BIOGRAPHICAL SKETCH

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NAME: Brossay, Laurent

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

POSITION TITLE: Professor

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
Rennes University, France	B. S.	1986	Biochemistry
Laval University, Quebec, QC, Canada	Ph. D.	1994	Microbiology
UCLA & LIAI, CA	Postdoctoral	1999	Immunology

A. Personal Statement

My laboratory is interested in understanding the molecular mechanisms controlling the development and activation of both Natural Killer (NK) and Natural Killer T cells (NKT). We use an animal model to determine the contribution of these innate-like cells during the immune response to infections, including murine cytomegalovirus (MCMV). During the last 20 years, we have generated several tools including an anti-CD1d antibody, an anti-KLRG1 antibody, the KLRG1 tetramer, and immunodeficient animals such as Qa-1 deficient mice and KLRG1 deficient mice.

I have served on numerous NIH study sections (~30) and I was a member of the *Immunity and Host Defense* study section. I also served as a Section Editor and Associate Editor for the *Journal of Immunology* and I am currently an Associate Editor for *Frontiers in NK Cell Biology*. I have been continually funded by the NIH since 2000 (one RO1 was renewed 3 times).

I was the chair of the Molecular Microbiology & Immunology Department from 2009 to 2021. As a chair, I recruited 6 tenure track Assistant Professors. They have been awarded NIH RO1s, NIH R21s, NIH K99, DARPA award, DOD discovery awards, SEARLE award and a multitude of local grants. Most of them have been project leader on NIH COBRE grants. Papers published by these junior members are *Immunity*, *Nature Immunology, Cell Host and Microbes, PloSPathogens* etc. Finally, I am the mentor for several successful Assistant Professors from other departments.

I have graduated ten graduate students, several of whom won presentation and/or poster awards at national or international conferences such as the American Association of Immunologist Conference or Keystone conferences. Several of my graduate students were from Historically Underrepresented Groups. Three of the last four graduate students I trained were awarded an NIH fellowship. Most of the graduate students I trained have published papers in top-tier journals as a first-author. Overall, I am committed to mentoring my trainees and helping them to become successful and visible immunologists.

<u>Ongoing and recently completed projects that I would like to highlight include:</u>

RO1 AI173163, 1-5
Brossay (PI)
05/12/23 - 06/30/28
Immune response to MCMV infection in the salivary glands

RO1 AI46709, 15-19
Brossay (PI)
05/08/18 - 04/30/24
NK T cell interaction with NK cells during viral infections

R01 AI46709-18S1

Brossay (PI)
07/20/21 - 04/30/24
NIH/NIAID
NK T cell interaction with NK cells during viral infections

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2011-2021 Chair, Department of Molecular Microbiology & Immunology
2009-2011 Acting chair, Department of Molecular Microbiology & Immunology
2014-Present Professor, Brown University, Providence, RI
2006-2014 Associate Professor, Brown University, Providence, RI
2000-2006 Assistant Professor, Brown University, Providence, RI
1997-2000 Research Scientist, La Jolla Inst. for Allergy & Immunology, San Diego, CA
1994-1997 Postdoctoral fellow, Department of Microbiology & Immunology, UCLA, Los Angeles, CA

Scientific Appointments

2020 Ad hoc Reviewer NIH, IHD Study Section, June 2020
2020 Ad Hoc Reviewer NIH NIAID ZRG1 IMM Study Section
2016-2019 Member of Finance Committee, American Association of Immunologists
2019 ZRG1-IMM-j03-2019 Study Section, ad hoc reviewer, July 2019
2018 Ad hoc Reviewer NIH, IHD Study Section, October 2018
2018 Ad hoc Reviewer, Belgian Foundation against Cancer,
2017 Ad hoc Reviewer NIH, IHD Study Section, October 2017
2017-Present NEIC steering committee
2016 Ad Hoc Reviewer for NIH NIAID ZRG1 IDM (December) Study Section
2016 Ad Hoc Reviewer for NIH NIAID ZRG1 IDM (April) Study Section
2015 Ad hoc Reviewer NIH, IHD Study Section, February 2015
2011-present Associate Editor for *Frontiers in NK Cell Biology*
2010-2014 Section Editor: *J. of Immunology*
2014 Ad Hoc Reviewer for NIH NIAID ZRG1 IMM Study Section
2013 Ad Hoc Reviewer for NIH NIAID Phase 1 Immune Mechanisms of Virus Control (U19)
2010-2014 Ad Hoc Reviewer ANR France
2009-2013 NIH IHD Study Section Member
2007-2010 Associate Editor: *J. of Immunology*
2009 Ad hoc Reviewer NIH, IHD Study Section
2009 Ad Hoc Reviewer for Stage 1 review of Challenge Grant Applications
2008 Ad Hoc Reviewer NIH, RCE Biodefense and Emerging Infectious Diseases Study Section
2008 Ad hoc Reviewer NIH, IHD Study Section
2004-2009 Ad Hoc Reviewer Belgium Fund Research
2008 Ad hoc Reviewer NIH, Program Project
2007 Ad hoc Reviewer NIH, Program Project
2004 Ad hoc Reviewer NIH, Program Project
2003 Ad hoc Reviewer NIH, Special Emphasis Study Section
2003 Ad hoc Reviewer NIH, Program Project
2002 Ad hoc Reviewer Swiss National Foundation and Irish Health Research Board
2002 Ad hoc Reviewer Swiss National Foundation and Irish Health Research Board
2002 Ad hoc Reviewer NIH, Special Emphasis Study Section
2001 Ad hoc Reviewer NIH, Special Emphasis Study Section
1999-Present Ad hoc Reviewer*: J. Exp. Medicine, Nature Immunology, J. of Clinical Investigation, Elife, PloS Pathogens, PNAS, European J. of Immunology, Blood, Nature Medicine, Nature Communications*

