

Università degli Studi di Siena
Dottorato di Ricerca in Medicina Molecolare

Scheda Relazione Annuale Dottorando
(da redigere in lingua inglese)

luogo e data Pisa, 29/09/25

Al Collegio Docenti del Dottorato in Medicina Molecolare

dr.ssa Sara Bernardi

ciclo 38° tutor Prof.ssa Federica Gemignani; Dott.ssa Maria Marchese

Attività scientifica svolta nel 3° anno di Dottorato, Anno Accademico 2024/2025

(massimo 2000 caratteri totali, spazi inclusi) descrivere brevemente la propria ricerca, suddividendola in:

- Introduzione

The neuronal ceroid lipofuscinoses (NCL) are a group of rare genetic neurodegenerative disorders, predominantly occurring during childhood and early adult life, multiple studies identified different forms of NCL associated with mutations in 13 genes (*CLN1-CLN8*, *CLN10-CLN14*), characterized by accumulation of autofluorescent storage material in lysosomes. The aim of my PhD project is to develop and characterized *cln1/3/5/8*-deficient knock-out zebrafish lines to unravel new pathomechanisms behind this disease and to test molecules through high-throughput drug screening.

- Metodiche utilizzate

cln1^{-/-} and *cln3*^{-/-} F2 homozygous zebrafish, generated using CRISPR/Cas9 method, were characterized to identify specific phenotypes, including locomotor impairments and protein downregulation. Locomotor behavior was assessed using video-tracking systems (DanioScope and DanioVision). In control and *cln5*^{-/-} larvae, electroencephalogram (EEG) recordings and optogenetic modulation were performed to investigate the epileptic phenotype. Standard molecular biology techniques were employed to validate gene and protein expression.

- Risultati ottenuti

During this year, we investigated different CLN models. Both *cln1*^{-/-} and *cln3*^{-/-} showed alterations in locomotor activity. In the *cln5*^{-/-} model, pharmacological screening revealed improvements with an already approved drug as well as with a compound synthesized at the University of Pisa. To further explore the epileptic phenotype of *cln5*^{-/-}, we applied optogenetic manipulation of Purkinje cells, suggesting that these neurons could act as potential pacemakers. In the *cln8*^{-/-} model, we further analyzed the lipid profile and found that the sulfatide group was inversely altered at two developmental stages, adult and juvenile.



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Treatment with a specific drug improved larval motility and increased the expression of *PARP-1*, a gene closely related to sulfatide metabolism.

- Elencare eventuali Pubblicazioni scientifiche: autori, titolo della pubblicazione, nome e numero della rivista, anno di pubblicazione (si ricorda che l'attività scientifica, a seguito di approvazione della relazione da parte del Collegio, consente l'acquisizione di 35 CFU per il I e II anno)

