Project Information

5R01AI099027-05

DESCRIPTION DETAILS RESULTS HISTORY SUBPROJECTS

Project Number: 5R01AI099027-05
Former Number: 5R01AI099027-04

Contact PI / Project Leader: HAMAD, ABDEL RAHIM

Title: MECHANISMS OF FAS LIGAND CONTROL OF INSULITIS IN AUTOIMMUNE DIABETES

Awardee Organization: JOHNS HOPKINS UNIVERSITY

Abstract Text:

DESCRIPTION (provided by applicant): Despite improvement in insulin delivery, maintaining tight control of glucose homeostasis continues to be a challenge that results in bouts of severe hypo and hyperglycemia and serious long-term complications in many type 1 diabetes (T1D) patients. Therefore, developing an immunotherapy for the disease remains a major goal. Reaching this goal, however, requires deep knowledge of all facets of the diabetogenic process - which is generally believed to be initiated by an imbalance between pathogenic and regulatory mechanisms that allows diabetogenic T cells to infiltrate pancreatic islets and destroy insulin-producing ß-cells. Therefore, identifying and understanding roles of various molecules and cell types that tip the balance towards the immunopathogenic pathways in susceptible individuals and animal models is important for developing effective immunotherapy. This proposal investigates mechanisms that powerfully control ß-cell specific autoreactive T cells when Fas ligand (FasL), an apoptosis-inducing member of TNF family, is genetically or pharmacologically inactivated. Previously, the lack of appropriate models and efficacious FasL blocking mAb has severely hampered such investigation. In this application, we will use NOD mice that are haploinsufficient for FasL (NOD-gld/+ mouse) and a FasL- neutralizing mAb (MFL4 clone) to investigate the underlying mechanisms and therapeutic significance of FasL blockade using the MFL4 mAb. NOD-gld/+ mice are completely protected from T1D, immunocompetent, and have normal immune homeostasis. In addition, MFL4 mAb protects NOD-wt mice from diabetes without altering immune homeostasis and, more importantly, our preliminary data show it has promising efficacy in reversing hyperglycemia in new-onset cases. Based on our preliminary data generated using these model systems, we hypothesize that an IL-10-producing regulatory B cell subset that suppresses diabetogenic autoreactive T cells are negatively regulated by FasL. In NOD-wt mice, FasL-mediated apoptosis eliminates IL- 10-producing regulatory B cells thereby removing the brakes on autoreactive T-cells (tested Aim 1). We hypothesize that the MFL4 mAb can be used to reverse new-onset diabetes (tested in Aim 2). In NOD mice, haploinsufficiency for FasL (gld/+) or mAb blockade of FasL prevents IL-10-producing B cell elimination, leading to control of diabetogenic T cells and suppression of insulitis (tested in Aim3). In this revised application, we will also assess relevance of our preclinical data to the humandisease in samples from newly diagnosed patients at Hopkins and tissues provided by the JDRF sponsored nPOD project (Aim 3). Because the role of FasL in normal immune response and ß-cell death are dispensable, understanding how FasL modulates the diabetogenic process can lead to new mechanistic insights into the disease pathogenesis that could have important therapeutic implications.

Public Health Relevance Statement:

PUBLIC HEALTH RELEVANCE: Developing an immunotherapy for type 1 diabetes is a major goal. Understanding how Fas ligand potently prevents the disease in mouse model, focus of this application, may lead to designing new therapeutic approaches.

NIH Spending Category:

Autoimmune Disease; Clinical Research; Diabetes; Health Disparities; Minority Health

Project Terms:

Animal Model; Anti-inflammatory; Anti-Inflammatory Agents; Apoptosis; Autoantigens; Autoimmune Diabetes; Autoimmune Process; autoreactive T cell; B-Lymphocyte Subsets; B-Lymphocytes; base; Beta Cell; Biological Models; blood glucose regulation; Cell Death; cell type; Cells; clinically significant; cytokine; Data; Defect; design; Diabetes Mellitus; diabetic; diabetogenic; Disease; Disease susceptibility; Equilibrium; Failure; Family; Frequencies; Genetic; Genetic study; Goals; Homeostasis; Hyperglycemia; Immune; Immune response; Immunocompetent; immunoregulation; Immunosuppressive Agents; Immunotherapy; Inbred NOD Mice; Individual; Injection of therapeutic agent; insight; Insulin; Insulin-Dependent Diabetes Mellitus; Interleukin-10; Investigation; islet; Islets of Langerhans; Knowledge; Lead; lymph nodes; Mediating; member; Modality; Modeling; mouse model; Mus; neutralizing monoclonal antibodies; Newly Diagnosed; Non obese; novel therapeutic intervention; Pancreas; Pathogenesis; Pathogenicity; Pathway interactions; Patients; Pharmacology; pre-clinical; Predisposition; prevent; Process; Production; public health relevance; Role; Sampling; Signal Transduction; Site; Structure of beta Cell of islet; System; T-Lymphocyte; Testing; Therapeutic; Tissues; TNF gene; Treatment Efficacy; Tumor Necrosis Factor Ligand Superfamily Member 6

Contact PI Information:

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Program Official Information:

Name: BOURCIER, KATARZYNA
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Other PI Information:

Not Applicable

Organization:

Name: JOHNS HOPKINS UNIVERSITY
City: BALTIMORE Country: UNITED STATES (US)

Department / Educational Institution Type:

PATHOLOGY
SCHOOLS OF MEDICINE

Congressional District:

State Code: MD
District: 07

Other Information:

FOA: PA-11-260
Study Section: Hypersensitivity, Autoimmune, and Immune-mediated Diseases Study Section (HAI)
Fiscal Year: 2017 **Award Notice Date:** 17-FEB-2017

DUNS Number: 001910777
Project Start Date: 1-MAR-2013
Budget Start Date: 1-MAR-2017

CFDA Code: 855
Project End Date: 28-FEB-2019
Budget End Date: 28-FEB-2019

Administering Institutes or Centers:

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Project Funding Information for 2017:

Total Funding: $405,000 **Direct Costs:** $250,000 **Indirect Costs:** $155,000

Year	Funding IC	FY Total Cost by IC
2017	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$405,000

Categorical Spending by IC: Click here for more information on NIH Categorical Spending

History:

Total project funding amount for 6 projects is **$2,385,103***

** Only NIH,CDC,and FDA funding data.*

Project Number	Sub #	Project Title	Contact Principal Investigator	Organization	FY	Admin IC	Funding IC	FY Total Cost by IC
5R01AI099027-05		MECHANISMS OF FAS LIGAND CONTROL OF INSULITIS IN AUTOIMMUNE DIABETES	HAMAD, ABDEL RAHIM	JOHNS HOPKINS UNIVERSITY	2017	NIAID	NIAID	$405,000
4R01AI099027-04		MECHANISMS OF FAS LIGAND CONTROL OF INSULITIS IN AUTOIMMUNE DIABETES	HAMAD, ABDEL RAHIM	JOHNS HOPKINS UNIVERSITY	2016	NIAID	NIAID	$414,503
5R01AI099027-03		MECHANISMS OF FAS LIGAND CONTROL OF INSULITIS IN AUTOIMMUNE DIABETES	HAMAD, ABDEL RAHIM	JOHNS HOPKINS UNIVERSITY	2015	NIAID	NIAID	$405,000
5R01AI099027-02		MECHANISMS OF FAS LIGAND CONTROL OF INSULITIS IN AUTOIMMUNE DIABETES	HAMAD, ABDEL RAHIM	JOHNS HOPKINS UNIVERSITY	2014	NIAID	NIAID	$405,000
1R01AI099027-01A1		MECHANISMS OF FAS LIGAND CONTROL OF INSULITIS IN AUTOIMMUNE DIABETES	HAMAD, ABDEL RAHIM	JOHNS HOPKINS UNIVERSITY	2013	NIAID	NIAID	$344,995
1R56AI099027-01		MECHANISMS OF FAS LIGAND CONTROL OF INSULITIS INITIATION IN AUTOIMMUNE DIABETES	HAMAD, ABDEL RAHIM	JOHNS HOPKINS UNIVERSITY	2012	NIAID	NIAID	$410,605

Subprojects:

Project Number	Sub #	Project Title	Contact Principal Investigator	Organization	FY	Admin IC	FY Total Cost by IC

No Subprojects information available for 5R01AI099027-05

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