

BIOGRAPHICAL SKETCH

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NAME: Deborah Chiabrando

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

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Milan, Milan, Italy	Master	01/2020	International Master in Peripheral Nervous System Disorders
Dept. of Molecular Biotechnology and Health Sciences, Molecular Biotechnology Center, University of Turin, Turin, Italy	Postdoctoral	2020	Regulation of heme metabolism
Dept. of Molecular Biotechnology and Health Sciences, Molecular Biotechnology Center, University of Turin, Turin, Italy	PhD	01/2011	Regulation of heme metabolism
Faculty of Biotechnology, University of Turin, Turin, Italy	Master Degree	07/2006	Molecular Biotechnology
Faculty of Biotechnology, University of Turin, Turin, Italy	Bachelor's Degree	07/2004	Molecular Biotechnology

A. Personal Statement

Since the beginning of my scientific activity, I specialized in the study of iron and heme metabolism in animal models. During the PhD and post-doctoral work, the focus of my research was the understanding of the physiological roles of the heme exporter FLVCR1. This allowed me to acquire strong competences in the generation and characterization of animal models, especially the analysis of mouse and zebrafish development. As an independent researcher, I focused on rare disorders caused by mutations in the *FLVCR1* gene that encompass milder forms characterized by the progressive degeneration of sensory neurons and photoreceptors, or more severe forms including congenital hydrocephalus. FLVCR1 has been implicated in the regulation of heme metabolism, choline/ethanolamine uptake and overall energetic metabolism but the pathogenetic mechanisms underlying the diseases are still unclear. The current focus of my laboratory is to elucidate the role of FLVCR1 in the nervous system and to uncover the molecular mechanisms responsible for these rare

disorders. Our long-term goal is to discover a therapeutic entry point to effectively treat rare neurological disorders.

My background on heme metabolism, neurodevelopment and cell metabolism suggests that I am well-suited to collaborate with Dr. Arnold and his interdisciplinary team in the project entitled “Molecular tools to study Flvcr2-mediated choline transport in brain angiogenesis and congenital hydrocephalus”.

B. Positions and Honors

Positions and Employment

2024- today	Associate Professor, Dept. of Molecular Biotechnology and Health Sciences, Molecular Biotechnology Center, University of Turin, Turin, Italy.
2021 - 2024	Assistant Professor (Researcher Type B), Dept. of Molecular Biotechnology and Health Sciences, Molecular Biotechnology Center, University of Turin, Turin, Italy.
2020 - 2021	Tenure Track Researcher (Researcher Type A), Dept. of Molecular Biotechnology and Health Sciences, Molecular Biotechnology Center, University of Turin, Turin, Italy.
2011 – 2020	Postdoc Fellow, Dept. of Molecular Biotechnology and Health Sciences, Molecular Biotechnology Center, University of Turin, Turin, Italy.

Other Experience and Professional Memberships

From 2020	Teaching activities at the School of Medicine (Biotechnology), University of Torino.
From 2020	Delegate for the Public Engagement (PE) registry, Dept. of Molecular Biotechnology and Health Sciences, Molecular Biotechnology Center, University of Torino, Torino, Italy.
From 2019	Member of the Research Commission, Dept. of Molecular Biotechnology and Health Sciences, Molecular Biotechnology Center, University of Torino, Torino, Italy.
2015-2017	Postdoc fellows Representative at the Faculty Committee, Dept. of Molecular Biotechnology and Health Sciences, Molecular Biotechnology Center, University of Torino, Torino, Italy.
2014-today	Reviewer for “Nature Communication”, “Cell Biology and Toxicology”, “BMC Medical Genetics”, “International Journal of Oncology”, “Pharmaceuticals”, “BMC Medical Genomics”, “Frontiers Pharmacology”.
2015-today	Member of the International “Peripheral Nerve Society” (2019), “Italian Association for the Study of Peripheral Nervous System” (AISNP) (2017-2019), “European Iron Club” (2016-2019), “European Hematology Association” (2015), “International BIOIRON Society (IBIS)” (2016-2019).
2011 – today	Co-supervisor of 4 PhD students and 4 master’s degree students
2022 – today	Supervisor of 2 PhD students and 3 master’s degree students

