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## MENINGES AS AN OVERLOOKED PHARMACOLOGICAL TARGET FOR GLOBOID CELL LEUKODYSTROPHY

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Globoid cell Leukodystrophy Disease (GLD) is an autosomal recessive disease caused by genetic defects in the lysosomal enzyme galactosylceramidase (GALC). It is a severe neurodegenerative life-threatening disease that manifests early in life (3 months to 6 years) with rapid progression (within 2 years). There is no cure for GLD.
Treatment options are still very poor. Enzyme reconstitution by protein or gene therapy (GT) provides variable results. However, early onset GLD remains a devastating disease with poor prognosis.
In this Telethon Project, we will consider GLD pathogenesis and therapy from an entirely new angle. We will study GLD neurodegeneration and therapy by changing the focus from the neurons and oligodendrocytes to the non-parenchymal brain cells. In particular, we will study the involvement of meninges in GLD pathogenesis and progression. Meninges are highly heterogeneous tissue with trophic, immune and neurogenic properties. Meninges are: - widely distributed into the brain; - a gateway for immune cell access into the CNS and - important source of trophic factors for the brain. Recently, we have identified neural progenitor cell (NPC) population in meninges that migrate to the cortex and differentiate into functional and integrated cortical neurons
(Bifari et al Cell Stem Cell 2017).
In this project, we will assess GLD-induced activation of meninges and meningeal NPCs. We will exploit meninges as effective complementary site for GALC gene transfer in GLD. Transduced meningeal cells may provide GALC secretion to the brain (cross-correction) and GALC-transduced meningeal NPCs can migrate to the brain and differentiate into GALC-overexpressing cortical neurons. Furthermore, we can culture, from adult human meninges, NPCs with neuronal differentiation potential. We will perform proof of concept of efficacy and safety of supra-physiological GALC expression in somatic, human meningeal NPCs (as potential therapeutic target for meningeal-directed in vivo GT).

La Malattia di Krebbe è una malattia genetica estremamente grave ed invalidante causata dall'assenza del gene GALC, che provoca la degenerazione delle cellule neurali del cervello. Attualmente, i tentativi di ripristinare i livelli dell'espressione di questo gene mancante non sono totalmente efficaci.

In questo progetto Telethon, il Dott. Francesco Bifari, responsabile del progetto del Dipartimento di Biotecnologie Mediche e Medicina Traslazionale (BIOMETRA) insieme alla Dott.ssa Angela Gritti, direttrice dell'Unità di Gene Therapy per la Leucodistrofia dell'ospedale San Raffaele, SR-Tiget e al neurochirurgo Dott. Marco Riva, BIOMETRA, propongono di valutare la Malattia di Krebbe da un nuovo punto di vista.
Valuteranno l'efficacia della correzione genica delle cellule che formano le meningi (membrane che avvolgono l'encefalo). Queste diventeranno quindi bioreattori capaci di esprimere il gene GALC e produrre la proteina che viene distribuita alle cellule neurali tramite il flusso di liquor che bagna e nutre

il cervello.

1. Wenger DA, Rafi MA, Luzi P: Molecular genetics of Krabbe disease (globoid cell leukodystrophy): diagnostic and clinical implications. Hum Mutat 1997, 10(4):268-279.
2. Lattanzi A, Neri M, Maderna C, di Girolamo I, Martino S, Orlacchio A, Amendola M, Naldini L, Gritti A: Widespread enzymatic correction of CNS tissues by a single intracerebral injection of therapeutic lentiviral vector in leukodystrophy mouse models. Hum Mol Genet 2010, 19(11):2208-2227.
3. Bifari F, Decimo I, et al: Neurogenic Radial Glia-like Cells in Meninges Migrate and Differentiate into Functionally Integrated Neurons in the Neonatal Cortex. Cell Stem Cell 2017, 20(3):360-373 e367.
4. Pino A, Fumagalli G, Bifari F, Decimo I: New neurons in adult brain: distribution, molecular mechanisms and therapies. Biochem Pharmacol 2017, 141:4-22.
5. Iliff JJ, et al: A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. Sci Transl Med 2012, 4(147):147ra111.
6. Sessa M, et al: Lentiviral haemopoietic stem-cell gene therapy in early-onset metachromatic leukodystrophy: an ad-hoc analysis of a non-randomised, open-label, phase 1/2 trial. Lancet 2016, 388(10043):476-487.

Malattia di Krebbe

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Partners: Angela Gritti, Marco Riva
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