Honors

2015 American Association of Immunologist Laboratory Travel Award
2015 American Association of Immunologist career in Immunology Fellowship Award
2013 American Association of Immunologist Laboratory Travel Award
2009 American Association of Immunologist Faculty Mentor Travel Award

C. Contribution to Science

1. NK cell response and non-classical T cell response during MCMV infection

We first characterized KLRG1 as a marker of recently activated NK and $CD8^+$ T cells. This is now widely accepted and this marker is used in many critical studies, which aim to understand the development of memory $CD8^+$ T cells. We then demonstrated that in response to MCMV, NK cells follow a kinetic parallel to $CD8^+$ T cells. In this system, we showed that NK cells undergo accelerated phenotypic maturation, expand and contract. This work has been in part the foundation of a novel concept called *memory NK cells* developed by several investigators. We also identified Qa-1 as a restricting element for non-classical $CD8^+$ T cells during MCMV infection. These cells can compensate for the absence of conventional T cells and protect against MCMV induced lethality.

- Robbins, S. H., K. B. Nguyen, N. Takahashi, T. Mikayama, C. A. Biron, and **L. Brossay**. 2002. Inhibitory Functions of the Killer Lectin-Like Receptor G1 Molecule during the Activation of Murine NK Cells. *J. Immunol. Cutting Edge* 168: 2585-2589
- Robbins, S. H., M. S. Tessmer, T. Mikayama, and **L. Brossay**. 2004. Expansion and contraction of the NK cell compartment in response to MCMV infection. *J. Immunol*. 173: 259-266
- Robbins, S. H., M. S. Tessmer, L. Van Kaer, and **L. Brossay**. 2005. Direct effects of T-bet and MHC class I expression, but not STAT1, on peripheral NK cell maturation. *Eur. J. Immunol*. 35: 757-765
- Anderson CK, Reilly EC, Lee AY, **Brossay L**. Qa-1-Restricted $CD8^+$ T Cells Can Compensate for the Absence of Conventional T Cells during Viral Infection. Cell Rep. 2019 Apr 9;27(2):537-548.e5. doi: 10.1016/j.celrep.2019.03.059. PubMed PMID: 30970256; PubMed Central PMCID: PMC6472915.

2. Identification of the KLRG1 ligands and role of KLRG1 as a checkpoint inhibitor

Using a reporter cell line and the KLRG1 tetramer, we identified E, and N-cadherin as ligands for KLRG1. The KLRG1 tetramer has been made available to the scientific community at the NIH tetramer facility.

- Tessmer, M. S., C. Fugère, F. Stevenaert, O. V. Naidenko, G. Leclercq, and **L. Brossay**. 2007. KLRG1 binds cadherins and preferentially associates with SHIP-1. *International Immunol*. 19: 391-400.
- Banh, C., C. Fugere and **L. Brossay**. Immunoregulatory functions of KLRG1 Cadherin interactions are dependent on forward and reverse signaling. 2009. *Blood*. 114: 5299-5306 PMCID: PMC2796135
- Tata, A., G. Dodard, C. Fugère, C. Leget, M. Ors, B. Rossi, E. Vivier and **L. Brossay**. 2021. Combination blockade of KLRG1 and PD-1 promotes immune control of local and disseminated cancers. *Oncoimmunology* 2021, VOL. 10, NO. 1, e1933808.

3. NK cell like behavior of iNKT cell during infection

iNKT cells are unique T cells that can respond within minutes to specific antigens mostly agonist such as α-GalCer. In the absence of specific antigen, iNKT cells have been shown to contribute directly or indirectly to the immune response to several pathogens leading to a second model of iNKT cell activation, which involves both TCR engagement and inflammatory cytokines. We hypothesized that in some cases such as viral infection, iNKT cells may not need TCR engagement to be activated. Using the MCMV system, we demonstrated that iNKT cell activation is mostly TCR independent. Therefore, iNKT cells essentially behave like NK cells during MCMV infection. These findings were recently confirmed by others using TCR reporter mice. In fact, the current view of iNKT cell activation during pathogen infection has shifted to a more important role of the cytokine-mediated activation than the TCR mediated activation during infections.

