BIOGRAPHICAL SKETCH

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NAME: Mathews, Clayton E.

eRA COMMONS USER NAME (credential, e.g., agency login): mathce

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
The North Carolina State University, Raleigh, NC	B.S.	05/1991	Biochemistry
The University of Georgia, Athens, GA	M.S.	05/1994	Foods & Nutrition
The University of Georgia, Athens, GA	Ph.D.	09/1997	Foods & Nutrition
The Jackson Laboratory, Bar Harbor, ME		04/2001	Genetics/Immunology

A. Personal Statement

Despite continuing improvements in the ability to treat individuals with type 1 diabetes (T1D, previously referred to as juvenile diabetes), the need to identify a true cure for the disease remains. In an attempt to meet this need, my group seeks to improve our collective understanding on the means by which T1D develops, both in humans as well as in mouse models of the disease. My overall research objective has been to identify the processes that result in the clinical symptoms of T1D. This effort has three main foci: 1) Identify the mechanisms whereby the pancreatic beta cell mass is functionally inhibited and reduced during the preclinical phase of T1D, and determine a means to prevent the beta cell dysfunction and death; 2) Elucidate the genetic elements that contribute to T1D as well as the mechanisms of action; and 3) Understand the interdependence of immunotherapy in conjunction with reviving the endogenous beta cell mass. The proposed studies tackle the first of these research foci

1. Mathews CE, Xue S, Posgai A, Lightfoot Y, Xie L, Wasserfall C, Haller M, Schatz D, Atkinson, MA Acute Versus Progressive Onset of Diabetes in NOD Mice –Potential Implications for Therapeutic Interventions in Type1 Diabetes. Diabetes. 2015 Nov;64(11):3885-3890. PMID: 26216853
2. Chen J, Chernatynskaya AV, Li J-W, Kimbrell MR, Cassidy RJ, Perry DJ, Muir AB, Atkinson MA, Brusko TM, Mathews CE. T cells display mitochondria hyperpolarization in human type 1 diabetes. Scientific Reports. Sci Rep. 2017 Sep 7;7(1):10835. doi: 10.1038/s41598-017-11056-9. PMID: 28883439
3. Newby BN, Brusko TM, Atkinson MA, Clare-Salzler MJ, Mathews CE. Type 1 Interferon Induced pSTAT4 Binds to the Granzyme B Promoter and Potentiates Human CD8+ T Cell Cytotoxicity. Diabetes. 2017 Dec;66(12):3061-3071. PMID: 28877912
4. Whitener RL, Gallo Knight L, Li J, Knapp S, Zhang S, Annamalai M, Pliner VM, Fu D, Radichev I, Amatya C, Savinov A, Yurdagul A Jr, Yuan S, Glawe J, Kevil CG, Chen J, Stimpson SE, **Mathews CE**. The Type 1 Diabetes-Resistance Locus Idd22 Controls Trafficking of Autoreactive CTLs into the Pancreatic Islets of NOD Mice. J Immunol. 2017 Dec 15;199(12):3991-4000. PMID: 29109122

B. Positions and Honors

Positions and Employment

1991-1997 Research Assistant, The University of Georgia, Athens, GA
1997-2001 Postdoctoral Fellow, The Jackson Laboratory, Bar Harbor, ME
2001-2007 Assistant Professor, Dept. of Pediatrics, University of Pittsburgh, Pittsburgh, PA
2007-2008 Associate Professor with Tenure, Dept. of Pediatrics, University of Pittsburgh, Pittsburgh, PA
2007-2008 Associate Professor, Department of Immunology, University of Pittsburgh, Pittsburgh, PA

