Neuropharmacology of NGF and proNGF

The pharmacology of nerve growth factor (NGF) has developed since the 1990s (Aloe et al, 2012). Clinical trials supported by solid pre-clinical foundations have been conducted to validate the use of NGF in peripheral neuropathies, Alzheimer's disease, re-epithelialization dysfunctions, retinal degeneration and, lately, in the treatment of the outcomes of severe neurotrauma. (Aloe et al, 2012; Chiaretti et al, 2017). To date, there is only one human recombinant NGF-based drug, produced with a eukaryotic expression system, registered and used for the treatment of neurotrophic ulcers of the cornea (Oxervate, Dompè Farmaceutici).

For more than two decades we have been dealing with the physiology and pathophysiology of NGF and its precursor proNGF, using models of neurodegenerative and neurotraumatic diseases in basic and preclinical studies. Since 2012, we have participated, as producers of the experimental drug, in clinical trials in which the efficacy of NGF, administered topically on the ocular surface, was evaluated in countering the effects of gliomas of the optic pathways (EudraCT Number: 2008 -001438-29; Falsini et al, 2017), and that of NGF, administered intranasally to the brain parenchyma, in reducing the devastating outcomes of severe neurotrauma (Chiaretti et al, 2017). For the latter application, a clinical trial has just been launched (EudraCT Nr. 2019-002282-35), in which we participate by collaborating with the Institute of Pediatrics and Pediatric Intensive Care at the Policlinico Gemelli and with the company Dompè Farmaceutici. As part of the same research project (funded by the Ministry of Health, RF-2018-12366594) we independently develop the preclinical component, using animal models of brain trauma and hypoxia. On these, we evaluate the effect of pharmacological treatments with NGF and with different mutated variants of proNGF, studying behavioral correlates, histopathological parameters, and identifying new biomarkers of neurodegeneration, neuroinflammation and neo-vascularization.

The recent development of our basic and preclinical research has led us to focus attention on the poorly characterized variant of the precursor of NGF, called proNGF-A. We have built a specific qPCR assay to discriminate the proNGF-A and proNGF-B sliping variants, with diagnostic and prognostic value in neurological diseases. Using this tool, we have identified the existence of the proNGF-A variant in human tissues, depositing the original sequence in GenBank (MH358394.1). We have therefore described for the first time the neurotrophic and neuroprotective effect of proNGF-A, associated with a relevant resistance to degradation by tissue proteases and a potentially advantageous safety profile compared to that of NGF (Patent Nr. 102018000003279. PCT / IB2019 / 051753) (Soligo et al, 2019; Soligo et al, 2020a). We have therefore designed and built, with a bio-computational approach, mutated variants of proNGF-A, which allow its production through eukaryotic expression systems (Patent application Nr. 02019000014646. European patent application Nr. EP20190214.5. US patent application Nr. 16/991517) (Soligo et al, 2020b).

The filing of the aforementioned patent applications also prompted us to undertake a path to enhance intellectual property through the start-up project ProNeuro, a spin-off of the CNR in which we collaborate with researchers from the Institute for Applied Mathematics (IAC-CNR) (third classified at Start-Cup Lazio 2019, participation in PNI 2019) and which we currently present on the web platforms Knowledge Share (https://www.knowledge-share.eu/brevetto/peptide-neurotropico-per-neurodegenerative-and-inflammatory-pathologies/ ) and Promo-TT (https://scouting.prom ott.cnr.it/#/entity/tecnologia/1162 ).
References:

Keywords: Nerve Growth Factor, Traumatic Brain Injury, Clinical Trials.

Contacts:
Luigi Manni  ORCID ID: 0000-0001-7844-6836  luigi.manni@ift.cnr.it
Marzia Soligo  ORCID ID: 0000-0002-1420-0914  marzia.soligo@ift.cnr.it

Funding: