

Vidofludimus Calcium Shows Potential Neuroprotective Effects in an In Vivo Multiple Sclerosis Model by Nurr1 Modulation

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Conflicts of Interest

Authors:

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Conflicts of interest:

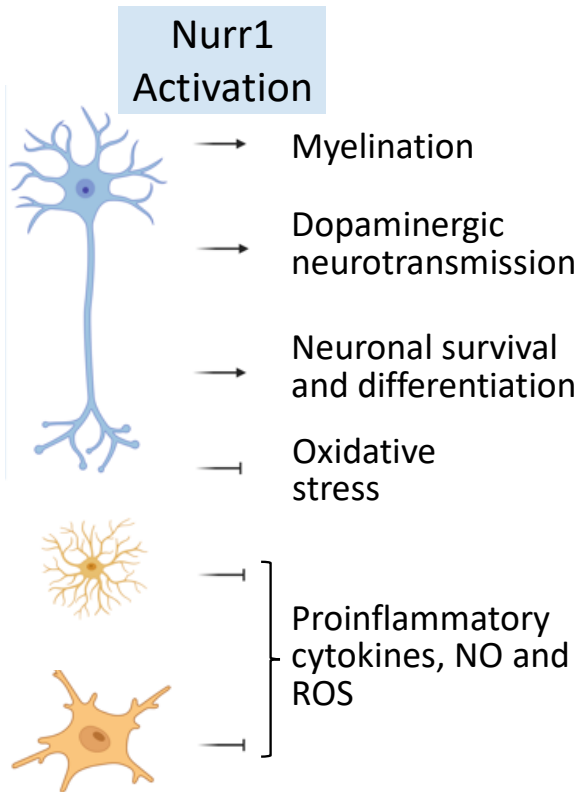
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- E.P., A.H., T.W., M.J., C.G., and H.K. are employees of Immunic AG, holding shares and/or stock options of the parent company, Immunic, Inc.
- A.M. is an employee of Immunic AG and Immunic Inc. and is a shareholders of Immunic Inc.
- D.V. is an employee of Immunic Inc. and is shareholder of Immunic Inc.
- E.P., C.G. A.M., D.V., and H.K. are inventors on a patent application covering the topic.
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Nurr1, a Transcription Factor, as a Potential Target to Address Neurodegeneration in Multiple Sclerosis



Nurr1 is Involved in Neuroprotection



Role of Nurr1 in MS Patients

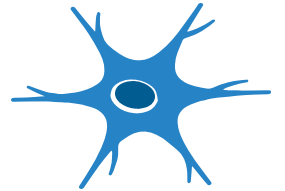
- In untreated relapsing remitting MS, Nurr1 was significantly downregulated compared to healthy controls.^[4]
- Nurr1 gene expression level negatively correlates with clinical parameters of MS, e.g., relapse rate and EDSS.^[5]
- In brain tissue from people with progressive MS, higher levels of Nurr1 are associated with less nerve loss.^[6]



VidoCa has a Dual Mode of Action

Nurr1 Activator^[1]

- Direct and indirect neuroprotective effects

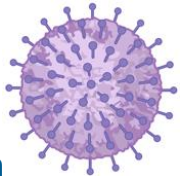


DHODH Inhibitor

- Selectively targets hyperactive immune cells
- Broad-spectrum antiviral effects prevent EBV reactivation



Blocking of Th17/Th1 cytokines



[1] Vietor et al., 2023, J Med Chem; [2] Schiro et al., 2022, Front. Neurol.; adapted from [3] Willems, Merk, 2022, J Med Chem.; illustrations created in BioRender.com. [4] Gilli et al., 2010, PLoS ONE; [5] Gilli et al., 2011, Arch. Neurol.; [6] Pansieri et al., 2023, Brain Commun.; DHODH = dihydroorotate dehydrogenase; EAE = experimental autoimmune encephalomyelitis; EBV = Epstein-Barr virus; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; Nurr1 = nuclear receptor-related 1; NO = nitric oxide; ROS = reactive oxygen species; VidoCa = vidofludimus calcium

