BIOGRAPHICAL SKETCH

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NAME: Roberta Brambilla

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POSITION TITLE: Associate 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
University of Milan, Milan, Italy	B.S.	11/1993	Pharmaceutical Chemistry & Technology
University of Milan, Milan, Italy	M.S.	11/1995	Pharmacology
University of Milan, Milan, Italy	Ph.D.	01/2000	Toxicology
University of Milan, Milan, Italy	Post-doc	02/2001	Neuropharmacology
University of Miami, Miami, USA	Post-doc	04/2003	Neuroscience

A. Personal Statement

I am an Associate Professor in the Department of Neurological Surgery at the University of Miami Miller School of Medicine, and my research centers on how neuroinflammation and neuro-immune interactions shape pathophysiology of neurodegenerative disorders, specifically multiple sclerosis, spinal cord injury, traumatic brain injury and stroke. I focus on glial cells with the goal of identifying targetable pathways to limit neurodegeneration and promote repair and recovery of the injured CNS. My work has been continuously supported by multiple federal and non-federal agencies (NIH, NMSS, FISM, State of Florida, etc.), and has resulted in over 60 publications in peer-reviewed journals.

I am a strong believer that excellence in research can only be achieved through multidisciplinary team science and a strong commitment to mentoring and training graduate students and postdoctoral researchers, as well as to contributing in the professional development of fellow faculty, particularly those in the early stages of their career. Thus, I made these principles the foundation and of my laboratory and academic career. A centerpiece of my work's mission is a commitment to inclusion and diversity, which I firmly believe are vital components of an enriching, open, and productive professional environment. This is reflected not only in the composition of my laboratory over the years, but of the University of Miami where I chose to work.

Mentoring and training are not only a priority but the aspects of academic life I most cherish. This is because I myself enjoyed being guided by exceptional mentors, attentive, caring and genuinely interested in helping me succeed. As testament of my commitment to training and mentoring, since joining the Graduate Faculty in our PIBS umbrella program and the Neuroscience Graduate Program in 2014, I have trained 6 University of Miami Ph.D. students and co-mentored 8 international Ph.D. students from Denmark and Italy, who have spent extended periods of time in my laboratory. Furthermore, I have served/currently serve on over 30 Ph.D. student dissertation committees, and mentored over 40 undergraduate and Masters' students. I also participated in the mentoring of a number of junior/early career investigators at the University of Miami (e.g. Dr. Hassan Al-Ali, Dr. Augusto Schmidt) and at international institutions (Dr. Bettina Clausen, University of Southern Denmark, Odense, Denmark; Dr. Marta Fumagalli, University of Milan, Milan, Italy), who have gone on to build exciting research programs and are making outstanding contributions.

B. Positions, Scientific Appointments and Honors

Professional Appointments

2003 - 2006 Assistant Scientist, The Miami Project to Cure Paralysis, Department of Neurological Surgery University of Miami Miller School of Medicine

2006 - 2010 Associate Scientist, The Miami Project to Cure Paralysis, Department of Neurological Surgery, University of Miami Miller School of Medicine

2010 - 2016 Research Assistant Professor, The Miami Project to Cure Paralysis, Department of Neurological Surgery, University of Miami Miller School of Medicine
2016 - 2018 Assistant Professor, The Miami Project to Cure Paralysis, Department of Neurological Surgery, University of Miami Miller School of Medicine
2018 - present Associate Professor, The Miami Project to Cure Paralysis, Department of Neurological Surgery, University of Miami Miller School of Medicine
2018 - present Adjunct Associate Professor of Neurobiology, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark.

Honors and Awards

06/2000 First Prize for a research project on "New Pharmacological Approaches to the Treatment of Inflammation", by the Italian Society of Pharmacology and Searle Pharmaceuticals.
02/2000 Research fellowship, University of Milan, Italy.
09/2001 Lois Pope LIFE Fellows Postdoctoral Fellowship in the Neurosciences, University of Miami.
01/2006 Travel award for Keystone Symposium "NF-kappa B: 20 years on the road to biochemistry to pathology", March 23-28, 2006, Banff, Canada.
05/2006 Travel award for the "8th International Congress of Neuroimmunology" (International Society for Neuroimmunology), October 15-19, 2006, Nagoya, Japan.
06/2010 Travel award for the "10th International Congress of Neuroimmunology" (International Society for Neuroimmunology), October 26-30, 2010, Sitges, Spain.
05/2022 Mentor of the year award, Neuroscience Graduate Program, University of Miami.

