

BIOGRAPHICAL SKETCH

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NAME: Alberto Pugliese, M.D.

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POSITION TITLE: Professor of Medicine, Microbiology and Immunology, tenured, The J. Enloe and Eugenia J. Dodson Chair in Diabetes Research

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
Liceo Scientifico V. Fardella, Trapani, Italy	B.S.	1980	Science
School of Medicine, University of Palermo, Italy	M.D.	1987	Medicine
School of Medicine, University of Palermo, Italy	Residency	1990	Diabetes & Metabolism
Internal Medicine Institute, University of Palermo	Residency	1995	Endocrinology
Internal Medicine Institute, University of Palermo	Research Fellow	1988-1990	T1D immunology, genetics, prevention
Joslin Diabetes Center & the Center for Blood Research, Harvard Medical School, Boston, MA	Research Fellow	1990-1992	T1D immunology, genetics, prevention
Barbara Davis Center for Childhood Diabetes, University of Colorado	Research Fellow	1991-1994	T1D immunology, genetics, prevention

A. Personal Statement

For 30 years I contributed to basic/clinical research about type 1 diabetes (T1D), studying its immunology, genetics, prediction, prevention and intervention. My contributions include: 1) the discovery of insulin gene transcription in the thymus, highlighting the role of thymic expression of tissue-restricted molecules in self-tolerance/autoimmunity; 2) the association of the HLA-DRB1*15:01-DQB1*06:02 haplotype with low risk of T1D development in autoantibody-positive relatives, leading to an exclusion criteria used in prevention trials; 3) the characterization of recurrent T1D in recipients of pancreas-kidney transplants, despite immune-suppression that prevents rejection; 4) the demonstration of low dose IL-2 selectivity for regulatory T cells, with implications for clinical trials; 5) For over 15 years, until 2017, I served as Steering Committee member of the Type 1 Diabetes TrialNet, a network that conducts clinical trials and natural history studies in at-risk relatives. I was co-PI of the Miami TrialNet Site, vice-Chair of the of the Ancillary Study Committee/Biomarker & Mechanisms Panel (and other committees); I have led and coauthored a number of studies involving TrialNet participants and clinical trials. 6) since 2010 I am Executive Co-Director of the JDRF nPOD (Network for the Pancreatic Organ Donors with Diabetes), a tissue bank and international collaborative project obtaining pancreatic and lymphoid tissues from organ donors with T1D/islet autoimmunity. I establish and oversee working groups to collaboratively address major questions about T1D (autoimmunity, viruses, extra-cellular matrix, etc.). With grant funding from the Helmsley Charitable Trust, I have identified, helped develop and supported novel projects that examine nPOD donors, by individual or by groups of investigators.

B. Positions and Honors**Academic appointments - Faculty**

1994-2000	Research Assistant Professor of Medicine, University of Miami
1999-2000	Research Assistant Professor of Medicine, Microbiology & Immunology; University of Miami
2000-2008	Research Associate Professor of Medicine, Microbiology and Immunology; University of Miami
2001-present	Graduate Faculty Member, Department of Microbiology & Immunology, University of Miami
2008-present	Research Professor of Medicine, Microbiology and Immunology, University of Miami
2013-present	Tenured Professor of Medicine, Microbiology and Immunology, University of Miami

Other Professional Positions

1998-2006 Chairman, T1D Component of the 13th & 14th International Histocompatibility Working Groups
2000-present TrialNet Steering Committee Member, with membership in several committees
2000-2005 Grant Review Panel Member, American Diabetes Association
2004-present Grant Reviewer for NIH, multiple study sections/review groups
2004-2005 Chair, Grant Review Panel, American Diabetes Association; Vice-chair (2003-2004)
2007-present Chair, Tissue Prioritization Committee, JDRF nPOD
2007-present Member, JDRF grant review panel, and chaired multiple review panels
2010-present Executive Co-Director, JDRF nPOD
2016-present Deputy Director for Immune Tolerance, Diabetes Research Institute

