

DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

Proposta di progetto per una borsa Dottorato Sapienza

Titolo della ricerca: "The complex link in neuromuscular disorders: from muscles to the nervous system and *vice versa*"

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Summary (max 300 parole)

Duchenne muscular dystrophy (DMD) is a severe x-linked myodegenerative disease caused by defective expression of the full-length dystrophin (Dp427), a large cortical cytoskeletal protein. A few studies from our laboratory described significant retrograde effects of muscle degeneration on peripheral autonomic innervation, as well as a direct impact of the lack of dystrophin on axonal dynamics *in vivo* and *in vitro* (1-3). However, little or none has been reported on the specific outcome that this disease has on motor neurons (MNs) innervating limb muscles (among the most severely affected) and on the crosstalk that their axons establish with Schwann cells (SCs), neither in DMD patients nor in animal models (e.g. *mdx* mice). This aspect is of particular importance as the impact that lack of Dp427 and other dystrophins on the nervous system begins during embryonic development, in some respect framing DMD among neurodevelopmental diseases.

The main goal of this project is to analyze the biomolecular mechanisms and intracellular pathways that are potentially altered in MNs and peripheral nerves in severe muscular pathologies, as the DMD. Particular attention will be paid to the repercussions that neuromuscular alterations have on intraspinal MN connectivity (i.e., sensory inputs, interneurons), axon growth, myelination, and regenerative capacities. The effects that potential epigenetic therapies (4,5) might have on some of these aspects will be also analyzed. The study will be conducted on the *mdx* mouse, a well-known experimental model of DMD, and their wild type.

Pertinent Publications of the proponent (last 5 years)

1. Cuenca-Bermejo L, Pizzichini E, **De Stefano ME**, Fernandez-Villalba EF, Herrero M-T (2020) *Octodon degus*: a natural model of multimorbidity for ageing research. *Aging Res Rev* (in press) **ISSN**: 1568-1637; **doi**: 10.1016/j.arr.2020.101204; **IF 2020**: 10.616; **5-year IF**: 10.401
2. Briatore F, Pregno G, Di Angelantonio S, Frola E, **De Stefano ME**, Vaillend C, Sassoè-Pognetto M, Patrizi A (2020) Dystroglycan mediates clustering of essential GABAergic components in cerebellar Purkinje cells. *Front Mol Neurosci* **13**: 164; **ISSN**: 1662-5099; **doi**: 10.3389/fnmol.2020.00164; **IF 2020**: 4.057
3. Persiconi I, Cosmi F, Guadagno NA, Lupo G **De Stefano ME** (2020) Dystrophin is required for the proper timing in retinal histogenesis: a thorough investigation on the *mdx* mouse model of Duchenne Muscular Dystrophy. *Front Neurosci* **14**: 760; **ISSN**: 1662-453X; **doi**: 10.3389/fnins.2020.00760; **IF 2020**: 3.707
4. Soligo M, Protto V, Chiaretti A, Piccinin S, **De Stefano ME**, Nisticò R, Bracci-Laudiero L, Manni L (2020) Effects of intranasally-delivered pro-nerve growth factors on the septohippocampal system in healthy and diabetic rats. *Neuropharmacology* **176**: 108223. **ISSN**: 0028-3908; **doi**: <https://doi.org/10.1016/j.neuropharm.2020.108223>; **IF 2018**: 4.36; **5-year IF**: 4.49
5. De Rosa A, Mastrostefano F, Di Maio A, Nuzzo T, Satoh Y, Napolitano F, Katane M, Isidori A, Caputo

- V, Falco G, Marotta P, **De Stefano ME**, Homma H, Usiello A, Errico F (2020) Prenatal expression of D-aspartate oxidase causes early cerebral D-aspartate depletion and influences brain morphology and cognitive functions at adulthood. *AminoAcids* **52**: 597-617. **ISSN**: 0939-4451; **doi**: <https://doi.org/10.1007/s00726-020-02839-y>; **IF 2018**: 2.52; **5-year IF**: 3.01
6. Fragapane P, Cosmi F, **De Stefano ME** (2020) Cultured hippocampal neurons of dystrophic mdx mice respond differently from those of wild type mice to an acute treatment with corticosterone. *Exp Cell Res* **386**: 111715. **doi**: 10.1016/j.yexcr.2019.111715. **IF 2018**: 3.329; **5-year IF 2018**: 3.317
 7. Protto V, Soligo M, **De Stefano ME**, Farioli-Vecchioli S, Marlier L, Nisticò R, Manni L (2019) Electroacupuncture in rats normalizes the diabetes-induced alterations in the septo-hippocampal cholinergic system. *Hippocampus* **29**, 891-904. **ISSN**: 1098-1063; **doi**: <https://doi.org/10.1002/hippo.23088>. **IF 2018**: 3.267; **5-year IF 2018**: 3.882
 8. Trobiani L, Favaloro FL, Di Castro MA, Di Mattia M, Cariello M, Miranda E, Canterini S, **De Stefano ME**, Comoletti D, Limatola C, De Jaco A (2018) UPR activation specifically modulates glutamate neurotransmission in the cerebellum of a mouse model of autism. *Neurobiol Dis* **120**:139-150. **ISSN**: 0969-9961; **doi**: <https://doi.org/10.1016/j.nbd.2018.08.026>. **IF**: 5.160; **5-year IF**: 5.304
 9. Soligo M, Piccinin S, Protto V, Gelfo F, **De Stefano ME**, Florenzano F, Berretta E, Petrosini L, Nisticò R, Manni L (2017) Electroacupuncture treatment in early diabetic rats improves important hippocampal physiological processes by regulating muscarinic receptor activity *Sci Rep* **7**:9077. **ISSN**: 2045-2322; **doi**: 10.1038/s41598-017-08556-z **IF**: 4.122; **5-year IF**: 4.609
 10. Canterini S, Dragotto J, Dardis A, Zampieri S, **De Stefano ME**, Battisti C, Mangia F, Erickson RP, Fiorenza MT (2017) Shortened primary cilia length and dysregulated Sonic hedgehog signalling in Niemann-Pick C1 disease. *Hum Mol Gen* **26**:2277-2289. **ISSN**: 0964-6906; **doi**: 10.1093/hmg/ddx118. **IF**: 4.902; **5-year IF**: 5.572
 11. Reggente M, Passeri D, Angeloni L, Scaramuzza FA, Barteri M, De Angelis F, Persiconi I, **De Stefano ME**, Rossi M (2017) Detection of stiff nanoparticles within cellular structures by contact resonance atomic force microscopy subsurface nanomechanical imaging. *Nanoscale* **9**:5671-5676. **ISSN**: 2040-3364; **doi**: 10.1039/c7nr01111c. **IF**: 7.233; **5-year IF**: 7.713;
 12. Lombardi L, Persiconi I, Gallo A, Hoogenraad CC, **De Stefano ME** (2017) NGF- dependent axon growth and regeneration are altered in sympathetic neurons of dystrophic mdx mice. *Mol Cell Neurosci*, **80**:1-17. **ISSN**: 1044-7431; **doi**: 10.1016/j.mcn.2017.01.006. **IF**: 3.312; **5-year IF**: 3.552
 13. **De Stefano ME** , Herrero MT (2017) The multifaceted role of metalloproteinases in physiological and pathological conditions in embryonic and adult brains. *Progr Neurobiol* **155**:36-56, **ISSN**: 0301-0082, **doi**: 10.1016/j.neurobio.2016.08.002. **IF**: 14.163; **5-year IF**: 13.530

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