

BIOGRAPHICAL SKETCH

NAME: Antonietta Gentile, Ph.D.

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

POSITION TITLE: Assistant Professor of Cellular and Applied Biology, Department of Biomedicine and Prevention, University of Rome Tor Vergata

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
"G. d'Annunzio" University, Chieti, IT	MPharm	10/2003	Pharmaceutical sciences
Consiglio Nazionale delle Ricerche (CNR), Rome, IT	Research Fellow	2004-2007	Cellular and molecular neuroscience
Istituto Dermopatico dell'Immacolata di Roma (IDI), Rome, IT	Research Fellow	2007-2010	Cellular biology
Tor Vergata University, Rome, IT	Specialization	11/2010	Clinical biochemistry
IRCCS Fondazione Santa Lucia-CERC, Rome, IT	Research Fellow	2011	Neuroimmunology
Tor Vergata University, Rome, IT	Ph.D.	05/2015	Neuroimmunology
Tor Vergata University, Rome, IT	Post-doc fellow	2014-2017	Neuroimmunology
"J. Gutenberg" University, Mainz, DE	Visiting Scientist	2016	Cellular neuroscience
IRCCS-Istituto Neurologico Mediterraneo Neuromed, Pozzilli (Is), IT	Post-doc fellow	2017-2018	Neuroimmunology
Tor Vergata University, Rome, IT	Post-doc fellow	2018-2020	Neuroimmunology
"J. Gutenberg" University, Mainz, DE	Visiting Scientist	2019-2021	Cellular, molecular, and behavioral neuroscience

A. Personal Statement

I am Assistant Professor of Cellular and Applied Biology with a broad background in cellular, biochemical and behavioral neuroscience. My career has always been characterized by strong motivation and the ability to embrace challenges in various areas of biomedical research, with a particular focus on neuroscience.

My main research interest is the interaction between the central nervous system and the immune system. In the last 20 years, the field of neuroimmunology has provided groundbreaking discoveries showing that physiologically the immune system controls mood, behavior, and cognition by modulating neuronal function, starting as early as the first developmental stages. Neuro-immune crosstalk is nowadays recognized as a central aspect of neurodevelopmental and neurodegenerative conditions. Deeply fascinated by this topic, during my PhD and later as a post-doctoral fellow and young PI, I have contributed to this field with my research aimed at understanding the neuron-immune crosstalk in the context of the prototypical neuroinflammatory disorder, the Multiple Sclerosis (MS). In the rodent model of MS, the experimental autoimmune encephalomyelitis (EAE), I

have characterized a mechanism of neurodegeneration arising from the detrimental effects of inflammation at synaptic level and called “inflammatory synaptopathy”, which also underlies behavioral alterations associated with this disorder. We have shown that under pathological circumstances, such as in MS, raises of cytokines induce long-lasting changes in synaptic transmission, leading to permanent dysfunctions of synapses and ultimately neurodegeneration. Thanks to the close collaboration with clinicians, immunologists and pharmaceutical companies, I carried out translational research bringing inputs from the clinical activity into preclinical research and vice versa.

In parallel to this research activity, during the work experience in Germany, I shifted my focus to the mechanisms of hippocampal neurogenesis and oligodendrogenesis in both physiological and stress-related contexts, deepening the intriguing aspects of stress resilience and vulnerability.

Upon my academic appointment as Assistant Professor, the accumulated neuroimmunology experience in the neurodegenerative context has prompted me to broaden my research interests and to investigate the contribution of immune cells and their released factors to synaptic malfunctioning in neurodevelopmental disorders such as autism spectrum disorder (ASD). Since then, I started my independent research activity with the goal of understanding how and to which extent microglia contribute to ASD pathophysiology.

