

BIOGRAPHICAL SKETCHNAME: **Chiara ZUCCATO**

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

POSITION TITLE: **Associate Professor, Department of Biosciences, University of Milan, and National Institute of Molecular Genetics "Romeo and Enrica Invernizzi"**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 (Italy)	PhD in Biotechnology applied to Pharmacology	December 2005	The role of BDNF in Huntington's Disease
University of Leeds (UK)	Research Stage	2004-2005	REST in Huntington's Disease
University of Insubria Varese (Italy)	Doctor in Biological Sciences	July 1998	Heterochromatin and epigenetics

A. Personal Statement

I have a strong background in Huntington's disease (HD) research, with a primary focus on synaptic dysfunction and its molecular determinants. My long-term goal is to develop disease-modifying therapeutic strategies capable of preventing synaptic failure and cognitive decline in HD. Since 2007, I have successfully led research projects funded by the Italian Ministry of University and Research (MIUR) and the Telethon Foundation, and I have participated as a collaborator in multiple projects supported by U.S. based foundations dedicated to Huntington's disease research, including the Huntington's Disease Society of America (HDSA), Hereditary Disease Foundation (HDF), and the CHDI Foundation.

Over the years, I have established a research line demonstrating that A Disintegrin and Metalloproteinase domain 10 (ADAM10) is a key downstream effector of mutant huntingtin (HTT) protein and a therapeutically relevant target in HD. This work has resulted in peer-reviewed publications in *Nature Neuroscience* (2012), *Journal of Clinical Investigation* (2019), *Human Molecular Genetics* (2021), and *Cellular and Molecular Life Sciences* (2024).

Building on the identification of ADAM10 as an HTT-regulated and disease-relevant target, I am currently pursuing translational strategies based on the chemical inhibition of ADAM10. In parallel, I am exploring minimally invasive delivery approaches for ADAM10 inhibitors, including intranasal

administration, with the aim of enhancing clinical translatability. My research team possesses the expertise, technological capabilities, and infrastructure required to investigate HD-related synaptic dysfunction and pharmacological agents targeting synapses at multiple levels, both *in vitro* and *in vivo*. I have extensive experience with preclinical HD mouse models, neurobehavioral assessments, and circuit-level analyses. I maintain long-standing national and international collaborations that reinforce the multidisciplinary nature of my research. These include a productive partnership with Prof. G. Biella (University of Pavia) for functional synaptic and electrophysiological studies; a collaboration with Dr. V. Maglione (Neuromed Institute Pozzilli), an expert in intranasal drug delivery and behavioral assessment in HD models; collaborations with international experts in synaptic biology such as D. Choquet (University of Bordeaux) and a collaboration with IRBM (Pomezia) focused on drug screening and chemical optimization of ADAM10 inhibitors.

As an active member of the European Huntington's Disease Network, I benefit from access to advanced experimental models and cutting-edge tools developed within the HD research community. I also have solid experience in leading and managing research projects, including personnel supervision, research integrity, and financial planning, ensuring the successful execution of complex, multidisciplinary research programs. I am confident that my expertise, research environment, and collaborative network position me well to successfully address the objectives and challenges of this project.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2015-present Associate Professor of Pharmacology, Dept. Biosciences, University of Milan
National Institute of Molecular Genetics "Romeo and Enrica Invernizzi" Milan

2012-2015 Assistant Professor of Pharmacology, Dept. Biosciences, University of Milan

2006-2012 Assistant Professor of Pharmacology, Dept. of Pharmacological Sciences, University of Milan

2004-2005 Senior research fellow, University of Leeds (UK), Dept. of Biochemistry

2001-2005 PhD student, Dept. of Pharmacological Sciences, University of Milan

1999-2001 Telethon Fellow, Dept. Pharmacological Sciences, University of Milan

1998-1999 Young research fellow, Dept. Pharmacology and Medical Chemoterapy, University of Milan

Membership

2023-present Chief Scientific Advisor Italian Federation for Life Sciences (FISV)
Since January 2023, I have been serving as the scientific director of the Italian Federation of Life Sciences (FISV), which represents over 10.000 university researchers and 19 scientific societies. I organize meetings for the Italian Life Science Community, training courses for young researchers, and conferences for high school students.

