BIOGRAPHICAL SKETCH

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NAME: CANDOTTI, Fabio

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

POSITION TITLE: Assoc. Prof. of Medicine, Head Physician, Division of Immunology and Allergy, Lausanne University Hospital, Switzerland

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
School of Medicine, University of Brescia, Italy	MD	1987	Medicine
Laboratory of Biotechnology, Univ. of Brescia, Italy	Postdoctoral Fellow	1991-1992	Molecular biology
Department of Pediatrics, University of Pavia, Italy	Specialty Board	1992	Pediatrics
Department of Pediatrics, University of Brescia, Italy	Subspecialty Board	1996	Pediatric Allergy and Immunology
National Cancer Institute, NIH, Bethesda, MD, USA	Postdoctoral Fellow	1992-1994	Gene therapy
National Human Genome Research Institute, NIH, Bethesda, MD, USA	Postdoctoral Fellow	1994-1996	Gene therapy

A. Personal Statement

I have a long-standing interest in defining the cellular and molecular bases of immunodeficiency diseases and in the development of new therapeutic approaches for these disorders. Through research and clinical activity in this field, I have been able to contribute to the discovery of the genes responsible for immunodeficiencies (e.g. JAK3-deficiency and reticular dysgenesis) and to define important clinical features of these disorders, as well as some of the immunological mechanisms leading to disease in affected patients. Over the years, my laboratory has developed Moloney virus- and HIV-based gene correction strategies for SCID-X1, ADA-SCID, Wiskott-Aldrich syndrome (WAS) and IL12Rβ1 deficiency that were tested in vitro and in mouse models. I have extensive experience in clinical applications of gene therapy through trials for the treatment of ADA-SCID using gamma-retroviral and lentiviral vectors. Since my joining the Lausanne University Hospital in 2014, I have been responsible for the clinical implementation of vaccine trials at its Vaccinology and Immunotherapy Center including protocols from the HVTN network, such as the HVTN106, HVTN704 and HVTN127 studies. My laboratory is currently developing gene editing strategies based on CRISPR/Cas-9-mediated approaches to correct models of immunodeficiency (e.g. ADA-SCID) that can be applied also to strategies against HIV infection.

B. Positions and Honors

Employment

1990-1992 Staff member, Bone Marrow Transplantation Unit, Department of Pediatrics, Univ. of Brescia, Italy
1991-1992 Faculty member, Italian National Health Service School for Nurses
1996-1997 Assistant Professor, Department of Pediatrics, University of Brescia, Italy
1996-1997 Attending Physician, Department of Pediatrics, City Hospital, Brescia, Italy
1998-2004 Investigator (tenure-track), NHGRI, NIH
1998-2014 Senior Member, Clinical Staff, Clinical Center, National Institutes of Health

2004-2014 Senior Investigator (tenured), NHGRI, NIH
2014-date Associate Professor of Medicine, Lausanne University, Switzerland
2014-date Clinical Director, Vaccine and Immunotherapy Center, Lausanne University Hospital
2014-2017 Attending Physician, Division of Immunology and Allergy, Lausanne University Hospital
2017-date Head Physician, Division of Immunology and Allergy, Lausanne University Hospital

Other Experience and Professional Memberships
Chair, NHGRI Institutional Review Board (2006-2014)

Member Editorial Board, Experimental Hematology (2003-2005)
Member Editorial Board, Clinical and Translational Science (2007-2014)
Member Editorial Board, The Open Gene Therapy Journal (2009-2014)
Member Editorial Board, The Journal of Clinical Immunology (2011-date)

1998-date American Society of Gene and Cell Therapy (ASGCT)
Member, Board of Directors, 2010-2013
1999-date Clinical Immunology Society (CIS)
Member, Membership Committee, 2004-2006
Chair, Membership Committee, 2006-2009
2004-date American Society Clinical Investigation
2004-date American Society of Hematology
Chair, Scientific Committee on Immunology and Host Defense (2012)
1992-date European Society of Immunodeficiency
Treasurer and Member Executive Board, 2016-2020

C. Contributions to Science

1. Development and application of viral vectors for gene transfer into hematopoietic cells: We developed a variety of vectors based on murine gamma-retroviruses, Foamy viruses and HIV and used them in preclinical experiments of gene therapy for primary immunodeficiency diseases. These experiments have demonstrated that lymphocyte- and hematopoietic stem cell-directed gene modification strategies can lead to correction of genetic diseases affecting the immune system.

