BIOGRAPHICAL SKETCH

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NAME: Lira, Sergio A

eRA COMMONS USER NAME (agency login): Sergiolira

POSITION TITLE: Director, Immunology Institute, Icahn School of Medicine at Mount Sinai

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

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Universidade Federal de Pernambuco, Recife	MD	1982	Medicine
Universidade Federal de Pernambuco, Recife	MS	1983	Physiology
University of California, San Diego, California	PHD	1988	Physiology & Pharmacology
Roche Institute for Molecular Biology, Nutley, NJ	Post-doc	1992	Cell & Developmental Biology

A. PERSONAL STATEMENT

I am an MD/PhD scientist with over 30 years of research experience in the pharmaceutical and academic settings. Throughout my career I have used genetically-modified mice to study the role of chemokines and cytokines in leukocyte trafficking, lymphoid organogenesis, inflammation, autoimmunity, and cancer. My laboratory has generated and characterized many of the chemokine mouse reagents described in the literature and has collaborated with groups in the US, Europe, Japan and South America. This work has resulted in over 150 peer-reviewed publications that have been extensively cited in the literature (>20,000 citations according to Google Scholar). Besides being a scientist with expertise in mucosal immunology and mouse genetics, I have extensive experience in grants management and administration, and serve as advisor in major national and international panels/study sections.

B. POSITIONS AND HONORS

Positions and Employment

1980 - Research Assistant, Max-Planck Institut fur Biophysikalische Chemie, Gottingen
1982 - 1983 Assistant Professor, Physiology Department, Universidade Federal de Pernambuco, Recife
1988 - 1992 Postdoctoral Fellow, Roche Institute for Molecular Biology, Nutley, NJ
1992 - 1996 Head, Transgenic Unit, Division of Oncology, Bristol-Myers Squibb Pharmaceutical Research Institute
1996 - 1999 Associate Director, Department of Immunology, Schering-Plough Research Institute
2000 - 2002 Director, Department of Immunology, Schering-Plough Research Institute
2002 - 2004 Irene Diamond Associate Professor, Immunobiology, Icahn School of Medicine at Mount Sinai
2004 - 2007 Professor, Immunobiology, Icahn School of Medicine at Mount Sinai
2007 - Professor, Medicine, Icahn School of Medicine at Mount Sinai
2007 - 2013 Co-Director, Immunology Institute, Icahn School of Medicine at Mount Sinai
2009 - The Leona M. and Harry B. Helmsley Chartiable Trust Professor of Immunology, Icahn School of Medicine at Mount Sinai
2013 - Director, Immunology Institute, Icahn School of Medicine at Mount Sinai

Other Experience and Professional Memberships

2003 - Co-organizer, 2003 Keystone Symposium on Chemokines and Chemokine Receptors
2006 - Chair, 2006 Gordon Research Conference on Chemotactic Cytokines and Chemokine Receptors, Aussois, France
2012 - Co-organizer, 2012 Keystone Symposium on Chemokines and Leukocyte Trafficking
2012 - 2015 Member of the Senior Research Award Study Section, Crohn's and Colitis Foundation of America
2013 - Appointed to the Scientific Advisory Board of the NCI (2013-2018)

2013 - Appointed Visiting Professor, Southern Medical University, Guangzhou, China

Honors

1980 Student Fellowship, Max Planck Gesellschaft (Germany)
1983 PhD Program Scholarship, Brazilian Research Council (CNPq)
1995 President's Award, Bristol-Myers Squibb Company
1998 Impact Award, Schering-Plough Rsearch Institute
2000 Inventor's Award, Schering-Plough Research Institute
2006 Elected to the Henry Kunkel Society
2008 Elected to the Association of American Physicians

C. Contribution to Science

1. Regulation of leukocyte trafficking by chemokines. At the beginning of the 90's little was known about the biological activities of the recently described group of molecules known as chemokines. Using genetic approaches in mice we showed for the first time that CXC and CC chemokines could promote recruitment of specific leukocyte subsets to specific organs. Our initial studies focused on the CXC chemokine KC (CXCL1). Using tissue-specific promoters we targeted expression of this chemokine to thymus, skin, and the brain, and observed that neutrophils accumulated in the vicinity of the cells expressing KC. These results showed for the first time that chemokines, once secreted by cells in the tissue were sufficient to direct trafficking of target cells from the endothelial lumen into the parenchyma. A set of complementary studies focused on the CC chemokine JE (mCCL2) and showed that its expression in vivo could direct trafficking of monocytes to specific organs such as the brain. To improve the understanding of the mechanism of action of chemokines in vivo our lab develop the first conditional models for chemokine expression in mice (using the tet-on system) and showed that tissue recruitment of neutrophils was dependent on the expression levels of CXCL chemokines. This study provided an explanation for the neutrophil paralysis observed in conditions such as sepsis, in which chemokines are highly elevated in circulation.