B. Positions, Scientific Appointments, and Honors

Academic appointments

2019-present	External Board Member Ph.D. in Neuroscience, Faculty of Medicine and Surgery, University of Rome Tor Vergata, Italy Adjunct Professor, post-graduate second level Master Experimental and Clinical Neuropsychimmunology, Faculty of Medicine and Surgery, University of Rome Tor Vergata, Italy
2019-2022	Guest lecturer, Webinar in Neuroscience for Ph.D. students in Neuroscience and medical doctor resident in Neurology, Univ. Tor Vergata and Sapienza, Rome (Italy)
2016-2019	Guest lecturer, summer school of “Neurobiology of fear” International Institute Lorenzo De’ Medici, Rome (Italy)
2018	Guest lecturer, “Animal models of Multiple Sclerosis” Science path-ISB Scuola Superiore IANUA-ISSUGE, University of Genoa (Italy)
2022	Assistant Professor (tenured track) in Cellular and Applied Biology Department of Biomedicine and Prevention, Faculty of Medicine and Surgery, University of Rome Tor Vergata, Italy

Scientific Appointments

2019-2024:	Researcher-Junior PI IRCCS San Raffaele Roma, IT
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Honors

2017:	Fondazione Veronesi postdoctoral fellowship
2018:	Federation of European Neuroscience Societies (FENS) travel grant, XI FENS Congress (Berlin, Germany)

C. Contributions to Science

Author of 60 peer-reviewed papers. Full list of publications on: <https://orcid.org/0000-0003-2456-0769>; Scopus Author ID:36911830900

1- IL-1 β drives anxiety- and depression-like behaviors in Multiple Sclerosis animal model

During my Ph.D. work I have shown that the cytokine IL-1 β is crucially involved in the behavioral syndromes associated with EAE by altering the dopaminergic and cannabinoid transmissions of the EAE striatum (*Gentile et al 2015, Neurobiol Dis*; *Gentile et al, 2016, J Neuroinflammation*). We have shown that both depression- and anxiety-like behavior in EAE occurs independently from clinical disability in the presymptomatic phase of the disease. I have shown that IL-1 β is critically increased in the striatum a subcortical area involved in MS. Blocking IL-1 β signaling by means of intracerebroventricular release of the IL-1 β antagonist reverses mood alterations in presymptomatic EAE model and dopaminergic and cannabinoid transmission synaptic alterations, contributing to clarify the synaptic basis of the so-called EAE-behavioral syndrome.

2- The inflammatory synaptopathy is a valuable pharmacological target

During my Ph.D. and in my postdoc, I have shown that the inflammatory synaptopathy affecting the striatum and the cerebellum of EAE mice can be targeted by immunomodulatory drugs, mainly via attenuation of microgliosis, providing evidence that this pathological feature can be a valuable pharmacological target (*Gentile et al, 2013, J Neuroimmune Pharmacol*; *Gentile et al, 2016, J Neuroinflammation*; *Gentile et al, 2018, J Neuroinflammation*; *Musella, Gentile et al, 2020, Cells*). Importantly, drugs tested in these studies are long-established or newly introduced in MS patients. Indeed, I showed that glatiramer acetate, which is one of the first compound used to treat MS and classically regarded as a T-cell modulator, attenuates glutamate excitotoxicity in the striatum of EAE mice by reducing TNF- α release by microglia cells (*Gentile et al, 2013, J Neuroimmune Pharmacol*). In 2016, I demonstrated that Siponimod, a sphingosine-1 receptor agonist that at that time was in clinical trial for progressive MS, had an anti-neurodegenerative effect in EAE, as it protected parvalbumin-positive interneurons from neurodegeneration, improving GABAergic transmission. This study pioneered the success of the compound for treating progressive MS (*Gentile et al, 2016 J Neuroinflammation*). I also showed that another S₁P_{1,5} agonist, namely Ozanimod, in contrast to Siponimod, showed a preferential effect on glutamatergic transmission: by using selective S₁P₁ and S₁P₅ agonists we showed that such an anti-excitotoxic effect was due to S₁P₁ agonism (*Musella, Gentile et al, 2020, Cells*). Finally, I demonstrated that another compound, namely Laquinimod, improved glutamatergic transmission of the EAE cerebellum by increasing expression and function of the glial glutamate transporter GLT-1 (*Gentile et al, 2018, J Neuroinflammation*).

