BIOGRAPHICAL SKETCH

Senior Trainer

NAME: Jon S. Odorico

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

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
Duke University, Durham, NC	BS	1983	Chemistry
New York University, New York, NY	MD	1987	Medicine
University of Pennsylvania, Philadelphia, PA		07/1987-06/1994	Surgery Residency
University of Pennsylvania, Philadelphia, PA		07/1990-06/1992	Postdoctoral Research Fellow
University of Wisconsin-Madison, Madison, WI		07/1994-06/1996	Transplant Fellowship

A. Personal Statement

My laboratory has studied pancreatic lineage differentiation from pluripotent stem cells, including ESCs and induced pluripotent stem cells (iPSCs). The work is designed to address two critical needs; the need to generate an unlimited supply of functional insulin-secreting beta cells to replace those destroyed in patients with diabetes, and the need for a culture-based model system to study, specifically, *human* pancreas and islet development, given known differences in pancreas and islet formation between humans and lower organisms and the inability to study human organ development *in vivo*. **With more than 15 years of experience in the field, we have pioneered an *in vitro* model of human pancreas development using a well-characterized protocol to differentiate pluripotent stem cells towards pancreatic lineages, resulting in glucose-responsive insulin producing islet-like clusters (ILCs).** Using this model we have investigated the role of transcription factors, such as Pdx1, Ngn3, and Ptf1a, as well as intercellular signaling pathways at different stages of differentiation. Other projects in the lab are directly addressing important preclinical questions related to stem cell-derived beta cell therapies, namely whether autologous human iPSC-derived cells will fulfill their promise of providing patient-customized cell replacement therapies that do not require immunosuppression or immunoprotection and whether manipulation of key immunologically relevant molecules in hESCs using genome editing can prevent or delay graft rejection using a humanized mouse transplant model.

a. Realizing the importance of organ-specific extracellular matrix in cell fates, we have recently developed novel methods for decellularizing human pancreatic tissue and have successfully produced a hydrogel which affords the opportunity to study the matrisome and matrix/stem cell-derived islet/human islet interactions, which is the topic of the present study. The recently published studies listed below were the result of an ongoing collaboration with the lab of Dr. Lingjun Li, who is co-PI on Dr. Tremmel's F31 application.
b. Sackett SD, Tremmel DM, Ma F, Feeney AK, Maguire RM, Brown ME, Zhou Y, Li X, O'Brien C, Li L, Burlingham WJ, Odorico JS. Extracellular matrix scaffold and hydrogel derived from decellularized and delipidized human pancreas. *Sci Rep*, 2018. 8(1): p. 10452. PMID 29993013
c. Ma F, Sun R, Tremmel DM, Sackett SD, Odorico J, Li L. Large-scale differentiation and site specific discrimination of hydroxyproline isomers by electron transfer/high-energy collision dissociation (EThcD) Mass Spectrometry. *Anal Chem* 2018. 90(9): 5857-5864. PMID29624053.

B. Positions and Honors

Positions

1996-2005	Assistant Professor, Department of Surgery, Division of Organ Transplantation, University of Wisconsin Hospital & Clinics, Madison, WI
2001-present	Principal Investigator, WiCell Research Institute, Madison, WI
2002-present	Co-Director, Islet Cell Transplantation Program, Division of Organ Transplantation, University of Wisconsin Hospital and Clinics, Madison, WI
2005-2014	Associate Professor, Department of Surgery, Division of Organ Transplantation, University of Wisconsin Hospital & Clinics, Madison, WI
2009-present	Director, Pancreas Transplantation, Division of Organ Transplantation, University of Wisconsin Hospital and Clinics
2014-present	Professor of Surgery, Department of Surgery, Division of Organ Transplantation, University of Wisconsin School of Medicine and Public Health