Honors and Awards

1987-1990 First Resident Award, School on Diabetes & Metabolism, Univ. Palermo, Italian Education Ministry
1990-1992 Research Fellowship Award from the Italian "Consiglio Nazionale Ricerche"
1992 Research Travel Award from the Italian Society of Diabetology
1992-1994 Research Fellowship Award from Juvenile Diabetes Foundation International (JDRF)
1996-2000 Career Development Award from Juvenile Diabetes Foundation International (JDRF)
1997 Travel Award to the Annual Meeting of the American Diabetes Association
1999 Dean's Award, University of Miami School of Medicine
2011 Selected by University of Miami Chairs of Basic Departments to deliver lecture for the inaugural series of the UM Discovery Science Grand Rounds
2014 Recipient (with Mark Atkinson) of the 2014 JDRF Mary Tyler Moore and S. Robert Levine Excellence in Clinical Research Award
2016 Recipient of The J. Enloe and Eugenia J. Dodson Chair in Diabetes Research

C. Contributions to Science

1. Studies of insulin gene polymorphisms in T1D/insulin expression in the thymus. I described insulin gene polymorphisms in T1D cohorts from the Joslin and Barbara Davis Center (*J. Autoimmunity*, 1994). I demonstrated insulin gene transcription in human thymus and that this is modulated by insulin gene alleles that influence T1D risk (*Nature Genetics*, 1997). This discovery highlighted a previously unknown role of central tolerance for self-molecules with tissue-restricted expression. We found other T1D autoantigens (GAD, IA-2, IGRP) expressed in thymus and peripheral lymphoid tissues and regulated by alternative splicing (*Diabetes*, 2001; *Diabetologia*, 2006). With Alice Tomei we showed that CCL21 promotes tolerogenic expression of self-antigens in stromal cells (*Diabetes*, 2020).

-Pugliese A, Zeller M, Fernandez A Jr, Zalberg LJ, Bartlett RJ, Ricordi C, Pietropaolo M, Eisenbarth GS, Bennett ST, Patel DD. The insulin gene is transcribed in the human thymus and transcription levels correlated with allelic variation at the INS VNTR-IDD3 susceptibility locus for type 1 diabetes. **Nat Genet.** 1997; 15(3):293-7. PMID: 9054945.

-Pugliese A, Brown D, Garza D, Murchison D, Zeller M, Redondo MJ, Diez J, Eisenbarth GS, Patel DD, Ricordi C. Self-antigen-presenting cells expressing diabetes-associated autoantigens exist in both thymus and peripheral lymphoid organs. **J Clin Invest.** 2001; 107(5):555-64. PMID: 11238556.

-Diez J, Park Y, Zeller M, Brown D, Garza D, Ricordi C, Hutton J, Eisenbarth GS, Pugliese A. Differential splicing of the IA-2 mRNA in pancreas and lymphoid organs as a permissive genetic mechanism for autoimmunity against the IA-2 type 1 diabetes autoantigen. **Diabetes.** 2001; 50(4):895-900. PMID: 11289059.

-Gonzalez Badillo FE, Zisi Tegou F, Abreu MM, Masina R, Sha D, Najjar M, Wright SH, Bayer AL, Korpos É, Pugliese A, Molano RD, Tomei AA. CCL21 Expression in β -Cells Induces Antigen-Expressing Stromal Cell Networks in the Pancreas and Prevents Autoimmune Diabetes in Mice. **Diabetes.** 2019; 68(10):1990-2003. PMID: 31371518.

2. The T1D-protective role of the HLA-DRB1*15:01, DQB1*06:02 haplotype in relatives of T1D patients, and contributions to genetic and miRNA studies and clinical trials. I showed that autoantibody-positive relatives with this haplotype have very low risk of progressing to T1D (*Diabetes*, 1995), which led to using presence of this protective haplotype for the Diabetes Prevention Trial-Type 1 (DPT-1) and subsequent prevention trials. I verified the identity of the protective DQ alleles by sequencing (*JCEM*, 1999). I described the immunologic and metabolic features of autoantibody-positive relatives with this protective allele (*Diabetes*, 2016). I contributed to several other genetic studies (*JCEM*, 2017; *Diabetes Care*, 2018) and to the development of a genetic risk score in TrialNet subjects (*Diabetes Care*, 2018). My group identified circulating miRNAs associated

with increased risk of T1D among autoantibody positive TrialNet relatives (*Diabetologia*, 2017) and other biomarkers of disease progression (*JCI Insight*, 2019).