Honors

2010	Best Oral Presentation Award. “European Iron Club Meeting” – Nimegen, The Netherlands.
2011	<u>Gunshin Levy Award 2011</u> . Awarded to Young Researchers for their dedication, commitment and contributions to the field area of iron homeostasis. Vancouver, Canada.
2012	Best Oral Presentation Award. “European Iron Club Meeting” - Rennes, France.
2014	Finalist at Under40 in Hematology – Final Contest in Rome, Italy.
2017	<u>Gunshin Levy Award 2017</u> . Awarded to Young Researchers for their dedication, commitment and contributions to the field area of iron homeostasis. Los Angeles, CA, USA.
2018	Italian National Academic Qualification as Associate Professor in Applied Biology.

Interruption of Research Activity:

I maternity leave: from 16/12/2013 to 16/05/2014

II maternity leave: from 08/07/2017 to 07/03/2018

C. Contributions to Science

Total of 29 Publications, h-index = 19, Citations > 1400, Field-Weighted Citation Impact: 1.52

Insights into the mechanism of mitochondrial heme export

Heme is endogenously synthesized in mitochondria but must be exported to be incorporated into most hemoproteins and to play regulatory functions. Until 2012, the heme biosynthetic reactions were well characterized but the mechanism of mitochondrial heme export was completely unclear. The major achievement of my PhD was the identification of a novel isoform of the FLVCR1 transporter, named FLVCR1b, which is crucially involved in the export of heme out of mitochondria and in erythroid differentiation:

- a. **Chiabrando D**, Marro S, Mercurio S, Giorgi C, Petrillo S, Vinchi F, Fiorito V, Fagoonee S, Camporeale A, Turco E, Merlo GR, Silengo L, Altruda F, Pinton P and Tolosano E.
THE MITOCHONDRIAL HEME EXPORTER FLVCR1B MEDIATES ERYTHROID DIFFERENTIATION.
Journal of Clinical Investigation, 2012.

These findings strongly contribute to the field of heme metabolism as the mechanism of mitochondrial heme export was completely unknown up to that time. This study was awarded at several international meetings and received more than 150 citations to date.

Subsequent studies in zebrafish models allowed me to dissect the specific contribution of FLVCR1 isoforms during the proliferation and differentiation of erythroid progenitors:

- b. Mercurio S, Petrillo S*, **Chiabrando D***, Bassi ZI, Gays D, Camporeale A, Vacaru A, Miniscalco B, Valperga G, Silengo L, Altruda F, Baron MM, Santoro MM and Tolosano E.
HEME EXPORTER FLVCR1 REGULATES EXPANSION AND DIFFERENTIATION OF COMMITTED ERYTHROID PROGENITORS BY CONTROLLING INTRACELLULAR HEME ACCUMULATION.
Haematologica, 2015.

2. Investigation of the physio-pathological implications of FLVCR1a

In the last years, I strongly contributed to the definition of FLVCR1 function in physio-pathological conditions. The analysis of different conditional knockout mouse models of FLVCR1a showed its crucial role in the regulation of hepatic homeostasis, developmental angiogenesis as well as in cancer.