2022-present Co-chair Scientific and Bioethics Advisory Committee (SBAC), European Huntington's Disease Network

2019-2020 Chair Huntington Onlus, the Italian Network of Huntington's Disease

2008-2019 Scientific Advisor AICH Milano and Huntington Onlus

Since the very beginning of my research activity in the HD field, I have had the privilege to know patients and their families. I funded "The Italian Network of Huntington's Disease" and launched the "Huntington Days," a 10-day event in which scientists, physicians, social workers, volunteers, and families from North to South Italy work together to break the silence surrounding this condition, communicate the progress of HD research, and raise awareness about the disease.

Selected Honors

2018 Habilitation as a Full Professor in Pharmacology. Valid until 2030.

2008 *Ricerca.Tissimi, Premio Ricerca & Internazionalizzazione* - Lombardy Region (Italy)

2006 Prize "Le Scienze 2006" conferred by the President of the Italian Republic

2003 Awarded by the association "Ricerca in Movimento" (Rome, Italy)

2003 Award "The Outstanding Young Persons" (TOYP) - Junior Chamber International (Italy)

Teaching

2013-present Faculty of Science and Technology, University of Milan

Lecturer for:

Biological Medicinal Products and Advanced Therapies (48 hours/year)

Stem Cells and Genetic Diseases (48 hours/year)

Neurobiology (32 hours/year)

2008-2012 Faculty of Pharmacy, Univ. of Milan

2011-2014 Faculty of Pharmacy University Our Lady of Good Counsel, Tirana

2018/2019 Master Communication of Science and Innovation, University of Trento

2010/2015 Annual school "Science-Communication-Society (SCS)", Turin

Tutor Activity

2001-present Tutor of 32 young researchers (master students and PhD students)

Oral presentations

2002-present 36 oral presentations to national and international meetings

21 invited seminars

59 presentations to HD patients association, high school students and general public

Organization of scientific conferences and courses

2025 FISV days: online event for high school students – 15.600 participants

FISV for Young "Advanced Technologies in single cell Omics" – 740 participants

2024 FISV days: online event for high school students – 8.000 participants

FISV Congress 2024 – 500 participants

FISV for Young "Genomics: advanced technologies" – 500 participants

2023 FISV days: online event for high school students – 3300 participants

2022 European Huntington's Disease Network Meeting (Bologna)

2020 "New advances in basic and applied virology" Online Course for PhD students

2019 Kick-off meeting Project of Excellence 2018-2022, Dept. Biosciences (Milan)

C. Contributions to Science

Since 1999, my research has been focused on Huntington's disease (HD), with the goal of identifying new pharmacological targets and neuroprotective drugs.

List of publications: ORCID: [HTTPS://ORCID.ORG/0000-0003-1771-3392](https://orcid.org/0000-0003-1771-3392)

Original manuscripts 48; Reviews: 10; Book chapters: 4

H index (Scopus, January 2026): 36

Citations (Scopus, January 2026): 8794

Average IF: 7.3

1. ADAM10 in HD synaptic dysfunctions

A major focus of my research team is to elucidate the molecular mechanisms underlying synaptic dysfunction in HD. We were the first to discover a link between HTT and ADAM10 in HD. In 2012, by studying neurulation in embryonic stem cells depleted of HTT, we found that the homotypic interaction between neuroepithelial cells is dependent on the presence of normal HTT, which acts physiologically to inhibit ADAM10 and the shedding of its substrate, N-Cadherin, allowing cell-cell contacts. We also reported that, in the adult brain, normal HTT can similarly affect synapse remodeling through inhibition of ADAM10 activity on N-Cadherin. In 2019, we extended this study by showing that this pathway is hyperactive in HD, with deleterious consequences for the morphology and functionality of the glutamatergic synapse. In particular, we found that active ADAM10 accumulates at the postsynaptic

density and causes excessive N-CAD proteolysis, leading to loss of excitatory synaptic contacts, synapse deficiencies, and cognitive decline in HD mice. Conversely, normalization of active ADAM10 is beneficial in HD mice. In 2021, we were the first to report that ADAM10 also exerts a crucial role in the regulation of presynaptic activities, suggesting that hyperactivity of presynaptic ADAM10 could be a major component of HD synaptic dysfunctions. More recently, we have found that ADAM10 inhibition protects from synapse loss in HD by enhancing BDNF levels. This discovery holds significance for HD treatment as inhibiting ADAM10 can prevent two critical molecular dysfunctions in the HD synapse: synaptic cell adhesion defects and downregulation of BDNF, a hallmark of HD pathogenesis.