-**Pugliese A**, Boulware D, Yu L, Babu S, Steck AK, Becker D, Rodriguez H, DiMeglio L, Evans-Molina C, Harrison LC, Schatz D, Palmer JP, Greenbaum C, Eisenbarth GS, Sosenko JM; Type 1 Diabetes TrialNet Study Group. The HLA-DRB1*15:01-DQA1*01:02-DQB1*06:02 haplotype protects autoantibody-positive relatives from type 1 diabetes throughout the stages of disease progression. **Diabetes**. 2016 Apr;65(4):1109-19. PMID: 26822082.

-Snowwhite IV, Allende G, Sosenko J, Pastori RL, Messinger Cayetano S, **Pugliese A**. Association of serum microRNAs with islet autoimmunity, disease progression and metabolic impairment in relatives at risk of type 1 diabetes. **Diabetologia**. 2017 Aug;60(8):1409-1422. PMID: 28500393.

-Steck AK, Xu P, Geyer S, Redondo MJ, Antinozzi P, Wentworth JM, Sosenko J, Onengut-Gumuscu S, Chen WM, Rich SS, **Pugliese A**; Type 1 Diabetes TrialNet Study Group. Can non-HLA Single Nucleotide Polymorphisms Help Stratify Risk in TrialNet Relatives at Risk for Type 1 Diabetes? **JCEM** 2017;102(8):2873-2880. PMID: 28520980.

-Redondo MJ, Geyer S, Steck AK, Sharp S, Wentworth JM, Weedon MN, Antinozzi P, Sosenko J, Atkinson M, **Pugliese A**, Oram RA; Type 1 Diabetes TrialNet Study Group. A Type 1 Diabetes Genetic Risk Score Predicts Progression of Islet Autoimmunity and Development of Type 1 Diabetes in Individuals at Risk. **Diabetes Care**. 2018;41(9):1887-1894. PMID: 30002199.

-Sosenko JM, Skyler JS, Herold KC, Schatz DA, Haller MJ, **Pugliese A**, Cleves M, Geyer S, Rafkin LE, Matheson D, Palmer JP; Type 1 Diabetes TrialNet Study Group. Slowed Metabolic Decline after One Year of Oral Insulin Treatment among Individuals at High Risk for Type 1 Diabetes in the Diabetes Prevention Trial-Type 1 and TrialNet Oral Insulin Prevention Trials. **Diabetes** 2020 Aug;69(8):1827-1832. doi: 10.2337/db20-0166. Epub 2020 May 21. PMID: 32439823.

-I Snowwhite, R Pastori, J Sosenko, S Messinger Cayetano, **A Pugliese**. Baseline Assessment of Circulating microRNAs Near Diagnosis of Type 1 Diabetes Predicts Future Stimulated Insulin Secretion. **Diabetes**. 2021 Feb;70(2):638-651. PMID: 33277338.

-Redondo MJ, Nathan BM, Jacobsen LM, Sims E, Bocchino LE, **Pugliese A**, Schatz DA, Atkinson MA, Skyler J, Palmer J, Geyer S, Sosenko JM; Type 1 diabetes TrialNet Study Group. Index60 as an additional diagnostic criterion for type 1 diabetes. **Diabetologia**. 2021 Jan 26. doi: 10.1007/s00125-020-05365-4. Online ahead of print. PMID: 33496819.

3. T1D recurrence in pancreas-kidney transplantation, despite immunosuppression that prevents rejection. With George Burke we demonstrated recurrence of autoimmunity (*Diabetes*, 2010) and identified autoantibodies as risk factors for this condition (*AJT*, 2016). We showed experimentally that autoreactive CD4 T cells from patients with recurrent T1D mediate beta cell destruction in vivo (*Diabetes*, 2010). We observed trans-differentiation of ductal cells into insulin-positive cells in pancreas transplant biopsies from recipients with recurrent T1D (*Diabetologia*, 2008).

-Martin-Pagola A, Sisino G, Allende G, Dominguez-Bendala J, Gianani R, Reijonen H, Nepom GT, Ricordi C, Ruiz P, Sageshima J, Ciancio G, Burke GW, **Pugliese A**. Insulin protein and proliferation in ductal cells in the transplanted pancreas of patients with type 1 diabetes and recurrence of autoimmunity. **Diabetologia**. 2008;51(10):1803-13. PMID: 18696047.

-Diamantopoulos S, Allende G, Ferreira JM, Ciancio G, Burke GW, **Pugliese A**. Retrospective assessment of islet cell autoantibodies in pancreas organ donors. **Diabetes Care**. 2008 Sep;31(9):1741-2. doi: 10.2337/dc08-0652. Epub 2008 Jun 12. PubMed PMID: 18556338; PubMed Central PMCID: PMC2518336.

