BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Kathryn Haskins	Professor
eRA COMMONS USER NAME HASKINS.KATIE	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Univ. of Kansas, Lawrence, KS	Ph.D.	1981	Biochemistry
National Jewish Hospital, Denver, CO	Postdoc	1981-1986	Immunology

A. Personal Statement

Our overall research focus over the past 25 years has been the investigation of pathogenic and regulatory processes mediated by CD4 T cells in type 1 diabetes (T1D) and the identification of new autoantigens for diabetogenic T cells. For this work, we have a unique panel of diabetogenic CD4 T cell clones from NOD mice, including the prototype clone BDC-2.5, the TCR of which was used to make a TCR-transgenic mouse that has been used by many investigators to study islet-reactive T cells in vivo; the antigen for this clone in particular has been considered a high priority research objective. Recent progress has led to the successful identification of two new secretory granule proteins as autoantigens for CD4 T cells: chromogranin A (ChgA) as the BDC-2.5 antigen and islet amyloid polypeptide (IAPP). We showed that a natural peptide cleavage product from ChgA, WE14, is a weakly stimulating ligand, but subsequent work has demonstrated that WE14 and other secretory granule peptides undergo a novel post-translational modification (PTM) involving the formation of hybrid peptides that are highly antigenic for the T cell clones. Investigating the role of modified peptides as ligands for autoreactive T cells is now one of our highest priorities. In addition, we are developing new hybrid peptide tetramer reagents to detect autoreactive T cells and investigating whether hybrid peptides could be used to induce antigen-specific tolerance. The investigators in my lab are a well-unified team and we have unparalleled experience and tools with which to approach these highly challenging projects. Together with our collaborators we are now moving these studies into the translational arena to identify and characterize autoreactive T cells in human subjects with T1D.

B. Positions and Honors:

Positions and Employment

1981-1986	Postdoctoral Fellow, Div. Basic Immunology, Natl. Jewish Hosp. & Res. Ctr., Denver, CO
1986-1999	Member, Barbara Davis Ctr. for Childhood Diabetes, U. Colo. Health Sci. Center (UCHSC), Denver, CO
1999-	Associate Member, Barbara Davis Ctr. for Childhood Diabetes, UCHSC
1986-1991	Assistant Professor, Dept. Microbiol./Immunol., UCHSC, Denver, CO
1991-1993	Associate Professor, Dept. of Microbiol./Immunol., UCHSC, Denver, CO
1993-1999	Interim Chair, Dept of Immunology, UCHSC, Denver, CO
1997-1999	Professor, Dept. of Immunology, School of Medicine, UCHSC, Denver, CO
1999-2014	Professor, Integrated Dept. Immunology, U Colorado Denver & Natl. Jewish Health, Denver, CO
2014-	Professor, Dept of Immunology and Microbiology, U. Colorado School of Medicine

Professional Memberships, Honors

Member, American Association of Immunologists
Member, American Diabetes Association
Member, Immunology of Diabetes Society
Member, American College of Rheumatology
NIH New Investigator Award 1985-1988
Diabetes Res. & Education Foundation Award 1989
JDRF Career Development Award 1990-1993
Regular member, NIH AITRC Study Section (2002-05)
ADA Mentor Award (2006-2010)
National Jewish Health Outstanding Scientific Achievement Award (2010)
Regular member, NIH DDK-B Study Section (2006-11)
Regular member, HAI Study Section (2011-15)
Regular member, ADA Review Committee (2015-18)
Associate Editor, Diabetes (2011-16)

C. Contribution to Science

1. **Development of antigen-specific diabetogenic T cell clones.** By the mid-1980's it was realized that both CD4 T cells and CD8 T cells were vital participants in the pathogenesis of T1D. A variety of studies in the NOD mouse model provided evidence for the critical role of T cells, but which T cells are more important to disease initiation has remained controversial. Our lab was the first to successfully isolate and characterize autoreactive T cell clones from the NOD mouse; we developed a panel of CD4 T cell clones that have been maintained for over 20 years. These T cell clones react to islet antigens, are highly pathogenic when transferred to young NOD or NOD.scid recipients, and provided the first demonstration that CD4 T cell clones alone could induce disease. The best known of these clones is the BDC-2.5 T cell that was subsequently used to make the BDC-2.5 T cell receptor transgenic (TCR-Tg) mouse, an animal model widely used by many investigators of autoimmune diabetes.

