DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO
40° Cycle

Project proposal for a PhD scholarship (with no financial support from Sapienza)

Title of the research: Characterization of pre-symptomatic phases in mouse models of Rett syndrome: potential new diagnostic tools and early pharmacological interventions

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Summary

The project aims to characterize the early stages of the neurobehavioral development and investigate early pharmacological interventions for Rett syndrome (RTT), a rare, monogenic disorder caused by sporadic mutations in the gene encoding the epigenetic factor methyl-CpG-binding protein 2 (MECP2). Females are primarily affected and acquire severe cognitive, social, motor and physiological impairments at toddlerhood. As the early stages of development appear normal, diagnosis usually occurs around two years of age, after the closure of multiple critical periods of brain development. The recent approval (March 2023) of the first-ever treatment for RTT makes early diagnosis the main forthcoming clinical challenge, to allow timely intervention. Given the urgency of improving the quality of life of girls with clear symptoms, only a few research groups have so far studied the mild alterations that are nonetheless already noticeable in the early stages of development. However, the complex nature of RTT, combined with the small number of patients, challenges the finding of consistent signs of pathogenesis that could be tailored for diagnosis acceleration.
This project aims to characterize in detail the postnatal stages of development in RTT mouse models to identify early molecular and behavioral alterations that may inform diagnosis acceleration and spot druggable targets, and to evaluate early interventions tailored at counteracting the pathogenic process leading to regression. The use of 4 distinct mouse lines carrying mutations commonly found in patients with RTT, together with state-of-the-art molecular and computational tools will allow us to draw robust and potentially generalizable conclusions about the role performed by MeCP2 in neurobehavioral development.

Pertinent Publications of the proponent (last 5 years)

1. Cosentino L, Vigli D, Franchi F, Laviola G, **De Filippis B** (2019). Rett syndrome

before regression: a time window of overlooked opportunities for diagnosis and intervention. *Neurosci Biobehav Rev. 2019* DOI: *10.1016/j.neubiorev.2019.05.013*
2. Zhang D, Bedogni F, Boterberg S, Camfield C, Camfield P, Charman T, Curfs L, Einspieler C, Esposito G, **De Filippis B**, Goin-Kochel RP, Höglinger GU, Holzinger D, Iosif AM, Lancioni GE, Landsberger N, Laviola G, Marco EM, Müller M, Neul JL, Nielsen-Saines K, Nordahl-Hansen A, O'Reilly MF, Ozonoff S, Poustka L, Roeyers H, Rankovic M, Sigafoos J, Tammimies K, Townend GS, Zwaigenbaum L, Zweckstetter M, Bölte S, Marschik PB (2019). Towards a consensus on developmental regression. *Neurosci Biobehav Rev.* 2019 DOI: 10.1016/j.neubiorev.2019.08.014.
3. Zuliani I, Urbinati C, Valenti D, Quattrini MC, Medici V, Cosentino L, Pietraforte D, Di Domenico F, Perluigi M, Vacca RA, **De Filippis B** (2020). The Anti-Diabetic Drug Metformin Rescues Aberrant Mitochondrial Activity and Restrains Oxidative Stress in a Female Mouse Model of Rett Syndrome*. J Clin Med*. 2020 DOI: 10.3390/jcm9061669. PMID: 32492904
4. Vigli D, Cosentino L, Pellas M, **De Filippis B** (2021). Chronic Treatment with Cannabidiolic Acid (CBDA) Reduces Thermal Pain Sensitivity in Male Mice and Rescues the Hyperalgesia in a Mouse Model of Rett Syndrome. *Neuroscience*. 2021;453:113-123. DOI: 10.1016/j.neuroscience.
5. Napoletani G, Vigli D, Cosentino L, Grieco M, Talamo MC, Lacivita E, Leopoldo M, Laviola G, Fuso A, d'Erme M, **De Filippis B** (2021)**.** Stimulation of the Serotonin Receptor 7 Restores Brain Histone H3 Acetylation and MeCP2 Corepressor Protein Levels in a Female Mouse Model of Rett Syndrome. *J Neuropathol Exp Neurol*. 2021;80(3):265-273. DOI: 10.1093/jnen/nlaa158.
6. Urbinati C, Cosentino L, Germinario EAP, Valenti D, Vigli D, Ricceri L, Laviola G, Fiorentini C, Vacca RA, Fabbri A, **De Filippis B** (2021). Treatment with the Bacterial Toxin CNF1 Selectively Rescues Cognitive and Brain Mitochondrial Deficits in a Female Mouse Model of Rett Syndrome Carrying a MeCP2-Null Mutation. Int J Mol Sci. 2021;22(13):6739. DOI: 10.3390/ijms22136739.
7. Fuchs C, Cosentino L, Urbinati C, Talamo MC, Medici G, Quattrini MC, Mottolese N, Pietraforte D, Fuso A, Ciani E, **De Filippis B** (2022). Treatment with FRAX486 rescues neurobehavioral and metabolic alterations in a female mouse model of CDKL5 deficiency disorder. CNS Neurosci Ther. 2022 ;28(11):1718-1732. DOI: 10.1111/cns.13907.
8. Urbinati C, Lanzillotta C, Cosentino L, Valenti D, Quattrini MC, Di Crescenzo L, Prestia F, Pietraforte D, Perluigi M, Di Domenico F, Vacca RA, **De Filippis B** (2023). Chronic treatment with the anti-diabetic drug metformin rescues impaired brain mitochondrial activity and selectively ameliorates defective cognitive flexibility in a female mouse model of Rett syndrome. Neuropharmacology. 2023; 224:109350. DOI: 10.1016/j.neuropharm.2022.109350.

REFERENCES

1. Chahrour M, Zoghbi HY. Neuron. 2007 Nov 8;56(3):422-37. doi: 10.1016/j.neuron.2007.10.001.
2. Ip JPK, et al. Nat Rev Neurosci. 2018 Jun;19(6):368-382. doi: 10.1038/s41583-018-0006-3.
3. Ricceri L, et al. Behav Pharmacol. 2008 Sep;19(5-6):501-17. doi: 10.1097/FBP.0b013e32830c3645.

4. Cosentino L, et alNeurosci Biobehav Rev. 2019 Dec;107:115-135. doi: 10.1016/j.neubiorev.2019.05.013.
5. De Filippis B et al. Genes Brain Behav. 2010 Mar 1;9(2):213-23. doi: 10.1111/j.1601-183X.2009.00551.x. Epub 2009 Nov 2.
6. Pino Lket al.. Mol Cell Proteomics. 2020 Jul;19(7):1088-1103. doi: 10.1074/mcp.P119.001913. Epub 2020 Apr 20.
7. Gupta C, et al. J Neurodev Disord. 2022 May 2;14(1):28. doi: 10.1186/s11689-022-09438-w.
8. De Filippis et al. Neuropharmacology. 2013 May;68:174-83. doi: 10.1016/j.neuropharm.2012.05.048.