- Wesley, J., M. S. Tessmer, D. Chaukos, and **L. Brossay**. 2008. NK cell-like behavior of Va14i NK T cells during MCMV infection. *Plos Pathogens*. 4(7):e1000106. PMCID: PMC2442879
- Anderson, C. K. Reilly S. P. and **L. Brossay**. 2021. The Invariant NKT Cell Response Has Differential Signaling Requirements during Antigen-Dependent and Antigen-Independent Activation. *J. Immunol.* doi: https://doi.org/10.4049/jimmunol.2000870

4. Role of phosphatases during NK cell and NKT cell development

NK cell and NKT cell inhibitory receptors associate predominantly with SHP-1 or SHP-2, which are thought to dephosphorylate key players of cellular activation. Using mice deficient for SHP-1, SHP-2 or SHIP1, we have defined the roles of these phosphatases during NK and iNKT cell development.

- Banh, C., S. Miah S.M., G. Kerr, and **L. Brossay**. 2012. The development and maturation of NK cells

are differentially regulated by SHIP-1. *Blood, 120:* 4583-4590 PMCID: PMC3512235

- Anderson, C. K., A. I. Salter, L. E., Toussaint, E. C. Reilly, C. Fugere, N. Srivastava, W. G. Kerr, and **L. Brossay**. 2015. Role of SHIP1 in iNKT cell development and functions. *J. Immunol.* 195*:* 2149-2156. PMCID: PMC4546909
- Miah SMS, Jayasuriya CT, Salter AI, Reilly EC, Fugere C, Yang W, Chen Q, **Brossay L**. Ptpn11 Deletion in CD4+ Cells Does Not Affect T Cell Development and Functions but Causes Cartilage Tumors in a T Cell-Independent Manner. *Frontiers in immunology*. 2017;8:1326. Epub 2017/11/01. doi: 10.3389/fimmu.2017.01326. PubMed PMID: 29085371; PMCID: PMC5650614.
- Niogret C, Miah SMS, Rota G, Fonta NP, Wang H, Held W, Birchmeier W, Sexl V, Yang W, Vivier E, Ho PC, ***Brossay L**, *Guarda G. Shp-2 is critical for ERK and metabolic engagement downstream of IL-15 receptor in NK cells. *Nature communications*. 2019; 10(1):1444. PubMed PMID: 30926899 PMCID: PMC6441079. *Corresponding authors

5. Unique population of NK cells in the liver, salivary glands and lacrimal glands

NK cells are critical effector cells during the immune response to viral infections, yet despite their presence in the salivary glands, several viruses persist in this organ for several weeks to months. We demonstrated that salivary gland NK cells have a unique phenotype with reduced effector functions. New findings in the laboratory indicate that this mucosal tissue harbors several subsets of NK cell like cells. We are currently testing the hypothesis that although NK cells cannot clear viral infections in this organ, NK cell response is sufficient to prevent viral reactivation while limiting tissue injury***.***

- Tessmer M. S., Reilly E. C., and **L. Brossay**. Salivary gland NK cells are phenotypically and functionally unique. 2011. *Plos Pathogens*. 7(1):e1001254 PMCID: PMC3020929
- Erick, T. K., C. K. Anderson, E. C. Reilly, J. R. Wands and **L. Brossay**. 2016. NFIL3 expression distinguishes tissue-resident NK cells and conventional NK-like cells in the mouse submandibular glands. *J. Immunol*. 197. 2485-2491 PMCID: PMC5010994
- Erick T, Grigoryan L, **Brossay L**. Lacrimal Gland NK Cells Are Developmentally and Functionally Similar to Conventional NK Cells. *Immunohorizons*. 2017;1(2):2-9. Epub 2017/10/03. doi: 10.4049/immunohorizons.1700008. PubMed PMID: 28966997; PMCID: PMC5616209.
- Dodard G., Tata, A., Erick, T.K., Jaime D., Mia S. M.S., Quatrini, L., Escaliere B, Ugolini S., Vivier E., and **L. Brossay**. 2020. Inflammation-Induced Lactate Leads to Rapid Loss of Hepatic Tissue-Resident NK Cells. *Cell Reports,* doi:10.1016/j.celrep.2020.107855. PubMed PMID: 32640221; PMCID: PMC7383148

Link to full list of 74 peer-reviewed publications:

http://www.ncbi.nlm.nih.gov/sites/myncbi/laurent.brossay.1/bibliography/40347211/public/?sort=date&direction=descending.