BIOGRAPHICAL SKETCH

NAME: Center, David

eRA COMMONS USER NAME (credential, e.g., agency login): dcenter@bu.edu

POSITION TITLE: Associate Provost, Translational Research; Gordon and Ruth Snider Professor of Pulmonary Medicine; Chief, Allergy, Pulmonary and Critical Care Medicine, Boston University Medical Campus

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	Completion Date	FIELD OF STUDY
Boston University School of Medicine, Boston, MA	AB, MD	1972	Medicine
Boston University Medical Center, Boston, MA	Resident	1974	Medicine
Boston University Medical Center, Boston, MA	Fellow	1975	Pulmonary Medicine
Robert B. & Peter B. Brigham Hospital/Harvard Medical School, Boston, MA (K. Frank Austen Lab)	Fellow	1978	Research

A. Personal Statement

I am the Associate Provost of Translational Research and Gordon and Ruth Snider Professor of Pulmonary Medicine at Boston University School of Medicine, and I have served as Chief of Pulmonary, Allergy, Sleep, and Critical Care Medicine since 1986. I have directed and served as PI for BU's Clinical and Translational Science Institute (CTSI) since 2008, focusing on facilitating translational research and advancing team science on the Boston University Medical Campus, which occupies half my time. My individual research focuses on the biological effects of Interleukin 16, which I co-discovered, as an immunomodulatory cytokine in inflammation. I also defined all the functional properties of the IL-16 precursor protein, Pro-IL-16, as a PDZ containing nuclear scaffold that coordinates a multiple protein complex that acts as a transcriptional suppressor. Mutations in the scaffold predispose to T cell malignancies, while the secreted cytokine acts a necessary growth factor for myeloma cells. This work has been funded by NIH-sponsored R, P, and U grants beginning in 1978. In the past several years I have shifted from a lifetime of traditional NIH P01, P50 and R01 research to concentrate my efforts on developing the intellectual property (in collaboration with industry) on inhibitors of IL-16 function, in particular human and humanized monoclonal antibodies to IL-16, as treatments for neuro-inflammatory diseases and multiple myeloma. Since 1996, I have directed this T32, the largest at Boston University. We train PhD pre- and post- doctoral fellows and MD postdoctoral fellows in multiple fields of lung health and disease from clinical outcomes to traditional lab science, from genetic epidemiology to developmental biology. Since 2015, I have chaired the NHLBI Division of Lung Diseases Pulmonary Trials Cooperative, which oversees 4 simultaneous overlapping pragmatic trials. My personal commitment to leading multidisciplinary research and research training and mentorship will continue as I will continue to Chair the T32 executive committee with oversight of career development and mentorship quality.

B. Positions and Honors

Positions and Employment

1978 – 1983 Assistant Professor of Medicine, Boston University School of Medicine
1978 – 1983 Chief, Allergy Unit, Boston University School of Medicine
1983 – 1989 Associate Professor of Medicine, Boston University School of Medicine
1987- Chief, Pulmonary, Allergy and Critical Care Medicine, Boston University School of Medicine
1989- Professor of Medicine and Research Professor of Biochemistry, Boston University School of Medicine
2000- Gordon and Ruth Snider Professor of Pulmonary Medicine, Boston University School of Medicine
2006- Assistant Provost for Translational Research; Director, Clinical and Translational Science Institute, Boston University School of Medicine

2007- Associate Provost for Translational Research, Boston University School of Medicine
2008- Director, Boston University Clinical and Translational Science Institute, Boston University School of Medicine
2014- Professor of Biomedical Engineering, Boston University School of Medicine

Other Experience and Professional Memberships

American Association of Immunologists
American Thoracic Society
Elected, American Society for Clinical Investigation
Elected, Association of American Physicians
Society for Clinical and Translational Science
Fellow, American Association for the Advancement of Science
American Academy of Asthma, Allergy and Immunology

Honors and Notable Leadership Positions

1981 Edward Livingston Trudeau Fellow of the American Thoracic Society
1985 – 1990 Career Investigator of the American Lung Association
1987 – 1988 National Secretary/Treasurer, A.F.C.R.
1987 – 1990 Respiration Study Section, Veteran's Administration Merit Review
1989 Co-Chairperson, Fellowship Fellow Review Committee, American Lung Association
1992 – 1994 Chairman, NIH Lung Biology Pathology Study Section
1992 – 1995 Chairman, American Lung Association Research Grant Review Committee
1995 – 1996 NIH DRG Advisory Council
1996 – 2000 Charter Member, NIH Peer Review Oversight Group (PROG)
1999 – 2003 Chair, American Thoracic Society Publications Policy Committee
1999 – 2006 NHLBI Board of Extramural Advisors
2000 – 2001 Chair, ATS Nomination Committee
2002 Distinguished Alumnus Award, Boston University School of Medicine
2002 Best Physicians in America
2003 – 2009 Best of Boston, Pulmonary Physicians
2006 – NHLBI LRP Reviewer
2007 – 2013 NHLBI T32 Review Committee
2008 Chadwick Medal of the Massachusetts Thoracic Society
2008 – NIH Director's New Innovator Award Reviewer
2009 – NIH Director's Pioneer Awards Reviewer
2009 – 2010 Board Member, Society for Clinical and Translational Science
2011 Secretary/Treasurer, Society for Clinical and Translational Medicine
2011 Commencement Speaker, Boston University Seven Year Medical Department Graduation
2013 Edward Livingston Trudeau Medal of the American Thoracic Society
2013 Elected, National Academy of Inventors
2014 – Distinguished Editor, NIH Director's New Innovator Award Review Editorial Board
2014 – Elected Fellow, American Association for the Advancement of Science
2015- Chair, DLD/NHLBI Pulmonary Trials Cooperative
2017 Breathing for Life Award, American Thoracic Society
2017- Treasurer, Association for Clinical and Translational Science (ACTS)

C. Contributions to Science

1. **Chemotactic Factor for Lymphocytes:** These back-to-back papers represent the first description of a naturally derived chemotactic factor for lymphoctyes. This represented a complete paradigm shift in the thinking of lymphocyte homing and accumulation, for before these papers lymphocytes were thought not to respond along concentration gradients as part of accumulation in lymph nodes and tissue sites of inflammation but homed via adhesion molecules. These papers also set the stage for the discovery of the entire family of lymphocyte specific chemotactic cytokines (chemokines). The Lymphocyte Chemoattractant Factor described here was later renamed Interleukin 16 and began a series of over 50 papers describing the functions of IL-16 from which over 30 patents have been issued to BU.

a) **Center DM**, Cruikshank W. Modulation of lymphocyte migration by human lymphokines. I. Identification and characterization of chemoattractant activity for lymphocytes from mitogen-stimulated mononuclear cells. *J Immunol*. 1982;128(6):2563-8. PMID: 7042840.
b) Cruikshank W, **Center DM**. Modulation of lymphocyte migration by human lymphokines. II. Purification of a lymphotactic factor (LCF). *J Immunol*. 1982;128(6):2569-74. PMID: 7042841.

2. **Gene Products of HIV-1:** This paradigm shifting work demonstrated for the first time that gene products of HIV-1, known to be present in the circulation of infected individuals, had specific functions independent of viral infection. The study shows that gp120 is responsible for CD4+ T cell homing and activation, making T cells more susceptible to infection. A follow up paper in Nature (Mackiewicz C, Levy J, Cruikshank W, Kornfeld H, Center D. Role of IL-16 in HIV Replication. *Nature*. 1996;383:488-9) defined the mechanism of IL-16 repression of HIV1 replication; and a J. Virology paper (Green, DS, Center, DM, Cruikshank, WW. HIV-1 gp120 reprogramming of T cell migration provides a mechanism for lymphadenopathy. *J Virol.* 83:5765-5770. PMCID: PMC2681967) demonstrated that HIV-1gp120 was capable of heterologous chemotactic factor desensitization and deactivating responses to S1P, therefore explaining the lymphadenopathy in early HIV-1 infection.

   a) Kornfeld H, Cruikshank WW, Pyle SW, Berman JS, **Center DM**. Lymphocyte Activation by HIV-1 Envelope Glycoprotein. *Nature*. 1988;335:445-448. PMID: 2843775.
   b) Mackewicz CE, Levy JA, Cruikshank WW, Kornfeld H, **Center DM**. Role of IL-16 in HIV Replication. *Nature*. 1996;383:488-9. PMID: 8849720.
   c) Green DS, **Center DM,** Cruikshank WW. Human immunodeficiency virus type 1 gp120 reprogramming of CD4+ T-cell migration provides a mechanism for lymphadenopathy. *J Virol*. 2009;83(11):5765-72. PMCID: PMC2681967

3. **Interleukin-16:** Cloning of Interleukin-16 and identification of its function as a CD4 ligand inducing migration and activation of CD4+ cells led to the naming of this cytokine as IL-16 and provided the neutralizing antibodies for all the subsequent studies of function and for the issue of 33 patents related to immune modulation by IL-16 in a variety of diseases, ranging from multiple myeloma to multiple sclerosis and asthma.