2008-2013 Associate Professor with Tenure, Department of Pathology, Immunology, and Laboratory Medicine, University of Florida, Gainesville, FL
2008-2013 Associate Professor, Dept. of Pediatrics, University of Florida, Gainesville, FL
2008-2013 Associate Professor, Dept. of Food Science and Human Nutrition, University of Florida
2008- Sebastian Family Professor for Diabetes Research
2010- Director, Immunology/Microbiology Graduate Program, College of Medicine, University of Florida, Gainesville, FL
2013- Professor with Tenure, Dept. of Pathology, Immunology, and Laboratory Medicine, University of Florida, Gainesville, FL
2013- Professor, Dept. of Pediatrics, University of Florida, Gainesville, FL
2013- Professor, Dept. of Food Science and Human Nutrition, University of Florida, Gainesville, FL

Other Experience and Professional Memberships

2009 NIH-NIDDK Diabetes Research Strategic Plan, Autoimmunity/T1D Sub-group
2010-2013 Chairman of the American Diabetes Association Research Grant Review Committee
2014- Regular Member of the DDK-B (Diabetes, Endocrinology and Metabolic Diseases B) study section

Honors

1994 (ERTA) National Institutes of Health, NIDDK
1999 Centro Internazionale Studi Diabete Young Investigator Award
1999-2001 National Research Service Award
2001-2006 JDFI Career Development Award
2009-2014 University of Florida Student-Recognized Outstanding Professor
2013 University of Florida Exemplary Teacher Award

C. Contributions to Science

1. Genetic resistance to autoimmune type 1 diabetes (T1D). Despite continuing improvements in the ability to treat individuals with T1D (commonly referred to as juvenile diabetes), the need to identify a true cure for the disease remains. In an attempt to meet this need, we have performed studies seeking to improve our collective understanding on the means by which T1D develops, both in humans and in mouse models of the disease. These efforts have been extremely novel in that while the majority of researchers addressing the notion of how the disease develops focus on identifying defects in cells of the immune system, the guiding hypothesis of my research is that insulin-secreting pancreatic beta cells are active contributors to the processes that leads to T1D. This concept was birthed through early works, demonstrating that beta cells had unusual reductions in their self-defense mechanisms and that this reduction was important in the initiation of T1D. Later studies demonstrated that beta cells from different strains of mice varied in their resistance to destruction by the immune system. These novel findings proved to be highly influential to the research community since prior to these efforts, evidence suggesting that beta cells could resist immune destruction did not exist. These findings also led us to postulate that genetic factors related to this feature may underlie natural resistance to T1D; a concept for which has recently found significant support. Our continuing attempts to discover genes that beta cells naturally employ to ward off destructive mechanisms used by the immune system will undoubtedly have important ramifications for efforts in organ transplantation, stem cell engineering and pharmacological-based studies seeking to cure T1D.

a. **Mathews CE**, Leiter EH, Spirina O, Bykhovskaya Y, Ringquist S, Gusdon AM, Fischel-Ghodsian N. 2005 *mt-Nd2* Allele of the ALR/Lt Mouse Confers Resistance Against both Chemically-Induced and Autoimmune Diabetes. Diabetologia 48:261-267.
b. Chen J, Gusdon AM, Piganelli J, Leiter EH, Mathews CE. *mt-Nd2*[a] modifies resistance against autoimmune Type 1 diabetes in NOD mice at the level of the pancreatic beta cell. Diabetes. 2011, 60:355-359. PMID: 20980458
c. Whitener RL, Gallo Knight L, Li J, Knapp S, Zhang S, Annamalai M, Pliner VM, Fu D, Radichev I, Amatya C, Savinov A, Yurdagul A Jr, Yuan S, Glawe J, Kevil CG, Chen J, Stimpson SE, Mathews CE. The Type 1 Diabetes-Resistance Locus Idd22 Controls Trafficking of Autoreactive CTLs into the Pancreatic Islets of NOD Mice. J Immunol. 2017 Dec 15;199(12):3991-4000. PMID: 29109122
d. Newby BN, Brusko TM, Atkinson MA, Clare-Salzler MJ, Mathews CE. Type 1 Interferon Induced pSTAT4 Binds to the Granzyme B Promoter and Potentiates Human CD8+ T Cell Cytotoxicity. Diabetes. 2017 Dec;66(12):3061-3071. PMID: 28877912