Awards & Honors

Merck Index Award, 1983; Phi Lambda Upsilon Chemical Honor Society, 1983; Magna Cum Laude, Duke University, 1983; National Research Service Award, National Institutes of Health, 1990-1992; Jonathan E. Rhoads Research Award, Harrison Department of Surgical Research, University of Pennsylvania, School of Medicine, 1992-1993; Finalist, Sandoz Fellowship Award, 1994; Best Abstract Award, OrthoBiotech Transplant Fellows Workshop, 1994; American Society of Transplant Surgeons, Fujisawa Faculty Development Award, 1996; Young Investigator Travel Award, Stem Cells and Pancreatic Development Workshop, NIH, 2000; Special Advisory Committee to the NIH Director on Stem Cell Differentiation 2000; Howard Hughes Medical Institute Faculty Development Award, 2000; "Top Doctor", *Madison Magazine*, 2004, 2012; Featured Clinical Scientist, American Society of Transplantation Newsletter, 2005; American Society of Transplant Surgeons Wyeth Midlevel Faculty Award, 2006-2008; Mary Jane Kugel Award, JDRF, 2006; Best Doctors in America, 2011; Vilas Association Professorship Award, 2011; ASTS Collaborative Scientist Award, 2013; President-Elect, International Pancreas and Islet Transplant Association, 2013-2015; Vice-Chair, UNOS Pancreas Committee 2014-2017; Member, American Surgical Association; President, IPITA, 2015-2017; Chair, UNOS Pancreas Committee 2017-present; 2016 UNICO Marconi Scientific Achievement Award

Other Experiences and Professional Memberships

JDRF – Medical Science Review Committee, Islet Biology and Transplantation, Encapsulation, Beta cell biology study sections, 2003 to 2016; California Institute of Regenerative Medicine (CIRM) –member of the Scientific and Medical Research Funding Working Group (Grants Review Working Group), 2006 to 2012; NIH Metabolism study section 2003; Member Stem Cell Committee NIH Beta Cell Biology Consortium 2003-5; Grant reviewer for NMRC, ASTS, and Diabetes Research Connection; Co-founder, CSO and Scientific Advisory Board Chair, Regenerative Medical Solutions, Inc. 2012- present; Patents: US 7,585,672 "Differentiation of stem cells to endoderm and pancreatic lineage" Sept. 8, 2009; US 8,247,229 "Method of differentiating stem cells into the endoderm and pancreatic lineage" Aug. 21, 2012; US 8,685,730 "Method and devices for differentiating pluripotent stem cells into cells of the pancreatic lineage" April 1, 2014;US 9,765,302 "Composition and methods for differentiating stem cells into cell populations comprising beta-like cells" Mar. 29, 2018; US9,371,516 "Composition and methods for differentiating stem cells into cell populations comprising beta-like cells" June 21, 2016, US 9,540,613 "Methods for producing insulin-secreting beta cells from human pluripotent stem cells" Jan. 10, 2017. Editorial Board: *American Journal of Transplantation, Transplantation Reviews, American Journal of Stem Cells, Journal of Diabetes Research and Clinical Metabolism*, *Journal of Regenerative Medicine and Tissue Engineering, Transplantation Direct*; Reviewer*: American Journal of Transplantation, Annals of Surgery, Diabetes, Stem Cells, Diabetologia, Nature Biotechnology, Journal of Clinical Investigation, PNAS, Transplantation, Clinical Transplantation, Current Biology, Journal of Molecular Medicine, Transplant International, Transplantation, Transplantation Proceedings;* Co-chair Cellular Transplantation Committee, ASTS 2003-6 and AST 2004-7; Member, Public Education Committee, ISSCR 2004-7; Member, Juvenile Diabetes Research Foundation – Western Wisconsin Chapter Board of Directors, 2012- 2018; Chaired and moderated numerous scientific sessions at American Transplant Congresses, International Transplant Congresses, and meetings of the ADA, ACS, ASC and IPITA; Advisory Board JDRF Beta Cell Replacement Strategy; Co-Chair Key Opinion Leaders meeting of "Stem Cell-derived Beta Cells" Sept 2016 and May 2018.

