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: Primary astrocyte dysfunction in the pathogenesis of the MLC leukodystrophy: searching for shared pathological mechanisms of myelin degeneration in astrocytopathies

Supervisor: Dott.ssa Angela Lanciotti (angela.lanciotti@iss.it; Dipartimento di Neuroscienze, Istituto Superiore di Sanità, Viale Regina Elena, 299 - 00161 Roma)

Tutor: Prof.ssa Adamaria Tata, adamaria.tata@uniroma1.it

Host Institution: Istituto Superiore di Sanità, Department of Neuroscienze

Summary

Leukodystrophies (LD) are rare devastating genetic disorders causing myelin disruption in the central nervous system. Some LD are primarily due to gene mutations affecting the function of astrocytes, the main regulators of CNS homeostasis. The so called "astrocytopathies" revealed that functional astrocytes are required for myelin integrity, but the molecular mechanisms of myelin degeneration are still elusive. Among these, megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a LD characterized by macrocephaly, brain cysts, edema, motor/cognitive decline and epilepsy mainly due to mutations in the astrocytic protein MLC1.

MLC is incurable but the clinical improvement observed in some patients suggests that the pathological process can be reversed and that rescuing MLC functions might arrest disease progression.

By an integrated experimental approach combining astrocytes derived from control/MLC patient iPSC, cell co-cultures, electrophysiology, imaging and proteomic analysis, the present project aim to: 1) unravel molecular pathways/biological processes altered in MLC and 2) test potential drugs to correct astrocyte defects.

Preliminary studies revealed that MLC patient-astrocytes activate stress signaling, as seen in other astrocytopathies, suggesting common molecular bases of astrocyte-mediated myelin damage whose understanding is mandatory for therapy development.

REFERENCES

1) Verkhratsky A et al. Adv Exp Med Biol. 2019,1175:149-179
2) Jorge MS, Bugiani M Adv Exp Med Biol. 2019,1175:199-225
3) van der Knaap MS et al. Ann Neurol. 1995,37:324-34
4) Ambrosini E et al. Mol Cell Neurosci. 2008 37(3):480-93
5) van der Knaap MS et al. Lancet Neurol. 2012 11(11):973-85
6) Bosch A, Estévez R. Front Cell Neurosci. 2021 14:627887.
7) Lanciotti A et al. Human Molecular Genetics. 2016,25:1543-155
8) Elorza-Vidal X et al. Neurobiol Dis. 2018,119:88-99
9) Brignone MS et al. Mol Neurobiol. 56(12):8237-8254
10) Lanciotti A et al. IJMS. 2021. 23 (1), 274.
11) Mohanty V et al. OMICS. 2019, 23(2):98-110

12) Hamann S et al. Journal of Fluorescence 2002.Vol.12,N.2, 139¿145
13) Awadova T et al. J Neurosci Methods 2018 1;306:38-44
14) Sforna L et al.J Cell Physiol. 2022. 237(3):1857-1870
15) Aldana IB et al. Mol Brain. 2020. 14;13(1):125
16) Bernardo A et al. Int J Mol Sci. 2021. 30;22(17):9434
17) Olla S et al. Pharmaceutics. 2021. 2;13(12):2064
18) Eleuteri C et al. Sci Rep. 2017. 7;7:45780
19) Martorana F et al., Oxid Med Cell Longev. 2019,8056904
20) Petrini S et al.,Mol Cell Neurosci. 2013, 56:307-21

Pertinent Publications of the proponent (last 5 years):

1) Brignone MS, Lanciotti A, Molinari P, Mallozzi C, De Nuccio C, Caprini ES, Petrucci TC, Visentin S, Ambrosini E. Megalencephalic leukoencephalopathy with subcortical cysts protein-1: A new calcium-sensitive protein functionally activated by endoplasmic reticulum calcium release and calmodulin binding in astrocytes. Neurobiol Dis. 2024 Jan;190:106388. doi: 10.1016/j.nbd.2023.106388. Epub 2023 Dec 22. PMID: 38141856

2) Brignone MS, Lanciotti A, Michelucci A, Mallozzi C, Camerini S, Catacuzzeno L, Sforna L, Caramia M, D'Adamo MC, Ceccarini M, Molinari P, Macioce P, Macchia G, Petrucci TC, Pessia M, Visentin S, Ambrosini E. The CaMKII/MLC1 Axis Confers Ca2+-Dependence to Volume-Regulated Anion Channels (VRAC) in Astrocytes. Cells. 2022 Aug 26;11(17):2656. doi: 10.3390/cells11172656. PMID: 36078064 Free PMC article.

3) Lanciotti A, Brignone MS, Macioce P, Visentin S, Ambrosini E. Human iPSC-Derived Astrocytes: A Powerful Tool to Study Primary Astrocyte Dysfunction in the Pathogenesis of Rare Leukodystrophies. Int J Mol Sci. 2021 Dec 27;23(1):274. doi: 10.3390/ijms23010274. PMID: 35008700 Free PMC article. Review.

4) Lanciotti A, Brignone MS, Belfiore M, Columba-Cabezas S, Mallozzi C, Vincentini O, Molinari P, Petrucci TC, Visentin S, Ambrosini E.Megalencephalic Leukoencephalopathy with Subcortical Cysts Disease-Linked MLC1 Protein Favors Gap-Junction Intercellular Communication by Regulating Connexin 43 Trafficking in Astrocytes. Cells. 2020 Jun 8;9(6):1425. doi: 10.3390/cells9061425. PMID: 32521795 Free PMC article.

5) Brignone MS, Lanciotti A, Serafini B, Mallozzi C, Sbriccoli M, Veroni C, Molinari P, Elorza-Vidal X, Petrucci TC, Estévez R, Ambrosini E.Megalencephalic Leukoencephalopathy with Subcortical Cysts Protein-1 (MLC1) Counteracts Astrocyte Activation in Response to Inflammatory Signals. Mol Neurobiol. 2019 Dec;56(12):8237-8254. doi: 10.1007/s12035-019-01657-y. Epub 2019 Jun 17. PMID: 31209783