1. Lo Sardo V, Zuccato C, Gaudenzi G, Vitali B, Ramos C, Tartari M, Myre MA, Walker JA, Pistocchi A, Conti L, Valenza M, Drung B, Schmidt B, Gusella J, Zeitlin S, Cotelli F, Cattaneo E. An evolutionary recent neuroepithelial cell adhesion function of huntingtin implicates ADAM10-Ncadherin. *Nat Neurosci*. 2012 May;15(5):713-21.
2. Vezzoli E, Caron I, Talpo F, Besusso D, Conforti P, Battaglia E, Sogne E, Falqui A, Petricca L, Verani M, Martufi P, Caricasole A, Bresciani A, Cecchetti O, Rivetti di Val Cervo P, Sancini G, Riess O, Nguyen H, Seipold L, Saftig P, Biella G, Cattaneo E, Zuccato C. Inhibiting pathologically active ADAM10 rescues synaptic and cognitive decline in Huntington's disease. *J Clin Invest*. 2019 May 6;129(6):2390-2403.
3. Cozzolino F, Vezzoli E, Cheroni C, Besusso D, Conforti P, Valenza M, Iacobucci I, Monaco V, Birolini G, Bombaci M, Falqui A, Saftig P, Rossi RL, Monti M, Cattaneo E, Zuccato C. ADAM10 hyperactivation acts on piccolo to deplete synaptic vesicle stores in Huntington's disease. *Hum Mol Genet*. 2021 Jun 17;30(13):1175-1187.
4. Scolz A, Vezzoli E, Villa M, Talpo F, Cazzola J, Raffin F, Cordiglieri C, Falqui A, Pepe G, Maglione V, Besusso D, Biella G, Zuccato C. Neuroprotection by ADAM10 inhibition requires TrkB signaling in the Huntington's disease hippocampus. *Cell Mol Life Sci*. 2024 Aug 7;81(1):333.

2. BDNF in HD

One of my main contributions in the field of HD has been the discovery that huntingtin, in its normal form, has neuroprotective function because it stimulates the expression of brain-derived neurotrophic factor (BDNF). I also contributed to demonstrating that the reduced production of BDNF in HD contributes to the observed selective neurodegeneration. The BDNF measurement is now deemed necessary to validate new models of HD, and it is used as a read-out in the evaluation of the efficacy of new therapeutic approaches. I also found that HTT regulates BDNF gene transcription through a mechanism that implicates the transcriptional repressor REST, which binds to the NRSE silencer within BDNF promoter II. Thanks to the collaboration developed with Prof. Noel Buckley of King's College, one of the leading experts on the NRSE silencer, I contributed to demonstrating the presence of a large genomic alteration of the NRSE silencer in HD. These findings prompted researchers to look into REST and the NRSE silencer as potential targets for developing drugs that can restore BDNF gene transcription in HD. These studies indicate that gene silencing strategies for HD must consider selective targeting of the mutant huntingtin allele.

1. Zuccato C, Ciammola A, Rigamonti D, Leavitt BR, Goffredo D, Conti L, MacDonald ME, Friedlander RM, Silani V, Hayden MR, Timmusk T, Sipione S, Cattaneo E. Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. *Science*. 2001 Jul 20;293(5529):493-8.
2. Zuccato C, Tartari M, Crotti A, Goffredo D, Valenza M, Conti L, Cataudella T, Leavitt BR, Hayden MR, Timmusk T, Rigamonti D, Cattaneo E. Huntingtin interacts with REST/NRSF to modulate the transcription of NRSE-controlled neuronal genes. *Nat Genet*. 2003 Sep;35(1):76-83.
3. Zuccato C, Belyaev N, Conforti P, Ooi L, Tartari M, Papadimou E, MacDonald M, Fossale E, Zeitlin S, Buckley N, Cattaneo E. Widespread disruption of repressor element-1 silencing transcription factor/neuron-restrictive silencer factor occupancy at its target genes in Huntington's disease. *J Neurosci*. 2007 Jun 27;27(26):6972-83.
4. Marullo M, Valenza M, Mariotti C, Di Donato S, Cattaneo E, Zuccato C. Analysis of the repressor element-1 silencing transcription factor/neuron-restrictive silencer factor occupancy of non-neuronal

genes in peripheral lymphocytes from patients with Huntington's disease. *Brain Pathol.* 2010 Jan;20(1):96-105.