a. Candotti F. et al.: Retroviral-mediated gene correction for X-linked severe combined immunodeficiency (XSCID). Blood 1996; 87:3097-3102.
b. Candotti F. et al.: In vitro correction of JAK3-deficient severe combined immunodeficiency by retroviral-mediated gene transduction. J Exp Med 1996; 183:2687-2692.
c. Wada T., …, Candotti F.: Retrovirus-mediated WASP gene transfer corrects Wiskott-Aldrich syndrome T cell dysfunction. Hum Gene Ther, 2002;13:1039-1046
d. Bosticardo M., …, Candotti F.: Retroviral-Mediated Gene Transfer Restores IL-12 and IL-23 Signaling Pathways in T Cells from IL-12 Receptor β1 Deficient Patients. Mol Ther 2004; 9:895-901.
e. Uchiyama T., …, Candotti F.: Foamy virus vector-mediated gene correction of a mouse model of Wiskott-Aldrich syndrome. Mol Ther 2012; 20:1270-9.

2. Conduction of clinical trials of gene therapy for human immunodeficiency: We have developed and conducted four clinical trials of gene therapy for adenosine deaminase (ADA) deficiency using an evolving combination of approaches that has resulted in the definition of ideal viral vectors and efficient clinical procedures.

a. Engel B.C., …, Candotti F., Kohn D.B.: Prolonged pancytopenia in a gene therapy patient with ADA-deficient SCID and trisomy 8 mosaicism – A case report. Blood 2007; 109:503-506.
b. Candotti F. et al.: Gene Therapy for Adenosine Deaminase-Deficient Severe Combined Immune Deficiency: Clinical Comparison of Retroviral Vectors and Treatment Plans. Blood 2012; 120:3635-46.
c. Shaw K.L., ..., Candotti F., Kohn D.B.: Clinical efficacy of gene-modified stem cells in adenosine deaminase-deficient immunodeficiency. J Clin Invest 2017, 127(5):1689-1699.
d. Cooper A.R., …, Candotti F., Pellegrini M., Kohn D.B.: Cytoreductive conditioning intensity predicts clonal diversity in ADA-SCID retroviral gene therapy patients. Blood 2017; 129(19):2624-2635.

e. Otsu M., …, Candotti F. et al..: Outcomes in Two Japanese Adenosine Deaminase-Deficiency Patients Treated by Stem Cell Gene Therapy with No Cytoreductive Conditioning. J Clin Immunol 2015, 35:384-98.

3. Characterization of human severe combine immunodeficiency (SCID): We have performed extensive clinical and modeling studies that have elucidated the clinical, pathophysiological, and genetic features of ADA deficiency and reticular dysgenesis, two forms of SCID that feature some of the most profound immunodeficiency known in humans, as well as extra-immunological complications that provide insights into the multifaceted function of adenosine deaminase and adenylate kinase-2 in the development and function of the hematopoietic, lymphoid, respiratory and auditory systems.

a. Sokolic, R., ..., Candotti F.: Myeloid dysplasia and bone marrow hypocellularity in adenosine deaminase-deficient severe combined immune deficiency. Blood, 2011. 118(10): p. 2688-94.
b. Kesserwan, C., ..., Candotti F.: Multicentric dermatofibrosarcoma protuberans in patients with adenosine deaminase-deficient severe combined immune deficiency. The Journal of allergy and clinical immunology, 2012. 129(3): p. 762-769 e1.
c. Komarow, H.D., ..., Candotti F.: Impulse oscillometry identifies peripheral airway dysfunction in children with adenosine deaminase deficiency. Orphanet J Rare Dis, 2015. 10(1): p. 159.
d. Lagresle-Peyrou, C., …, Candotti F. et al.: Human adenylate kinase 2 deficiency causes a profound hematopoietic defect associated with sensorineural deafness. Nature genetics, 2009. 41(1): p. 106-11.
e. Rissone, A., …; Candotti F.: Reticular dysgenesis-associated AK2 protects hematopoietic stem and progenitor cell development from oxidative stress. J Exp Med, 2015. 212(8): p. 1185-202.