Other Experience

Invited lectures (last 5 years):

February 2018. Neurological Disorder Study Group, Dept. Neurology, University of Miami, Miami, FL
February 2018. Peggy and Harold Katz Family Drug Discovery Center, University of Miami, Miami, FL.
March 2018. Symposium: "Signaling Pathway Dysfunction in Neurologic Diseases" ASN2018 Meeting, March 24-28, 2018, Riverside, CA. *Symposium Co-chairperson*
April 2019. Dept. Neurobiology and Anatomy, Drexel University College of Medicine, Philadelphia, PA.
June 2019. The 17th international TNF Superfamily Conference, June 3-7, 2019, Asilomar, Monterey, CA.
August 2019. Dept. Neurobiology Research, University of Southern Denmark, Odense, Denmark.
December 2019. Keynote speaker, "MS Breakthroughs: research update". National MS Society Breakthroughs, December 14, 2019, Boca Raton, FL.
October 2020. Bascom Palmer Eye Institute Research Retreat, University of Miami.
October 2020. Dept. Drug Design and Pharmacology, University of Copenhagen, Copenhagen, Denmark.
October 2020. Dept. Neurobiology and BRIDGE program, University of Southern Denmark, Odense, Denmark
November 2020. Italian Multiple Sclerosis Foundation Annual Conference, November 25-27, Italy.
February 2021. Meet the Scholar Seminars, Dept. Neuroscience, University of Montreal, Montreal, Canada.
October 2021. Master Course: Multiple Sclerosis, form bench to clinic. University of Southern Denmark, Odense, Denmark.
November 2021. BIOGEN, Boston, MA
November 2021. Dept. Immunology, University of Miami Miller School of Medicine.
April 2022. Neurosurgery Grand Rounds, University of Miami Miller School of Medicine
November 2022. Research Week, Keynote Speaker, University of Southern Denmark, Odense, Denmark.
March 2023. TNFR2 regulates the immunomodulatory properties of oligodendrocytes in neuroimmune disease. ASN2023, American Society for Neurochemistry Meeting, March 18-22, 2023, Lexington, KY. *Invited Speaker and Symposium Co-chairperson.*

Other:

Ad hoc grant reviewer: NIH; Department of Defense Spinal Cord Injury Research Program; Department of Defense Multiple Sclerosis Research Program; Italian Ministry of Health; Italian Multiple Sclerosis Foundation; French Multiple Sclerosis Society; MS Research Australia.

2016 - present Member, Biomedical Research Scientific Committee, Italian Multiple Sclerosis Foundation
2018 - present Member, Editorial Board, Acta Neuropathologica
2018 - present Member, Editorial Board, Frontiers in Cellular Neuroscience
2018 - present Member, Steering Committee, Neuroscience Graduate Program, University of Miami

2020 - present Member, Steering Committee, MSTP program, University of Miami
2020 - present Member, University of Miami Research Council
1999 - present Society for Neuroscience membership
2018 - present Society for Neurochemistry membership
2023 - present Director, Neuroscience Graduate program, University of Miami
2023 - present Associate Editor, Frontiers in Neuroinflammation

C. Contributions to Science

1) Purinergic signaling in the CNS. My interest in the role of glial cells in CNS neuroinflammation began during my undergraduate and graduate studies in the laboratory of Professors Mariapia Abbracchio and Flaminio Cattabeni at the University of Milan (Milan, Italy), where we studied purinergic signaling in the CNS. We made two seminal discoveries in the field: we were the first to identify phospholipase C as the second messenger activated downstream of the newly discovered G-protein-coupled A_3 adenosine receptor in the brain, as well as the first to report on the gliotic and pro-inflammatory response of astrocytes to ATP and its analogs.

a. Abbracchio MP, **Brambilla R**, Ceruti S, Kim HO, von Lubitz DKJE, Jacobson KA and Cattabeni F (1995) G-protein-dependent activation of phospholipase C by adenosine A3 receptors in rat brain. Mol. Pharmacol., 48: 1038-1045. PMID: 8848003.
b. **Brambilla R**, Burnstock G, Bonazzi A, Ceruti S, Cattabeni F and Abbracchio MP (1999) Cyclooxygenase-2 mediates P2Y receptor-induced reactive astrogliosis. Br. J. Pharmacol., 126: 563-567. PMCID: PMC1565841.
c. **Brambilla R**, Neary JT, Cattabeni F, Cottini L, D'Ippolito G, Schiller PC and Abbracchio MP (2002) Induction of COX-2 by P2Y receptors in rat cortical astrocytes is dependent on ERK1/2 but independent of calcium signaling. J. Neurochem., 83: 1285-1296. PMID: 12472883.
d. Fumagalli M, **Brambilla R^**, D'Ambrosi N, Volonte' C, Matteoli M, Verderio C, and Abbracchio MP (2003) Nucleotide-mediated calcium signalling in rat cortical astrocytes: role of P2X and P2Y receptors. GLIA, 43:218-230. PMID: 12898701. (^Co-first author)

