

BIOGRAPHICAL SKETCH

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NAME: Roberto Chiesa

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

POSITION TITLE: Ph.D., Head of the Laboratory of Prion Neurobiology

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)	YEAR(s)	FIELD OF STUDY
University of Pavia, Pavia, Italy	M.S.	1987-1991	Biological Sciences – Major in Genetics
Mario Negri Institute for Pharmacological Research Milan, Italy	Ph.D.	1992-1994	Neurodegenerative diseases
Washington University School of Medicine, St. Louis, MO, USA	Post-doctoral training	1996-2000	Prion disease

A. Personal Statement.

I graduated in Biology, majoring in genetics, at the University of Pavia, Italy, and became interested in neurodegeneration during my PhD, where I investigated amyloid neurotoxicity *in vitro*. I then focused on mechanisms of neurodegeneration *in vivo* and how abnormally folded proteins are neurotoxic. At Washington University, St. Louis, USA, I worked on genetic prion diseases. I generated Tg(PG14) mice, which express an insertional PrP mutation and show marked progressive neurodegeneration. Only another model existed, the Tg(P101L) made in Prusiner lab, and together these strengthened the case for pathogenicity of PrP mutations. I pursued this line of research when I returned to Italy in 2001. Since then I led an independent group in the Neuroscience Department at the Mario Negri Institute, focusing on two central questions: 1) What causes neuronal dysfunction in inherited prion diseases? 2) How do different PrP mutations direct the disease phenotype? I developed a program whose main objectives were to explore the mechanisms of neurodegeneration in transgenic mice and neuronal cultures, with the ultimate goal of devising therapeutic approaches. I am also interested in the role of prion-like propagation of tau in chronic neurodegeneration following traumatic brain injury, and in studying cerebellar degeneration in Marinesco-Sjögren syndrome, a rare genetic neurological disease of infancy.

B. Positions, Scientific Appointments, and Honors

Positions

1988-1991: Undergraduate student in the Laboratory of Immunogenetics at the Institute of Genetics, Biochemistry and Evolutionistic (I.G.B.E.) of the Italian National Research Council (C.N.R.), Pavia, Italy.

1992-1996: Graduate student, then postdoctoral fellow in the Laboratory of Biology of Neurodegenerative Disorders, Mario Negri Institute for Pharmacological Research, Milan, Italy

1996-2000: Research associate in the Laboratory of Prof. David A. Harris, at the Department of Cell Biology and Physiology, Washington University Medical School, Saint Louis, Missouri, USA

2000-2001: Research associate in the Department of Neuroscience, Mario Negri Institute for Pharmacological Research, Milan, Italy

2001-2008: Assistant Telethon Scientist, Dulbecco Telethon Institute c/o Department of Neuroscience, Mario Negri Institute for Pharmacological Research, Milan, Italy

2009-2013: Associate Telethon Scientist, Dulbecco Telethon Institute c/o Department of Neuroscience, Mario Negri Institute for Pharmacological Research, Milan, Italy

2009-present: Head of the Prion Neurobiology Lab, Department of Neuroscience, Mario Negri Institute for Pharmacological Research, Milan, Italy

Scientific Appointments

2006-present: Member of the Biochemical Journal Editorial Advisory Panel

2012-present: Academic Editor of PLoS ONE

2013: Guest Editor of the Special Issue on Protein Misfolding and Neurodegenerative Diseases of International Journal of Cell Biology
2017-2021: Review Editor in Neurodegeneration of Frontiers in Neuroscience
2019: Section Editor for a Special Issue on Prion diseases of Current Opinion in Pharmacology

Honors

1998: *James L. O'Leary Prize for Research in Neuroscience*, from Washington University of St. Louis, MO, USA
1999: Honorable mention in the 75th Annual Meeting of the American Association of Neuropathologists. Portland, OR, USA
2000: *Bruno Ceccarelli Prize for Research in Neuroscience*, from the "Bruno Ceccarelli" Association, Milan, Italy
2001: Telethon Career Award (Assistant Telethon Scientist)
2009: Telethon Career Award (Associate Telethon Scientist)

C. Contributions to Science

1. Mechanisms of phenotypic heterogeneity in genetic prion diseases. My laboratory developed transgenic mouse models to determine how prion protein (PrP) molecules carrying pathogenic mutations are handled differently by neurons than their normal counterparts, and how these differences contribute to neurodegeneration and disease phenotype. Our work contributed to define experimentally the distinction between the infectious and neurotoxic properties of mutant prion proteins, and established that mutant PrPs cause mutation-specific alterations in secretory transport of synaptic proteins, leading to neuronal dysfunction. Based on these results, we put forward a new hypothesis to explain the phenotypic heterogeneity of genetic prion diseases., and begun to test potential therapeutic approaches.

