BIOGRAPHICAL SKETCH

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NAME: **David Marshall Harlan**

eRA COMMONS USER NAME: **DAVIDMH**

POSITION TITLE: **William & Doris Krupp Professor of Medicine, UMass Chan Medical School**

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Michigan, Ann Arbor, MI	B.S.	08/1977	Physiology
Duke University School of Medicine, Durham, NC	M.D.	12/1980	Medicine
Duke University Medical Center, Durham, NC		07/1984	Internal Med Residency
Duke University Medical Center, Durham, NC		11/1989	Endocrine Fellowship

A. Personal Statement: For over 35 years, I have conducted both basic and clinical research exploring the pathophysiology underlying type 1 diabetes (T1D) and working to improve treatment for those with the disease. My efforts have spanned from epidemiological studies relating to patient outcomes following pancreas transplantation, to clinical trials (islet transplantation, immunotherapy trials, and efforts attempting to promote β cell regeneration), to animal models using (as appropriate for the question being addressed) non-human primates or mice, to cellular (studying pancreatic β cells and the islet inflammatory infiltrate underlying T1D), to molecular (gene expression studies, promoter analyses, insulin splice forms). Since 2010 when I moved to UMass Chan, my team has developed innovative techniques to sort human pancreatic islet endocrine cell subsets, including from donors with diabetes (T1D and T2D) to determine the transcriptome from those purified cells to identify new potential therapeutic targets, and to characterize the immune cells infiltrating the islets. We have also developed the ability to differentiate stem cells (embryonic or induced pluripotent) into stem cell derived islets (SC-islets), and techniques to recover isolated human islets transplanted into immunodeficient rodents. Ongoing and recently completed projects I wish to highlight include:

5UO1DK104218-05
Greiner (PI)
9/20/19- 5/31/23
Humanized Mouse Avatars for T1D

3-COE-2023-1308-A-N
Harlan (PI)
A Cure for Type 1 Diabetes
10-01-20- 9/30/25

*Citation*s:

a. Blodgett DM, Nowosielska A, Afik S, Pechhold S, Cura AJ, Kennedy NJ, Kim S, Kucukural A, Davis RJ, Kent SC, Greiner DL, Garber MG, **Harlan DM***, diIorio P: Novel Observations from Next Generation RNA Sequencing of Highly Purified Human Adult and Fetal Islet Cell Subsets. Diabetes **64**: 3172-81, 2015. (*corresponding author) PMCID: PMC4542439
b. Babon JA, DeNicola ME, Blodgett DM, Crevecoeur 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. Nature Medicine **22**, 1482-1487, 2016 PMCID: PMC5140746
c. Russell MA, Redick SD, Blodgett DM, Richardson SJ, Leete P, Krogvold L, Dahl-Jørgensen K, Bottino R, Brissova M, Spaeth JM, Babon JAB, Haliyur R, Powers AC, Yang C, Kent SC, Derr AG, Kucukural A, Garber MG, Morgan NG, **Harlan DM**. HLA Class II antigen procession and presentation pathway

components demonstrated by transcriptome and protein analysis of islet β-cells from donors with type 1 diabetes. Diabetes **68**, 988-1001, 2019 PMCID: PMC6477908

d. Redick SD, Leehy L, Rittenhouse AR, Blodgett DM, Derr AG, Kucukural A, Garber MG, Shultz, LD, Greiner DL, Wang JP, **Harlan DM**, Bortell R, Jurczyk, A. Recovery of viable endocrine-specific cells and transcriptomes from human pancreatic islet-engrafted mice. FASEB Journal. **34**, 1901-1911, 2020 PMCID: PMC6972551

B. Positions, Scientific Appointments, and Honors

Academic

1987-1988	Assistant Clinical Professor of Medicine, University of California, San Diego, CA
1989-1991	Associate, Department of Medicine, Duke University Medical Center, Durham, NC
1992-1998	Assistant Professor of Medicine, Uniformed Services University of Health Sciences
1998-2004	Associate Professor of Medicine, Uniformed Services University of Health Sciences
2004-2009	Professor of Medicine, Uniformed Services University of Health Sciences, Bethesda, MD
2009-2020	Professor of Medicine and Chief, Diabetes Division, UMass. Med. School, Worcester, MA
2010-	William and Doris Krupp Professor of Medicine, UMass Med. School, Worcester, MA