2) Role of astrocytes in neuroinflammation. After my graduate studies, I became interested in addressing neuroinflammation from an *in vivo* perspective, studying the role of glial cells in animal models of neurodegenerative disorders. I developed and characterized a transgenic mouse (GFAP-IκBα-dominant negative mice) where the transcription factor NF-κB, a master regulator of inflammation, is inactivated in astrocytes. With this model, we produced the first *in vivo* evidence that selective inhibition of the astrocyte-driven inflammatory response leads to functional recovery after spinal cord injury, experimental autoimmune encephalomyelitis (EAE, a model of multiple sclerosis), and neuropathic pain.

a. **Brambilla R***, Bracchi-Ricard V, Hu W-H, Frydel B, Bramwell A, Karmally S, Green EJ, and Bethea JR (2005) Inhibition of astroglial nuclear factor kappaB reduces inflammation and improves functional recovery after spinal cord injury. J. Exp. Med., 202:145-56. PMCID: PMC2212896.
b. **Brambilla R***, Persaud T, Hu X, Karmally K, Shestopalov VI, Dvoriantchikova G, Ivanov D, Nathanson L, Barnum SR, and Bethea JR (2009) Transgenic inhibition of astroglial NF-κB improves functional outcome in experimental autoimmune encephalomyelitis by suppressing chronic central nervous system inflammation. J. Immunol., 182:2628-40. PMCID: PMC4291126.
c. **Brambilla R***, Dvoriantchikova G, Barakat D, Ivanov D, Bethea JR, and Shestopalov VI (2012) Transgenic inhibition of astroglial NF-κB protects from optic nerve damage and retinal ganglion cell loss in experimental optic neuritis. J. Neuroinflammation, 9:213. PMCID: PMC3490907.
d. **Brambilla R***, Morton PD, Ashbaugh JJ, Karmally S, Lambertsen K, and Bethea JR (2014) Astrocytes play a key role in EAE pathophysiology by orchestrating in the CNS the inflammatory response of resident and peripheral immune cells and by suppressing remyelination. GLIA, 62:452-457. PMID: 24357067.

3) **Protective TNFR2 signaling in MS.** As I continued my career as an independent investigator, I expanded my research to studying the role of tumor necrosis factor (TNF), both membrane-bound and soluble, in the processes of neuroinflammation, demyelination and remyelination associated with multiple sclerosis. I am especially interested in TNF signaling via TNFR2, the receptor that has been associated with neuroprotective and anti-inflammatory properties in the CNS. I have been studying TNFR2 function *in vivo* using pharmacological and genetic approaches, particularly cell-specific TNFR2 conditional knockout mice with ablation of TNFR2 in various CNS and immune-cell populations that we developed in the laboratory. This has led to the discovery that TNFR2 is a key signal for oligodendrocyte differentiation (Madsen et al., J Neurosci,

2016), as well as an important driver of microglia host defense and anti-inflammatory functions (Gao et al., Cell Rep, 2017) following EAE. This indicates that TNFR2 may be a viable target for neuromodulatory and remyelinating therapies.

a. **Brambilla R*,** Jopek Ashbaugh J, Magliozzi R, Dellarole A, Karmally S, Szymkowski DE, and Bethea JR (2011) Inhibition of soluble tumor necrosis factor is therapeutic in experimental autoimmune encephalomyelitis and promotes axon preservation and remyelination. Brain, 134:2736-2754. PMCID: PMC3170538.
b. Madsen PM, Motti D, Karmally S, Szymkowski DE, Lambertsen KL, Bethea JR, **Brambilla R*** (2016) Oligodendroglial TNFR2 mediates membrane TNF-dependent repair in experimental autoimmune encephalomyelitis by promoting oligodendrocyte differentiation and remyelination. J Neurosci, 36:5128-43. PMCID: PMC4854972.
c. Gao H, Danzi MC, Choi CS, Taherian M, Dalby-Hansen C, Ellman DG, Madsen PM, Bixby JL, Lemmon VP, Lambertsen KL, **Brambilla R*** (2017) Opposing functions of microglial and macrophagic TNFR2 in the pathogenesis of experimental autoimmune encephalomyelitis. Cell Re., 18:198:212. PMCID: PMC5218601.
d. Madsen PM, Desu HL, Vaccari JPR, Florimon Y, Ellman DG, Keane RW, Clausen BH, Lambertsen KL, **Brambilla R*** (2020). Oligodendrocytes modulate the immune-inflammatory response in EAE via TNFR2 signaling. Brain Behav Immun, 84:132-146. PMCID: PMC7010565.