a. Lira SA, Zalamea P, Heinrich JN, Fuentes ME, Carrasco D, Lewin AC, Barton DS, Durham S, Bravo R. Expression of the chemokine N51/KC in the thymus and epidermis of transgenic mice results in marked infiltration of a single class of inflammatory cells. J Exp Med. 1994 Dec 1;180(6):2039-48. PubMed PMID: 7964481; PubMed Central PMCID: PMC2191760.

b. Fuentes ME, Durham SK, Swerdel MR, Lewin AC, Barton DS, Megill JR, Bravo R, Lira SA. Controlled recruitment of monocytes and macrophages to specific organs through transgenic expression of monocyte chemoattractant protein-1. J Immunol. 1995 Dec 15;155(12):5769-76. PubMed PMID: 7499865.

c. Tani M, Fuentes ME, Peterson JW, Trapp BD, Durham SK, Loy JK, Bravo R, Ransohoff RM, Lira SA. Neutrophil infiltration, glial reaction, and neurological disease in transgenic mice expressing the chemokine N51/KC in oligodendrocytes. J Clin Invest. 1996 Jul 15;98(2):529-39. PubMed PMID: 8755666; PubMed Central PMCID: PMC507459.

d. Wiekowski MT, Chen SC, Zalamea P, Wilburn BP, Kinsley DJ, Sharif WW, Jensen KK, Hedrick JA, Manfra D, Lira SA. Disruption of neutrophil migration in a conditional transgenic model: evidence for CXCR2 desensitization in vivo. J Immunol. 2001 Dec 15;167(12):7102-10. PubMed PMID: 11739532.

2. Biological function of chemokine and their receptors. We used loss-of-function approaches to generate and study mouse strains deficient in many chemokine receptors, including CCR6, CCR8, D6 (ACKR2), CX3CR1, CCR11 (ACKR4); and chemokine ligands, including CXCL1, CX3CL1 and CXCL15. These studies revealed a critical role for these molecules in a variety of immune processes beyond cell trafficking, including mucosal cell responses, T helper cell responses, microglial toxicity, cell survival, resolution of inflammation, and autoimmunity. Together these and other studies not listed here have contributed to the understanding of the role of chemokines in homeostasis and disease.

a. Cook DN, Prosser DM, Forster R, Zhang J, Kuklin NA, Abbondanzo SJ, Niu XD, Chen SC, Manfra DJ, Wiekowski MT, Sullivan LM, Smith SR, Greenberg HB, Narula SK, Lipp M, Lira SA. CCR6 mediates dendritic cell localization, lymphocyte homeostasis, and immune responses in mucosal tissue. Immunity. 2000 May;12(5):495-503. PubMed PMID: 10843382.

b. Chensue SW, Lukacs NW, Yang TY, Shang X, Frait KA, Kunkel SL, Kung T, Wiekowski MT, Hedrick JA, Cook DN, Zingoni A, Narula SK, Zlotnik A, Barrat FJ, O'Garra A, Napolitano M, Lira SA. Aberrant in vivo T

helper type 2 cell response and impaired eosinophil recruitment in CC chemokine receptor 8 knockout mice. J Exp Med. 2001 Mar 5;193(5):573-84. PubMed PMID: 11238588; PubMed Central PMCID: PMC2193397.
c. Jamieson T, Cook DN, Nibbs RJ, Rot A, Nixon C, McLean P, Alcami A, Lira SA, Wiekowski M, Graham GJ. The chemokine receptor D6 limits the inflammatory response in vivo. Nat Immunol. 2005 Apr;6(4):403-11. PubMed PMID: 15750596.
d. Martin AP, Marinkovic T, Canasto-Chibuque C, Latif R, Unkeless JC, Davies TF, Takahama Y, Furtado GC, Lira SA. CCR7 deficiency in NOD mice leads to thyroiditis and primary hypothyroidism. J Immunol. 2009 Sep 1;183(5):3073-80. PubMed PMID: 19675158.

3. Lymphoid organogenesis. My laboratory has contributed to understanding the role of chemokines (CCL21 and CXCL13) and cytokines (TNF and LT) in the development of secondary and tertiary lymphoid organs. Our first contribution to this field was the demonstration of the existence of at least two distinct forms of CCL21 in the mouse (one with predominant expression in lymph nodes and the other in lymphatics). We showed that deletion of the lymph-node specific form of CCL21 was the cause of a natural mutation in the mouse known as plt (paucity of lymph nodes). We also showed for the first time that the chemokine CCL21 had organogenic properties and could induce development of tertiary lymphoid structures with well defined and topographically distinct B and T cell zones and specialized vasculature (HEV and lymphatics), when expressed ectopically in the pancreas or the thyroid. The discovery of the lymphoid organogenic properties of chemokines led us to study the mechanisms underlying these properties. Using again genetic models we showed that the initial steps in the formation of these organs include interactions between CD4+ T cells and dendritic cells and development of high endothelial venules and lymphangiogenesis, mechanisms requiring TNF and lymphotoxin. More recently we have demonstrated that RORc+ cells are not absolutely required for organogenesis of secondary lymphoid organs, as previously believed.