2. Role of Reactive Oxygen Species (ROS) in the Pathogenesis of T1D: Beta Cells.

Destruction of pancreatic beta cells is mediated by aberrant immune responses against islet antigens resulting in the development of T1D. During the early stages of disease, an insulitic infiltrate consisting of dendritic cells [DC], T cell subsets, macrophages, and B cells accumulates in the pancreatic islets. Effector mechanisms, including direct T cell cytotoxicity and indirect methods mediated by leukocytes have been linked to β cell destruction and overt diabetes. Production of reactive oxygen species [ROS] has been proposed to be an important contributor to β cell loss during T1D pathogenesis. Using NADPH Oxidase 2 deficient mice we were able to determine that cytoplasmic ROS production was not essential for T cell mediated beta cell death. However, by reducing mitochondrial ROS production with *mt-Nd2*, beta cell death was significantly reduced, both *in vivo* and *in vitro*. Further, when beta cells produced nitric oxide or superoxide these cells were killed, however when cells were forced to generate both NO and superoxide the cells survived. Our overall novel studies have led to the conclusions that ROS production in beta cell death is essential, however the timing, location, and species are major contributors to beta cell life and death.

a. Gusdon AM, Votyakova TV, Reynolds IJ, Mathews CE. 2007 Nuclear-Mitochondrial Interaction Involving mt-Nd2 Leads to Increased Mitochondrial Reactive Oxygen Species Production. J Biol Chem. 282:5171-517. PMID: 17189252
b. Gusdon AM, Votyakova TV, Mathews CE. 2008 *mt-Nd2*^{a} Suppresses Mitochondrial Reactive Oxygen Species Production. J Biol Chem. 283:10690-10697. PMID: 18281288
c. Broniowska KA, Oleson BJ, McGraw J, Naatz A, Mathews CE, Corbett JA. How the location of superoxide generation influences the β-cell response to nitric oxide. J Biol Chem. 2015 Mar 20;290(12):7952-7960. PMID: 25648890
d. Oleson BJ, McGraw JA, Broniowska KA, Annamalai M, Chen J, Bushkofsky JR, Davis DB, Corbett JA, Mathews CE. Distinct differences in the responses of the human pancreatic beta-cell line EndoC-βH1 and human islets to proinflammatory cytokines. Am J Physiol. Am J Physiol Regul Integr Comp Physiol. 2015 Sep;309(5):R525-34. doi: 10.1152/ajpregu.00544.2014. Epub 2015 Jun 17. PMID: 26084699

3. Role of Reactive Oxygen Species (ROS) in the Pathogenesis of T1D: Immune Cells.

Destruction of pancreatic beta cells is mediated by aberrant immune responses against islet antigens resulting in the development of T1D. During the early stages of disease, an insulitic infiltrate consisting of dendritic cells [DC], T cell subsets, macrophages, and B cells accumulates in the pancreatic islets. Effector mechanisms, including direct T cell cytotoxicity and indirect methods mediated by leukocytes have been linked to beta cell destruction and overt diabetes. Production of reactive oxygen species [ROS] has been proposed to be an important contributor to β cell loss during T1D pathogenesis. However the cellular sources and mechanistic actions of ROS during the development of this autoimmune disease have not been fully defined.

To investigate the function of ROS in the pathogenesis of T1D, we have utilized a number of mouse models. These include the T1D-prone NOD, the highly T1D-resistant ALRs well as an NADPH oxidase 2 [NOX2] deficient NOD mouse [NOD.*Ncf1*^{m1J}], which harbor a point mutation in *Ncf1* [a.k.a. *p47*^{phox}], the regulatory subunit of this enzyme. We identified that ALR mice Our recent reports, using NOD mouse models of T1D, have demonstrated that NOX2 modulates immune cells in the pathogenesis of T1D, as NOX-deficient NOD.*Ncf1*^{m1J} mice were resistant to spontaneous T1D and NOD.*Ncf1*^{m1J} splenocytes transferred T1D poorly in adoptive transfer experiments. Furthermore, our published work as well as the preliminary have identified that the loss of NCF1 has a major impact on CD8^{+} Cytotoxic T Lymphocyte [CTL] function, as well as appearing to significantly hamper DC cross-presenting capability. These findings are highly significant to our understanding of how ROS regulate T1D as well as CD8+ T cell mediated immune responses.