4) TNF signaling in neurological disease. My interest in role of TNF in neurodegenerative disorders has led me to expand my studies to CNS diseases other than multiple sclerosis, including stroke, spinal cord injury, neuropathic pain, retinal ischemia and traumatic neuropathy. These studies have consistently uncovered an important role for TNF in the neuroinflammatory response associated with neurological/neurodegenerative disease, and highlighted how TNF has beneficial or detrimental functions in CNS damage and repair depending upon the type and phase of disease and/or injury.

a. Dellarole A, Morton PD, **Brambilla R**, Walters W, Summers S, Bernardes D, Grilli M, and Bethea JR (2014) Neuropathic pain-induced depressive-like behavior and hippocampal neurogenesis and plasticity are dependent on TNFR1 signaling. Brain Behavior and Immunity, 41:65-81. PMCID: PMC4167189.
b. Madsen PM, Clausen BH, Degn M, Thyssen S, Kellemann Kristensen L, Svensson M, Ditzel N, Finsen B, Deierborg T, **Brambilla R***, Lambertsen KL (2016) Genetic ablation of soluble TNF with preservation of membrane TNF is associated with neuroprotection after focal cerebral ischemia. J. Cereb. Blood Flow and Metab. 36:1553-69. PMCID: PMC5012516.
c. Clausen BH, Degn M, Sivasaravanaparan M, Fogtmann T, Gammelstrup Andersen M, Trojanowsky MD, Gao H, Hvidsten S, Baun C, Deierborg T, Finsen B, Kristensen BW, Thornby Bak S, Meyer M, Lee JK, Nedospasov SA, **Brambilla R**, Lambertsen KL (2016) Conditional ablation of myeloid TNF increases lesion volume after experimental stroke in mice, possibly via altered ERK1/2 signaling. Sci. Rep. 6:29291. PMCID: PMC4935869.
d. Yli-Karjanmaa M, Larsen KS, Fenger CD, Kristensen LK, Martin NA, Jensen PT, Breton A, Nathanson L, Nielsen PV, Lund MC, Carlsen SL, Gramsbergen JB, Finsen B, Stubbe J, Frich LH, Stolp H, **Brambilla R**, Anthony DC, Meyer M, Lambertsen KL (2019) TNF deficiency causes alterations in the spatial organization of neurogenic zones and alters the number of microglia and neurons in the cerebral cortex. Brain Behav Immun, 82:279-29. PMID: 31505254.

5) Oligodendrocyte dysfunction in MS pathogenesis. A question I am interested in addressing is whether oligodendrocyte dysfunction plays a role in MS etiopathology. To address this question we generated a tet-off PLP:mtPstI transgenic mouse model where mitochondrial DNA (mtDNA) depletion can be timely and reversibly induced in myelinating oligodendrocytes. With this model we demonstrated that mtDNA damage can cause primary oligodendropathy which in turn triggers demyelination, proving PLP:mtPstI mice to be a useful tool to study the pathological consequences of mitochondrial dysfunction in oligodendrocytes. In addition, PLP:mtPstI mice recapitulate some of the key features of chronic demyelinating syndromes, including progressive MS forms, which are not accurately reproduced in the models currently available. For this reason, the PLP:mtPstI mouse model is an excellent tool to test the efficacy of remyelinating therapies. The key question though is whether intrinsic oligodendrocyte dysfunction is found in individuals with MS and this is being investigated in the laboratory by single-nucleus RNA sequencing of normal appearing white matter samples from the spinal cord of individuals with primary progressive MS and in oligodendrocytes derived from iPSCs from individuals with primary progressive MS (Plastini et al., 2022, under review).

a. Madsen PM, Pinto M, Patel S, McCarthy S, Gao H, Taherian M, Karmally S, Pereira CV, Dvoriantchikova G, Ivanov D, Tanaka KF, Moraes CT, **Brambilla R*** (2017) Mitochondrial DNA double-strand breaks in

oligodendrocytes cause demyelination, axonal injury and CNS inflammation. J Neurosci. 37:10185-10199. PMCID: PMC5647772.

*Corresponding author

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/roberta.brambilla.1/bibliography/45030419/public/?sort=date&direction=ascending