a. Vassileva G, Soto H, Zlotnik A, Nakano H, Kakiuchi T, Hedrick JA, Lira SA. The reduced expression of 6Ckine in the plt mouse results from the deletion of one of two 6Ckine genes. J Exp Med. 1999 Oct 18;190(8):1183-8. PubMed PMID: 10523616; PubMed Central PMCID: PMC2195659.
b. Chen SC, Vassileva G, Kinsley D, Holzmann S, Manfra D, Wiekowski MT, Romani N, Lira SA. Ectopic expression of the murine chemokines CCL21a and CCL21b induces the formation of lymph node-like structures in pancreas, but not skin, of transgenic mice. J Immunol. 2002 Feb 1;168(3):1001-8. PMID: 11801632.
c. Marinkovic T, Garin A, Yokota Y, Fu YX, Ruddle NH, Furtado GC, Lira SA. Interaction of mature CD3+CD4+ T cells with dendritic cells triggers the development of tertiary lymphoid structures in the thyroid. J Clin Invest. 2006 Oct;116(10):2622-32. PubMed PMID: 16998590; PubMed Central PMCID: PMC1570377.
d. Furtado GC, Pacer ME, Bongers G, Bénézech C, He Z, Chen L, Berin MC, Kollias G, Caamaño JH, Lira SA. TNFα-dependent development of lymphoid tissue in the absence of RORγt^{+} lymphoid tissue inducer cells. Mucosal Immunol. 2014 May;7(3):602-14. PubMed PMID: 24129162; PubMed Central PMCID: PMC4264842.

4. Role of virus encoded molecules affecting the chemokine system. Viruses encode a variety of mechanisms to evade host immune pathways and cause disease. Large DNA viruses (herpesviruses and poxviruses) encode proteins that mimic chemokines and chemokine receptors. My lab was the first to show that chemokine receptors encoded by herpes-viruses had oncogenic properties. We also showed that the oncogenic activity of these receptors could be modulated in vivo by endogenous chemokines. Some viruses also encode secreted proteins that bind chemokines and have structure unrelated to host proteins. We have taken advantage of these chemokine binding proteins to probe the inflammatory response in vivo and shown that blockade of multiple chemokines by the chemokine binding proteins M3 or CrmD had a marked impact on the development of autoimmunity and inflammation in the mouse. These studies have provided a rational for the development of therapeutic strategies blocking multiple chemokine ligands.

a. Yang TY, Chen SC, Leach MW, Manfra D, Homey B, Wiekowski M, Sullivan L, Jenh CH, Narula SK, Chensue SW, Lira SA. Transgenic expression of the chemokine receptor encoded by human herpesvirus 8 induces an angioproliferative disease resembling Kaposi's sarcoma. J Exp Med. 2000 Feb 7;191(3):445-54. PubMed PMID: 10662790; PubMed Central PMCID: PMC2195818.
b. Holst PJ, Rosenkilde MM, Manfra D, Chen SC, Wiekowski MT, Holst B, Cifire F, Lipp M, Schwartz TW, Lira SA. Tumorigenesis induced by the HHV8-encoded chemokine receptor requires ligand modulation of high constitutive activity. J Clin Invest. 2001 Dec;108(12):1789-96. PubMed PMID: 11748262; PubMed Central PMCID: PMC209468.

c. Bongers G, Maussang D, Muniz LR, Noriega VM, Fraile-Ramos A, Barker N, Marchesi F, Thirunarayanan N, Vischer HF, Qin L, Mayer L, Harpaz N, Leurs R, Furtado GC, Clevers H, Tortorella D, Smit MJ, Lira SA. The cytomegalovirus-encoded chemokine receptor US28 promotes intestinal neoplasia in transgenic mice. J Clin Invest. 2010 Nov;120(11):3969-78. PubMed PMID: 20978345; PubMed Central PMCID: PMC2964974.

d. Shang L, Thirunarayanan N, Viejo-Borbolla A, Martin AP, Bogunovic M, Marchesi F, Unkeless JC, Ho Y, Furtado GC, Alcami A, Merad M, Mayer L, Lira SA. Expression of the chemokine binding protein M3 promotes marked changes in the accumulation of specific leukocytes subsets within the intestine. Gastroenterology. 2009 Sep;137(3):1006-18, 1018.e1-3. PubMed PMID: 19501588; PubMed Central PMCID: PMC2736321.

