

BIOGRAPHICAL SKETCH

NAME: Absinta, Martina, MD, PhD

December 19th, 2024

eRA COMMONS USER NAME: mabsint1

POSITION TITLE

Associate Professor of Neurology, Humanitas University

Head of Experimental Neuropathology Lab, IRCCS Humanitas Research Hospital

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Vita-Salute San Raffaele University- Hospital, Milan, Italy	M.D.	07/2006	Medicine
Vita-Salute San Raffaele University- Hospital, Milan, Italy	Residency	09/2012	Neurology
Vita-Salute San Raffaele University- Hospital, Milan, Italy	Ph.D.	04/2016	Molecular medicine, experimental neurology
National Institute of Neurological Disorders and Stroke (NINDS), NIH	Postdoctoral fellowship	07/2019	MRI-neuropathology of multiple sclerosis

A. Personal Statement

Prof. Martina Absinta is an Associate Professor of Neurology and Head of the Experimental Neuropathology Lab at Humanitas University Hospital in Milan, Italy. She is a physician-scientist with clinical and research activities focused on neuroinflammatory diseases of the central nervous system. She has dedicated her research work to studying MRI–human neuropathological correlations in multiple sclerosis and identifying novel imaging biomarkers of chronic inflammation, with a special focus on glia-mediated and leptomeningeal inflammation. Her research has highlighted the clinical relevance of compartmentalized inflammation and chronic active lesions in driving progression in multiple sclerosis and the need of novel treatments with bioactivity within the central nervous system. Her scientific work has been published in high impact scientific journals, including *Nature*, *Nature Reviews Neurology*, *JCI*, *eLife*, and *JAMA Neurology*.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2012-2014	Visiting Postdoctoral Fellow, Neurological Disorders and Stroke (NINDS), NIH, Bethesda, MD
2016-2019	Research Fellow, Neurological Disorders and Stroke (NINDS), NIH, Bethesda, MD
2019-2020	Assistant Professor, Department of Neurology at the Johns Hopkins University School of Medicine, Baltimore, MD
2020-ongoing	Adjunct Assistant Professor of Neurology, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD
2020-2023	Junior PI, Neuroimmunology, IRCCS San Raffaele Scientific Institute, Milan
2023-2024	Group leader of Translational Neuropathology Lab, IRCCS San Raffaele Scientific Institute, Milan

2024-ongoing Associate Professor of Neurology, Humanitas University
Group Leader of Experimental Neuropathology Lab, IRCCS Humanitas Research Hospital

Honors

2009 Award for best poster - Italian Society of Neurology
2016 Award for best paper with impact factor between 10 and 20 - Italian Society of Neurology
2018 NIH Fellows Award for Research Excellence competition, Bethesda, USA
2021 Rita Levi Montalcini Prize from the Italian MS Society
2022 Young Physician-Scientist Award - The American Society for Clinical Investigation (ASCI)

C. Contribution to Science

Multiple sclerosis lesion staging: role of chronic active/smoldering lesions. I implemented cutting-edge ultra-high-field imaging (in vivo and postmortem 7-tesla MRI) and neuropathology correlations to narrow the gap between pathology and imaging in MS lesion development and evolution, with the ultimate aim to find innovative biological markers to test novel repair-promoting treatments. In the context of lesion evolution, my work has especially contributed to identify the subset of newly forming MS lesions at high risk of complete remyelination failure and compartmentalized smoldering inflammation (chronic active/slowly expanding lesions). In the last few years, my work highlighted their clinical relevance in driving clinical progression in multiple sclerosis and prompted for the planning of novel-designed MRI-based clinical trials aimed at treating such perilesional chronic inflammation. To better understand the immunological mechanism operating at the chronic active lesion edge and to identify new therapeutical targets, I recently built a detailed cellular blueprint of multiple sclerosis lesions using single-nucleus RNA sequencing of human MS tissue and identified C1q as critical mediator of microglia activation.