Assignments

1984-1988	Staff Internist, Naval Hospital, San Diego, CA
1991-1995	Head, Preclinical Studies, Immune Cell Biology Program, Naval Medical Research Inst.
1995-1999	Director, Immune Cell Biology Program, Naval Medical Research Institute, Bethesda, MD
1999-2007	Head, NIDDK-Navy Transplantation and Autoimmunity Branch, NIH
2007-2010	Head, NIDDK Diabetes Branch, NIH

Certification and Licensure

1985-present	California Medical License
2009-present	Massachusetts Medical License
1984-present	American Board of Internal Medicine certification
1991-present	ABIM Endocrinology, Diabetes, & Metabolism certification

Consultants, Editorial Board Memberships

1996-1999	National Institute for Diabetes and Digestive and Kidney Diseases Advisory Council
1997-2000	Medical Science Review Committee of the Juvenile Diabetes Foundation International
2002-2006	Member, Biological Response Modifiers Advisory Committee for the FDA
2005-2007	Member (& Chair in 2006-07) American Diabetes Association Session Scientific Planning
2008-2009	Consultant, Geron Corporation's Scientific Advisory Panel
2009	Howard Hughes Medical Institute Scientific Review Board *ad hoc* member
2011	Member, Glucagon Receptor Antagonist – Advisory Board (Pfizer)
2011-2013	Member, Advisory Board for AstraZeneca LP
2013-2018	Member, Scientific Advisory Board, Nutritional Science Initiative (NuSI)
2013-2016	Integrated Islet Distribution Program Oversight Committee
2014-present	Mentor Advisory Group, American Diabetes Association
2015-present	American Diabetes Association Community Volunteer Leadership Board member
2017-2020	Data Safety Monitoring Board (DSMB) for Technological Advances in Glucose Management in Older Adults or "The Tango Study"
2019-present	Editor, Current Opinion in Endocrinology, Diabetes, and Obesity
2020-present	Data Safety Monitoring Committee for Clinical Trial Protocol CCVZ533X2207 (Novartis)
2020	Advisory Board, VielaBio, Inc
2021	Special Government Employee "voting non-member" for the 69th meeting of the FDA Cellular, Tissue, and Gene Therapies Advisory Committee
1999-present	Several study sections for the NIH and JDRF

Honors

1977	Phi Beta Kappa, University of Michigan
1979	Alpha Omega Alpha, Duke School of Medicine
1984	Haskel Schiff Award in Clinical Medicine, Duke Medical Center
1997	Frank Brown Berry Prize for Federal Medicine
2000	Legion of Merit, United States Navy

2004	Peter Forsham Award for Academic Excellence, Society of Uniformed Endocrinologists
2005	Ray A. Kroc & Robert L. Kroc Visiting Professor at Stanford University
2006	U.S. PHS Physician Researcher of the Year Award
2009	Friend for Life Award, Children with Diabetes Foundation
2009	Jerry Ross Sustaining Member Lecture, Association of Military Surgeons of the United States
2011	Massachusetts Medical Law Report Rx for Excellence Award for "Leader in Quality"
2022	Rachiel Levine Award for Excellence in Clinical Research and Mentoring

C. Contributions to Science

1. Rodent models to study pathogenic mechanisms underlying diabetes. I developed and patented a transgenic mouse model (β cell specific expression of the costimulatory receptor CD80) to study the mechanisms underlying the pancreatic β cell destruction underlying T1D. The model allowed diabetes to be induced by virus infection, low dose β cell toxins, or by immunizing with β cell autoantigens. The model was utilized to study islet biology as diabetes develops, and to develop new analytical techniques which we later transitioned to the study of human islets. We have recently moved on to the study of rat models which appear more congruent with human T1D pathophysiology.