a. Mathews CE, Dunn BD, Hannigan MO, Huang C-K, Leiter EH. 2002. Genetic Control Of Neutrophil Superoxide Burst Activity In Diabetes Resistant ALR/Lt Mice. Free Radical Biol. Med. 32:744-751. PMID: 11937300
b. Tse HM, Thayer TC, Steele C, Cuda CM, Morel L, Piganelli JD, Mathews CE. NADPH oxidase deficiency regulates Th lineage commitment and modulates autoimmunity. J Immunol. 2010, 185:5247-5258. PMID: 20881184
c. Thayer TC, Delano MJ, Liu C, Chen J, Padgett L, Annamali M, Piganelli JD, Tse HM, Moldawer LL, Mathews CE. Superoxide Production by Macrophages and T cells is Critical for the Induction of Autoreactivity and Type 1 Diabetes. Diabetes. Diabetes. 2011 Aug;60(8):2144-51. PMID: 21715554

d. Chen J, Stimpson SE, Fernandez-Bueno GA, Mathews CE. Mitochondrial Reactive Oxygen Species and Type 1 Diabetes. Antioxidant and Redox Signaling. 2018 Jan 2. doi: 10.1089/ars.2017.7346. PMID: 29295631

4. Metabolic Defects and Diabetes: Beta cell dysfunction is a common theme in the pathogenesis of both autoimmune Type 1 Diabetes and obesity-associated Type 2 Diabetes. Genetic as well as metabolic derangements at the beta cell level result in impaired beta cell function and the inability of beta cells to compensate for the demand of insulin resistance as well as the increasingly toxic levels of circulating lipids and glucose. In type 1 diabetes the immune system is thought to play the major role and destroy the beta cell mass until there are no remaining beta cells and this dearth of insulin production gives way to hyperglycemia. However, recent findings have called into question the severity of autoimmunity as well as have questioned the impact of beta cells on this disease. Our histological studies have demonstrated that insulin positive beta cells exist in patients with established T1D, a finding that supports several previous publications that have observed the presence of meal-stimulated c-peptide release in T1D patients. Our findings have also implicated mitochondria as a major site of beta cell dysfunction in pre-T1D. Mitochondria are essential for glucose-stimulated insulin secretion and in both NOD mice as well as humans. Our results, as well as those from many other groups, have clearly demonstrated that genetics at the mitochondrial level can perturb beta cell insulin secretory function. However, mitochondrial haplotypes can also positively impact beta cell function in response to stress. These studies are paving the way for a more indepth investigation of beta cell dysfunction in human pre-T1D as well as the mechanistic underpinnings of beta cell failure and death that result in this devastating disease.
   a. Lightfoot YL, Chen J, Mathews CE. Role of the Mitochondria in Immune-Mediated Apoptotic Death of Human Beta β Cells. PLoS One. 2011;6(6):e20617. PMID: 21738580
   b. Ize-Ludlow D, Lightfoot YL, Parker MJ, Xue S, Wasserfall CH, Haller MJ, Schatz DA, Becker DJ, Atkinson MA, Mathews CE. Progressive Erosion of Beta Cell Function Precedes the Onset of Hyperglycemia in the NOD Mouse Model of Type 1 Diabetes. Diabetes. 2011. PMID: 21659497
   c. Zhang S, Mathews CE. Metabolic abnormalities in the pathogenesis of type 1 diabetes. Curr Diab Rep. 2014 Sep;14(9):519. PMID: 25023213
   d. Chen J, Chernatynskaya AV, Li J-W, Kimbrell MR, Cassidy RJ, Perry DJ, Muir AB, Atkinson MA, Brusko TM, Mathews CE. T cells display mitochondria hyperpolarization in human type 1 diabetes. Scientific Reports. Sci Rep. 2017 Sep 7;7(1):10835. doi: 10.1038/s41598-017-11056-9. PMID: 28883439

