
NOD mouse, tissue /cell culture

Institution:	UNIVERSITY OF NORTH CAROLINA CHAPEL HILL CHAPEL HILL, NC 27514
Fiscal Year:	1997
Department:	
Project Start:	
Project End:	
ICD:	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
IRG:	

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Grant Number:	5P60AR030701-160034
PI Name:	TISCH, ROLAND MICHAEL.
PI Email:	rmtisch@med.unc.edu
PI Title:	ASSOCIATE PROFESSOR
Project Title:	ANTIGEN-SPECIFIC IMMUNOTHERAPY BY DNA VACCINATION

Abstract: Currently, there is growing evidence indicating that a functional imbalance between Th1 (pathogenic) and Th2 (regulatory) T helper cell subsets is a key factor in the pathogenesis of T cell mediated autoimmune diseases such as insulin dependent diabetes mellitus, multiple sclerosis and rheumatoid arthritis. As a result, one approach to immunotherapy is to promote 'immune deviation' as a means to induce antigen-specific regulatory Th2 cells to suppress the activity of the relevant autoreactive Th1 cells. We and others have shown that this approach is indeed effective in various animal models of T cell mediated autoimmunity. The current challenge, however, is to establish methods of immune deviation which can effectively induce and establish long term protection in a safe manner and in turn be directly applicable to a clinical setting. Recently, DNA vaccination has proven to be a highly successful method to establish protective immunity to a plasmid DNA encoded antigen. The immunity that is induced is maintained over long periods of time and there is no detectable response to the DNA itself. The approach is highly flexible in that virtually any antigen can be expressed in vivo and there is no limit in the number of plasmid DNAs that can be injected at any one time. Therefore, DNA vaccination provides several advantages that make this method a potentially effective and novel means of immunotherapy. Using the nonobese diabetic mouse, a spontaneous murine model for insulin dependent diabetes mellitus, we will test whether plasmid DNAs encoding beta cell autoantigens and appropriate cytokines can under a number of conditions: i) effectively induce regulatory antigen-specific Th2 cells, and ii) prevent and/or treat the diabetogenic response. In this way, we will be able to determine the feasibility of DNA vaccination as a general approach to treat T cell mediated autoimmunity.

Thesaurus Terms:
DNA, active immunization, autoantigen, autoimmunity, gene therapy, insulin dependent diabetes mellitus, vaccine
autoimmune disorder, chimeric protein, diabetes mellitus therapy, disease /disorder prevention /control, disease model, glutamate decarboxylase, helper T lymphocyte, immune tolerance /unresponsiveness, insulin, interleukin 4, lymphocyte proliferation, nonhuman therapy evaluation, pancreatic islet

enzyme linked immunosorbent assay, laboratory mouse, polymerase chain reaction, transfection vector

Institution:	UNIVERSITY OF NORTH CAROLINA CHAPEL HILL CHAPEL HILL, NC 27514
Fiscal Year:	1997
Department:	
Project Start:	
Project End:	
ICD:	NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES
IRG:	

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Grant Number:	1R01DK052365-01
PI Name:	TISCH, ROLAND MICHAEL.
PI Email:	rmtisch@med.unc.edu
PI Title:	ASSOCIATE PROFESSOR
Project Title:	T CELL REACTIVITY TO GAD65 IN DIABETES

