BIOGRAPHICAL SKETCH

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NAME: Kevan Herold

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

POSITION TITLE: Professor of Immunobiology and Medicine

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
Penn State University, State College, PA	B.S	1977	Pre-Medicine
Jefferson Medical College, Philadelphia, PA	M.D.	1979	Medicine
Temple University Hospital, Philadelphia, PA	Intern & Resident	1982	Internal Medicine
The University of Chicago, Chicago, IL	Fellow	1984	Endocrinology
The University of Chicago, Chicago, IL	Post-doc	1986	Immunology

A. Personal Statement: My career has been focused on studies of the pathogenesis and treatment of immune diseases. My training and research work began in murine models and has involved studies of human samples from clinical trials: I have been the PI of 5 multicenter clinical trials of teplizumab for treatment and prevention of Type 1 diabetes and have also led other single and multicenter clinical trials. As part of this work, we have analyzed cellular immune responses in patients and determined the effects of immune therapies on these responses. We have also studied changes in β cell function and mass in humans with diabetes and animal models. We described epigenetic changes that occur in β cells in response to immune attack and identified a subpopulation of β cells that resists immune killing. To identify how immune responses are associated with the decline in β cells we developed an assay to measure β cell death in vivo. We described changes in β cells that occur in response to immunologic stressors which, we have postulated, may lead to survival. My laboratory has a long standing interest in developing tools to analyze autoantigen specific T cells in patients with Type 1 diabetes. We have used Class I MHC tetramers to analyze these cells in clinical trials and have developed T cell libraries for this purpose. My group was the first to identify autoimmune diabetes induced with checkpoint inhibitors (Diabetes Care 1995) which has provided insights into the mechanisms of Type 1 diabetes. In addition to clinical studies of anti-CD3 mAb I am and have been the Co-PI of early Phase trials of regulatory T cells to treat Type 1 diabetes, and others. I am a member of the Immune Tolerance Network Steering committee and the PI of the Yale Trial Net Center. I serve as Deputy Director for Translational Medicine in the Yale CTSA, and the Director of the Autoimmunity program in the Human Translational Immunology section of the Department of Immunobiology.

B. Positions and Honors

Positions and Employment

1977-1979 Associate Professor, Dept of Medicine, The University of Chicago, Chicago, IL
1977-1979 Assoc Professor (Tenured), Dept of Medicine, Univ of Illinois at Chicago, Chicago, IL
1980-1986 Clinical Assoc Professor of Medicine, Albert Einstein College of Medicine, Bronx, NY
1986-1987 Staff Scientist Hagedorn Research Laboratory, Gentofte, Denmark
1987-1988 Research Associate (Asst Professor), Dept. of Medicine, The University of Chicago, Chicago, IL
1988-1995 Assistant Professor, Department of Medicine, The University of Chicago, Chicago, IL

1988-1995 Assistant Professor, Committee on Immunology, The University of Chicago, Chicago, IL
1995-1998 Scientific Director, Juvenile Diabetes Foundation, Int., New York, New York
1998-2004 Associate Professor of Clinical Medicine, Columbia University, New York, New York
2004-2006 Associate Professor of Medicine, Columbia University, New York, New York
2006 Professor of Immunobiology and Medicine, Yale University, New Haven, CT

Professional Review Committees

1992-1999 Medical Science Review Committee, Juvenile Diabetes Foundation Int.
1995-96, 99 Ad hoc reviewer, Medical Research Council of Canada
1998, 02, 03 Ad hoc Reviewer, Metabolism and Immunologic Sciences Study Section, NIH
2002-2003 Ad hoc reviewer, Medical Research Council of Canada
2004-2007 Permanent member Reviewer, Metabolism and Immunologic Sciences Study Section, NIH

Honors and Awards

1978 Alpha Omega Alpha Honor Medical Society
1983, 85, 88 Young Investigators' Research Award, ADA, Northern Illinois Affiliate
1988-1990 Career Development Award, Juvenile Diabetes Foundation Int.
1990 Clinical Investigator Award, NIH
2005 Excellence in Clinical Research Award, Juvenile Diabetes Research Foundation
2008 Elected, Kunkel Society