(a) Haskins, K., Portas, M., Bergman, B., Lafferty, K., and Bradley, B. (1989) Pancreatic Islet-Specific T Cell Clones from NOD Mice. *Proc. Natl. Acad. Sci.* 86: 8000.

(b) Haskins, K. and McDuffie, M. 1990. Acceleration of diabetes in young NOD mice with a CD4+ islet-specific T cell clone. *Science* 249: 1433.

(c) Katz, J.D., Wang, B., Haskins, K., Benoist, C. and Mathis, D. 1993. Following a diabetogenic T cell from genesis through pathogenesis. *Cell* 74:1089. PMID: 8402882.

(d) Haskins, K. 2005. Pathogenic T cell clones in autoimmune diabetes: more lessons from the NOD mouse. *Advances in Immunol. 87*: 123-62. PMID: 16102573.

2. **Characterization of Th1 T cell effector function and inflammatory role of macrophages in the NOD mouse.** Although many studies indicated that T cells were participants in the disease process, mechanistic information on how pathogenic T cells functioned was somewhat scarce. In a series of studies using our CD4 T cell clones to transfer disease, we developed methods to retrieve these cells from the pancreas and characterize their activity *ex vivo*.

a) Cantor, J. and Haskins, K. 2005. Effector Function of Diabetogenic CD4 Th1 T cell clones: A Central Role for TNFα. *J. Immunol*. 175: 7738-45. PMID: 16301684.

b) Cantor, J. and Haskins, K. 2007. Recruitment and activation of macrophages by pathogenic CD4 T cells in T1D: Involvement of CCR8 and CCL1. *J. Immunol.* 179: 5760-67.

3. **Demonstration of antigen-specific requirement for T regs.** The Treg field in autoimmune diabetes has been very competitive and we and others worked out successful methods for converting T cells from the BDC-2.5 TCR-Tg mouse into Tregs. We extended this work to another TCR-Tg mouse that was produced with the TCR of a second T cell clone from our panel, BDC-6.9, and as described in the first publication listed under this paragraph, this TCR is also available on a NOD background that lacks the antigen for the BDC-6.9 clone. These two TCR-Tg mice provided a useful and unique system for examining how Tregs function in vivo in the presence and absence of their antigen.

(a) Pauza, M. E., Dobbs, C. M., He, J., Patterson, T., Wagner, S., Anobile, B., Bradley, B., Lo, D. and Haskins, K. (2004) TCR transgenic response to an endogenous polymorphic autoantigen determines susceptibility to diabetes. *Diabetes* 53: 978-988.

(b) Tonkin, D.R., He, J., Barbour, G. and Haskins, K. 2008. Regulatory T cells prevent transfer of type 1 diabetes in NOD mice only when their antigen is present in vivo. *J. Immunol.* 181: 4516-22

(c) Tonkin, D.R. and Haskins, K. 2009. Regulatory T cells enter the pancreas during suppression of type 1 diabetes and inhibit effector T cells and macrophages in a TGF-β-dependent manner. *Eur. J. Immunol.* 39: 1313-22.

4. **Identification of new beta-cell autoantigens for CD4 T cells in T1D.** Over the last 20 years, the prevailing view has been that insulin is the initiating, most critical antigen for development of diabetes. As most of the T cell clones in our panel do not respond to peptides of insulin, we pursued identification of the antigens for these clones using biochemical approaches. By the year 2000, we had biochemically characterized properties of antigenic fractions obtained from chromatographic separations of beta cell lysates. When Dr. Delong joined the lab in 2006 as a postdoctoral fellow, he moved our antigen studies forward with a proteomic approach which led to his identification by mass spectrometry of two new secretory granule proteins, chromogranin A (ChgA) and islet amyloid polypeptide (IAPP). Whereas IAPP had previously been shown to be an autoantigen through identification of autoantibody and human CD8 T cell reactivity to IAPP epitopes, ChgA had no previous history in autoimmune disease. Since ChgA turned out to be the antigen for BDC-2.5 and other clones in the panel, this discovery was met with wide interest. The proteomic identification of proteins and their ligands formed the basis for the first five years of the current R01 grant. The importance of ChgA as an antigen has been underscored by our recent finding that NOD mice deficient in ChgA do not develop diabetes (Baker et al, manuscript submitted).