5. Inflammation and cancer. My lab has a longstanding interest in the connection between inflammation and cancer. We have contributed to the identification of two viral-induced chemokine receptor oncogenes, and have studied for many years the influence of the inflammation in tumor development. In recent years we have focused our research on the interplay between growth factors such as EGFR and immune molecules such as TLR4 and CX3CL1 in cancer. In a recent study we examined the mechanisms dictating the site-specific development of neoplasms in the intestine, using an animal model of serrated polyps developed in our lab. We showed that the geographic localization of the polyps was dependent on a host-specific, site-specific microbiota. We demonstrated that the presence of the microbiota within the tumors triggered a significant inflammatory response that included recruitment of neutrophils to the polyp. Blockade of neutrophil recruitment reduced the number and size of the polyps, suggesting an important role for inflammation in the process. These results strongly implicate the microbiota as a major factor contributing to development of this specific kind of neoplasms, in addition to the well established somatic mutations in BRAF, and K-Ras.

a. Bongers G, Muniz LR, Pacer ME, Iuga AC, Thirunarayanan N, Slinger E, Smit MJ, Reddy EP, Mayer L, Furtado GC, Harpaz N, Lira SA. A role for the epidermal growth factor receptor signaling in development of intestinal serrated polyps in mice and humans. Gastroenterology. 2012 Sep;143(3):730-40. PubMed PMID: 22643351; PubMed Central PMCID: PMC3431560.

b. Tardáguila M, Mira E, García-Cabezas MA, Feijoo AM, Quintela-Fandino M, Azcoitia I, Lira SA, Mañes S. CX3CL1 promotes breast cancer via transactivation of the EGF pathway. Cancer Res. 2013 Jul 15;73(14):4461-73. PubMed PMID: 23720051.

c. Santaolalla R, Sussman DA, Ruiz JR, Davies JM, Pastorini C, España CL, Sotolongo J, Burlingame O, Bejarano PA, Philip S, Ahmed MM, Ko J, Dirisina R, Barrett TA, Shang L, Lira SA, Fukata M, Abreu MT. TLR4 activates the β-catenin pathway to cause intestinal neoplasia. PLoS One. 2013;8(5):e63298. PubMed PMID: 23691015; PubMed Central PMCID: PMC3653932.

d. Bongers G, Pacer ME, Geraldino TH, Chen L, He Z, Hashimoto D, Furtado GC, Ochando J, Kelley KA, Clemente JC, Merad M, van Bakel H, Lira SA. Interplay of host microbiota, genetic perturbations, and inflammation promotes local development of intestinal neoplasms in mice. J Exp Med. 2014 Mar 10;211(3):457-72. PubMed PMID: 24590763; PubMed Central PMCID: PMC3949565.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/16AcQxr2prVk7/bibliography/41571514/public/?sort=date&direction=ascending

D. RESEARCH SUPPORT

Ongoing Research Support

5P01DK072201-10, NIH/NIDDK **09/15/2006-08/31/2016**
Lira, Sergio A (PI)
Innate/Adaptive Immune Interactions in Gut Inflammation
Project 2 - Role of chemokines and IL-23 in the biology of Rorgt+ cells - To investigate the functional role of chemokines in inflammatory bowel disease
Core A – Animal Core - Provide the technical expertise and support for performing all mice study-related

330239, Crohn's & Colitis Foundation of America **01/01/2015-12/31/2017**
Lira, Sergio A (PI)
Interplay of TNF and dysbiosis in the pathogenesis of IBD - Explore the interaction between the host mucosal immune system and microbes, both at the epithelial cell surface and within the gut lumen.

Anonymous Foundation (SUCCESS project) **02/01/2014-01/31/2017**

Colombel, Jean-Frederic M. (PI)
Project 3: Define the contributions of the genes and the microbiome to the development of UC - Define how mutations in specific genes increase the risk of UC.
Role: PI

Janssen Biotech **07/01/2013-06/30/2016**
Schadt, Eric E (PI)
Project 2: MIND/IL33 - Establish relevance/connectivity of IBD mouse models to human CD and/or UC.
Role: PI

5R01CA161373-05, NIH/NIDDK **07/01/2011-06/30/2016**
Lira, Sergio A (PI)
Molecular Pathogenesis of Intestinal Serrated Polyps - Define the mechanisms that contribute to development of serrated polyps in HB28 mice

5P01AI061093-12, NIH/NIAID **07/01/2004-08/31/2016**
Cerutti, Andrea (PI)
Project 2: Development of B Cell Memory in CVID - The major goal of this project is to determine mechanisms by which B cell memory is not developed in CVID.
Role: Co-Investigator

10030, Boehringer Ingelheim Pharmaceuticals, Inc. **11/01/2015-10/31/2018**
Collaboration Between BI and the Immunology Institute
Project 3 – To generate 5 new mouse mutants by CRISPR/Cs9 technology