C. Contributions to Science

1. **Development of anti-CD3 monoclonal antibody (mAb) for treatment of Type 1 diabetes**. Beginning with preclinical rodent studies, I showed that anti-CD3 mAb would prevent autoimmune diabetes in mice treated with low doses of streptozotocin and then in NOD mice in later studies. Based on these and other preclinical results from others, I wrote an Investigator IND for a clinical trial of teplizumab,that was manufactured by Dr. Jeffrey Bluestone, and performed the trial. The trial showed significant improvement in C-peptide responses for 2 years after diagnosis in children and adults. The successful results led to new trials by the Immune Tolerance Network a Phase III trial by pharma (MacroGenics) and another clinical trial that I conducted with NIH/JDRF support in patients with longer duration disease. All of these trials confirmed the effects of anti-CD3 mAb on clinical responses. We used Class I MHC tetramers to track antigen specific T cells in trial participants and showed that the mechanism of the drug effect did not involve cell depletion.
   a. **Herold KC**, Hagopian W, Auger JA, Poumian-Ruiz E, Taylor L, Donaldson D, Gitelman S, Harlan D, Xu D, Zivin R, and Bluestone JA. Anti-CD3 monoclonal antibody in new-onset Type 1 diabetes mellitus. *N Engl J Med.* 2002. 346:1692-1698.
   b. **Herold KC**, Gitelman SE, Willi SM, Gottlieb PA, Waldron-Lynch F, Devine L, Sherr J, Rosenthal SM, Adi S, Jalaludin MY, Michels AW, Dziura J, Bluestone JA Teplizumab treatment may improve C-peptide responses in participants with type 1 diabetes after the new-onset period: a randomised controlled trial. Diabetologia. 2013 Feb;56(2):391-400
   c. **Herold KC,** Gitelman SE, Ehlers MR, Gottlieb PA, Greenbaum CJ, Hagopian W, Boyle KD, Keyes-Elstein L, Aggarwal S, Phippard D, Sayre PH, McNamara J, Bluestone JA; AbATE Study Team. Teplizumab treatment improves C-peptide responses in subjects with Type 1 diabetes after the new onset period. *Diabetes*. 2013. 62(11):3766-74. PMCID: PMC3537871
   d. Tooley JE, Vudattu N, Choi J, Cotsapas C, Devine L, Raddassi K, Ehlers MR, McNamara JG, Harris KM, Kanaparthi S, Phippard D, **Herold KC.** Changes in T-cell subsets identify responders to FcR-nonbinding anti-CD3 mAb (teplizumab) in patients with type 1 diabetes. Eur J Immunol. 2016 Jan;46(1):230-41.
2. **Immune biomarkers and monitoring in patients with immune disease.** We have studied the ways in which anti-CD3 modifies immune responses as a biomarker of efficacy of the drug and evaluated the effects of the microbiome on immune responses. We first identified the occurrence of autoimmune diabetes in patients treated with checkpoint inhibitors.
   a. Gülden E, Vudattu NK, Deng S, Preston-Hurlburt P, Mamula M, Reed JC, Mohandas S, Herold BC, Torres R, Vieira SM, Lim B, Herazo-Maya JD, Kriegel M, Goodman AL, Cotsapas C, **Herold** KC. Microbiota control immune regulation in humanized mice. JCI Insight. 2017 Nov 2;2(21).

b. Long SA, Thorpe J, DeBerg HA, Gersuk V, Eddy E, Harris K, Ehlers M, **Herold KC**, Nepom G and Linsley PS Partially exhausted CD8 T cells are associated with clinical response to teplizumab in new-onset type 1 diabetes Science Immunology Nov;1(5). pii: eaai7793..
c. Stamatouli AM, Quandt Z, Perdigoto AL, Clark PL, Kluger H, Weiss SA, Gettinger S, Sznol M, Young A,Rushakoff R, Lee J, Bluestone JA, Anderson M, and **Herold KC**. Collateral Damage: Insulin dependent diabetes induced with checkpoint inhibitors. Diabetes 2018 67:1471-80.
d. Ogura H, Preston-Hurlburt P, Perdigoto AL, Amodio M, Krishnaswamy K, Clark P, Yu H, Egli D, Fouts A, Steck AK, and **Herold KC**. Identification and analysis of islet antigen specific CD8+ T cells with T cell libraries. J Immunol 2018 201:1662-1670.