a. **Harlan DM**, Hengartner H, Huang ML, Kang YH, Abe R, Moreadith RW, Pircher H, Gray GS, Ohashi PS, Freeman GJ, Nadler LM, June CH, and Aichele P. Transgenic mice expressing both B7-1 and viral glycoprotein on pancreatic β cells along with glycoprotein-specific transgenic T cells develop diabetes due to a breakdown of T lymphocyte unresponsiveness. Proceedings of the National Academy of Sciences, U S A 1994; **91**: 3137-3141. PMID: 7512724 PMCID: PMC43530
b. Pechhold K, Zhu X, Lee J, Chakrabarty S, Periwal V, Koczwara K, **Harlan DM**. Dynamic changes in pancreatic hormone secreting cell abundance and distribution during development of β cell specific autoimmune diabetes. Diabetes; **58**: 1175-1184, 2009. PMCID: PMC2671059
c. Pechhold S, Stouffer M, Walker G, Martel R, Seligmann B, Hang Y, Stein R, **Harlan DM**, Pechhold K. Gene expression profiling of FACS-sorted pancreatic endocrine islet cell subsets by quantitative nuclease protection array (qNPA) technology suggests facultative β cell neogenesis in adult mice. Nature Biotechnology; **27**: 1038-1042, 2009. PMCID: PMC4638177
d. Fuchs YF, Adler K, Lindner A, Karasinsky A, Wilhelm C, Weigelt M, Balke H, Fortsch K, Mortler-Hildebrandt LF, **Harlan DM,** Pechhold K, Ziegler AG, Bonifacio E. Igrp and insulin vaccination induce CD8 T cell mediated autoimmune diabetes in the RIP-CD80GP mouse. Clin Exp Immunol 2014; **176**: 199-206. PMID:24387268 PMCID: PMC3992032

2. Employed non-human primate models to evaluate novel immunomodulatory approaches to prevent allograft rejection and transplanted pancreatic islet biology. With new immunomodulatory therapies focused on islet transplantation, we developed non-human primate models to test safety and efficacy. We reported the remarkable efficacy of anti-CD154 to prevent allograft rejection (kidney, islets, and skin). We also explored other potentially safer approaches to transplant isolated islets, the detailed metabolic function promoted by islet allografts, and techniques that may obviate immunosuppression following an islet allograft.

a. Kirk AD, Burkly L, Batty DS, Baumgartner RE, Berning JD, Fechner JH Jr, Germond RL, Kampen RL, Patterson NB, Swanson SJ, Tadaki DK, Tenhoor C, White L, Knechtle SJ, **Harlan DM.** Treatment with humanized monocloncal antibody against CD154 prevents acute renal allograft rejection in non-human primates. Nature Medicine 1999: **5**:686-693. PMID: 10371508
b. Soleimanpour SA, Hirshberg B, Brunnell DJ, Sumner AE, Ader M, Remaley AT, Rother KI, Rickels MR, **Harlan DM**. Metabolic function of a suboptimal transplanted islet mass in nonhuman primates on rapamycin monotherapy. Cell Transplantation; **21**: 1-7, 2012 PMID: 22080915 PMCID: PMC3508173
c. Conrad E, Dai C, Spaeth J, Guo M, Cyphert HA, Scoville D, Carroll J, Yu WM, Goodrich LV, **Harlan DM**, Grove KL, Roberts CT Jr, Powers AC, Gu G, Stein R. The MAFB transcription factor impacts islet α-cell function in rodents and represents a unique signature of primate islet β-cells. Am J Physiol Endocrinol Metab. **310**: E91-102, 2016 PMCID: PMC4675799
d. Vegas AJ, Veiseh O, Doloff JC, Ma M, Tam HH, Bratlie K, Li J, Bader AR, Langan E, Olejnik K, Fenton P, Kang JW, Hollister-Locke J, Bochenek MA, Chiu A, Siebert S, Tang K, Jhunjhunwala S, Aresta-Dasilva S, Dholakia N, Thakrar R, Vietti T, Chen M, Cohen J, Siniakowicz K, Qi M, McGarrigle J, Lyle S, **Harlan DM**, Greiner DL, Oberholzer J, Weir GC, Langer R, Anderson DG. Combinatorial hydrogel library enables identification of materials that mitigate the foreign body response in primates. Nature Biotechnology **34**: 341-352, 2016 PMCID: PMC4904301.