C. Contributions to Science

Initially, my lab collaborated with Dr. James Thomson and focused on embryoid-body based early endoderm lineage differentiation from pluripotent stem cells. We also developed methods to remove residual undifferentiated stem cells based on magnetic bead selection. This work led to several publications, a patent (see above) and editing an textbook on human embryonic stem cell biology and applications.

a. Thomson JA, **Odorico JS**: Human embryonic stem cell and embryonic germ cell lines. *Trends in Biotechnol* 18(2):53-57, 2000. PMID 10652509.
b. Kaufmann DS, **Odorico JS**, Thomson JA. Transplantation therapies for human embryonic stem cells-circumventing immune rejection. *E-biomed: The Journal of Regenerative Medicine* 1:11-15, 2000.
c. **Odorico JS**, Kaufman DS, Thomson JA. Multilineage differentiation from human embryonic stem cell lines. *Stem Cells* 19(3):193-204, 2001. PMID 11359944.
d. **Odorico JS**, Zhang SC, Pedersen RA (eds.) *Human Embryonic Stem Cells*, Garland Science/BIOS Scientific Publishers, Oxford, 2005.

Since 1998 my lab has worked on understanding how to differentiate human and murine pluripotent stem cells into definitive endoderm, pancreatic progenitors and beta cells as potential cellular therapies for patients with diabetes. We were among the first to address this question and subsequently a robust field with many investigators has developed over the last 15 years. Indeed, my interests in this question stemmed from my longstanding understanding of the limitations of existing transplantation therapies for these patients. We and others have made significant progress towards these goals, first understanding the phenotype of human definitive endoderm, then subsequently describing differentiation protocols based on developmental principles of lower organisms to produce endoderm and pancreatic progenitors in vitro from human stem cells, and most recently refining differentiation conditions that are effective for generating beta-like cells from multiple human pluripotent stem cell lines which function in vitro and produce insulin in murine models of diabetes. This work has led to several patents as noted above. Based on this achievement we are actively studying the function of cells in encapsulation devices in vitro and in a variety of transplant models in the autologous and allogeneic setting.

a. Kahan BW, Jacobson LM, Hullett DA, Ochoada JM, Oberley,TD, Lang KM, **Odorico JS**. Pancreatic precursors and differentiated islet cell types from murine embryonic stem cells: an in vitro model to study islet differentiation. Diabetes 52(8): 2016-2024, 2003. PMID 12882918.
b. Xu X, Kahan B, Forgianni A, Jing P, Jacobson L, Browning V, Treff N, **Odorico J**. Endoderm and pancreatic islet lineage differentiation from human embryonic stem cells. Cloning & Stem Cells 2006; 8(2): 96-107. PMID 16776601.
c. Xu X, Browning VL, **Odorico JS**. Culture Protocols for Producing Definitive Endoderm and Pancreatic Lineage Cells from Human ES or iPS Cells. In Methods in Bioengineering: Cell Transplantation, eds. Soto-Gutierrez A, Navarro-Alvariez N, Fox I. Artech House Publishers, Boston, 2011, Chapter 11:173-181.
d. Xu X, Browning V, **Odorico J**. Activin, BMP and FGF pathways cooperate to promote endoderm and pancreatic lineage cell differentiation from human embryonic stem cells. Mechanisms of Development, 2011, 128:412-27. PMID 21855631.
e. Sackett SD, Brown M, Tremmel D, Ellis T, Burlingham WJ, **Odorico J**. Modulation of human allogeneic pluripotent stem cells and implications for organ transplantation. Transplantation Reviews,30(2):61-70, 2016. PMID 26970668

Building on the development of robust in vitro differentiation protocols we have focused on using stem cells to model pancreatic development and interrogate the function of a number of pancreatic transcription factors. In 2006, before efficient methods were available to genetically modify human ESCs we successfully engineered murine ESCs to have inducible overexpression of any transcription factor or gene of interest. So far, we have used these cell lines to study the role of genes such as Ngn3 and Ptf1a in pancreatic development. We intend to extend this work to human pluripotent stem cells now that efficient means for expressing inducible constructs through TALEN and CRISPR systems are available.

a. Vincent R, Treff N, Budde M, Kastenberg Z, **Odorico J**. Generation and characterization of novel tetracycline-inducible pancreatic transcription factor-expressing murine embryonic stem cell lines. *Stem Cells Dev* 2006; 15(6): 953-962. PMID 17253956.
b. Treff NR, Vincent RK, Budde ML, Browning VL, Magliocca JF, Kapur V, **Odorico JS**. Differentiation of

embryonic stem cells conditionally expressing neurogenin 3. *Stem Cells* 2006; 24(11): 2529-2537. PMID 16809427.