a) Stadinski, B.D.*, Delong, T.*, Reisdorph, N., Reisdorph, R., Powell, R.L., Armstrong, M., Piganelli, J.D., Barbour, G., Bradley, B., Crawford, F., Marrack, P., Mahata, S.K., Kappler, J.W. and Haskins, K. 2010. Chromogranin A is an autoantigen in type 1 diabetes. *Nature Immunol.* 11: 225-31. PMID: 20139986. **Denotes equal contributions.* PMCID: PMC3166626

(b) Delong, T., Reisdorph, N., Reisdorph, R., Powell, R.L., Armstrong, M., Baker, R.L., Barbour, G., Bradley, B., and Haskins, K. 2011. Islet amyloid polypeptide is the autoantigen for a diabetogenic CD4 T cell clone BDC-5.2.9. *Diabetes* 60: 2325-30.

(c) Baker, R.L., Delong, T., Barbour, G., Bradley, B., Nakayama, M. and Haskins, K. 2013. *Cutting Edge:* CD4 T cells reactive to a peptide from IAPP accumulate in the pancreas of NOD mice. *J. Immunol.*191: 3990-4. PMCID: PMC3815676

(d) Gottlieb, P.A., Delong, T., Baker, R.L., Fitzgerald-Miller, L., Wagner, R., Cook, G., Rewers, M.J., Michels, A. and Haskins, K. 2014. Chromogranin A is a T Cell Antigen in Human Type 1 Diabetes. *J. Autoimmunity* 50: 38-41.

(e) Baker, R.L., Bradley, B., Wiles, T.A., Lindsay, R.S., Barbour, G., Delong, T., Friedman, R.S. and Haskins, K. 2016. NOD mice deficient in chromogranin A do not develop diabetes. *J. Immunol Cutting Edge* 196: 39-43.

5. **Identification of a unique post-translation modification involved in the formation of peptide ligands for autoreactive T cells in T1D.** Our identification of two new secretory granule proteins constituted important discoveries, but left open the question of the ligands presented to T cells from these proteins. Through our collaboration with Dr. Kappler and his student, Stadinski (*Nat Immunol* 2010), we had found that WE14, a peptide of 14 amino acids and a natural cleavage product of ChgA, was a weakly stimulating ligand for the T cell clone, BDC-2.5. Because this peptide could only stimulate the clone at high concentrations, we hypothesized that some kind of modification must be involved in the generation of the natural ligand in vivo and were able to demonstrate that cross-linked or aggregated forms of WE14 were far more antigenic than the linear peptide (Delong et al, *Diabetes* 2012). Dr. Delong then discovered that the distribution of WE14 did not correspond to the antigenic fractions of beta cell extracts, but that C-peptides and fragments thereof did. He was able to demonstrate that some of the C-peptide fragments in antigenic fractions had activated C-termini, capable of forming peptide bonds with N-termini of other peptides. This led to the hypothesis and subsequent demonstration that hybrid peptides were forming between fragments of insulin and sequences of other secretory granule protein cleavage products such as WE14. In recognition of his discoveries and proposal to develop hybrid peptide libraries for screening human autoreactive T cells, Dr. Delong was awarded the new ADA Pathway to Stop Diabetes award in Jan 2015. The discovery of the hybrid peptides was described in *Science* early in 2016.

(a) Delong, T., Baker, R.L., He, J., Barbour, G., Bradley, B., and Haskins, K. 2012. Diabetogenic T cell clones recognize an altered peptide of Chromogranin A. *Diabetes* 61: 3239-46.

(b) Delong, T., Wiles T.A., Baker, R.L., Bradley, B., Barbour, G., Reisdorph, R., Kumar, N., Elso, C.M., Armstrong, M., Powell, R.L., Reisdorph, N., DeNicola, M., Bottino, R., Powers, A.C., Harlan, D.M., Kent, S.C., Mannering, S.I. and Haskins, K. 2016. Pathogenic CD4+ T cells in type 1 diabetes recognize epitopes formed by peptide fusion. *Science* 351: 711-14.

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/kathryn.haskins.1/bibliograpahy/40375677/public/?sort=date&direction=ascending