

Università degli Studi di Siena
Dottorato di Ricerca in Medicina Molecolare

Scheda Relazione Annuale Dottorando
(da redigere in lingua inglese)

Pisa, XX/10/2025

Al Collegio Docenti del Dottorato in Medicina Molecolare

dr.ssa Lorenza Di Marsico

ciclo XXXIX tutor Prof. Massimo Dal Monte

Scientific activity related to the 2nd year of PhD, Academic Year 2024/2025

- Introduction

The retina, as part of the central nervous system, represents a privileged site to investigate mechanisms of neurodegeneration, with neuroinflammation and oxidative stress recognized as major drivers of neuronal vulnerability. During the second year, my research activity focused on two projects addressing retinal neurodegeneration and potential therapeutic targets. The first investigated early retinal alterations in a mouse model of amyotrophic lateral sclerosis (ALS), aiming to characterize early mechanisms of retinal damage (1). The second explored the role of $\beta 3$ -adrenoceptor ($\beta 3$ -AR) in oxygen-induced retinopathy (OIR), a model of hypoxia-driven vascular pathology. This study specifically aimed to clarify the contribution of astrocyte in vascular template recovery following $\beta 3$ -AR activation (2).

- Methods: Intraperitoneal or subcutaneous injections; retinal dissection; electroretinogram (ERG) and optical coherence tomography (OCT); molecular analyses: Western blot, RT-PCR and immunofluorescence.

- Results

(1) In the ALS model, ERG revealed early dysfunction of both outer and inner retinal layers, in particular affecting retinal ganglion cells (RGC). OCT and immunofluorescence confirmed RGC loss and nerve fiber thinning. Mutant SOD1 protein was associated with oxidative stress, microglial activation and inflammatory responses, driven also by miRNAs dysregulation. These findings indicate that retinal impairment precedes motor symptom onset, supporting the retina as a non-invasive tool for early ALS diagnosis and therapeutic testing.

(2) In OIR, retinal astrocytes express $\beta 3$ -ARs, whose levels were modulated by hypoxia and normalized by pharmacological agonism. $\beta 3$ -AR stimulation restored the balance of angiogenic and



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neurotrophic factors, reduced reactive gliosis, and improved antioxidant responses. These results highlight astrocytes as key players in β 3-AR-mediated protection and suggest β 3-AR activation as a promising therapeutic strategy for proliferative retinopathies.

- Publications:

- Lucchesi M., Di Marsico L., Guidotti L., Lulli M., Filippi L., Marracci S., Dal Monte M.
“Hypoxia-Dependent Upregulation of VEGF Relies on β 3-Adrenoceptor Signaling in Human Retinal Endothelial and Müller Cells”
Int J Mol Sci. 2025 Apr 24;26(9):4043. doi: 10.3390/ijms26094043.
- Di Marsico L., Sturlese Verduri A., Marracci S., Amato R., Dal Monte M.
“Rodent models of glaucoma: how mice and rats can help human vision move out of the woods and into the light”
Cells, 2025 -Under Review

Didactic activity

- CFU totali conseguiti per le frequenze di didattica frontale: 9 CFU

• Seminars:

1. Dr. Danielle Beckman, 10/12/2024: “Combining Fluorescence Microscopy and 3D Reconstruction to Investigate Neuron-Glia Interaction in Neurological Diseases” (online)
2. Dr. Kista Rantanen, 11/12/2024: “The Paradigm Shift from Normoxia to Physoxia in Biomedical Research” (online)
3. Prof. Jean-Luc Balligand, 16/01/25: “Tweaking the adrenergic system for cardiac protection” (presence)
4. Dr- Elisa Adani, 17/01/25: “Contributions of metabolic dysregulations to photoreceptor cell death in Retinal Degeneration” (online)
5. Bio-Rad Laboratories, 28/01/25: “Blot Smarter, Not Harder: Real world troubleshooting, New techniques and best practices” (online)
6. Prof. Martin Michel, 9/05/25: “What can we learn from failed drug development in the field of beta3-adrenoceptor agonists?” (presence)

CFU conseguiti per questa attività: 4 CFU

• Soft Skills:

1. English for Research Publication and Presentation Purposes (UNIP CL), from January to April 2025.

CFU conseguiti per questa attività: 10 CFU



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- **Congresses:**

1. 15/11/2024 "PISA MUSCLE AWARD 2024 - MUSCLE DISEASES: PHENOTYPES AND THERAPIES": Pisa, auditor.
2. 21-22/03/2025 "INTERNATIONAL MEETING PISA FOR ALS: Artificial Intelligence driving research and cure in ALS, SMA, and other Motor Neuron Diseases", Pisa, Poster: *"Early retinal dysfunctions as a biomarker in amyotrophic lateral sclerosis: insights from the SOD1^{G93A} mouse model."*
Lorenza Di Marsico, E. Daghini, R. Amato, A. Cannavale, A. Canovai, G. Neri, U. Borello, M.C. Gargini, M. Pistello, G. Siciliano, G. Casini, M. Cammalleri, M. Dal Monte
3. 21-23/05/2025 - 18th Annual Meeting of Young Researchers in Physiology (YRP2025), Catania, Oral presentation: *"Retinal alterations in amyotrophic lateral sclerosis: insights from the SOD1^{G93A} mouse model."*
Lorenza Di Marsico, E. Daghini, R. Amato, A. Cannavale, A. Canovai, G. Neri, U. Borello, M. Cammalleri, M. Dal Monte
4. 17-19/09/2025 75th Congress of the Italian Society of Physiology (SIF), Torino, Poster: *"Exploring early neurodegenerative phenomena in amyotrophic lateral sclerosis: insights from the SOD1^{G93A} mouse model."*
Lorenza Di Marsico, E. Daghini, R. Amato, A. Cannavale, A. Canovai, G. Neri, U. Borello, M. Cammalleri, M. Dal Monte
5. 5-7/10/2025 PNRR annual meeting "RNA-based innovative therapies for neurological disorders", Napoli, Poster: *"Early retinal degeneration in Amyotrophic lateral sclerosis: preclinical evidence from SOD1^{G93A} mouse model"*
Lorenza Di Marsico, E. Daghini, R. Amato, A. Cannavale, A. Canovai, G. Neri, U. Borello, M.C. Gargini, M. Cammalleri, M. Dal Monte
6. 09-11/10/2025 28th EVER Congress 2025, Firenze, Short oral presentation and poster: *"Early retinal involvement in amyotrophic lateral sclerosis: functional and molecular characterization in SOD1^{G93A} mice"*
Lorenza Di Marsico, E. Daghini, R. Amato, A. Cannavale, A. Canovai, G. Neri, U. Borello, M.C. Gargini, M. Cammalleri, M. Dal Monte

CFU conseguiti per questa attività: 5.5 CFU

- Eventuali soggiorni in altri laboratori italiani o esteri: NO



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Tabella Riepilogativa CFU **primo anno**

Didattica	Seminari Webinar	Soft Skills	Congressi	PhD Day	TOTALE I ANNO (Inclusi 35 CFU per la ricerca)
9 CFU	11 CFU	8 CFU	1 CFU	1 CFU	65 CFU

Tabella Riepilogativa CFU **secondo anno**

Didattica	Seminari Webinar	Soft Skills	Congressi	PhD Day	TOTALE II ANNO (Inclusi 35 CFU per la ricerca)
9 CFU	4 CFU	10 CFU	5.5 CFU	1 CFU	64.5 CFU