Dossena S, Imeri L, Mangieri M, Garofoli A, Ferrari L, Senatore A, Restelli E, Balducci C, Fiordaliso F, Salio M, Bianchi S, Fioriti L, Morbin M, Pincherle A, Marcon G, Villani F, Carli M, Tagliavini F, Forloni G, Chiesa R. (2008). Mutant prion protein expression causes motor and memory deficits and abnormal sleep patterns in a transgenic mouse model. **Neuron** 60(4):598-609. doi: 10.1016/j.neuron.2008.09.008.

Senatore A, Colleoni S, Verderio C, Restelli E, Morini R, Condiliffe SB, Bertani I, Mantovani S, Canovi M, Micotti E, Forloni G, Dolphin AC, Matteoli M, Gobbi M, Chiesa R. (2012). Mutant PrP suppresses glutamatergic neurotransmission in cerebellar granule neurons by impairing membrane delivery of VGCC $\alpha 2\delta$ -1 subunit. **Neuron** 74(2):300-13. doi: 10.1016/j.neuron.2012.02.027.

Bouybayoune I, Mantovani S, Del Gallo F, Bertani I, Restelli E, Tapella L, Comerio L, Bianchi S, Fernández-Borges N, Mangieri M, Bisighini C, Beznoussenko GV, Paladini A, Balducci C, Micotti E, Forloni G, Castilla J, Fiordaliso F, Tagliavini F, Imeri L, Chiesa R. (2015). Transgenic fatal familial insomnia mice indicate prion infectivity-independent mechanisms of pathogenesis and phenotypic expression of disease. **PLOS Pathog** 11(4):e1004796. doi: 10.1371/journal.ppat.1004796.

Ghirardini E, Restelli E, Morin R, Bertani I, Ortolan D, Perrucci F, Pozzi D, Matteoli M, Chiesa R. (2020) Mutant prion proteins increase calcium permeability of AMPA receptors, exacerbating excitotoxicity. **PLoS Pathog** 16(7): e1008654. doi: 10.1371/journal.ppat.1008654

2. Therapeutic approaches for prion diseases. We have contributed to validate neuroinflammation, abnormal protein trafficking, and the cellular prion protein as potential therapeutic targets for prion diseases.

Bertani I, Iori V, Trusel M, Maroso M, Foray C, Mantovani S, Tonini R, Vezzani A, Chiesa R. (2017) Inhibition of IL-1 β signaling normalizes NMDA-dependent neurotransmission and reduces seizure susceptibility in a mouse model of Creutzfeldt-Jakob disease. **J Neurosci** 37(43):10278-10289. doi: 10.1523/JNEUROSCI.1301-17.2017.

Lavigna G, Masone A, Bouybayoune I, Bertani I, Lucchetti J, Gobbi M, Porcu L, Zordan S, Rigamonti M, Imeri L, Restelli E, Chiesa R. (2021) Doxycycline rescues recognition memory and circadian motor rhythmicity but does not prevent terminal disease in fatal familial insomnia mice. **Neurobiol Dis.** 158:105455. doi: 10.1016/j.nbd.2021.105455.

Restelli E, Capone V, Pozzoli M, Ortolan D, Quaglio E, Corbelli A, Fiordaliso F, Beznoussenko GV, Artuso V, Roiter I, Salles M, Chiesa R. (2021) Activation of Src family kinase ameliorates secretory trafficking in mutant prion protein cells. **J Biol Chem** 296:100490. doi: 10.1016/j.jbc.2021.100490.

Masone A, Zucchelli C, Caruso E, Lavigna G, Eraña H, Giachin G, Tapella L, Comerio L, Restelli E, Raimondi I, Elezgarai SR, De Leo F, Quilici G, Taiarol L, Oldrati M, Lorenzo NL, García-Martínez S, Cagnotto A, Lucchetti J, Gobbi M, Vanni I, Nonno R, Di Bari MA, Tully MD, Cecatiello V, Ciossani G, Pasqualato S, Van Anken E, Salmona M, Castilla J, Requena JR, Banfi S, Musco G, Chiesa R. (2023) A tetracationic porphyrin with dual anti-prion activity. **iScience** 26(9):107480. doi: 10.1016/j.isci.2023.107480.