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/clayton.mathews.1/bibliography/43786598/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

5-SRA-2018-557-Q-R Atkinson (PI) 03/01/18-12/30/22
JDRF
nPOD Organ Processing and Pathology Core
This Core provides organ procurement, processing, analysis, and distribution services for a human pancreas initiative
Role: Co-Investigator

2018PG-T1D053 Atkinson (PI) 01/01/18-12/31/20
Helmsley Charitable Trust
Collaborative Type 1 Diabetes Research Project: The Network for Pancreatic Organ donors with Diabetes (nPOD)
The goal of this project is Pancreas collection from organ donors, when combined with modern assessments of metabolic activity, immune function, clinical history, beta cell biology, developmental biology, as well as new areas of research (e.g., single cell technologies, “omics” in many forms) will allow for major improvements in our understanding of the pathogenesis of T1D.
Role: Co-Investigator

DP3 DK110845 Michels (PI) 08/02/16-07/31/19
UC Denver/NIH
Insulin Specific T and B cells in Type 1 Diabetes

The major goal of the project is to establish a repository of carrier cells transduced with TCRs obtained from laboratories worldwide.
Role: Co-Investigator

T32DK108736 Atkinson (PI) 09/01/17-08/31/22
NIH
Interdisciplinary Graduate Program in Type 1 Diabetes and Biomedical Engineering
The goal of this proposal is to propose that a training program designed for co-mentoring of pre-doctoral students in an environment and culture providing strong interdisciplinary support for bioengineering and type 1 diabetes, will result in a new generation of researchers poised to contribute to a fuller understanding of, and new technologies for disease management, prevention and reversal.

R01 DK112865 Sunny (PI) 04/01/17-03/31/22
Univ. of Maryland/NIH
Metabolic Origins of Nonalcoholic Steatohepatitis
The goal of this proposal is to identify how dysfunctional mitochondrial oxidative flux leads to the pathogenic development of NASH.
Role: Co-Investigator

P01 AI42288 Atkinson (PI) 6/20/2018-05/31/2023
NIH/NIAID
Immune function and the progression to Type 1 Diabetes
This is a program project investigating the relationship between genetic susceptibility for IDD and various immune functions. The project monitors same/similar patient populations and provides technical support including nurse time for subject recruitment.
Role: Co-Principal Investigator (project 1), Co-Investigator (Core B, director of immunology core)

UC4 DK104194 Mathews (PI) 09/30/14-06/30/19
NIH
Genetic regulation of human beta cell destruction
Our goal is to create an innovative platform to study how Type 1 Diabetes genetic risk factors precipitate autoimmunity leading to the loss of insulin producing cells.
Role: Principal Investigator

F30DK105788 Newby (PI) 05/16/16-05/15/20
NIH/NIDDK
Type 1 IFN in Type 1 Diabetes: Influencing Beta-Cell and CD8 + T Cell Interactions
The goal of this preparatory program is to develop the infrastructure and to generate critical preliminary data to allow our team to submit competitive program project grant (PPG) to the NIH and DOD within two years on the emerging field of immune metabolism.
Role: Mentor

323521 Qian (PI) 10/14/16-06/30/19
PNNL/NIH/NIDDK
Serum protein biomarkers for predicting type 1 diabetes development
The goal of the subproject is to provide clinical samples from the UFDI Study bank to address the notion of early biomarker development from serum/plasma/whole blood.
Role: Co-Investigator

Completed Research Support

UC4 DK104167 Qian/Kulkarni/Mathews (MPI) 09/20/14-08/31/18 nce
PNNL/NIH
Regulatory Networks and Biomarkers of Beta-cell Dysfunction and Apoptosis
Our goals are to identify novel signaling pathways and networks that contribute to early stage β-cell stress and death by applying highly sensitive mass spectrometry-based quantitative proteomics focusing on posttranslational modifications (PTMs) and using unique sets of clinical samples.
Role: Principal Investigator