-Vendrame F, Pileggi A, Laughlin E, Allende G, Martin-Pagola A, Molano RD, Diamantopoulos S, Standifer N, Geubtner K, Falk BA, Ichii H, Takahashi H, Snowwhite I, Chen Z, Mendez A, Chen L, Sageshima J, Ruiz P, Ciancio G, Ricordi C, Reijonen H, Nepom GT, Burke GW 3rd, **Pugliese A**. Recurrence of type 1 diabetes after simultaneous pancreas-kidney transplantation, despite immunosuppression, is associated with autoantibodies and pathogenic autoreactive CD4 T-cells. **Diabetes**. 2010; 59(4):947-57. PMID: 20086230.

-F. Vendrame, Y-Y. Hopfner, S. Diamantopoulos, S.K. Viridi, G. Allende, I.V. Snowwhite, H.K. Reijonen, L. Chen, P. Ruiz, G. Ciancio, J.C. Hutton, S. Messinger, G.W. Burke III, **A. Pugliese**. Risk factors for type 1 diabetes recurrence in immunosuppressed recipients of simultaneous pancreas-kidney transplants. **AJT** 2016; 16(1):235-245. PMID: 26317167.

4. The JDRF nPOD. Since 2010 I am Executive Co-Director of the JDRF nPOD, which identifies organ donors with T1D and distributes tissues to investigators worldwide after scientific review, which I chair. I promote collaboration among nPOD investigators and have organized many working groups, supported by grants from the Helmsley Charitable Trust allowing me to award funds to working groups and nPOD investigators for pilot studies. I am the PI of the nPOD-Virus Working Group, which investigates viruses in the etiology of T1D (*Diabetologia*, 2019). With Stephan Speier I oversaw the piloting and validation of using pancreas slices from organ donors (*JCI Insight*, 2020), and have now organized an integrated group of investigators utilizing nPOD pancreas slices for 12 new projects; I have supported pancreas slice studies with the Helmsley funds.

-Campbell-Thompson M, Fu A, Kaddis JS, Wasserfall C, Schatz DA, **Pugliese A**, Atkinson MA. Insulinitis and β -Cell Mass in the Natural History of Type 1 Diabetes. **Diabetes**. 2016; 65(3):719-31. PMID: 26581594.

-Seay HR, Yusko E, Rothweiler SJ, Zhang L, Posgai AL, Campbell-Thompson M, Vignali M, Emerson RO, Kaddis JS, Ko D, Nakayama M, Smith MJ, Cambier JC, **Pugliese A**, Atkinson MA, Robins HS, Brusko TM. Tissue distribution and clonal diversity of the T and B cell repertoire in type 1 diabetes. **JCI Insight**. 2016 20:e88242. PMID: 27942583.

-Babon JA, DeNicola ME, Blodgett DM, Crèvecoeur I, Buttrick TS, Maehr R, Bottino R, Naji A, Kaddis J, Elyaman W, James EA, Haliyur R, Brissova M, Overbergh L, Mathieu C, Delong T, Haskins K, **Pugliese A**, Campbell-Thompson M, Mathews C, Atkinson MA, Powers AC, Harlan DM, Kent SC. Analysis of self-antigen specificity of islet-infiltrating T cells from human donors with type 1 diabetes. **Nat. Med.** 2016;12:1482-1487. PMID: 27798614.

-Dunne JL, Richardson SJ, Atkinson MA, Craig ME, Dahl-Jørgensen K, Flodström-Tullberg M, Hyöty H, Insel RA, Lernmark Å, Lloyd RE, Morgan NG, **Pugliese A**. Rationale for enteroviral vaccination and antiviral therapies in human type 1 diabetes. **Diabetologia**. 2019; 62(5):744-753. PMID: 30675626.

-MMF Qadir, S Álvarez-Cubela, J Weitz, JK Panzer, D Klein, Y Moreno-Hernández, S Cechin, A Tamayo, J Almaça, H Hiller, M Beery, I Kusmartseva, M Atkinson, S Speier, C Ricordi, **A Pugliese**, A Caicedo, CA Fraker, RL Pastori, J Domínguez-Bendala. Long-term Culture of Human Pancreatic Slices as a Model to Study Real-Time Islet Regeneration. *Nat Commun*. 2020 Jun 29;11(1):3265. PMID: 32601271.