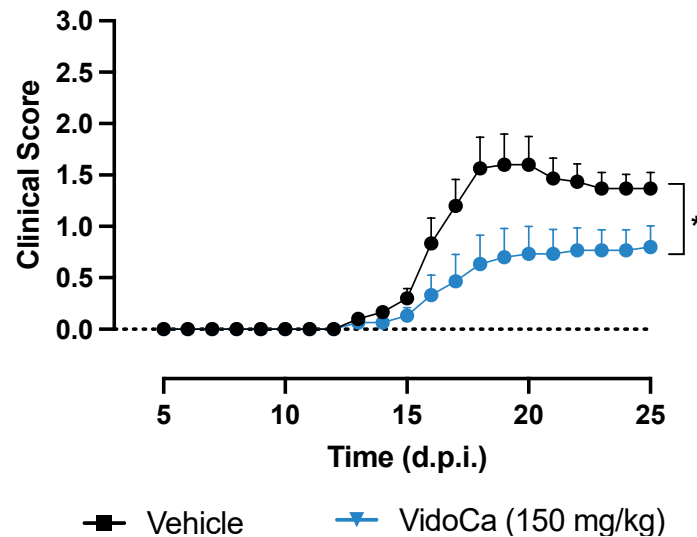
Vidofludimus Calcium Demonstrated Activity in a Prophylactic Murine EAE Model



VidoCa Reduces EAE Disease Severity^[1]

VidoCa treatment reduces:

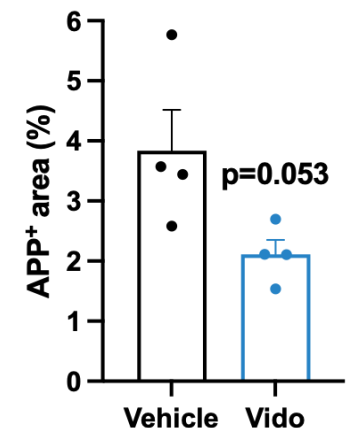
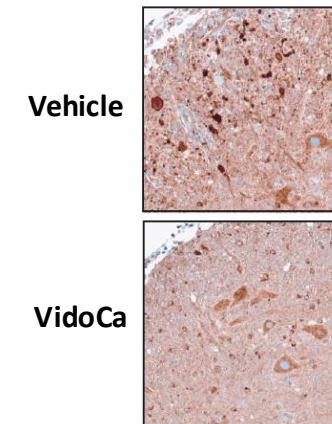
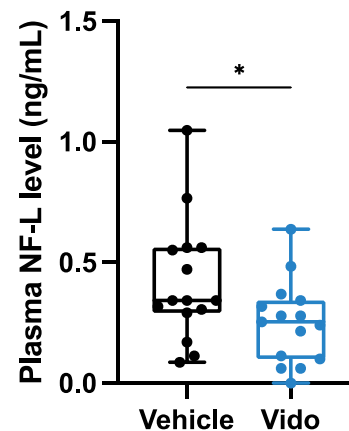
- disease severity,
- immune cell infiltration



VidoCa Reduces Axonal Injury *In Vivo* and *In Vitro* and Increases Neuronal Survival *In Vitro*^[1,2,3]

In vivo VidoCa treatment reduces:

- NfL plasma levels^[1] and
- axonal injury^[3]



In vitro, in a murine neuronal cell line (N2A) undergoing apoptosis, VidoCa reduces^[2]:

- NfL levels in supernatant and
- neuronal apoptosis

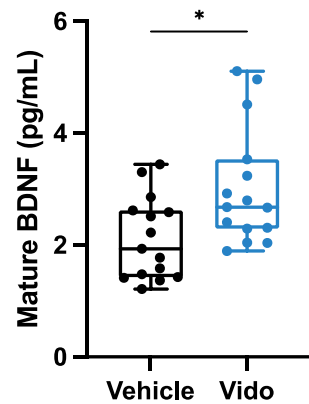
Data generated by Prof. Sun, City of Hope, unpublished; [1, 3] EAE was induced with MOG₃₅₋₅₅. Daily treatment per oral gavage was started 5 d.p.i. with vehicle (PEG400) or vidofludimus calcium (150 mg/kg). [1] n = 15 mice per group; [2] N2A cells were challenged with TNFα (50 ng/ml) and CHX (20 µg/ml) for 6h; [3] pilot study with n = 4 mice per group. APP = amyloid precursor protein; CHX = cycloheximide; d.p.i. = days post immunization; EAE = experimental autoimmune encephalomyelitis; MOG = myelin oligodendrocyte glycoprotein; NfL = neurofilament light chain; TNFα = tumor necrosis factor alpha; VidoCa/Vido = vidofludimus calcium

