



Painless NGF: testing the rescue of Rett syndrome neuronal degeneration through its actions on microglia

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Scientific Abstract:

The aim of this project is to test the hypothesis that painless human Nerve Growth factor (hNGFp), the neuroprotective therapeutic candidate we are currently developing for various clinical indications, might rescue Rett Syndrome (RTT) neurodegeneration, thanks to its actions on microglia.

In the past, NGF has been linked to RTT because of the reduced levels observed in brain and blood of patients. This reduction of NGF, a well-established neurotrophic factor for cholinergic neurons, can be linked to the cholinergic hypofunction observed in RTT. Despite this promising potential, the clinical application of NGF in RTT, as well as in other neurological diseases, has been hampered by the fact that NGF cannot cross the blood brain barrier and has a strong pro-nociceptive activity. This has limited not only the clinical application of this neurotrophin, but also its testing in RTT mouse models.

To overcome these limits, we have developed over the past years a two tier approach: (1) we developed hNGFp, a variant of NGF with a tenfold reduced pain-sensitizing activity; (2) we demonstrated that NGF and hNGFp can be effectively delivered to the brain using an intranasal route of administration.

In a previous study, and in subsequent work, we demonstrated that a widespread biodistribution of intranasally delivered hNGFp is necessary to obtain the full rescue of the neurodegenerative phenotype in a mouse model for Alzheimer's disease. In that study, we showed that the neuroprotective action of hNGFp does not involve a mere action on cholinergic neurons but it necessarily implies a new neuroprotective mechanism by acting on astrocytes and microglia. Thus, we showed that cellular targets of hNGFp in the brain are glial cells, in addition to basal forebrain cholinergic neurons. Indeed, the non-invasive intranasal delivery of hNGFp, facilitating its access to the CNS and minimizing its systemic biodistribution, shows broad anti-neurodegenerative effects in two mouse models of Alzheimer's disease, through a mechanism that involves microglia, modulation of TNF α and CXCL12. hNGFp acts on microglia to decrease the bioavailability of TNF α (Capsoni et al., Brain 2017). Moreover, in a second study we showed that NGF reduces the pro-

inflammatory status of beta amyloid-treated microglia, thereby protecting neurons from the microglia-dependent pruning of its synapses (Rizzi et al., *Glia* 2018). This is particularly relevant for RTT, since it has been recently suggested that in *Mecp2* null mice the conditioned medium from microglia decreases neuronal branching and the number of synapses. Thus, painless NGF has broad neuroprotective and anti-inflammatory actions in the brain that justify its testing in RTT.

Here we propose to test the efficacy of hNGFp on *Mecp2* null mice, by verifying its effects on neurodegeneration and behaviour.