4, Characterization of the genetic and immunological features of the Wiskott-Aldrich syndrome: We have described the increased frequency of somatic revertant mosaicism in patients affected with the Wiskott-Aldrich syndrome (WAS), as well as other biological defects that lead to immunodeficiency in WAS patients. These findings have hinted to a multifaceted function of the WAS protein (WASp) in genomic stability and differentiation of the normal immune system.

a. Wada T, …, Candotti F. Somatic mosaicism in Wiskott--Aldrich syndrome suggests in vivo reversion by a DNA slippage mechanism. Proc Natl Acad Sci U S A. 2001 Jul 17;98(15):8697-702.
b. Wada T, …, Candotti F. Second-site mutation in the Wiskott-Aldrich syndrome (WAS) protein gene causes somatic mosaicism in two WAS siblings. J Clin Invest. 2003 May;111(9):1389-97
c. Konno A, …, Candotti F. Differential contribution of Wiskott-Aldrich syndrome protein to selective advantage in T- and B-cell lineages. Blood. 2004 Jan 15;103(2):676-8.
d. Shimizu M., …, Candotti F., Yachie A.: Aberrant glycosylation of IgA in Wiskott–Aldrich syndrome and X-linked thrombocytopenia. J Allergy Clin Immunol 2013; 131:587-590.
e. Simon KL, …, Candotti F. Molecular and phenotypic abnormalities of B lymphocytes in patients with Wiskott-Aldrich syndrome. J Allergy Clin Immunol. 2014 Mar;133(3):896-9.e4.

5. Role of the Wiskott-Aldrich syndrome protein (WASp) in immune regulation: We have made extensive use of mouse models of WAS to unravel the role of WASp in maintenance of tolerance. Our findings revealed new and multifaceted implications of WASp in immune regulation including regulation of TCR-induced apoptosis and FasL secretion, regulatory B cell function and functional interaction with N-WASp and indicate that WASp-deficient mice provide a good model for the study of autoimmune manifestations induced by WASp deficiency.
a. Adriani M, …, Candotti F. Defective inhibition of B-cell proliferation by Wiskott-Aldrich syndrome protein-deficient regulatory T cells. Blood 2011, 117(24):6608-11.
b. Nikolov N.P., …, Candotti F., Siegel R.M.: Systemic Autoimmunity and Defective Fas Ligand Secretion in the Absence of the Wiskott-Aldrich Syndrome Protein. Blood 2010; 116:740-7.
c. Yokoyama T., ..., Candotti F.: Age-dependent defects of regulatory B cells in Wiskott-Aldrich syndrome gene knockout mice. PLOS One 2015, 10(10):e0139729.
d. Volpi S., ..., Candotti F., Notarangelo L.D.: N-WASP is required for B cell-mediated autoimmunity in the Wiskott-Aldrich syndrome. Blood 2015, 127(2):216-20.
e. Crestani E., Volpi S., Candotti F. et al.: Broad spectrum of autoantibodies in Wiskott-Aldrich Syndrome (WAS) and Xlinked Thrombocytopenia (XLT). J Allergy Clin Immunol, 2015;136(5):1401-1404.

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

Ongoing Funding

Swiss National Science Foundation (310030-179251) Candotti (PI) 04/2018 – 03/2021
Role of the Wiskott-Aldrich syndrome protein (WASp) in the differentiation and regulation of the immune system.

Past Funding

NHGRI-NIH intramural funding Candotti (PI) 1998-2014

NIH Roadmap for Medical Research Segre (PI) 2009-2013
Human Microbiome Projects 1UH2AR057504, 4UH3AR057504-02
Skin Microbiota in Disease States: Atopic Dermatitis and Immunodeficiencies

UNIL-CHUV (CGRB 29583) Candotti (PI) 07/2014 – 06/2016
Molecular and immunological aspects of inherited immunodeficiencies and interferonopathies

Swiss National Science Foundation (310030-156795) Candotti (PI) 10/2014 – 09/2017
Role of the Wiskott-Aldrich syndrome protein (WASp) in immune regulation

Gebert Rüf Stiftung (GRS 061-14) Candotti (PI) 01/2015 – 12/2016
Molecular diagnosis of primary immunodeficiency diseases: a next generation sequencing and functional analysis platform.

H2020 (SCIDNET Consortium) Gaspar (Coordinator) 01/2016 – 12/2019
Developing genetic medicines for severe combined immunodeficiency (SCID)
Gene editing of adenosine deaminase deficiency