- a. **Absinta M**, Maric D, Gharagozloo M, Garton T, Smith MD, Jin J, Fitzgerald KC, Song A, Liu P, Lin JP, Wu T, Johnson KR, McGavern DB, Schafer DP, Calabresi PA, Reich DS. A lymphocyte-microglia-astrocyte axis in chronic active multiple sclerosis. *Nature* 2021
- b. Maggi P, Kuhle J, Schädelin S, van der Meer F, Weigel M, Galbusera R, Mathias A, Lu PJ, Rahmanzadeh R, Benkert P, La Rosa F, Bach Cuadra M, Sati P, Théaudin M, Pot C, van Pesch V, Leppert D, Stadelmann C, Kappos L, Du Pasquier R, Reich DS, **Absinta M***, Granziera C*. Chronic White Matter Inflammation and Serum Neurofilament Levels in Multiple Sclerosis. *Neurology* 2021
- c. **Absinta M**, Sati P, Masuzzo F, Nair G, Sethi V, Kolb H, Ohajon J, Wu T, Cortese I, Reich DS. Chronic active multiple sclerosis lesions are associated with disability in vivo. *JAMA Neurol.* 2019
- d. **Absinta M**, Sati P, Schindler M, Leibovitch E, Ohayon J, Wu T, Meani A, Filippi M, Jacobson S, Cortese I, Reich DS. Poor outcome in MS lesions with persistent 7-tesla phase rim. *J Clin Invest* 2016
- e. **Absinta M**, Sati P, Reich DS. Advanced MRI and Staging of Multiple Sclerosis Lesions. *Nature Reviews Neurology* 2016
- f. **Absinta M**, Sati P, Gaitán MI, Maggi P, Cortese IC, Filippi M, Reich DS. Seven-tesla phase imaging of acute multiple sclerosis lesions: A new window into the inflammatory process. *Ann Neurol.* 2013

Modelling chronic inflammation in multiple sclerosis using hiPSC-derived glia-enriched neural organoid

The lack of animal models harboring chronic active lesions is a major obstacle in the field. In the last 3 years, my lab team developed a novel hiPSC-derived glia-enriched neural organoid (composed of neurons, astrocytes, oligodendroglia, and invading hiPSC-derived microglia) which exhibits single-cell transcriptional profiles similar to the adult human brain. Neural precursor cells commitment towards oligodendrogenesis was achieved through ectopic and transient SOX10 induction. When exposed to inflamed cerebrospinal fluid (CSF) from MS patients, organoids properly mimic macroglia-microglia neurodegenerative phenotypes and intercellular communication seen in chronic active MS. Oligodendrocyte vulnerability emerged by day 6 post-

MS-CSF exposure, with nearly 50% reduction. Temporally resolved organoid data support and expand on the role of soluble CSF mediators in sustaining downstream events leading to oligodendrocyte death and inflammatory neurodegeneration. Such findings support implementing this organoid model for mechanistic studies and drug screening to halt inflammatory neurodegeneration.

- a. Fagiani F, Pedrini E, Taverna S, Brambilla, Murtaj V, Podini P, Ruffini F, Butti E, Braccia C, Andolfo A, Magliozzi R, Smirnova L, Kuhlmann T, Quattrini A, Calabresi PA, Reich DS, Martino G, Panina-Bordignon P, **Absinta M**. A glia-enriched stem-cell 3D model of the human brain mimics the glial-immune neurodegenerative phenotypes of multiple sclerosis. *Cell Rep Med* 2024
- b. Summers RA, Fagiani F, Rowitch DH, **Absinta M**, Reich DS. Novel human iPSC models of neuroinflammation in neurodegenerative disease and regenerative medicine. *Trends Immunol.* 2024

Leptomeningeal inflammation in multiple sclerosis. We visualized in vivo, on MRI, areas of leptomeningeal inflammation that lead to abnormalities of the blood-meningeal barrier (seen as restricted leakage of gadolinium in the subarachnoid space) and validated this finding pathologically. Imaging leptomeningeal inflammation in MS opened an original way to better understand not only the pathogenesis of the disease in vivo, but potentially the spatial link between neuroinflammation and cortical damage.