5. Conforti P, Mas Monteys A, Zuccato C, Buckley NJ, Davidson B, Cattaneo E. In vivo delivery of DN:REST improves transcriptional changes of REST-regulated genes in HD mice. *Gene Ther.* 2013 Jun;20(6):678-85.

6. Conforti P, Zuccato C, Gaudenzi G, Ieraci A, Camnasio S, Buckley NJ, Mutti C, Cotelli F, Contini A, Cattaneo E. Binding of the repressor complex REST-mSIN3b by small molecules restores neuronal gene transcription in Huntington's disease models. *J Neurochem.* 2013 Oct;127(1):22-35.

7. Schiffer D, Caldera V, Mellai M, Conforti P, Cattaneo E, Zuccato C. Repressor element-1 silencing transcription factor (REST) is present in human control and Huntington's disease neurones. *Neuropathol Appl Neurobiol.* 2014 Dec;40(7):899-910.

3. Huntingtin structure and function

Since 2005, my research activity has also been aimed at creating a multidisciplinary research network involving biologists, physicians, anthropologists, and zoologists to study the function and evolution of CAG repeat triplets in the HD gene. I contributed to collecting and analyzing samples from more than 200 species of vertebrates and mammals. These studies led to the reconstruction of the main evolutionary passages of the Huntington gene and the identification that the N500 aa of HTT is a domain endowed with neural functions. We also demonstrated that Huntington genes from species with progressively longer CAG tracts have greater neural capacity. More recently, I have contributed to discovering that, during evolution, natural selection promotes the conservation and purity of the CAG tract and that small increases in its physiological length influence the neural functions of HTT. I'm actually involved in a project that aims to understand the link between the polyP and the polyQ tract in HTT neuronal function and in HD pathogenesis.

1. Tartari M, Gissi C, Lo Sardo V, Zuccato C, Picardi E, Pesole G, Cattaneo E. Phylogenetic comparison of huntingtin homologues reveals the appearance of a primitive polyQ in sea urchin. *Mol Biol Evol.* 2008 Feb;25(2):330-8.

2. Lo Sardo V, Zuccato C*, Gaudenzi G, Vitali B, Ramos C, Tartari M, Myre MA, Walker JA, Pistocchi A, Conti L, Valenza M, Drung B, Schmidt B, Gusella J, Zeitlin S, Cotelli F, Cattaneo E. An evolutionary recent neuroepithelial cell adhesion function of huntingtin implicates ADAM10-Ncadherin. *Nat Neurosci.* 2012 May;15(5):713-21. *co-first author

3. Iennaco R, Formenti G, Trovesi C, Rossi RL, Zuccato C*, Lischetti T, Bocchi VD, Scolz A, Martínez-Labarga C, Rickards O, Pacifico M, Crottini A, Møller AP, Chen RZ, Vogt TF, Pavesi G, Horner DS, Saino N, Cattaneo E. The evolutionary history of the polyQ tract in huntingtin sheds light on its functional pro-neural activities. *Cell Death Differ.* 2022 Feb;29(2):293-305. *co-first author

4. Zobel M, Damaggio G, Mignogna ML, Besusso D, Scalzo D, Cossu A, Trovesi C, Crosti M, Cortina F, Campus I, Formenti G, Mazzara S, Gregoret F, Antonelli L, Oliva G, Zuccato C, Colonna V, Conforti P, Cereda M, Rossi RL, Maestri S, Scolz A, Iennaco R, Cattaneo E. A human CAGinSTEM platform for decoding HTT repeats' somatic instability links CAG interruption to HD pathology in neurons. *Cell Rep.* 2025 Dec 23;44(12):116685.