- a. Vinchi F, Ingoglia G, **Chiabrando D**, Mercurio S, Turco E, Silengo L, Altruda F and Tolosano E.
HEME EXPORTER FLVCR1A REGULATES HEME SYNTHESIS AND DEGRADATION AND CONTROLS ACTIVITY OF CYTOCHROMES P450.
Gastroenterology, 2014.
- b. Petrillo S, **Chiabrando D**, Genova T, Fiorito V, Ingoglia G, Vinchi F, Mussano F, Carossa S, Silengo L, Altruda F, Merlo GR, Munaron L and Tolosano E.
HEME ACCUMULATION IN ENDOTHELIAL CELLS IMPAIRS ANGIOGENESIS BY TRIGGERING PARAPTOSIS.
Cell Death and Differentiation, 2018.
- c. Fiorito V, Allocco AL, Petrillo S, Gazzano E, Torretta S, Marchi S, Destefanis F, Pacelli C, Audrito V, Provero P, Medico E, **Chiabrando D**, Porporato PE, Cancelliere C, Bardelli A, Trusolino L, Capitanio N, Deaglio S, Altruda F, Pinton P, Cardaci S, Riganti C, Tolosano E.
THE HEME SYNTHESIS-EXPORT SYSTEM REGULATES THE TRICARBOXYLIC ACID CYCLE FLUX AND OXIDATIVE PHOSPHORYLATION.
Cell Reports 2021
- d. Petrillo S, De Giorgio F, Bertino F, Garelo F, Bitonto V, Longo DL, Mercurio S, Ammirata G, Allocco AL, Fiorito V, **Chiabrando D**, Altruda F, Terreno E, Provero P, Munaron L, Genova T, Nóvoa A, Carlos AR, Cardoso S, Mallo M, Soares MP, Tolosano E.
ENDOTHELIAL CELLS REQUIRE FUNCTIONAL FLVCR1A DURING DEVELOPMENTAL AND ADULT ANGIOGENESIS. Angiogenesis. 2023.

I served as a co-investigator in all these studies. Specifically, I was involved in the generation and characterization of conditional knockout mouse models.

3. Identification of *FLVCR1* as a novel disease-causing gene for sensory neuropathy

Hereditary Sensory and Autonomic Neuropathy (HSAN) is a rare genetic disorder mainly characterized by the degeneration of sensory neurons that are responsible for pain perception. Mutations in different genes, involved in distinct cellular pathways, have already been discovered. However, the molecular mechanisms underlying sensory neurodegeneration are still incompletely understood and disease-causing mutations remain to be identified in a substantial number of patients. I identified for the first-time mutations in the *FLVCR1* gene in patients affected by HSAN. *FLVCR1* mutations were previously identified in patients with sensory ataxia and retinitis pigmentosa but never in patients with inability to sense pain. Specifically, I was involved in the functional validation of the consequences of *FLVCR1* mutations *in vitro*.

- a. **Chiabrando D#**, Castori M, di Rocco M, Ungelenk M, Gießelmann S, Di Capua M, Madeo A, Grammatico P, Bartsch S, Hübner CA, Altruda F, Silengo L, Tolosano E*#, Ingo Kurth*#.
MUTATIONS IN THE HEME EXPORTER FLVCR1 CAUSE SENSORY NEURODEGENERATION WITH LOSS OF PAIN PERCEPTION.
PLOS Genetics, 2016. IF (2018): 5.224
- b. Castori M, Morlino S, Ungelenk M, Pareyson D, Salsano E, Grammatico P, Tolosano E, Kurth I and **Chiabrando D#**.
POSTERIOR COLUMN ATAXIA WITH RETINITIS PIGMENTOSA COEXISTING WITH SENSORY-AUTONOMIC NEUROPATHY AND LEUKEMIA DUE TO A RECURRENT FLVCR1 MUTATION.
Am Journal Medical Genetics B, 2017.
IF (2018): 3.123
- c. Bertino F*, Firestone K*, Bellacchio E, Jackson KE, Asamoah A, Hersh J, Fiorito V, Destefanis F, Gonser R, Tucker ME, Altruda F, Tolosano E and **Chiabrando D#**.
HEME AND SENSORY NEUROPATHY: INSIGHTS FROM NOVEL MUTATIONS IN THE HEME EXPORTER FLVCR1. PAIN, 2019. IF (2018): 6.029

By identifying a novel disease-causing gene in HSAN, I strongly contributed to increase the basic knowledge on HSAN genetics, thus improving HSAN diagnosis. Indeed, following the first report, the number of patients affected by HSAN with *FLVCR1* mutations is growing. I served as the primary investigator or last author in all of these studies.