- a. Bhargava P, Kim S, Reyes AA, Grenningloh R, Boschert U, **Absinta M**, Pardo C, Van Zijl P, Zhang J, Calabresi PA. Imaging meningeal inflammation in CNS autoimmunity identifies a therapeutic role for BTK inhibition. *Brain* 2021
- b. **Absinta M**, Cortese IC, Vuolo L, Nair G, de Alwis M, Ohayon J, Meani A, Martinelli V, Scotti R, Falini A, Smith B, Nath A, Jacobson S, Filippi M, Reich DS. Leptomeningeal gadolinium enhancement across the spectrum of chronic neuroinflammatory diseases. *Neurology* 2017
- c. **Absinta M***, Vuolo L*, Rao A, Nair G, Sati P, Cortese IC, Ohayon J, Fenton K, Reyes-Mantilla MI, Maric D, Calabresi PA, Butman JA, Pardo CA, Reich DS. Gadolinium-based MRI characterization of leptomeningeal inflammation in multiple sclerosis. *Neurology* 2015

Lymphatic vessels of the dura mater in human beings and primates. Last 10-year animal research highlighted the existence of a network of dural lymphatic vessels in rodents (Louveau *Nature* 2015; Aspelund *JCI* 2015). We demonstrated that a similar network is present in human beings and nonhuman primates (marmoset monkeys). Not only we provided neuropathological evidence of their existence and distribution in both species, but we were able to directly and noninvasively image dural lymphatics with high-resolution MRI (in-plane resolution 270 x 270 µm or finer) in living human beings and nonhuman primates. This discovery holds promise for better understanding the normal physiology of lymphatic drainage from the central nervous system and potential aberrations in neurological diseases.

- a. **Absinta M***, Ha SK*, Nair G, Sati P, Luciano N, Palisoc M, Louveau A, Zaghloul K, Pittaluga S, Kipnis J, Reich DS. Human and nonhuman primate meninges harbor lymphatic vessels that can be visualized noninvasively by MRI. *eLife* 2017
- b. Okar SV, Fagiani F, **Absinta M**, Reich DS. Imaging of brain barrier inflammation and brain fluid drainage in human neurological diseases. *Cell Mol Life Sci.* 2024

Complete List of Published Work in MyBibliography: <https://www.ncbi.nlm.nih.gov/pubmed/?term=absinta>

Publications: 101 PubMed available manuscripts (23 first-authored, 7 last- or co-last-authored)

Number of total citations: 6.041 (Scopus)

H-index: 43 (Scopus)

Research Funding

- | | |
|------------|---|
| 2024-2027 | Italian MS Society #2023-R-Single-015 / "Glial-enriched stem-cell 3D model of smoldering inflammation in multiple sclerosis: towards a drug screening cellular platform" / role: PI |
| 2023- 2025 | National MS Society (NMSS, US) #RFA-2203-39325 / "MRI-single cell transcriptomic investigation of chronic active inflammation of the spinal cord in patients with multiple sclerosis" / |

role: PI

2024-2026 Italian Ministry of Health Ricerca Finalizzata 2023 / “Hybrid recto proteins: new tools to regulate neuroinflammation” / role: PI Muzio/co-PI Absinta

2021-2024 International Progressive MS Alliance #PA-2107-38081/ “Multi-omics predictors of chronic inflammation in multiple sclerosis”/ role: PI Fitzgerald/co-PI Absinta

2021-2024 FRRB Early Career Award #1750327 / “Personalized brain organoid model of premature aging in multiple sclerosis” / role: PI

2020-2023 Cariplo Foundation #1677 / “Inflammation-induced accelerated brain aging in multiple sclerosis” / role: PI

2019-2023 Conrad N. Hilton Foundation #17313 / “Limiting chronic inflammation in MS lesions: from MRI to molecular pathways” / role: PI

2016-2019 National MS Society (NMSS, US) FG-2093-A-1 / “Chronic inflammation and remyelination failure in MS lesions: in vivo and postmortem investigation of chronic lesions with phase rims” / role: postdoctoral fellowship