3. Studied isolated *human* islets to disclose important structural and functional biology, and to develop new analytical tools. Recognizing the unique resource isolated *human* islets afforded for discovery, we were the first

to report that hyperglycemia induces β cell TXNIP expression, and transcription of a novel insulin mRNA which is preferentially translated, the very different cellular structure of human and compared to rodent islets, and that adult human β proliferation rates are very low. We've recently moved to the study of islets isolated from donors with T2D and T1D- with the latter helping to identify novel T cell epitopes involved in the anti-β cell immune response.

a. Babon JAB, 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. Nature Medicine. **22**, 1482-1487, 2016. PMCID: PMC5140746
b. Russell MA, Redick SD, Blodgett DM, Richardson SJ, Leete P, Krogvold L, Dahl-Jørgensen K, Bottino R, Brissova M, Spaeth JM, Babon JAB, Haliyur R, Powers AC, Yang C, Kent SC, Derr AG, Kucukural A, Garber MG, Morgan NG, **Harlan DM**. HLA Class II antigen procession and presentation pathway components demonstrated by transcriptome and protein analysis of islet β-cells from donors with type 1 diabetes. Diabetes **68**, 988-1001, 2019 PMCID: PMC6477908
c. Nyalwidhe J, Jurczyk A, Satish B, Redick S, Qaisar N, Trombly M, Vangala P, Racicot R, Bortell R, **Harlan DM**, Greiner DL, Brehm M, Nadler J, Wang J. Proteomic and transcriptional profiles of human stem cell-derived beta cells following enteroviral challenge. Microorganisms, 2020 PMCID: PMC 7074978
d. Leite NC, Sintov E, Meissner TB, Brehm MA, Greiner DL, **Harlan DM**, Melton DA. Modeling type 1 diabetes in vitro using human pluripotent stem cells. Cell Reports 32: 107894, 2020. PMCID: PMC7359783

4. Conducted clinical trials to test novel therapies and elucidate important human biology as it relates to diabetes and its treatment. As an active diabetes clinician, I have tested novel diabetes treatments for safety and efficacy. I participated in testing immunotherapies (e.g. anti-CD3, oral interferon-alpha), led the NIH islet transplantation efforts, and have tested various approaches to promote pancreatic insulin producing capacity after T1D diagnosis.

a. Liu EH, Digon III, BJ, Hirshberg B, Chang R, Wood BJ, Neeman Z, Kam A, Wesley R, Polly S, Hofmann RM, Rother KI, **Harlan DM**. Pancreatic β cell function persists in many with chronic T1D but is not dramatically improved by prolonged immunosuppression and euglycemia from a β cell allograft. Diabetologia; **52**: 1369-1380, 2009. PMID: 19418039 PMCID: PMC2756111
b. Rother KI, Spain LM, Wesley R, Digon 3rd BJ, Baron A, Chen K, Nelson P, Dosch HM, Palmer J, Brooks-Worrell B, Ring M, **Harlan DM**. In chronic type 1 diabetes, functional pancreatic β cells survive despite ongoing autoimmunity but do not regenerate in response to exenatide and daclizumab. Diabetes Care; **32**: 2251-2257, 2009. PMCID: PMC2782986
c. Haliyur R, Tong X, Sanyoura M, Shrestha S, Lindner J, Saunders DC, Aramandla R, Poffenberger G, Redick SD, Bottino R, Prasad N, Levy SE, Blind RD, **Harlan DM**, Philipson LH, Stein RW, Brissova M, Powers AC. Human islets expressing HNF1A variant have defective beta cell transcriptional regulatory networks." J Clin Invest **129**: 246-251, 2019 PMCID: 6307934
d. Wright JJ, Saunders DC, Dai C, Poffenberger G, Cairns B, Serreze DV, **Harlan DM**, Bottino R, Brissova M, Powers AC. Decreased pancreatic acinar cel number in type 1 diabetes. Diabetologia **63**: 1418-1423 2020

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/david.harlan.1/bibliography/47740283/public/?sort=date&direction=ascending