- De Paolo, R., Sarti, S., **Bernardi, S.**, Cucco, F., Tavano, A., Pitto, L., & Poliseo, L. (2023). Differential impact of BRAFV600E isoforms on tumorigenesis in a zebrafish model of melanoma. *Cell & bioscience*, 13(1), 121.
 - Bernardi, S., Gemignani, F., & Marchese, M. (2023). The involvement of Purkinje cells in progressive myoclonic epilepsy: Focus on neuronal ceroid lipofuscinosis. *Neurobiology of disease*, 185, 106258.
 - Gammaldi, N., Doccini, S., **Bernardi, S.**, Marchese, M., Cecchini, M., Ceravolo, R., Rapposelli, S., Ratto, G. M., Rocchiccioli, S., Pezzini, F., Santorelli, F. M., & DEM-AGING Network (2024). Dem-AGING: autophagy-related pathologies and the "two faces of dementia". *Neurogenetics*, 25(1), 39–46.
 - Marchese M, **Bernardi S**, Ogi A, et al. Targeting autophagy impairment improves the phenotype of a novel CLN8 zebrafish model. *Neurobiol Dis.* 2024;197:106536.
 - Santucci, L., **Bernardi, S.**, Vivarelli, R., Santorelli, F. M., & Marchese, M. (2024). Glucose metabolism impairment as a hallmark of progressive myoclonus epilepsies: a focus on neuronal ceroid lipofuscinoses. *Frontiers in cellular neuroscience*, 18, 1445003. <https://doi.org/10.3389/fncel.2024.1445003>
 - Della Vecchia S, Imbriani P, Liantonio A, Naef V, Damiani D, Licita R, **Bernardi S**, Marchese M, Santorelli FM. Dapagliflozin ameliorates Lafora disease phenotype in a zebrafish model. *Biomed Pharmacother.* 2025 ;183:117800. doi: 10.1016/j.biopha.2024.117800.
 - Licita R, Della Vecchia S, Santucci L, Vivarelli R, **Bernardi S**, Santorelli FM, Marchese M. Trehalose Ameliorates Zebrafish Emotional and Social Deficits Caused by CLN8 Dysfunction. *Cells.* 2025 Jan 5;14(1):55. doi: 10.3390/cells14010055
 - **Bernardi S***, Vitolo S*, Gabellini C., Marchese M., Ferraro E. Trimetazidine stimulates intracellular Ca²⁺ transients and zebrafish locomotor activity in spinal neurons, 02 July 2025. *Sci Rep* 15, 22854 (2025). <https://doi.org/10.1038/s41598-025-06065-y>
 - Marchese M, **Bernardi S**, Vivarelli R, Doccini S, Santucci L, Ogi A, Licita R, Zang J, Soliymani R, Mero S, Neuhaus SC, Ciarmoli L, Signore G, Lalowski MM, Santorelli FM. CLN5 deficiency impairs glucose uptake and uncovers PHGDH as a potential biomarker in Batten disease. *Mol Psychiatry.* 2025. doi: 10.1038/s41380-025-03043-8
 - C. Merola, R. Licita, **S. Bernardi**, R. Rocchi, R. Scarpone, M. Marchese, P24-18 Neurotoxicity and developmental impact of the dinitroaniline herbicide pendimethalin in zebrafish early-life stages, *Toxicology Letters*, 2025. doi:10.1016/j.toxlet.2025.07.719
- Attività didattica (seguire le indicazioni [1](#) e [2](#) online per il calcolo CFU. Deve essere congruente con le schede mensili)
 - Methods to investigate striated muscle mechanics and energetics. Prof. Marco Linari (2023)
 - Applications of optogenetics to experimental cardiology, Prof. Leonardo Sacconi (2023)
 - -High-throughput sequencing: technologies and application in molecular medicine, Prof. Stefano Cagnin (2023)
 - Polygenic risk scores: from research to diagnosis and precision medicine, Prof.ssa Betti Giusti (2023)



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- Exploring the genomic and epigenomic landscape of diseases with Nanopore sequencing, Prof.ssa Betti Giusti (2023)
- Single cell sequencing in Molecular Medicine, Prof.ssa Nicoletta Piroddi (2023)
- Human iPSC-derived cardiomyocytes and muscle cells as a model of inherited cardiac & muscular diseases, Prof. Jose' Manuel Pioner (2023)
- How to study genetics in complex diseases, Prof. Stefano Landi (2023)
- The beta-adrenergic system in the retina: targeting beta adrenoceptors against retinal neovascular diseases, Prof. Massimo Dal Monte (2023)
- Functional role of beta 3 adrenoceptors in cancers: a new hope from in vitro and in vivo studies? Prof. Massimo Dal Monte (2023)
- Cancer Genetics, Prof. Stefano Landi (2023)
- Gene - environment interaction: from bench to bedside Prof. Stefano Landi (2023)
- Beyond the proteome: non-coding regulatory RNAs in cell pathophysiology. Part 1 and 2, Prof. Stefano Cagnin. (Siena, 20 e 21 maggio, 2024).
 - Dual filaments regulation of muscle contraction, Prof. Linari; The molecular motor of muscle studied in vitro mechanics, Prof. Bianco; Mechanical dysfunction in genetic-based cardiomyopathies: perspectives for the use of novel small molecules and biomimetic polymers, Prof.ssa Ferrantini; High-throughput sequencing: technologies and application in molecular medicine, Prof.ssa Giusti; Effects of SGLT-2 inhibitors in diseased myocardium, Prof.ssa Cerbai. (23/02/2024)
 - The beta-adrenergic system in the retina: targeting beta adrenoceptors against retinal neovascular diseases, Prof. Massimo Dal Monte; The beta-adrenergic system in the retina: targeting beta adrenoceptors against retinal neovascular diseases, Dr. Rosario Amato (11-04-2024, Pisa).
 - Cardiac mechano-electric coupling and arrhythmias (11-04-2025, Firenze)
 - Liquid crystalline elastomers: State of the art and cardiac applications (11-04-2025, Firenze)
 - Non-genetic optical manipulation of cardiac dynamics (11-04-2025, Firenze)
 - Of neurons and glucose: an unstable relationship (10-04-2025, Pisa)
 - New insights into the link between inflammation and electrogenesis (11-04-2025, Firenze)
 - Cardiac multiscale bioimaging: from nano- to mesoscales (11-04-2025, Firenze)
 - Measuring molecular forces across scales: from single molecules to cell collectives (11-04-2025, Firenze)
 - LCE-based enhancement of engineered heart tissue maturation (11-04-2025, Firenze)
 - Advanced Techniques in Neuroscience: optogenetics, magnetogenetics, sonogenetics (10-04-2025, Pisa)
 - Small-protein scaffold for targeted therapy in solid tumors (08-04-2025, Pisa)
 - Human primordial germ cells: Origin and maturation during embryonic development (10-06-2025, Siena)
 - Human primordial germ cell-like development in human hindgut organoids (10-06-2025, Siena)
 - Tuning leukocyte migration by atypical chemotactic receptors, (21/5/25, online)



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CFU **totali** conseguiti per le frequenze di didattica frontale: 27 CFU

- Seminari (indicare relatore e data del/i seminario/i. Aggiungere righe se necessario)
 1. Ethical issues in preclinical research, Prof.ssa Carla Gambarana (2023)
 2. Spermatogenesis and sperm in normal and pathological conditions, Prof.ssa Giulia Collodel (2023)
 3. Glucose-6- phosphatase 3, a new function for an old enzyme, Prof.ssa Paola Marcolongo (2023)
 4. Prof. Reggiani Diversity and specialization of skeletal muscle fibers: an omics point of view; Prof.ssa Kronnie Circular RNA: the salt of the transcriptome
 5. Application of nano-agents in cancer and cerebral ischemia. Dott. Attilio Marino, Fondazione Stella Maris, Pisa. (3/5/2024)
 6. Organoids revolutionizing biomedicine through-miniature organ models (08/05/24). Webinar.

CFU conseguiti per questa attività: (indicare CFU **totali** da Novembre '24 a Ottobre '25) 4 CFU

- Soft Skills (indicare nome e data del/i corso/i. Aggiungere righe se necessario)
 1. I finanziamenti europei nel settore digitale. 11/05/23.
 2. Europrogettazione: programmi, progetti e rendicontazione. 18/05/23.
 3. Science and Society: continuity and change. 29/05/23. Università di Siena.
 4. PhD and then? Overview on career paths inside and outside the academia. 12/06/23.
 5. Materiale promozione THRUST corso incentivazione imprenditorialità Ecosistema THE. 20-30/06/23.
 6. Last update in Sustainability reporting regulation. 07/09/23.
 7. Ricerche bibliografiche, bibliometria e open access & science. 14/09/23. Università di Siena.
 8. The role of standardization in innovation development. 20/09/23. Università di Siena.
 9. Corso Embase. Webinar (Università di Firenze, 31/05/24)
 10. Corso PubMed. Webinar (Università di Firenze, 7/6/24)
 11. Corso diritto d'autore e pubblicare in accesso aperto (Università di Firenze, 19/06/24)
 12. Corso trasversale "L'assicurazione della Qualità nell'Ateneo di Pisa e il ruolo dei dottorandi" (Università di Pisa, 20/9/24)
 13. Science and Society: continuity and change (17/9/24)
 14. Come la terapia genica sta cambiando la storia di malattie ereditarie e tumorali (27/9/24)
 15. The story of the European Union and how it funds research, (10/2024)
 16. Le caratteristiche principali di un brevetto, (10/2024)
 17. La nuova Commissione europea: priorità e obiettivi strategici, (20/02/25)
 18. Lezione 3 -Non solo mercato. L'UE e il modello sociale europeo (06/03/25)
 19. Aprirsi al nuovo, senza timore. La strategia dell'UE per l'Intelligenza artificiale, (13/03/25)
 20. Siamo ciò che mangiamo. La politica agricola comune: che cos'è ea cosa serve, (20/03/25)



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21. L'Unione europea e la resilienza idrica, (27/03/25)
22. L'Unione europea e la sua difesa: lo stato dell'arte, gli obiettivi, (03/04/25)
23. Il Business Plan, (17/6/25)

CFU conseguiti per questa attività: (indicare CFU **totali** da Novembre '24 a Ottobre '25) 20 CFU