Vidofludimus Calcium Enhances Nurr1 Target Gene Expression in an EAE Mouse Model



Increased Plasma BDNF levels^[1]

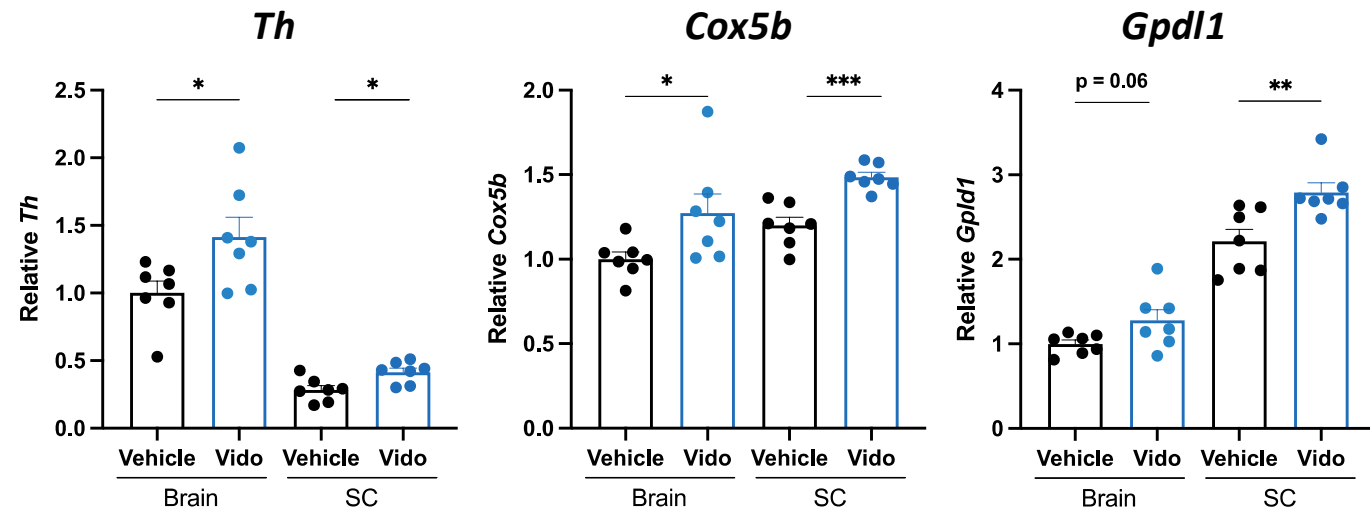
Brain-derived neurotrophic factor (BDNF) plays an important role in neuronal survival and growth and is a direct target of Nurr1.



Nurr1 Regulated Genes Are Increased in CNS of VidoCa Treated EAE Mice^[1]

Nurr1 target genes are regulated in brain and spinal cord.

- Th – Tyrosine hydroxylase.
- Cox5b – Mitochondrial function and reducing ROS.
- Gpld1 – Neurogenesis and cognition.



Data generated by Prof. Sun, City of Hope, unpublished; [1] EAE was induced with MOG₃₅₋₅₅. Daily treatment per oral gavage was started 5 d.p.i. with vehicle (PEG400) or vidofludimus calcium (150 mg/kg). n = 15 mice per group; Cox5b = cytochrome c oxidase subunit 5B; d.p.i. = days post immunization; EAE = experimental autoimmune encephalomyelitis; Gpld1 = glycosylphosphatidylinositol-specific phospholipase D1; MOG = myelin oligodendrocyte glycoprotein; ROS = reactive oxygen species; VidoCa/Vido = vidofludimus calcium

Vidofludimus Calcium Has the Potential to Address Both Relapses and Smoldering Neurodegeneration in Multiple Sclerosis

1

Improving the survival of neurons in a neurotoxic environment

Nurr1 Activation

2

Reducing the activation of microglia (which are a source of a neurotoxic environment)

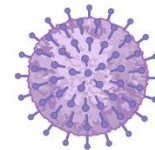
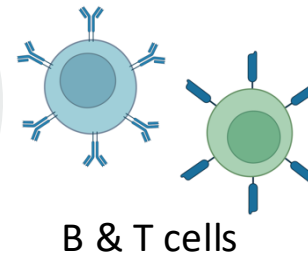
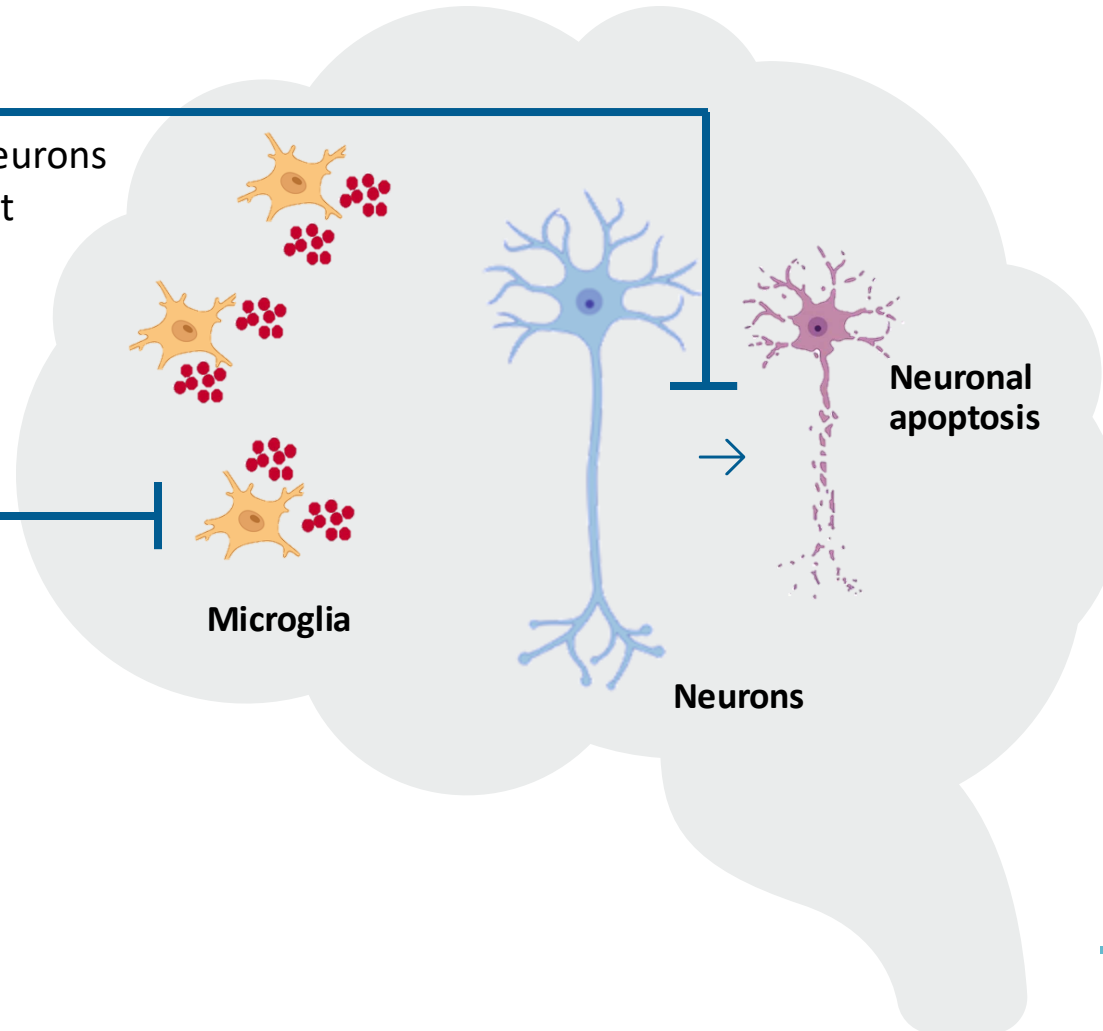
3

Targeting metabolically active immune cells involved in MS

DHODH Inhibition

4

Blocking the constant trigger of immune cells via inhibition of EBV reactivation



Thank you!

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