Masone A, Zucchelli C, Caruso E, Musco G, Chiesa R. (2024) Therapeutic targeting of cellular prion protein: toward the development of dual mechanism anti-prion compounds **Neural Regen Res** 20(4):1009-1014. doi: 10.4103/NRR.NRR-D-24-00181. Epub 2024 Jun 3.

3. The role of PrP^C as a cell-surface receptor for toxic oligomers. Our work contributed to understanding the role of PrP^C in mediating the neurotoxicity of protein oligomers involved in Alzheimer's and Parkinson's disease.

Balducci C, Beeg M, Stravalaci M, Bastone A, Scip A, Biasini E, Tapella L, Colombo L, Manzoni C, Borsello T, Chiesa R, Gobbi M, Salmona M, Forloni G. (2010). A β oligomers impair memory independently of cellular prion protein. **Proc Natl Acad Sci** 107(5):2295-300. doi: 10.1073/pnas.0911829107.

La Vitola P, Beeg M, Balducci C, Santamaria G, Restelli E, Colombo L, Caldinelli L, Pollegioni L, Gobbi M, Chiesa R, Forloni G. (2019) Cellular prion protein neither binds to alpha-synuclein oligomers nor mediates their detrimental effects. **Brain** 142(2):249-254. doi: 10.1093/brain/awy318.

Del Gallo F, Bianchi S, Bertani I, Messa M, Colombo L, Balducci C, Salmona M, Imeri L, Chiesa R. (2020) Sleep inhibition induced by amyloid- β oligomers is mediated by the cellular prion protein. **J Sleep Res** 30(3):e13187. doi: 10.1111/jsr.13187.

4. Role of prion-like propagation of tau in traumatic brain injury. Our work demonstrated for the first time that traumatic brain injury induces a self-replicating form of the protein tau that propagates throughout the brain in a prion-like manner. This may explain how a biomechanical insult may turn into a long-term neurodegenerative pathology.

Zanier ER*, Bertani I, Sammal E, Pischiutta F, Chiaravalloti MA, Vegliante G, Masone A, Corbelli A, Smith DH, Menon DK, Stocchetti N, Fiordaliso F, De Simoni MG, Stewart W, Chiesa R*. (2018) Induction of a transmissible tau pathology by traumatic brain injury. **Brain** 141(9):2685-2699. doi: 10.1093/brain/awy193. *Corresponding author

Zanier ER*, Barzago MM, Vegliante G, Romeo M, Restelli E, Bertani I, Natale C, Colnaghi L, Colombo L, Russo L, Micotti E, Fioriti L, Chiesa R*, Diomede L*. (2021) C. elegans detects toxicity of traumatic brain injury generated tau. **Neurobiol Dis** 153:105330. doi: 10.1016/j.nbd.2021.105330. *Corresponding author

5. PERK inhibition in Marinesco-Sjögren syndrome. Our work indicated a crucial role the PERK branch of the unfolded protein response in the pathogenesis of Marinesco-Sjögren syndrome, and provided evidence that pharmacological PERK inhibition ameliorates the disease phenotype in a mouse model.

Capone V, Clemente E, Restelli E, Di Campli A, Sperduti S, Ornaghi F, Pietrangelo L, Protasi F, Chiesa R, Sallese M. (2018) PERK inhibition attenuates the abnormalities of the secretory pathway and the increased apoptotic rate induced by SIL1 knockdown in HeLa cells. **Biochim Biophys Acta Mol Basis Dis** 1864(10):3164-3180. doi: 10.1016/j.bbadis.2018.07.003.

Grande V, Ornaghi F, Comerio L, Restelli E, Masone A, Corbelli A, Tolomeo D, Capone V, Axten JM, Laping NJ, Fiordaliso F, Sallese M, Chiesa R. (2018) PERK inhibition delays neurodegeneration and improves motor function in a mouse model of Marinesco-Sjögren syndrome. **Hum Mol Genet** 27(14):2477-2489. doi: 10.1093/hmg/ddy152.

Restelli E, Masone A, Sallese M, Chiesa R. (2019) Neuroprotective modulation of the unfolded protein response in Marinesco-Sjögren syndrome: PERK signaling inhibition and beyond. **Neural Regen Res** 14(1):62-64. doi: 10.4103/1673-5374.243708.

Complete list of publications in Scopus: <https://www.scopus.com/authid/detail.uri?authorId=56650259600>