BIOGRAPHICAL SKETCH

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NAME: **Maria Serena Longhi. M.D, Ph.D.**

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

POSITION TITLE: **Assistant Professor, Department of Anesthesia, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston MA**

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
University of Verona, Italy	M.D.	07/1998	Medicine and Surgery
University of Verona, Italy	Accredited Specialist	10/2002	Infectious Diseases
King's College London, United Kingdom	Ph.D.	07/2006	Immunology

A. Personal Statement

Dr. Maria Serena Longhi, M.D., Ph.D., is an Assistant Professor in the Department of Anesthesia, Critical Care and Pain Medicine at Beth Israel Deaconess Medical Center (BIDMC), Harvard Medical School in Boston. She also currently holds a Visiting Senior Lecturer position in the Department of Liver Sciences at King's College London, London, United Kingdom. Her main area of research focuses on central immune mechanisms modulating the balance between effector and regulatory cells in the context of inflammatory and autoimmune conditions of the liver and intestine. Specifically, she has recently focused on the role of the CD39 ectonucleotidase in regulating Th17-regulatory T-cell (Treg) balance and how this is regulated by interactions with the aryl hydrocarbon receptor and oxygen pathways in inflammatory bowel disease and autoimmune liver disease. Additional studies in her laboratory aim at defining the mechanisms regulating CD39 at post-transcriptional level in Treg and Th17 cells in experimental colitis and human IBD.

1. **Longhi MS**, Liberal R, Holder B, Robson SC, Ma Y, Mieli-Vergani G, Vergani D. Inhibition of interleukin-17 promotes differentiation of $CD25^-$ cells into stable T regulatory cells in patients with autoimmune hepatitis. Gastroenterology. 2012 Jun;142(7):1526-35.e6. doi: 10.1053/j.gastro.2012.02.041. Epub 2012 Feb 28. PMID: 22387392
2. Heneghan MA, Yeoman AD, Verma S, Smith AD, **Longhi MS**. Autoimmune hepatitis. Lancet. 2013 Oct 26;382(9902):1433-44. doi: 10.1016/S0140-6736(12)62163-1. Epub 2013 Jun 14. PMID: 23768844
3. Grant CR, Liberal R, Holder BS, Cardone J, Ma Y, Robson SC, Mieli-Vergani G, Vergani D, **Longhi MS**. Dysfunctional CD39(POS) regulatory T cells and aberrant control of T-helper type 17 cells in autoimmune hepatitis. Hepatology. 2014 Mar;59(3):1007-15. doi: 10.1002/hep.26583. Epub 2014 Jan 30. PMID: 23787765 PMCID: PMC6377365
4. **Longhi MS**, Moss A, Bai A, Wu Y, Huang H, Cheifetz A, Quintana FJ, Robson SC. Characterization of human CD39+ Th17 cells with suppressor activity and modulation in inflammatory bowel disease. PLoS One. 2014 Feb 5;9(2):e87956. doi: 10.1371/journal.pone.0087956. PMID: 24505337 PMCID: PMC3914873

B. Positions and Honors

1998-02 Specialist Registrar, Ospedale Civile Maggiore Borgo Trento, Verona, Italy
2002-06 Research Fellow, Institute of Hepatology (2002), University College London;
Institute of Liver Studies, King's College London (2003-2006), London, United Kingdom

2006-10 Post-doctoral Research Associate, Institute of Liver Studies, King's College London, London, United Kingdom
2010 Clinical Lecturer in Liver Immunopathology, Institute of Liver Studies, King's College London, London, United Kingdom
2010-14 MRC Clinician Scientist Fellow/Senior Lecturer/Honorary Consultant in Hepatology, Institute of Liver Studies, King's College London, London, United Kingdom
Research Fellow (from 2011), Division of Gastroenterology, BIDMC, Harvard Medical School, Boston
2011-16 Research Fellow, Division of Gastroenterology, BIDMC, Harvard Medical School, Boston
2015- Visiting Senior Lecturer, King's College London, London, United Kingdom
2017-18 Instructor in Medicine, BIDMC, Harvard Medical School, Boston
2018- Assistant Professor of Anesthesia/Medicine
2018- Deputy Director, Center for Inflammation Research, Department of Anesthesia, Critical Care and Pain Medicine

Other Experience and Professional Memberships:

2004- Reviewer for Hepatology, Journal of Hepatology, Gut, Journal of Autoimmunity, Immunology, Liver International, Cancer Immunology and Immunotherapy, Clinical and Experimental Immunology, Trends in Molecular Medicine, Liver Transplantation, Oncotarget
2010- Grant reviewer for the Medical Research Council (United Kingdom), the Swiss National Science Foundation (Switzerland) and the Israel Science Foundation (Israel)
2011- Junior Writer for the 'Autoimmune hepatitis section' within the iLiver Project (European Association for the Study of the Liver, EASL)
2017- Member of the American Association of Immunologists (AAI) and the American Association for the Study of Liver Diseases (AASLD)
2018- Member of the Harvard Digestive Diseases Center (HDDC)
2018- Guest Associate Editor for Frontiers in Immunology (Research topic on 'The role of ectonucleotidases in acute and chronic inflammation
2019- Abstract Selection Committee, AASLD: Inflammation and Immunobiology
2019- Associate Editor for Cells

Select Honors:

2005 Award recipient at the 58th Annual Meeting of the American Association for the Study of Liver Diseases (November 2-6, 2005, Boston, USA)
2009 IAS-NIH Scholarship Recipient (July 19-22, 2009, Cape Town, South Africa)
2009 Dame Sheila Sherlock Research Prize and Lecture (British Association for the Study of the Liver, September 9-11, 2009, London, UK)
2013 Dame Sheila Sherlock Fellowship (Royal College of Physicians, June 2013, London, UK)
2019 Early Career Faculty Travel Grant (American Association of Immunologists, May 9-13, 2019, San Diego, CA)

C. Contributions to Science

1. Identification of intrahepatic cell subsets involved in the execution of tissue damage in autoimmune liver disease (AILD), including autoimmune hepatitis (AIH) and sclerosing cholangitis. Reported the involvement of both adaptive and innate immune responses in the pathogenesis of these conditions. Described the relationship between autoreactive CD4 and CD8 T-cells with disease activity and severity. Reported heightened pro-inflammatory properties (increased spontaneous migration and TNF-α production) of monocytes isolated from AIH patients.

    a. Ma Y, Bogdanos DP, Hussain MJ, Underhill J, Bansal S, **Longhi MS**, Cheeseman P, Mieli-Vergani G, Vergani D. Polyclonal T-cell responses to cytochrome P450IID6 are associated with disease activity in autoimmune hepatitis type 2. Gastroenterology. 2006 Mar;130(3):868-82. PMID: 16530525
    b. **Longhi MS**, Hussain MJ, Bogdanos DP, Quaglia A, Mieli-Vergani G, Ma Y, Vergani D.

Cytochrome P450IID6-specific CD8 T cell immune responses mirror disease activity in autoimmune hepatitis type 2. Hepatology. 2007 Aug;46(2):472-84. PMID: 17559153

c. **Longhi MS**, Mitry RR, Samyn M, Scalori A, Hussain MJ, Quaglia A, Mieli-Vergani G, Ma Y, Vergani D. Vigorous activation of monocytes in juvenile autoimmune liver disease escapes the control of regulatory T-cells. Hepatology. 2009 Jul;50(1):130-42. doi: 10.1002/hep.22914. PMID: 19437492
d. **Longhi MS**, Ma Y, Mieli-Vergani G, Vergani D. Aetiopathogenesis of autoimmune hepatitis. J Autoimmun. 2010 Feb;34(1):7-14. doi: 10.1016/j.jaut.2009.08.010. Epub 2009 Sep 18. Review. PMID: 19766456

2. Established links between overwhelming effector immune responses and Treg functional impairment in AILD. Described for the first time that enhanced effector immune responses in AIH are linked to Treg inability to promote infectious tolerance. As part of these investigations defective Galectin-9/Tim-3 pathway has been reported in Treg/Th1 effectors in AIH.

   a. **Longhi MS**, Ma Y, Mitry RR, Bogdanos DP, Heneghan M, Cheeseman P, Mieli-Vergani G, Vergani D. Effect of CD4+ CD25+ regulatory T-cells on CD8 T-cell function in patients with autoimmune hepatitis. J Autoimmun. 2005 Aug;25(1):63-71. PMID: 16005184
   b. **Longhi MS**, Hussain MJ, Mitry RR, Arora SK, Mieli-Vergani G, Vergani D, Ma Y. Functional study of CD4+CD25+ regulatory T cells in health and autoimmune hepatitis. J Immunol. 2006 Apr ;176(7):4484-91. PMID: 16547287
   c. Liberal R, Grant CR, Holder BS, Ma Y, Mieli-Vergani G, Vergani D, **Longhi MS**. The impaired immune regulation of autoimmune hepatitis is linked to a defective galectin-9/tim-3 pathway. Hepatology. 2012 Aug;56(2):677-86. doi: 10.1002/hep.25682. Epub 2012 Jul 6. PMID: 22371007
   d. Liberal R, Grant CR, Holder BS, Cardone J, Martinez-Llordella M, Ma Y, Heneghan MA, Mieli-Vergani G, Vergani D, **Longhi MS**. In autoimmune hepatitis type 1 or the autoimmune hepatitis-sclerosing cholangitis variant defective regulatory T-cell responsiveness to IL-2 results in low IL-10 production and impaired suppression. Hepatology. 2015 Sep;62(3):863-75. doi: 10.1002/hep.27884. Epub 2015 Jun 18. PMID: 25953611