4. Identification of *FLVCR1* as a novel disease-causing gene for congenital hydrocephalus

Congenital hydrocephalus (CH), occurring in approximately 1/1000 live births, represents an important clinical challenge due to the limited knowledge of underlying molecular mechanisms. The discovery of novel CH-genes is thus essential to shed light on the intricate processes responsible for ventricular dilatation in CH. We recently identified *FLVCR1* as a novel gene responsible for a severe form of CH in humans and mice. Interestingly, subsequent studies from independent laboratories confirmed that loss of function mutations in *FLVCR1* severely impairs CNS development (PMID: 39306721). Of note, mice lacking *FLVCR1* in neuronal progenitors died perinatally and showed a severe impairment of central nervous system development: reduced corticogenesis and secondary expansion of ventricles. Mechanistically, our data reveal that *FLVCR1a* interacts with the IP3R3-VDAC complex located on mitochondria-associated membranes (MAMs) that controls mitochondrial calcium handling. Loss of *Flvcr1a* in mouse neural stem cells (NSCs) affects mitochondrial calcium levels and energy metabolism, leading to defective cortical neurogenesis and brain ventricle enlargement. These data point to defective NSC calcium handling and metabolic activity as one of the pathogenetic mechanisms driving CH.

- a. Bertino F, Mukherjee D, Bonora M, Bagowski C, Nardelli J, Metani L, Zanin Venturini DI, Chianese D, Santander N, Salaroglio IC, Hentschel A, Quarta E, Genova T, McKinney AA, Allocco AL, Fiorito V,

Petrillo S, Ammirata G, De Giorgio F, Dennis E, Allington G, Maier F, Shoukier M, Gloning K, Munaron L, Mussano F, Salsano E, Pareyson D, Di Rocco M, Altruda F, Panagiotakos G, Kahle KT, Gressens P, Riganti C, Pinton PP, Roos A, Arnold T, Tolosano E and **Chiabrando D**.
DYSREGULATION OF FLVCR1-DEPENDENT MITOCHONDRIAL CALCIUM HANDLING IN NEURAL STEM CELLS CAUSES CONGENITAL HYDROCEPHALUS.
Cell Reports Medicine 2024.

By analyzing a unique mutation in the *FLVCR1* gene responsible for CH, we unexpectedly uncovered new mechanistic insights into the disease pathogenesis. I served as the PI of this study.

Complete List of Published Work: <http://orcid.org/0000-0002-8968-8029>.

D. Additional Information: Research Support and/or Scholastic Performance

Current Research Support:

2022PX3SR3 Deborah Chiabrando Years: 2023-2025
Title: Unlocking the structure and function of the heme transporter FLVCR1, Funded by the *Italian Ministry of University and Research* (Progetti di Rilevante Interesse Nazionale - PRIN), € 73,132 euro
Project goal: Elucidation of the mechanism of action of the FLVCR1 isoforms.
Role: PI

GMR22T1076 Deborah Chiabrando Years: 2023-2025
Title: Posterior Column Ataxia and Retinitis Pigmentosa: new pathogenetic insights from the study of mitochondria-associated membranes, Funded by *Fondazione Telethon ETS*, €160.000
Project goal: Development of cellular and animal models to study the pathogenetic mechanisms responsible for PCARP.
Role: PI

R01 NS123168-01 Deborah Chiabrando Years: 2021-2025
Title: Defective heme transport in the development of congenital hydrocephalus", supported by the *National Institute of Health (NIH)*.
Project goal: Understanding the role of FLVCR1 in congenital hydrocephalus.
Role: Co-PI

Completed Research Support:

GFI Deborah Chiabrando Year: 2023
Title: Impact of iron deficiency on the bioelectrical communications between gut bacteria and neurons, Funded by the *University of Torino* (Grant for Internalization – GFI), €15.233
Project goal: Study of the impact of iron on bacteria membrane polarization in the context of the gut-brain axis.
Role: PI

GEP13065 Deborah Chiabrando Year: 2013
Title: "Investigation of the molecular basis of Posterior Column Ataxia and Retinitis Pigmentosa", funded by *Telethon* (Telethon Exploratory Project), € 40.100.
Project goal: Understanding the pathogenetic mechanisms underlying Posterior Column Ataxia and Retinitis Pigmentosa.
Role: PI