



**UNIVERSITÀ
DI SIENA**
1240

DIPARTIMENTO DI
**MEDICINA MOLECOLARE
E DELLO SVILUPPO**
— DMMS

Università degli Studi di Siena
Dottorato di Ricerca in Medicina Molecolare

Scheda Relazione Annuale Dottorando

Milan, 3th October 2025

Al Collegio Docenti del Dottorato in Medicina Molecolare

dott./dr.ssa **Renna Giorgia Maria**

ciclo **XXXIX** tutor **Ester Zito**

Attività scientifica svolta nel 2° anno di Dottorato, Anno Accademico **2024/2025**

Introduction:

RYR1- and SEPN1-related myopathies (RYR1-RM and SEPN1-RM) are classified as multi-minicore diseases and are associated with mutations in the RYR1 and SEPN1 genes, respectively. Affected patients present with a wide range of symptoms, including skeletal abnormalities as well as proximal and respiratory muscle weakness. Currently, there are no pharmacological treatments available for these conditions. This project focuses on investigating the role of endoplasmic reticulum (ER) stress and the mevalonate pathway as potentially druggable pathogenic mechanisms for the treatment of RYR1-RM and SEPN1-RM.

Methods:

These analyses were conducted using murine and patient-derived primary cells. I performed RT-PCR, immunofluorescence analysis, Western blotting of detergent-soluble and -insoluble protein fractions, cycloheximide (CHX) chase assays, and tetramethylrhodamine (TMRM) analysis.

Results:

Transcriptomic analysis of primary myotubes derived from RYR1^{I4895T/WT} mice revealed ER stress and dysregulation of the cell cycle, suggesting impaired differentiation. Immunofluorescence analysis of myosin heavy chain in these myotubes further confirmed this defect. Western blotting of detergent-soluble and -insoluble protein fractions showed upregulation of ERO1 and BiP, along with a reduction in RYR1 levels in RYR1^{I4895T/WT} primary myotubes. TMRM analysis demonstrated that mitochondrial activity decreased following treatment with the ER stress inducer thapsigargin, whereas ERO1 inhibition increased mitochondrial membrane potential. These results suggest that elevated ERO1 levels may disrupt calcium homeostasis and bioenergetics, contributing to myopathy progression.

In the context of SEPN1-RM, RT-PCR on patient-derived primary myotubes revealed ER stress and dysregulation of the mevalonate pathway. Cycloheximide (CHX) chase assays in SEPN1 knockdown myotubes showed that mevalonolactone treatment increases SEPN1 protein levels. Furthermore,



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TMRM analysis indicated that treatment with either mevalonolactone or tauroursodeoxycholic acid (TUDCA), an ER stress inhibitor, improves mitochondrial bioenergetics in SEPNI knockout primary myotubes.

Publications:

“Myotube-Specific Vulnerability to Clozapine”. Gloria Buffi, Mara Fiorani, Andrea Guidarelli, Nazanin Bagherlou, Andrea Spina, Lorenzo Scocchia, Giorgia Maria Renna, Ester Zito, and Orazio Cantoni. (submitted to Biomedicine and Pharmacotherapy);

“Structure–Activity relationship studies of pyrazolone-based ERO1 inhibitors and their therapeutic potential in ERO1A-upregulated diseases”. Michele Retini, Alessandro Cherubini, Alice Marrazza, Ersilia Varone, Serena Germani, Giorgia Maria Renna, Andrea Recchia, Andrea Guidarelli, Stefano Fumagalli, Chiara Grasselli, Michele Mari, Giovanni Piersanti, Giovanni Bottegoni, Roberto Tonelli, Marco Gobbi, Jaehyung Cho, Orazio Cantoni, Ester Zito. (submitted to Pharmacological Research);

PhD courses:

1. Pisa, Thursday, 10th April 2025;
2. Firenze, Friday, 11th April 2025;
3. Siena, Friday, 10th October 2025

Total CFU for PhD courses: **9 CFU**

Seminars:

1. “TSP-1 in the bone marrow microenvironment: a key player in breast cancer dormancy”- Elena Carlessi, Mario Negri Institute (Milan), 14/11/2024
2. “Impact of post-translational modifications of albumin on the organ crosstalk”- Joachin Jankowski, Mario Negri Institute (Milan), 05/12/2024;
3. “Reaching barriers for superior AAV brain gene therapy”- Vania Broccoli, Mario Negri Institute (Milan), 13/12/2025;
4. “Multifaced Organometallic Chemistry for Therapy and Imaging”- Angela Casini, Mario Negri Institute (Milan), 30/01/2025;
5. “How early-life insults shape adult behaviors: from the clinic to the lab and back”- Tallie Z. Baram, Mario Negri Institute (Milan), 19/03/2025;
6. “Bio-responsive Nanomaterials for Sensing Controlled Treatments”- Giorgia Giovannini, Mario Negri Institute (Milan), 14/03/2025;
7. “Treatment of mitochondrial aminoacyl-tRNA synthetases (mt-ARS) defects with specific aminoacids: a pilot study”- Alessia Catania, Mario Negri Institute (Milan), 14/04/2025;
8. “The RANKL cytokine maintains stemness features of skeletal stem and progenitor cells and supports the hematopoietic niche in the bone microenvironment”- Crisitina Sobacchi, Mario Negri Institute (Milan), 06/05/2025;
9. “Progress in 3D printing research and future applications in biomedical research”- Malgorzda Wlodarczyk-Biegun, Mario Negri Institute (Milan), 12/05/2025;



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10. “Planetary Health: una visione olistica per un futuro sostenibile”- Walter Ricciardi, Mario Negri Institute (Milan), 09/06/2025;

Total CFU for seminars: **10 CFU**

Soft Skills:

1. “Aprirsi al nuovo, senza timore. La strategia dell’UE per l’Intelligenza Artificiale- 13/03/2025;
2. “NetLogo course” -25/03/2025 and 01-08-15/04/2025
3. “Siamo ciò che mangiamo. La politica agricola comune: che cos’è e a cosa serve 20/03/2025;
4. “L’Unione Europea e la resilienza idrica”- 27/03/2025;
5. “L’Unione Europea e la sua difesa: lo stato dell’arte, gli obiettivi”- 03/04/2025;
6. “TLC-Soft Skills & Didattica”- 28/04/2025;
7. “Demystifying false myths around dyslexic minds”- 12/05/2025;
8. “International Perspective on Teaching and Learning Centre”- 21/05/2025;
9. “Europrogettazione”- 13-15/05/2025;
10. “OPEN SCIENCE, OPEN ACCES, OPEN EDUCATION”- 21/05/2025;
11. “Assessment design laboratory”- 28/05/2025;
12. “Anatomy of assessment”- 29/05/2025

Total CFU for soft skills: **8,5 CFU**

Congresses:

1. 10th PhD meeting-Mario Negri Institute (Milan), 09-10-11/06/2025. Poster: “***ER stress and mevalonate pathway: a possible target for the treatment of RYR1 and SEPNI-RM***”. *Giorgia Maria Renna, Serena Germani, Stefano Fumagalli, Luca Guarrera, Ester Zito*
2. FEBS-IUBMB-enable Conference. 4th International Molecular Biosciences PhD and Postdoc Conference. Poster: ***ER STRESS AND MEVALONATE PATHWAY: TWO POSSIBLE TARGETS FOR THE TREATMENT OF RYR1-IT AND SEPNI-RM***. *Giorgia Maria Renna, Serena Germani, Ersilia Varone, Stefano Fumagalli, Ester Zito*

Total CFU for Congresses: **2 CFU**

Anna accademico_ 2024/2025

Nome e Cognome: Giorgia Maria Renna

Numero di Matricola: 143974

Mese	Webinar - Seminari	Didattica	PhD Day / Graduation day	Congressi	Soft Skills
novembre	1	0	0	0	0
dicembre	2	0	0	0	0
gennaio	1	0	0	0	0
febbraio	0	0	1	0	0
marzo	2	0	0	0	1,25
apirle	1	6	0	0	1,25
maggio	2	0	0	0	4
giugno	1	0	0	1	2
luglio	0	0	0	0	0
agosto	0	0	0	0	0
settembre	0	0	0	1	0
ottobre	0	3	0	0	0
	Totale: 10	Totale: 9	Totale: 1	Totale: 2	Totale: 8,5

Anna accademico_ 2023/2024

Nome e Cognome: Giorgia Maria Renna

Numero di Matricola: 143974

Mese	Webinar - Seminari	Didattica	PhD Day / Graduation day	Congressi	Soft Skills
novembre	0		0	0	
dicembre	2		0	0	
gennaio	1		0	0	
febbraio	2	3	1	0	
marzo	1		0	0	
apirle	1	3	0	0	
maggio	1	3	0	1	2
giugno	1		0	1	2
luglio	1		0	0	0.5
agosto	0		0	0	
settembre	2		0	0	1
ottobre	0		0	0	0.5
	Totale: 12	Totale: 9	Totale: 1	Totale: 2	Totale: 6