3- Exercise improves behavioral, synaptic and neuropathological hallmarks of human and experimental Multiple Sclerosis

Exercise is well known to exert beneficial effects on brain functioning in humans and rodents. I have tested the disease-modifying efficacy of exercise in MS. I have unraveled the anti-inflammatory, neuroprotective and anti-demyelinating effects of physical exercise (running wheel) in two mouse models of MS, showing that attenuation of microglia activation anticipates neuroprotection (*Mandolesi et al, 2019; Rizzo et al, 2021, Brain Behav Behavior*). In the pure demyelinating model of MS, the cuprizone (CPZ) model, I have shown that preventive exercise induced an early protection against axonal damage and the loss of the myelin in the striatum and the corpus callosum, in coincidence of a strongly attenuated microglia activation in both brain areas. During the late phase of the treatment, exercise in CPZ mice reduced the recruitment of new oligodendrocytes compared to sedentary CPZ mice, likely due to the precocious protection against myelin damage (*Mandolesi et al, 2019, Neurobiol Dis*). In the EAE model, I showed that preventive exercise improved cognitive function and prevented EAE-induced synaptic plasticity abnormalities in the CA1 area of the hippocampus, by promoting the survival of parvalbumin-positive (PV+) interneurons and by attenuating inflammation. Indeed, exercise significantly reduced microgliosis in the CA1 area. Notably, exercise exerted a precocious and long-lasting mitigating effect on microgliosis that preceded its neuroprotective action, likely underlying the improved cognitive function observed in both presymptomatic and acute phase EAE mice (*Rizzo et al, 2021, Brain Behav and Immunity*). Recently in collaboration with neurologists, we conducted a cross-sectional study on 235 relapsing-remitting MS patients at the time of the diagnosis. We have shown that the CSF levels of the interleukin-2 and 6 (IL-2, IL-6) were increased in MS patients compared with control individuals. In MS subjects exercise was associated with normalized CSF levels of IL-2 and reduced anxiety and depression, suggesting that exercise in the early phase may act as a disease-modifying therapy (*Gilio et al, 2022, Neurobiol Dis*). Another clinical study to which I contributed, has shown that both preventive and therapeutic exercise improve long-term plasticity explored using paired associative stimulation (PAS) (*Stampanoni Bassi et al, 2024, Eur J Neurol*).

4- Establishment of an ex vivo chimeric model of MS

By using an ex vivo chimeric model of MS I have proved the translational value of the animal studies showing that human T cells taken from MS subjects alter synaptic transmission similarly to murine EAE T cells (*Gentile*

et al, 2020, Neurophatol and Applied Neurobiol). I have shown for the first time that peripheral T cells taken from active MS subject, and those isolated from non-active MS or healthy age- and sex- matched individuals induce an increase of the kinetic properties of the glutamatergic transmission in striatal neurons of healthy mice. Such alterations, reminiscent of those induced by EAE T cells, was blocked by incubation of the slices with etanercept, a TNF receptor antagonist. These data highlight the synaptotoxic potential retained by MS T cells, suggesting that during the inflammatory phase of the disease infiltrating T cells could influence the neuronal activity contributing to the TNF-mediated mechanisms of glutamate excitotoxicity in central neurons.

5- Role of brain derived neurotrophic factor released by serotonergic neurons in promoting hippocampal neurogenesis during social defeat stress

I have contributed to clarify the interplay between BDNF/TrkB signaling and serotonergic system in the modulation of stress response (*Leschik et al, 2022, Progr Neurobiol*). This goal was reached by exposing transgenic mice overexpressing BDNF in serotonergic neurons in an inducible manner to chronic social defeat stress (CSDS). This mouse line was found to be less affected by stress and enhanced hippocampus-dependent contextual learning. In parallel the BDNF-overexpressing mice showed enhanced serotonergic axonal sprouting in the dentate gyrus and increased neural stem/progenitor cell proliferation. We showed here that BDNF overexpression by adult 5-HT neurons is protective and buffers CSDS-induced behavioral responses. Concomitantly, we observed increased serotonergic axonal sprouting and upregulated adult neurogenesis in the DG, which might constitute one of the mechanisms in the observed stress protection.