3. Identified a key role of the purinergic pathway and particularly the CD39 ectonucleotidase in the modulation of Treg and Th17 cell immune responses in AILD and inflammatory bowel disease. Reported for the first time that CD39 confers regulatory properties to Th17 cells favoring the limitation of their pathogenic potential. Established that the immunoregulatory properties of unconjugated bilirubin are mediated through CD39 upregulation in an AhR-dependent manner.

   a. Grant CR, Liberal R, Holder BS, Cardone J, Ma Y, Robson SC, Mieli-Vergani G, Vergani D, **Longhi MS**. Dysfunctional CD39(POS) regulatory T cells and aberrant control of T-helper type 17 cells in autoimmune hepatitis. Hepatology. 2014 Mar;59(3):1007-15. doi: 10.1002/hep.26583. Epub 2014 Jan 30. PMID: 23787765 PMCID: PMC6377365
   b. **Longhi MS**, Moss A, Bai A, Wu Y, Huang H, Cheifetz A, Quintana FJ, Robson SC. Characterization of human CD39+ Th17 cells with suppressor activity and modulation in inflammatory bowel disease. PLoS One. 2014 Feb 5;9(2):e87956. doi: 10.1371/journal.pone.0087956. eCollection 2014. PMID: 24505337 PMCID: PMC3914873
   c. Liberal R, Grant CR, Ma Y, Csizmadia E, Jiang ZG, Heneghan MA, Yee EU, Mieli-Vergani G, Vergani D, Robson SC, **Longhi MS.** CD39 mediated regulation of Th17-cell effector function is impaired in juvenile autoimmune liver disease. J Autoimmun. 2016 Aug;72:102-12. doi: 10.1016/j.jaut.2016.05.005. Epub 2016 May 20. PMID: 27210814 PMCID: PMC6348153
   d. **Longhi MS**, Vuerich M, Kalbasi A, Kenison JE, Yeste A, Csizmadia E, Vaughn B, Feldbrugge L, Mitsuhashi S, Wegiel B, Otterbein L, Moss A, Quintana FJ, Robson SC. Bilirubin suppresses Th17 immunity in colitis by upregulating CD39. JCI Insight. 2017 May 4;2(9). pii: 92791. doi: 10.1172/jci.insight.92791. [Epub ahead of print]. PMID: 28469075 PMCID: PMC5414551

4. Made significant contributions to translational research, particularly the development of strategies for generating polyclonal and antigen-specific Tregs for clinical application. Showed for the first time that polyclonal and antigen-specific Tregs, generated and expanded from AIH patients, can effectively suppress target cell effector function. Reported that Treg conditioning confers suppressor abilities to activated Teff in

AILD. The findings of these investigations are crucial to the clinical use of Tregs to re-establish immune-tolerance in AIH and other autoimmune conditions with similar pathogenesis.

a. **Longhi MS**, Meda F, Wang P, Samyn M, Mieli-Vergani G, Vergani D, Ma Y. Expansion and de novo generation of potentially therapeutic regulatory T cells in patients with autoimmune hepatitis. Hepatology. 2008 Feb;47(2):581-91. doi: 10.1002/hep.22071. PMID: 18220288
b. **Longhi MS**, Hussain MJ, Kwok WW, Mieli-Vergani G, Ma Y, Vergani D. Autoantigen-specific regulatory T cells, a potential tool for immune-tolerance reconstitution in type-2 autoimmune hepatitis. Hepatology. 2011 Feb;53(2):536-47. doi: 10.1002/hep.24039. Epub 2010 Dec 28. PMID: 21274874
c. **Longhi MS**, Liberal R, Holder B, Robson SC, Ma Y, Mieli-Vergani G, Vergani D. Inhibition of interleukin-17 promotes differentiation of CD25- cells into stable T regulatory cells in patients with autoimmune hepatitis. Gastroenterology. 2012 Jun;142(7):1526-35.e6. doi: 10.1053/j.gastro.2012.02.041. Epub 2012 Feb 28. PMID: 22387392
d. Liberal R, Grant CR, Yuksel M, Graham J, Kalbasi A, Ma Y, Heneghan MA, Mieli-Vergani G, Vergani D, **Longhi MS**. Treg conditioning endows activated Teff with suppressor function in autoimmune hepatitis/autoimmune sclerosing cholangitis. Hepatology. 2017 Jun 9. doi: 10.1002/hep.29307. [Epub ahead of print]. PMID: 28597951 PMCID: PMC5689077

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