c. Vincent RK, **Odorico JS**: Isolating endoderm and understanding developmental signals: defining sequential steps of embryonic stem cell differentiation to β cells. *Curr Opin Organ Transplant* 12:49-54, 2007. PMID: 27792089
d. Nair GG, Vincent RK, **Odorico JS**. Ectopic Ptf1a expression in Murine ESCs potentiates endocrine differentiation and models pancreas development in vitro. *Stem Cells.* 2014 May;32(5):1195-207. PMID 24375815.
e. Sackett SD, Rodriguez A, **Odorico JS.** The Nexus of Stem Cell-Derived Beta Cells and Genome Engineering. *Rev. Diabet. Stud.* 14:39-50, 2017. PMID28632820.

As a clinical scientist, I direct the UW pancreas transplant program, which is among the busiest in the world. We have performed over 1700 pancreas transplants since the inception of the program and have a world-renowned reputation for achieving excellent results. My expertise is highly sought after in many topics related to pancreas transplantation including donor and recipient selection, surgical technique, immunosuppression, use of pediatric and donation after cardiac death donors, management of transplant pancreatitis and other surgical complications, and the diagnosis and treatment of antibody mediated rejection (AMR). I was the first to describe use of a new immunosuppressant mycophenolate mofetil in pancreas transplantation in 1998 reporting significantly improved rejection rates. We were also the first to report the use of Alemtuzumab, an anti-CD52 monoclonal antibody, for induction immunosuppression in a large series of pancreas transplants, as well as transplantation with enteric drainage without use of nasograstric tubes. With our pathologist collaborator Dr. Torrealba, we were the first to systematically describe the pathological findings of C4d staining in AMR of the pancreas allograft and subsequently described the incidence and risk factors for biopsy proven AMR in a large series of pancreas transplants.

a. **Odorico JS**, Pirsch JD, Knechtle SJ, D'Alessandro AM, Sollinger HW: A study comparing mycophenolate mofetil to azathioprine in simultaneous pancreas-kidney transplantation. *Transplantation* 66(12):1751-1759, 1998. PMID: 9884272
b. Sollinger HW, **Odorico JS**, Becker YT, D'Alessandro AM, Pirsch JD: One thousand simultaneous pancreas-kidney transplants at a single center with 22-year follow-up. *Ann Surg*. Aug 27. 250(4): 618-30, 2009. PMID: 19730242
c. Torrealba JR, Samaniego M, Pascual J, Becker Y, Pirsch J, Sollinger H, **Odorico J**: C4d-positive interacinar capillaries correlates with donor-specific antibody-mediated rejection in pancreas allografts. *Transplantation* 86(12):1849-1856, 2008. PMID: 19104433
d. Niederhaus SV, Leverson GE, Lorentzen DF, Robillard DJ, Sollinger HW, Pirsch JD, Torrealba JR, **Odorico JS**. Acute cellular and antibody-mediated rejection of the pancreas allograft: incidence, risk factors and outcomes. *Am J Transplant*. Nov;13(11): 2945-55, 2013. PMID: 24102905

Islet transplantation is another less invasive option for restoring beta cell mass in patients with diabetes. Although still experimental, I initiated a clinical islet transplantation program at UW in 2002 which remains the only active islet transplant program in the state of Wisconsin. My interest in islet transplantation originates with my post-doctoral studies when I described the transfer of donor immune cells to the thymus to induce tolerance and donor-specific unresponsiveness to a variety of organ and cellular transplants including islet transplants in collaboration with Dr. Andrew Posselt. I also studied the mechanisms of intrathymic tolerance and immune responses to Class I deficient murine islet grafts with Dr. James Markmann. Since this early experimental work, my focus in islet transplantation research has been more clinically focused. We have reported on the negative impact of pre-transplant donor specific antibodies on human islet allograft outcomes with Dr. Mohanakumar at Washington University. Working with Dr. Fernandez in a cross-institutional collaboration I have evaluated our own islet transplant recipients using a variety of metabolic studies describing early metabolic markers that predict loss of insulin independence. In addition, with Dr. Michael Macdonald we identified important differences between human and rodent islets related to the activity of several metabolic enzymes. As a member of the Collaborative Islet Transplant Registry, we have helped identify factors that correlate with improved clinical islet transplant outcomes.