-Panzer JK, Hiller H, Cohrs CM, Almaça J, Enos SJ, Beery M, Cechin S, Drotar DM, Weitz JR, Santini J, Huber MK, Muhammad Fahd Qadir M, Pastori RL, Domínguez-Bendala J, Phelps EA, Atkinson MA, **Pugliese A**, Caicedo A, Kusmartseva I, Speier S. Pancreas tissue slices from organ donors enable in situ analysis of type 1 diabetes pathogenesis. **JCI Insight**. 2020 Apr 23;5(8):e134525. PMID: 32324170.

-I Kusmartseva, W Wu, F Syed, V Van Der Heide, M Jorgensen, P Joseph, X Tang, E Candelario-Jalil, C Yang, H Nick, JL Harbert, AL Posgai, JD Paulsen, R Lloyd, S Cechin, **A Pugliese**, M Campbell-Thompson, RS Vander Heide, C Evans-Molina, D Homann, and MA Atkinson. Expression of SARS-CoV-2 Entry Factors in the Pancreas of Normal Organ Donors and Individuals with COVID-19. **Cell Metab**. 2020 Dec 1; 32(6): 1041–1051. PMID: 33207244.

5. Low-dose IL-2 as a therapeutic agent for T1D. I collaborate with Tom Malek in studying low dose IL-2 to treat islet autoimmunity. We showed (*Diabetes*, 2015) that low-dose IL-2 selectively targets regulatory T cells (Tregs) in healthy individuals and T1D patients. This selective Treg responsiveness is explained by Treg higher expression of IL-2R α and γ c and other mechanisms. We found that human Tregs possess an IL-2-dependent transcriptional amplification mechanism that widens their selective responses to low-dose IL-2. These studies provide a molecular underpinning for clinical trials with low dose IL-2 to enhance Tregs in T1D. Our group has collaborated in studying immunological effects of low-dose IL-2 in the T1D trial led by David Klatzmann (*J. Autoimmunity*, 2015). We obtained a NIAID U01 grant for a clinical trial in T1D with low dose IL-2; unfortunately, severe delays impacting drug supply compromised funding in March 2020; we plan to reapply. I collaborate with Allison Bayer in experimental therapeutic manipulations of Treg cells (*Diabetes*, 2020).

-A Yu, I Snowwhite, F Vendrame, M Rosenzweig, D Klatzmann, **A Pugliese**, TR Malek. Selective responsiveness of regulatory T cells through multiple intrinsic mechanisms support the use of low-dose IL-2 therapy in Type-1 diabetes. **Diabetes**. 2015; 64(6):2172-83. PMID: 25576057.

-Rosenzweig M, Churlaud G, Mallone R, Six A, Dérian N, Chaara W, Lorenzon R, Long SA, Buckner JH, Afonso G, Pham HP, Hartemann A, Yu A, Pugliese A, Malek TR, Klatzmann D. Low-dose interleukin-2 fosters a dose-dependent regulatory T cell tuned milieu in T1D patients. **J Autoimmunity**. 2015; 58:48-58. PMID: 25634360.

-Churlaud G, Rosenzweig M, Cacoub P, Saadoun D, Valteau-Couanet D, Chaput N, **Pugliese A**, Klatzmann D. IL-2 antibodies in type 1 diabetes and during IL-2 therapy. **Diabetologia**. 2018 Sep;61(9):2066-2068. doi: 10.1007/s00125-018-4649-4. Epub 2018 Jun 2. PMID: 29860627.

-Cabello-Kindelan C, Mackey S, Sands A, Rodriguez J, Vazquez C, **Pugliese A**, Bayer AL. Immunomodulation Followed by Antigen-Specific T(reg) Infusion Controls Islet Autoimmunity. **Diabetes**. 2020 Feb;69(2):215-227. PubMed PMID: 31712320.

-N Nagy, G Kaber, MJ Kratochvil, HF Kuipers, SM Ruppert, K Yadava, J Yang, SC Heilshorn, S Alice Long, **A Pugliese**, PL Bollyky. Weekly injection of IL-2 using an injectable hydrogel reduces autoimmune diabetes incidence in NOD mice. **Diabetologia**. 2021 Jan;64(1):152-158. PMID: 33125521

Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/alberto.pugliese.1/bibliography/48109013/public/?sort=date&direction=ascending>