Abstract: DESCRIPTION (Adapted from Investigator's abstract): The investigator proposes to characterize the properties of T-cell responses to GAD65 in NOD mice. Preliminary studies, have produced an extensive panel of GAD65-specific T-cell clones derived from 4 week old female NOD mice. His initial characterizations of these clones, which were isolated using intact GAD65 as the stimulating antigen, predominantly recognize p216-235 (27/28) with a single clone recognizing p280-299 (1/28). Interestingly, all 27 of the T-cell clones recognizing p216-235 exhibit a Th1-like phenotype (IFN-gamma secretion), while the lone clone recognizing p280-299 has a Th2-like phenotype (IL-4 secretion). In addition, characterizations of the Vbeta usage of these clones demonstrate that the response to p216-235 was oligo- or poly-clonal. These findings support the hypothesis that Th1/Th2 of GAD65-specific T-cells are dictated at least in part by the specific peptide epitope recognized. In addition, preliminary data obtained by adoptive transfer of the lone Th2 clone into 10 day old NOD mice indicates that this clone suppresses the development of insulitis, while transfer of one of the Th1 clones in an identical fashion accelerated insulitis. These studies proposes to continue with the goal of characterizing the epitope specificity and functional properties of T-cells spontaneously responding to GAD65 in NOD females. Three specific aims: Isolate GAD65-specific Th1 and Th2 clones from unimmunized NOD mice representing different stages of disease development and determine the immunodominant epitopes that are recognized. Preliminary data, discusses the isolation of 80 T-cell clones from 4 week old unimmunized NOD females. Clones will be isolated from 10 and 30 week old female NOD. These clones will be characterized with respect to their Th phenotype by cytokine secretion and their TCR will be analyzed. 2. Determine the pathogenic and regulatory functions in IDDM of GAD65-specific Th1 and Th2 clones, respectively. These experiments will involve transfer of clones into young NOD female mice and assessing the acceleration of disease and/or insulitis. 3. Determine the relative binding affinity of GAD65-specific immunodominant epitopes to I-Ag7 and the effect this has on stability and cell surface I-Ag7 half-life. The binding affinities will be done using a competition assay Preliminary results indicate that p216-235 bound with about 10-fold greater affinity than p280-299 to I-Ag7. The half-life studies will be performed The long-term goal of these studies will be to accurately assess the molecular mechanisms mediating the development of

autoimmune responses to GAD65 in NOD and determining the role of these responding T-cells in IDDM pathogenesis.

Thesaurus Terms:
autoantigen, glutamate decarboxylase, helper T lymphocyte, insulin dependent diabetes mellitus, leukocyte activation /transformation
MHC class II antigen, T cell receptor, antigen presentation, cellular pathology, chemical binding, cytokine
NOD mouse, clone cell, molecular cloning, tissue /cell culture

Institution:	UNIVERSITY OF NORTH CAROLINA CHAPEL HILL CHAPEL HILL, NC 27514
Fiscal Year:	1997
Department:	MICROBIOLOGY AND IMMUNOLOGY
Project Start:	26-APR-1997
Project End:	30-NOV-2002
ICD:	NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES
IRG:	IMS

Version 2.0

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Grant Number:	1R21AI042616-01
PI Name:	TISCH, ROLAND MICHAEL.
PI Email:	rmtisch@med.unc.edu
PI Title:	ASSOCIATE PROFESSOR
Project Title:	SENSITIZED LIPOSOMES FOR HIV VACCINATION

Abstract: DESCRIPTION (adapted from applicant's abstract): The long-term objective of the proposed research is to establish an effective form of vaccination to prevent HIV-1 infection. The general strategy, as presented, is to employ sensitized liposomes to encapsulate and deliver HIV-1-specific proteins to the gut lumen in order to elicit mucosal immunity. The use of liposomes has proven to be an efficient approach to elicit antigen-specific humoral responses, and more recently T cell immunity in the mucosa. The applicants propose to assess the feasibility of employing liposomes to elicit protective CD8+ T and CD4+ T cell responses specific for HIV-1 encoded proteins. Specifically, liposomes containing HIV-specific gag (pr55gag) will be used to target M cells of Peyer's patches of mice transgenic for a chimeric HLA-A2.1/Kb molecule. The investigators will then determine the effectiveness of this approach to elicit: (i) CD8+ cytotoxic T cell (CTL) activity specific for known, HLA-A2.1 restricted, gag-specific epitopes, and (ii) CD4+ T helper cell reactivity. The proposed work is expected to provide the necessary insight to develop rational liposome-based vaccine strategies to establish effective mucosal immunity for the prevention of HIV-1 infection.

Thesaurus Terms:
AIDS vaccine, drug delivery system, gag protein, human immunodeficiency virus, liposome, mucosal immunity, vaccine development
Peyer's patches, cytotoxic T lymphocyte, hapten, helper T lymphocyte, intestinal mucosa, oral administration
laboratory mouse, transgenic animal

Institution:	UNIVERSITY OF NORTH CAROLINA CHAPEL HILL CHAPEL HILL, NC 27514
Fiscal Year:	1997
Department:	MICROBIOLOGY AND IMMUNOLOGY
Project Start:	30-SEP-1997
Project End:	29-SEP-1999
ICD:	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
IRG:	ZAI1