a. Posselt AM, **Odorico JS**, Barker CF, Naji A. Promotion of pancreatic islet allograft survival by intrathymic transplantation of bone marrow. *Diabetes* 41:771-776, 1992. PMID 1534058.
b. Markmann JF, Bassiri H, Desai NM, **Odorico JS**, Kim JI, Koller BH, Smithies O, Barker CF: Indefinite survival of MHC class I deficient murine pancreatic islets allografts. *Transplantation* 54:1085-1089, 1992.

PMID 1465773.

c. Mohanakumar T, Narayanan K, Desai N, Ramachandran S, Shenoy S, Jendrisak M, Susskind BM, Olack B, Benshoff N, Phelan DL, Brennan DC, Fernandez LA, **Odorico JS**, Polonsky KS. A significant role for histocompatibility in human islet transplantation. *Transplantation* 2006 82(2):180-7. PMID 16858280.

d. Macdonald MJ, Longacre MJ, Stoker SW, Kendrick MA, Thonpho A, Brown LJ, Hasan NM, Jitrapakdee S, Fukao T, Hanson MS, Fernandez LA, **Odorico J**. Differences between human and rodent pancreatic islets: low pyruvate carboxylase, ATP citrate lyase, and pyruvate carboxylation; high glucose-stimulated acetacetate in human pancreatic islets. *Journal of Biological Chemistry* 2011 May 27; 286(21): 18383-96. PMCID 3099655.

Complete list of published work in My Bibliography
https://www.ncbi.nlm.nih.gov/pubmed/?term=odorico+j

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

Ongoing Research Support

JDRF 1-PNF-2016-250-S-B (Odorico PI; Palecek Co-I) 08/01/16- 07/31/18
A natural human pancreatic matrix hydrogel- and endothelial cell-based platform for transplanting pluripotent stem cell-derived beta cells
This project will test the effectiveness of a human pancreatic matrix hydrogel in various beta cell transplant platforms.

NIH R21AI126419 (Odorico, PI; Li Co-I; Hematti Co-I) 07/01/16 – 6/30/18, NCE
Transformational platform for regenerating autologous transplantable endocrine tissue from human pancreatic matrix and pluripotent stem cells
The immediate objectives are to characterize human pancreatic extracellular matrix using state-of-the-art quantitative MS methods and to use this natural matrix in combination with stem cell-derived beta cells, ECs and MSCs to reconstruct endocrine tissue capable of glucose-stimulated insulin-secretion in mice.

JDRF 3-SRA-2017-364-S-B (Odorico, PI; Huangfu Co-I) 2/01/17-1/31/20
An inducible genome engineering approach for preventing immune rejection of hESC-derived beta cells
The goals of this project are to generate and validate various hESC lines that harbor modifications in relevant immunomodulatory genetic loci and test these in a kidney subcapsule diabetic mouse model and assess immune responses.

Completed Research Support

ASTS (Odorico, PI) 07/01/13-06/30/15
The goal of this research is to study the function and survival of transplanted hESC-derived pancreatic progenitors and beta cells.

JDRF (Odorico, PI) 07/01/12-09/1/15
The objective of this study is to overcome the differentiation block in deriving endocrine cells in culture by growing endocrine progenitors in a 3D extracellular matrix derived from decellularized human pancreata.

NIH –CTOT-15 (Stock – PI) 11/1/14-10/30/16
Optimization of NULOJIX® (Belatacept) Usage as a Means of Minimizing CNI Exposure in Simultaneous Pancreas and Kidney Transplantation. This is a multicenter randomized prospective clinical trial evaluating the efficacy of co-stimulatory blockade with Belatacept as induction and maintenance therapy.

JDRF 1-SRA- 2016-168-S-B (Odorico PI; Graham Co-I; O'Brien Co-I) 04/01/16-04/01/18
Encapsulation of human PSC-derived beta cells in a novel device combining dynamic nutrient delivery and a matrix based niche microenvironment