***DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO***

**XXXIX 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

**Supervisor:**

Bianca De Filippis,

Centro di Riferimento per le Scienze comportamentali e la Salute mentale,

Istituto Superiore di Sanità

Email: bianca.defilippis@iss.it

**Tutor:**

Prof. M. Egle De Stefano, egle.destefano@uniroma1.it

**Host Institution:**

Istituto Superiore di Sanità

**Summary**

The project aims to characterize the early stages of the neurobehavioral development of mouse models of Rett syndrome (RTT), a rare genetic disorder occurring in early childhood and predominantly affecting females, which is characterized by a progressive loss of both the intellectual abilities and motor skills previously acquired. Diagnosis usually occurs around two and a half years of age, as the early stages of development appear normal and the mutations responsible for the disorder are sporadic. Given the lack of a resolutive therapy and the urgency of improving the quality of life of patients, most of the preclinical studies conducted to date have been performed in mouse models in an advanced stage of the disease, when symptoms are fully evident. Although still not much explored, the early stages of development are characterized by slight behavioral alterations that, if identified in time, could be useful for a prompt diagnosis and for an early intervention with targeted therapies. The complex nature of RTT, combined with the small number of patients, makes difficult to investigate the pathogenesis of the disease, and to identify effective therapies. To date, there is no cure for the RTT. Furthermore, given the need to find therapies for girls with clear symptoms, only a few research groups have so far studied the mild metabolic and behavioral alterations that are nonetheless already measurable in the early stages of life. This project aims to characterize in detail the pre- and post-natal stages of Rett model mice, carriers of mutations on the Mecp2 gene, to identify early molecular and behavioral alterations that may be exploited to accelerate the development of tools for the diagnosis and early treatment of patients. This project will also allow us to draw robust and potentially generalizable conclusions about the role performed by MeCP2 in neurobehavioral development, as it will be conducted using 4 models murine carriers of mutations on the Mecp2 gene commonly found in RTT patients.

**Pertinent Publications of the proponent (last 5 years)**

1. Vigli D., Rusconi L., Valenti D., La Montanara P., Cosentino L., Lacivita E., Leopoldo M., Amendola E., Gross C., Landsberger N., Laviola G., Kilstrup-Nielsen C., Vacca R.A., **De Filippis B.** (2018). Rescue of prepulse inhibition deficit and brain mitochondrial dysfunction by pharmacological stimulation of the central serotonin receptor 7 in a mouse model of CDKL5 Deficiency Disorder. *Neuropharmacology*. 18, 30802-5. DOI: 10.1016/j.neuropharm.2018.10.018
2. Vigli D., Cosentino L., Raggi C., Laviola G., Woolley-Roberts M., **De Filippis B.** (2018). Chronic treatment with the phytocannabinoid Cannabidivarin (CBDV) rescues behavioural alterations and brain atrophy in a mouse model of Rett syndrome. *Neuropharmacology*. 140,121-129. DOI: 10.1016/j.neuropharm.2018.07.029
3. 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*
4. 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.
5. 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
6. 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.
7. 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.
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.
9. 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.
10. 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.
11. 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 brainitochondrial activity and selectively ameliorates defective cognitive flexibility in a female mouse model of Rett syndrome.](https://pubmed.ncbi.nlm.nih.gov/36442649/) Neuropharmacology. 2023;224:109350. DOI: 10.1016/j.neuropharm.2022.109350.