   a) Cruikshank WW, **Center DM**, Nisar N, Wu M, Natke B, Theodore AC, Kornfield H. Molecular and functional analysis of a lymphocyte chemoattractant factor: association of biologic function with CD4 expression. *Proc Natl Acad Sci U S A.* 1994;91(11):5109-13. PMCID: PMC43941.
   b) **Center DM**, Kornfeld H, Ryan TC, Cruikshank WW. Interleukin 16: implications for CD4 functions and HIV-1 progression. *Immunol Today.* 2000 Jun;21(6):273-80. PMID: 10825739.
   c) **Center DM**, Kornfeld H, Cruikshank WW. Interleukin 16 and its function as a CD4 ligand. *Immunol Today.* 1996 Oct;17(10):476-81. PMID: 8908813.
   d) **Center DM**, Kornfeld H, Wu MJ, Falvo M, Theodore AC, Bernardo J, Berman JS, Cruikshank WW, Djukanovic R, Teran L, et al. Cytokine binding to CD4+ inflammatory cells: implications for asthma. Am *J Respir Crit Care Med.* 1994 Nov;150(5 Pt 2):S59-62. PMID: 7952594.

4. **IL-16 Selective Chemotactic Activity:** We demonstrated IL-16 selective chemotactic activity for T regulatory cells via CD4 ligands and the induction of the FoxP3+IL-2Rhi phenotype of CD4+ T regulatory cells, thus providing a mechanism for the immunosuppressive effects of IL-16 and a TGFbeta independent pathway for generating T regulatory cells.

   a) McFadden CS, Green D, Yamasaki H, **Center DM**, Cruikshank WW. Preferential migration of T regulatory cells induced by IL-16. *J Immunol*. 2007;179:6439-45. PMID: 17982032.
   b) Lynch EA, Heijens CA, Horst NF, **Center DM**, Cruikshank WW. Cutting edge: IL-16/CD4 preferentially induces Th1 cell migration: requirement of CCR5. *J Immunol.* 2003 Nov 15;171(10):4965-8. PMID: 14607889.

5. **Pro-IL-16:** The first paper listed defined Pro-IL-16 as first (described) PDZ domain containing nuclear scaffold. It is the most highly regulated gene following T cell activation and is the limiting factor in Skp2

transcription, and thus p27levels permitting T cell exit from G1. It also defines IL-16 as a dual function Alarmin.

a) Zhang Y, Tuzova M, Xiao Z-XJ, Hanson SK, Xie H, Kornfeld H, Cruikshank WW, **Center DM**. Pro-Interleukin-16 is a scaffold protein which targets Histone Deacetylase 3 to Transcription Factor GABP in the Skp2 Core Promoter. *J Immunol*. 2008;180:402-408. PMID 18097041.

b) **Center DM**, Cruikshank WW, Zhang Y. Nuclear pro-IL-16 regulation of T cell proliferation: p27(KIP1)-dependent G0/G1 arrest mediated by inhibition of Skp2 transcription. J Immunol. 2004 Feb 1;172(3):1654-60. PMID: 14734747.

c) Zhang Y, Tuzova M, Xiao ZX, Cruikshank WW, **Center DM**. Pro-IL-16 recruits histone deacetylase 3 to the Skp2 core promoter through interaction with transcription factor GABP. *J Immunol.* 2008 Jan 1;180(1):402-8. PMID: 18097041.

D. Additional Information: Current Research Support only

Ongoing Research Support

T32 HL 07035 Center (PI) 07/01/75 – 06/30/21
NIH/NHLBI
*Biology of the Lung: A Multidisciplinary Approac*h
This is the current T32 which provides training for PhD predoctoral students and PhD and MD postdoctoral fellows in diagnosis, prevention and treatment of lung diseases including developmental biology and regenerative medicine; immunity; genomics and genetics; biomedical engineering; and outcomes research.
Role: PI

U54 TR001430 Center (PI) 05/01/08 – 03/31/25
2020-2025 pending NOA; priority score 15; $38m
NIH/NCATS
Boston University Clinical and Translational Science Award (CTSA)
This is the parent CTSA award for Boston University. It provides support for infrastructure for clinical and translational scientists, including pilot awards, junior faculty and trainee positions, assistance in bioinformatics, biostatistics, human subjects research approval, study design and recruitment and engagement of the community in translational research efforts.
Role: PI