3. **Development of combinatorial approaches to enable a long term treatment and prevention of T1D** None of the therapies that have been tested to date have resulted in permanent remission of the disease. The problems with relapse may be failure of the immunologics, irreparable beta cell damage, or a combination of these problems. We found that there was a population of degranulated beta cells at diagnosis of diabetes in NOD mice that recovered function with anti-CD3 mAb therapy. The observation accounts for the "honeymoon" of T1D. We used information from our pre- and clinical studies to design combination regimens with GLP-1 receptor agonists, IL-1beta blockade, and with antigen.
   a. Bresson D, Togher L, Rodrigo E, Chen Y, Bluestone JA, **Herold KC,** and vonHerrath M. Anti-CD3 and nasal proinsulin combination therapy enhances remission from recent-onset autoimmune diabetes by inducing Tregs. *J Clin Invest* 2006. 116(5):1371-81. PMCID: PMC1440705
   b. Sherry NA, Chen W, Kushner JA, Glandt M, Tang Q, Tsai S, Santamaria P, Bluestone JA, Brillantes AM, **Herold KC**. Exendin-4 improves reversal of diabetes in NOD mice treated with anti-CD3 monoclonal antibody by enhancing recovery of beta-cells. *Endocrinology* 2007. 148(11):5136-44.
   c. Bluestone JA, Buckner JH, Fitch M, Gitelman SE, Gupta S, Hellerstein MK, **Herold KC**, Lares A, Lee MR, Li K, Liu W, Long SA, Masiello LM, Nguyen V, Putnam AL, Rieck M, Sayre PH, Tang Q. Type 1 diabetes immunotherapy using polyclonal regulatory T cells. Sci Transl Med. 2015 Nov 25;7(315):315ra189.
   d. Perdigoto AL, Preston-Hurlburt P, Clark P, Long SA, Linsley PS, Harris KM, Gitelman SE, Greenbaum CJ, Gottlieb PA, Hagopian W, Woodwyk A, Dziura J, and **Herold, KC**. Treatment of Type 1 diabetes with teplizumab: clinical and immunological follow-up after 7 years from diagnosis. Diabetologia (in press)

4. **Analysis of beta cells in autoimmune diabetes**. The goal of therapy of Type 1 diabetes is to stop metabolic studies that are performed to evaluate β cell mass and function in diabetes do not identify β cell killing. We developed an assay to measure beta cell death in vivo and have used it in clinical settings. We described the development of a β cells that can resist immune killing in NOD mice and in human islets.
   a. Rui J, Deng S, Arazi A, Perdigoto AL, Liu Z, **Herold** KC. β Cells that Resist Immunological Attack Develop during Progression of Autoimmune Diabetes in NOD Mice. Cell Metab. 2017;25(3):727-738 PMID: 28190773
   b. **Herold KC**, Usmani-Brown S, Ghazi T, Lebastchi J, Beam CA, Bellin MD, Ledizet M, Sosenko JM, Krischer JP, Palmer JP. β Cell death and dysfunction during type 1 diabetes development in at-risk individuals. J Clin Invest. 2015. pii:78142. doi: 10.1172/JCI78142. PubMed PMID: 25642774.
   c. Akirav EM, Lebastchi J, Galvan EM, Henegariu O, Akirav M, Ablamunits V, Lizardi PM, **Herold KC**. Detection of β cell death in diabetes using differentially methylated circulating DNA. *Proc Natl Acad Sci U S A.* 2011. 108(47):19018-23. PMCID: PMC3223447
   d. Lebastchi J, Deng S, Lebastchi A, Beshar I, Gitelman S, Willi S, Gottlieb P, Akirav E, Bluestone JA, and **Herold KC.** Analysis of beta cell death in type 1 diabetes: Effects of immune therapy. *Diabetes.* 2013. PMCID: PMC3636605

