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## BIOGRAPHICAL SKETCH

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NAME: Brossay, Laurent

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

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POSITION TITLE: Professor

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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 24 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. Most reagents are shared freely or/and donated to Jackson lab or NIH tetramer facility

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 continuously funded by the NIH since 2000.

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 leaders on NIH COBRE grants. Papers published by these junior members are *Immunity*, *Nature Immunology*, *Cell Host and Microbes*, *PLoS Pathogens* etc. Finally, I am the mentor for several successful Assistant Professors from other departments.

I have graduated twelve graduate students and I am currently training three, 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. Six graduate students from my laboratory were awarded an NIH F31 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.

### Ongoing and recently completed projects that I would like to highlight include:

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 - 04/30/25

*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 <i>Frontiers in NK Cell Biology</i>
2010-2014	Section Editor: <i>J. of Immunology</i>
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: <i>J. of Immunology</i>
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: <i>J. Exp. Medicine, Nature Immunology, Science Immunology, J. of Clinical Investigation, Elife, PLoS Pathogens, PNAS, European J. of Immunology, Blood, Nature Medicine, Nature Communications etc</i>

### **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
2004	American Association of Immunologist Junior Faculty 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<sup>+</sup> 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<sup>+</sup> T cells. We then demonstrated that in response to MCMV, NK cells follow a kinetic parallel to CD8<sup>+</sup> 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<sup>+</sup> 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., 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<sup>+</sup> 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.
- Hogan M.J., N. Maheshwari, B.E. Begg, A. Nicastrì, E.J. Hedgepeth, H. Muramatsu, N. Pardi, M.A. Miller, S.P. Reilly, **L. Brossay**, K.W. Lynch, N. Ternette, and L.C. Eisenlohr. 2023. Cryptic MHC-E epitope from influenza elicits a potent cytolytic T cell response. *Nature Immunol.* doi: 10.1038/s41590-023-01644-5

## 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. The KLRG1 deficient animals have been donated to Jackson laboratories.

- 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  $\alpha$ -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 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 cytokine-mediated activation than 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.* PMCID: PMC7855310

## 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. PMID: 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; PMID: 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 PMID: PMC6441079. **\*Corresponding authors**

## 5. Unique population of NK cells and T cells in the salivary 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. We also recently demonstrated that NK cells regulate CD8<sup>+</sup> T cell number and frequency in the salivary glands.

- Tessmer M. S., Reilly E. C., and **L. Brossay**. Salivary gland NK cells are phenotypically and functionally unique. 2011. *Plos Pathogens.* 7(1):e1001254 PMID: 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 PMID: PMC5010994
- 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; PMID: PMC7383148.
- Borys, S.M., S.P. Reilly, I. Magill, D. Zemmour, and **L. Brossay**. 2024. NK cells restrain cytotoxic CD8<sup>+</sup> T cells in the submandibular gland via PD-1–PD-L1. *Science Immunol.* 9:ead12967

**Link to the full list of 78 peer-reviewed publications:**

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