- Partecipazione a congressi (indicare nome e data del/i congressi/i, titolo della/e presentazione-i/poster/abstract, autori)
 1. 18th NCL2023 Congress- Hamburg 25-30 September 23. Poster presentation; Disentangling Batten disease through a zebrafish modelling: characterization of a new cln3-deficient zebrafish line; **Bernardi S.**, Ogi A., Mero S., Gemignani F., Santorelli F. M., Marchese M.
 2. XXI Scientific Convention Telethon, Riva Del Garda 13-15 March 23. Poster presentation; Insight CLN5: Approaching therapies in the neuronal ceroid; **Bernardi S.**, Ogi A., Licitra R., Mero S., Galatolo D., Naef V., Gemignani F., Ratto G. M., Nardi G., Rapposelli S., Zang J., Neuhauss S., Santorelli F. M., Marchese M.
 3. Pisa Zebrafish Day 3.0, Pisa 15 September 23.
 4. 4th Italian Zebrafish Meeting, Palermo 7-9 February 2024; Disentangling Batten disease through a zebrafish modelling: characterization of a new cln3-deficient zebrafish line; **Sara Bernardi**, Asahi Ogi, Federica Gemignani, Filippo M. Santorelli, Maria Marchese.
 5. 6th International Congress IRPES2024 – Pisa, December, 6th 2024; Targeting autophagy in a novel zebrafish (Danio rerio) model on neuronal ceroid lipofuscinosis 8; **Sara Bernardi**; Asahi Ogi; Rosario Licitra, Giada Silvi; Serena Mero; Daniele Galatolo; Nicola Gammaldi; Stefano Doccini; Federica Gemignani; Gian Michele Ratto; Simona Rapposelli; Filippo M. Santorelli; Maria Marchese.
 6. 7th Brayn Conference, Poster session, Verona 9-11/10/24; Investigating Purkinje cells role in seizures through optogenetic manipulation in zebrafish; **Bernardi S.**, Gemignain F., Santorelli F. M., Marchese M.
 7. 4° Congresso nazionale A-NCL, Roma, 19/10/2024;
 8. 2° Zeb-ONE, poster session, Roma 24-25/10/2024; Insight on CLN5 dysfunction using novel zebrafish model: reveals impaired glucose metabolism, brain calcium homeostasis and new trans-species biomarkers; **Bernardi S.**, Vivarelli R.; Santucci L., Ogi A., Licitra R., Mero S., Galatolo D., Naef V., Gemignani F., Ratto G. M., Nardi G., Rapposelli S., Zang J., Neuhauss S., Santorelli F. M., Marchese M.
 9. Pisa Zebrafish Day, 02/07/25, Pisa; Speaker; Purkinje cells as gatekeepers of seizure susceptibility: insights from optogenetics; **Bernardi S.**, Gemignain F., Santorelli F. M., Marchese M.
 10. 21st national congress of the Italian Society for Neuroscience, 10-13/09/25, Pisa, Poster session, Purkinje cells as gatekeepers of seizure susceptibility: insights from optogenetics; **Bernardi S.**, Gemignain F., Santorelli F. M., Marchese M.

CFU conseguiti per questa attività: (indicare CFU **totali** da Novembre '24 a Ottobre '25) 9 CFU



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- Eventuali soggiorni in altri laboratori italiani o esteri

From August 14th to September 13th 2024 in Dr. Wendy E. Heywood's laboratory, Translational Mass Spectrometry Research group, Genetics and Genomic Medicine Research and Teaching Dept, UCL Institute of Child Health, London. For lipidomic profile analysis in Neuronal Ceroid Lipofuscinoses on Zebrafish samples.

Tabella Riepilogativa CFU **primo anno**

Didattica	Seminari Webinar	Soft Skills	Congressi	PhD Day	TOTALE I ANNO (Inclusi 35 CFU per la ricerca)
9 CFU	0 CFU	8 CFU	2,5 CFU	1 CFU	55,5 CFU

Tabella Riepilogativa CFU **secondo anno** (lasciare in bianco se del primo anno)

Didattica	Seminari Webinar	Soft Skills	Congressi	PhD Day	TOTALE II ANNO (Inclusi 35 CFU per la ricerca)
9 CFU	3,5 CFU	6 CFU	4,5 CFU	1 CFU	59 CFU

Tabella Riepilogativa CFU **terzo anno**

Didattica	Seminari Webinar	Soft Skills	Congressi	PhD Day	TOTALE III ANNO (Inclusi 35 CFU per la ricerca)
9 CFU	0,5 CFU	6 CFU	2 CFU	1 CFU	53,5 CFU