5. **The role of RAGE in adaptive immune responses**. Our studies began in NOD mice in which we found that transfer of diabetes by splenocytes from diabetic mice into NOD/scid recipients could be attenuated with soluble RAGE. In other rodent models we confirmed the role of RAGE in adaptive responses. Subsequent studies showed that RAGE was important in cytokine production and differentiation of T cells. We then turned to human cells but found that RAGE was expressed *intracellularly* in T cells and was associated with increased production of cytokines including IL-17. These studies have also shown that RAGE expression on T cells can prolong cell survival. This may be a mechanism whereby antigen specific T cells may be activated by ligands other than antigen itself, and may explain the kinetics and precipitating events in Type 1 diabetes.
   a. Moser B, Desai DD, Downie MP, Chen Y, Yan SF, **Herold K**, Schmidt AM, Clynes R. Receptor for

advanced glycation end products expression on T cells contributes to antigen-specific cellular expansion in vivo. *J Immunol*. 2007. 179(12):8051-8.

b. Chen Y, Akirav EM, Chen W, Henegariu O, Moser B, Desai D, Shen JM, Webster JC, Andrews RC, Mjalli AM, Rothlein R, Schmidt AM, Clynes R, **Herold KC**. RAGE ligation affects T cell activation and controls T cell differentiation. *J Immunol*. 181(6):4272-8. PMCID: PMC2643976

c. Akirav EM, Preston-Hurlburt P, Garyu J, Henegariu O, Clynes R, Schmidt AM, **Herold KC**. RAGE expression in human T cells: a link between environmental factors and adaptive immune responses. *PLoS One*. 2012. 7(4):e34698. PMCID: PMC3324532

d. Durning SP, Preston-Hurlburt P, Clark PR, Xu D, **Herold KC**; Type 1 Diabetes TrialNet Study Group. The Receptor for Advanced Glycation Endproducts Drives T Cell Survival and Inflammation in Type 1 Diabetes Mellitus. J Immunol. 2016 Oct 15;197(8):3076-3085. 2016 Sep 21.

Complete List of Published Works in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/kevan.herold.1/bibliography/45937776/public/?sort=date&direction=ascending

D. Additional Information: Research Support

Ongoing Research Support

UL1 TR000142-10 Sherwin (PI) 07/01/16 – 06/30/21
Yale Clinical and Translational Science Award Program
This proposal is to use a new method to determine beta cell mass in type 1 diabetes. The studies include analysis of NOD mice that have been treated with anti-CD3 or anti-CD20 antibodies as well as patients with type 1 diabetes who will receive treatment with Rituximab.
Role: Co-PI

2R01 DK057846-11A1 Herold (PI) 04/01/14 – 03/31/18 (NCE)
Phase II Trial of HOKT3gamma 1 (ALA-ALA) in Type 1 Diabetes
Major goals of this project are to analyze antigen specific T cells in patients at risk of T-1D. Role: PI

Completed research (within the last 3 years):

U01AI1U01-02011-01 Hafler/Herold (PI) 07/01/12 - 06/30/17
"The role of the innate immune system on Treg reprogramming in human autoimmune diseases"
This project will investigate how regulatory T cells are generated in health and disease and identify key molecules that could be targeted therapeutically to restore normal processes in Multiple Sclerosis and Type I diabetes
Role: PI

2R42 DK095639-02 Herold (PI) 09/01/14 – 08/31/17
STTR Phase II: Analysis of Beta Cell Death with L2 Diagnostics, LLC
The objective of this study is to identify changes in methylation patterns of DNA released from dying β cells in patients with T1D.
Role: PI

1UC4 DK104205-01 Herold (PI) 09/18/14 – 08/31/18
Epigenetic, Protein, and Cellular Biomarkers of Beta Cell Function in T1D
The major goals of this project are aimed at defining specific parameters during the dysfunction and eventual demise of beta cells, though those cells are asymptomatic in subjects at-risk for T1D.
Role: PI