

# Neurology and Therapeutics

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## Repurposing the NRF2 activator dimethyl fumarate as therapy against synucleinopathy in Parkinson's disease

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This preclinical study was aimed at determining if pharmacological targeting of transcription factor NRF2 might provide a disease modifying therapy in the animal model of Parkinson's disease (PD) that best reproduces the main hallmark of this pathology, i.e.  $\alpha$ -synucleinopathy, and associated events including nigral dopaminergic cell death, oxidative stress and neuroinflammation. Pharmacological activation of NRF2 was at the basal ganglia by repurposing dimethyl fumarate (DMF), a drug already in use for the treatment of multiple sclerosis, leading to up-regulation of a battery of cytoprotective genes. Daily oral gavage of DMF protected nigral dopaminergic neurons against  $\alpha$ -SYN toxicity and decreased astrocytosis and microgliosis after 1, 3 and 8 weeks from stereotaxic delivery to the ventral midbrain of recombinant adeno-associated viral vector expressing human  $\alpha$ -synuclein. This protective effect was not observed in *Nrf2*-knockout mice. *In vitro* studies indicated that this neuroprotective effect was correlated with altered regulation of autophagy markers p62, LC3 and LAMP2 in MN9D, BV2 and IMA 2.1 and with a shift in microglial dynamics towards a less pro-inflammatory and more wound-healing phenotype. In postmortem samples of PD patients, the cytoprotective proteins associated with NRF2 expression, NQO1 and SQSTM1/p62, were partly sequestered in Lewy bodies, suggesting impaired neuroprotective capacity of the NRF2 signature. These experiments provide a compelling rationale for targeting NRF2 with DMF as a therapeutic strategy to reinforce endogenous brain defense mechanisms against PD-associated synucleinopathy.

### Biography

Isabel Lastres-Becker is Associate Professor at the Autonomous University of Madrid, Spain. Her main focus is to uncover the molecular basis of neurodegenerative disorders like Parkinson and Alzheimer's disease, to try to find a therapeutic target to develop a cure

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