

Tuesday, September 10, 2024



Nuclear Receptor-Related 1 protein (NURR1) in Multiple Sclerosis (MS)



**Vidofludimus Calcium's Profile and Positioning as a Potentially
Groundbreaking Multiple Sclerosis Therapy**

Could vidofludimus calcium become the first oral treatment option offering neuroprotective benefits for relapsing and progressive forms of multiple sclerosis?

Francesca Montarolo, PhD

Immunic's Onsite Multiple Sclerosis R&D Day in New York City



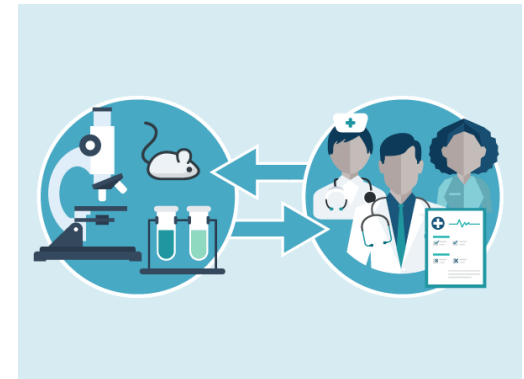
NICO
Neuroscience Institute Cavalieri Ottolenghi



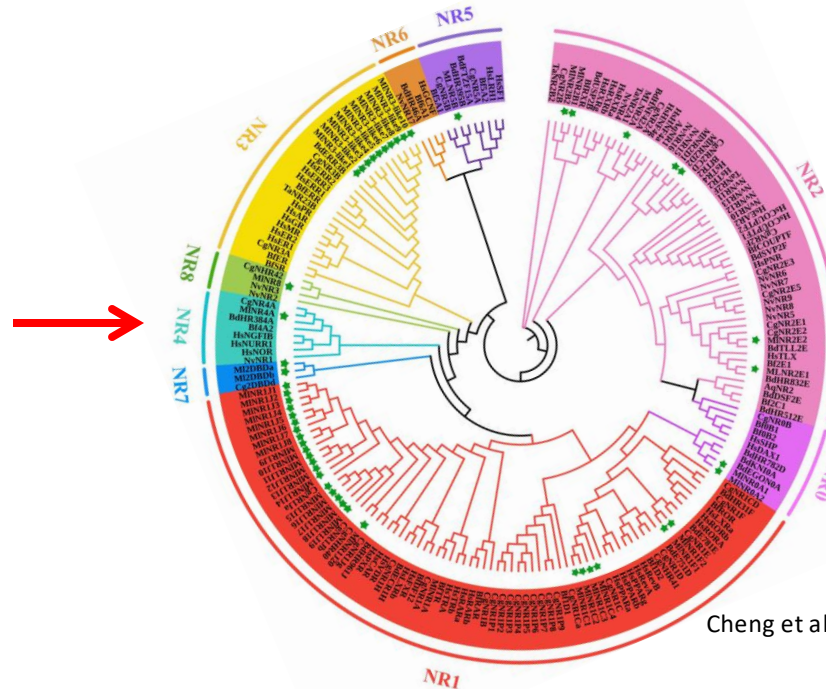
UNIVERSITÀ
DI TORINO

AGENDA

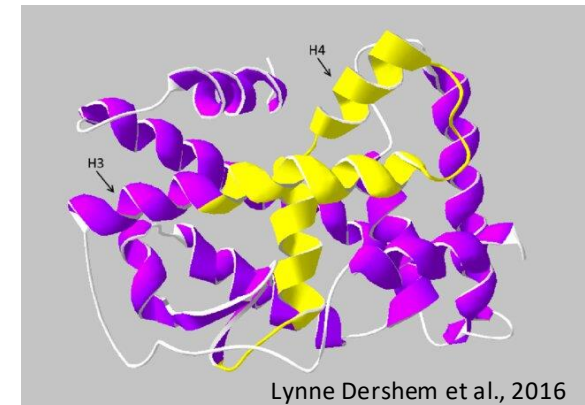
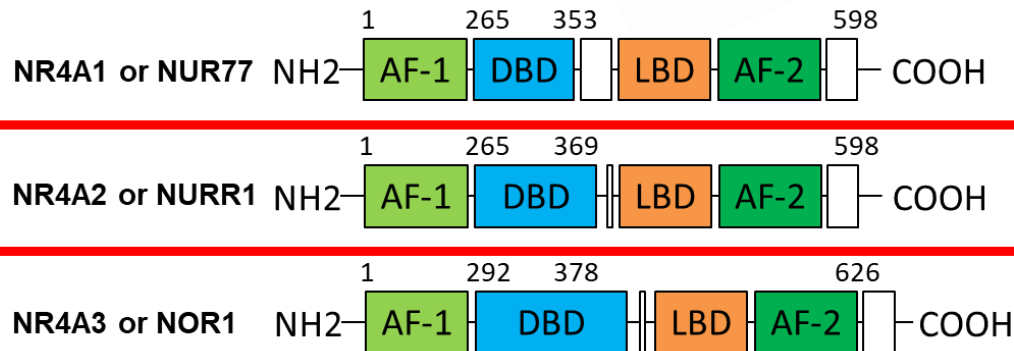
- **Role of NURR1 – neuro-protective and anti-inflammatory**
 - NURR1 in Multiple Sclerosis (MS)
 - Human data / pregnancy
 - Murine model data
 - NURR1: a target for DMTs



The **Nuclear related protein 1 (NURR1)** also called **Nuclear receptor 4A2** is a transcription factor belonging to the **nuclear receptor 4A** subfamily



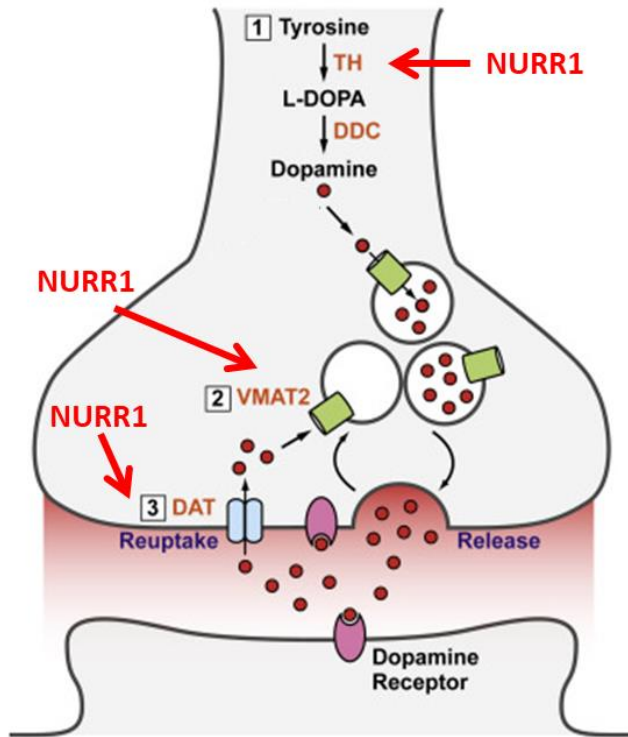
Cheng et al., 2021



Lynne Dershem et al., 2016

NURR1 ligand binding domain (LBD) is close due to the proximity of hydrophobic residues

NURR1 induces neuronal survival and development



Proc. Natl. Acad. Sci. USA
Vol. 95, pp. 4013–4018, March 1998
Neurobiology

Nurr1 is essential for the induction of the dopaminergic phenotype and the survival of ventral mesencephalic late dopaminergic precursor neurons

ODILA SAUCEDO-CARDENAS^{*}, JUAN D. QUINTANA-HAU^{*}, WEI-DONG LE[†], MARTEN P. SMIDT[‡], JOKE J. COX[‡], FRANCESCO DE MAYO^{*}, J. PETER H. BURBACH[‡], AND ORLA M. CONNEELY^{*§}

Departments of ^{*}Cell Biology and [†]Neurology, Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030; and [‡]Department of Medical Pharmacology, Rudolf Magnus Institute for Neurosciences, Utrecht University, 3584 CG Utrecht, The Netherlands

Dopamine Neuron Agenesis in Nurr1-Deficient Mice

Rolf H. Zetterström, Ludmila Solomin, Lottie Jansson, Barry J. Hoffer, Lars Olson, Thomas Perlmann*

SCIENCE • VOL. 276 • 11 APRIL 1997 • <http://www.sciencemag.org>

modified by Bruning et al., 2019

In NURR1 gene, polymorphisms and mutations resulting in reduced expression of NURR1 are associated with **Parkinson's disease (PD)**, where selective degeneration of mDA neurons occurs

GENERAL ARTICLE

Nurr1 repression mediates cardinal features of Parkinson's disease in α -synuclein transgenic mice

Maria Argyrothalmidou¹, Athanasios D. Spathis¹, Matina Maniati¹, Amalia Poula¹, Maira A. Katsianou^{1,†}, Evangelos Sotiriou¹, Maria Manousaki¹, Celine Perier², Ioanna Papapanagiotou¹, Zeta Papadopoulou-Daifoti^{3,†}, Pothitos M. Pitychoutis^{3,4}, Pavlos Alexakos¹, Miquel Vila², Leonidas Stefanis^{1,5} and Demetrios K. Vassilatis^{1,*}

Neuroscience Letters 457 (2009) 75–79



Contents lists available at ScienceDirect

Neuroscience Letters

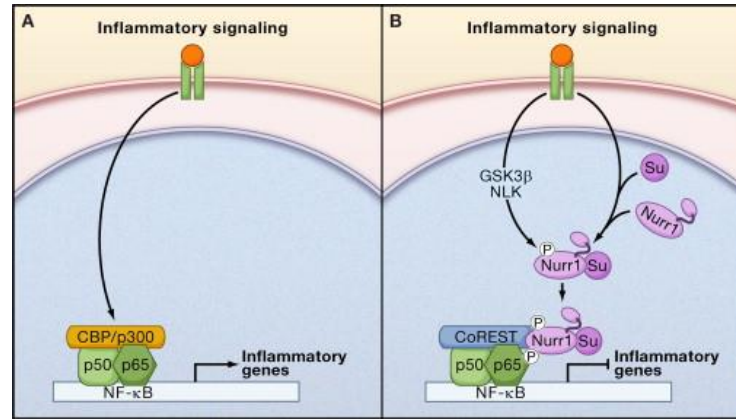
journal homepage: www.elsevier.com/locate/neulet



Characterisation of a novel NR4A2 mutation in Parkinson's disease brain

P.M.A. Sleiman^{a,g,1,2}, D.G. Healy^{a,1}, M.M.K. Muqit^{a,b,1,3}, Y.X. Yang^b, M. Van Der Brug^c, J.L. Holton^a, T. Revesz^d, N.P. Quinn^d, K. Bhatia^d, J.K.J. Diss^b, A.J. Lees^{a,c}, M.R. Cookson^c, D.S. Latchman^{b,f}, N.W. Wood^{a,*}

NURR1 exerts anti-inflammatory function by blocking the NF-κB pathway

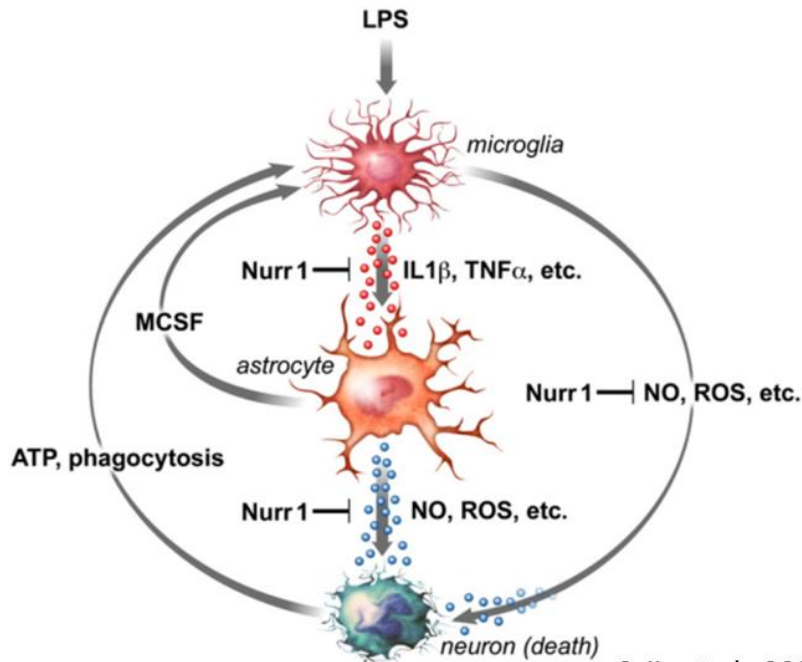


Bensinger et al., 2009



Cell 137, 47–59, April 3, 2009

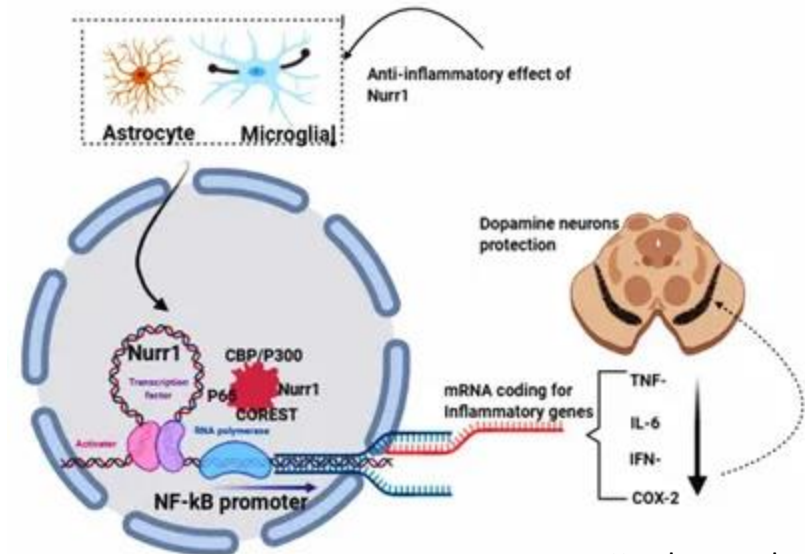
NURR1 exerts neuro-protection through glial cells



Saijo et al., 2009

A Nurr1/CoREST Pathway in Microglia and Astrocytes Protects Dopaminergic Neurons from Inflammation-Induced Death

Kaoru Saijo,^{1,*} Beate Winner,^{5,6} Christian T. Carson,^{5,6,7} Jana G. Collier,^{1,6} Leah Boyer,^{4,5} Michael G. Rosenfeld,^{2,3} Fred H. Gage,⁵ and Christopher K. Glass^{1,2,*}



Kambey et al., 2021



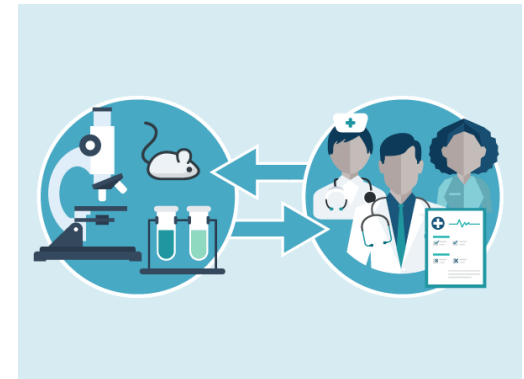
NICO
Neuroscience Institute Cavalieri Ottolenghi



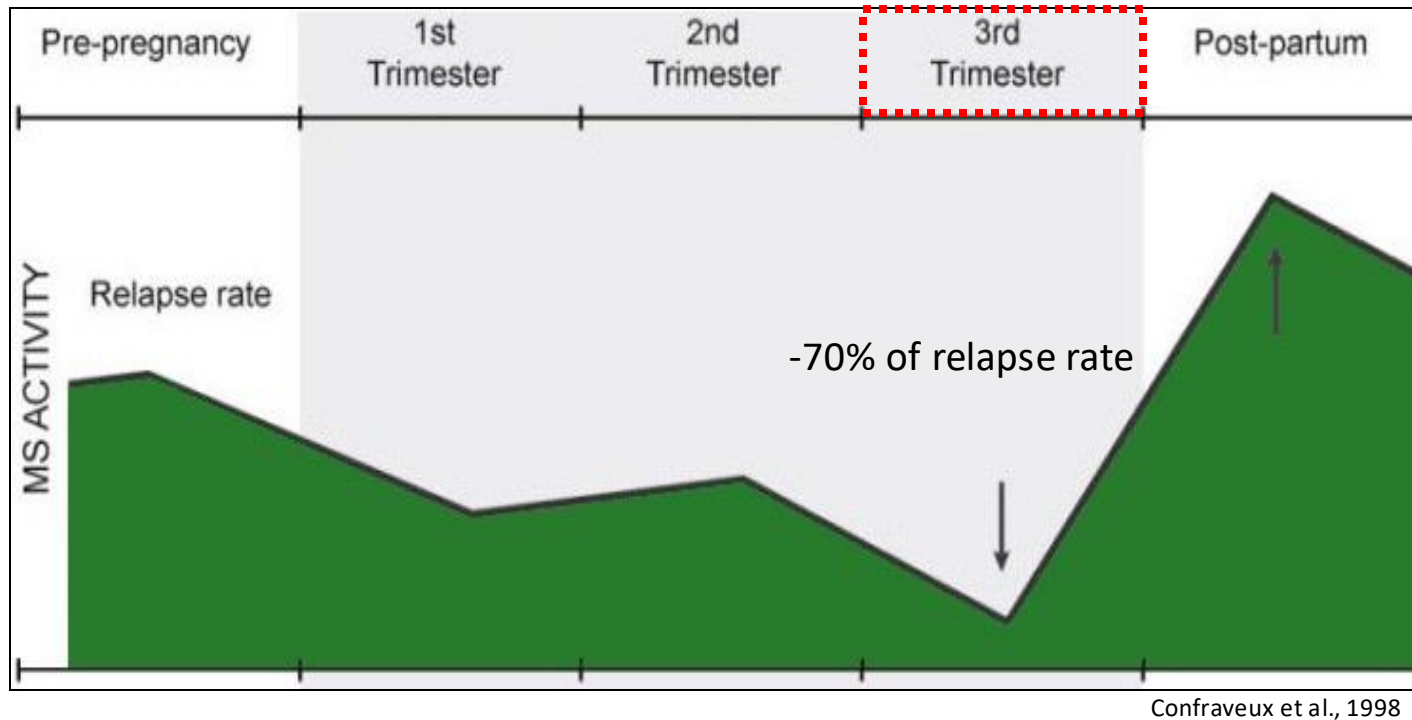
**UNIVERSITÀ
DI TORINO**

AGENDA

- Role of NURR1 – neuro-protective and anti-inflammatory
 - **NURR1 in Multiple Sclerosis (MS)**
Human data / pregnancy
Murine model data
 - NURR1: a target for DMTs



Pregnancy's impact on MS disease activity



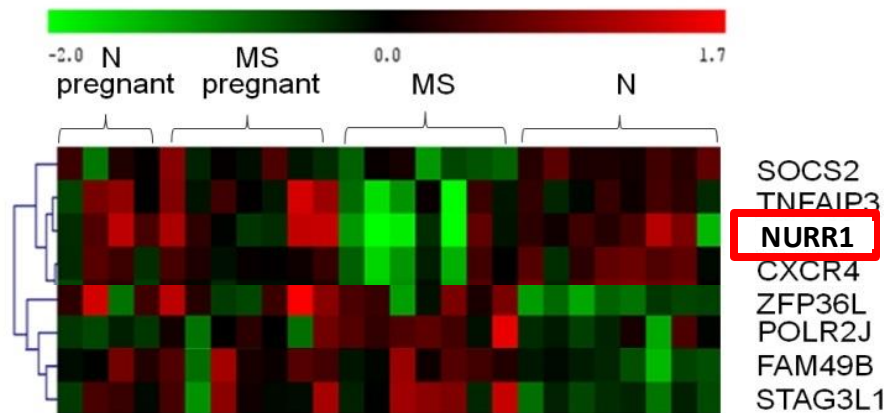
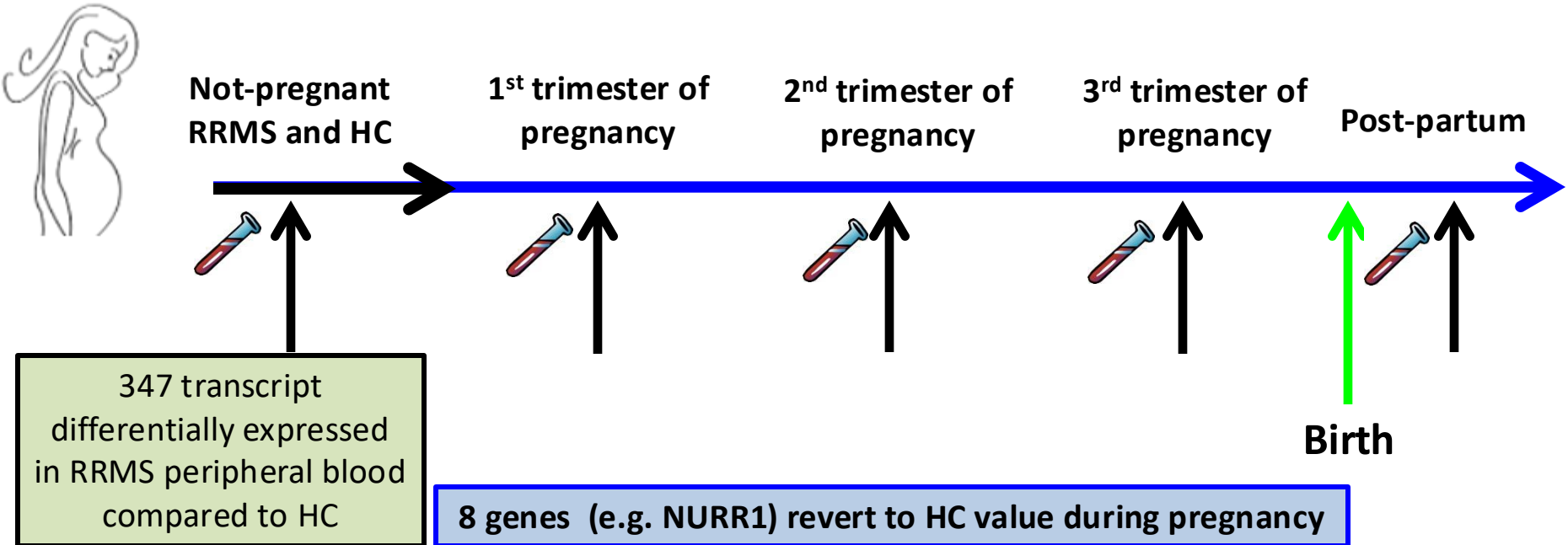
Women with MS experience a substantial **reduction of disease activity** during pregnancy, particularly in the 3rd trimester
relapses worsen further in the post-partum, returning to higher levels than pre-pregnancy

Pregnancy is a unique state of immune-modulation in which the maternal immune system transiently tolerates the paternal antigens of the semi-allogenic foetus

The exact mechanism by which pregnancy influences MS is not already full understood

Multiple Sclerosis (MS) transcript signature

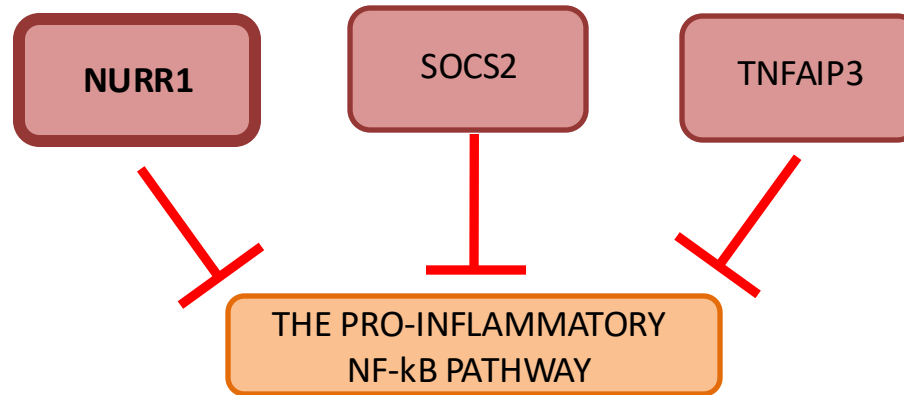
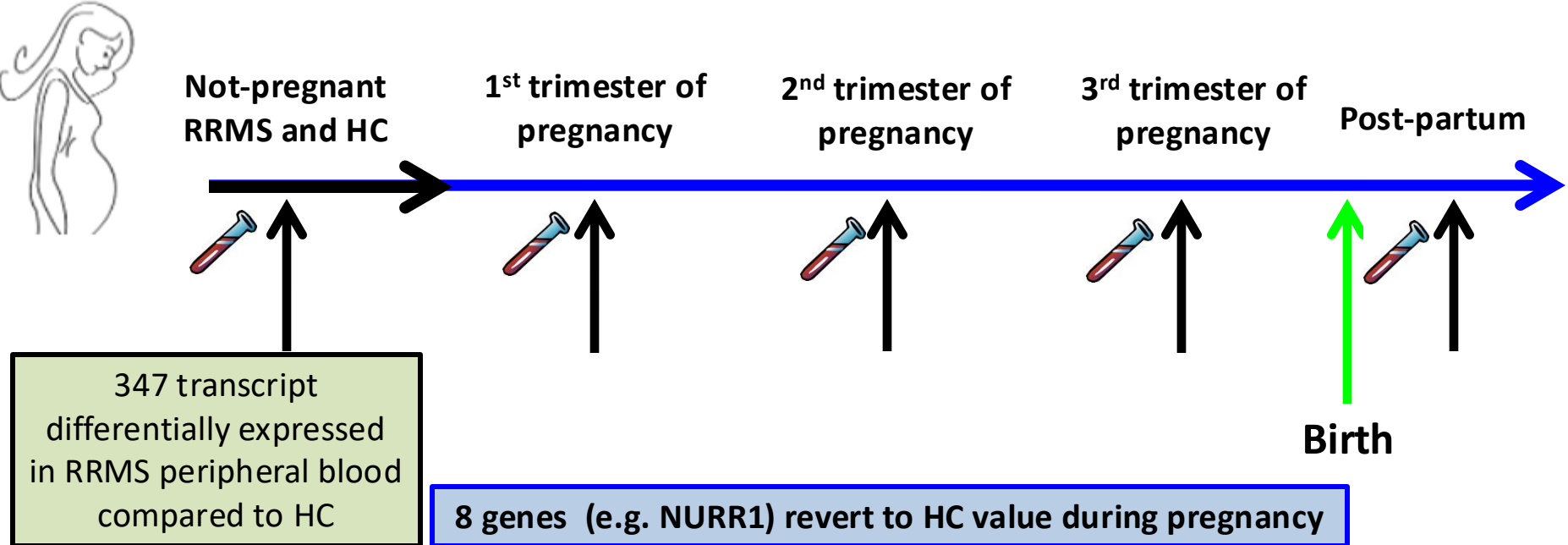
The gene expression level of NURR1 is **down-regulated** in treatment naive RRMS blood in comparison to HC, but during pregnancy its imbalance expression returns to HC value



Dr. A. Bertolotto
 CReSM –
 Regional referral MS center,
 AOU San Luigi Gonzaga,
 Orbassano (TO), Italy

Multiple Sclerosis (MS) transcript signature

3 of the 8 genes whose expression level is down-regulated in RRMS and is completely restored to the HC value during pregnancy **block the pro-inflammatory pathway of NF-kB**

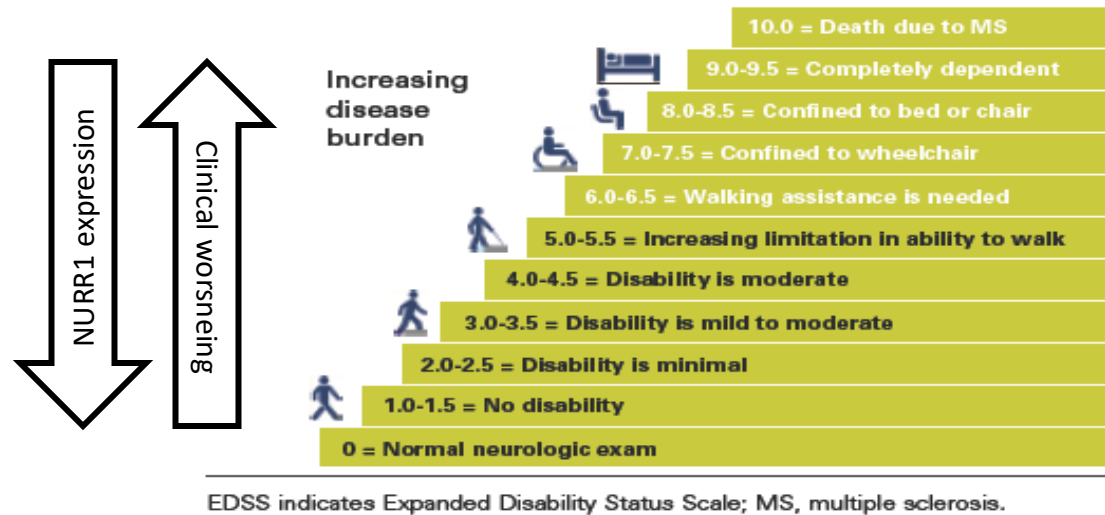


loss of braking signal of inflammation in MS



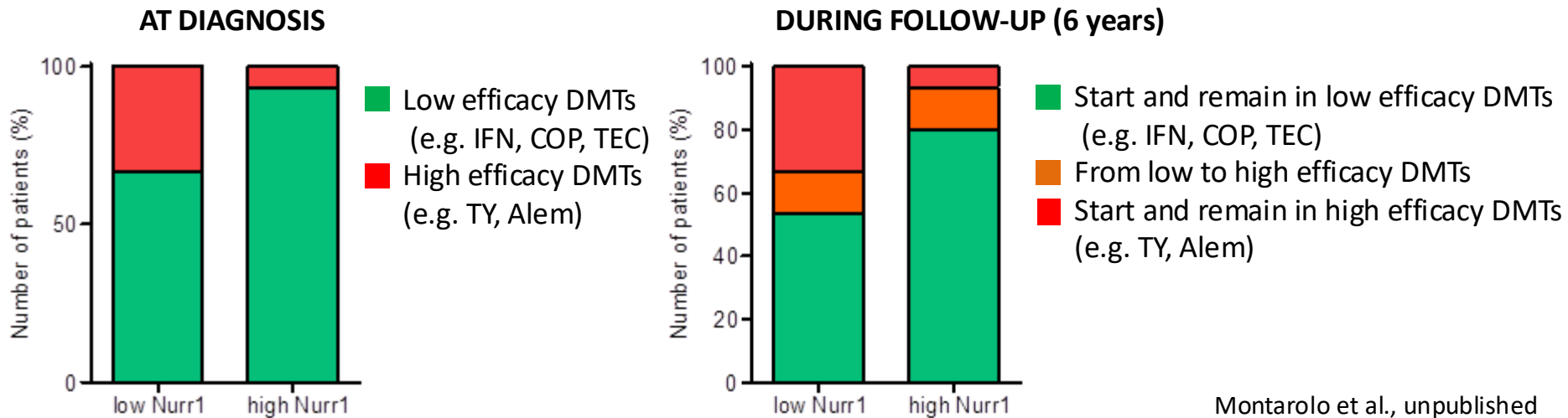
Dr. A. Bertolotto
 CRéSM –
 Regional referral MS center,
 AOU San Luigi Gonzaga,
 Orbassano (TO), Italy

NURR1 gene expression level negatively correlates with relapse rate and EDSS (aggressive MS)



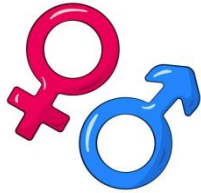
Gilli et al., 2010, 2011

Lower levels of NURR1 expression correlate with increased probability of initiating or switching to high efficacy disease modifying treatment (DMT) necessary for the most aggressive form of the disease



Montarolo et al., unpublished

NURR1 gene expression level is down-regulated in treatment naive RRMS in comparison to HC



whole blood	Gilli et al., 2011; Montarolo et al., 2019
peripheral blood mononuclear cell (PBMCs)	Gilli et al., 2010
CD4+ T cells (lymphocytes)	Navone et al., 2014
CD14+ cells (monocytes)	Navone et al., 2014



Blood Transcriptional Signatures of Multiple Sclerosis: Unique Gene Expression of Disease Activity

Anat Achiron, MD, PhD,¹ Michael Gurevich, PhD,¹ Nir Friedman, PhD,² Naftali Kaminski, MD,³ and Mathilda Mandel, MD⁴

Ann Neurol 2004;55:410–417

ONLINE FIRST

2011

Loss of Braking Signals During Inflammation

A Factor Affecting the Development and Disease Course of Multiple Sclerosis

Francesca Gilli, PhD; Nicole Désirée Navone, MSc; Simona Perga, PhD;
Fabiana Marnetto, MSc; Marzia Caldano, PharmD; Marco Capobianco, MD;
Annalisa Pulizzi, MD; Simona Malucchi, MD; Antonio Bertolotto, MD

OPEN ACCESS Freely available online

2010 PLOS one

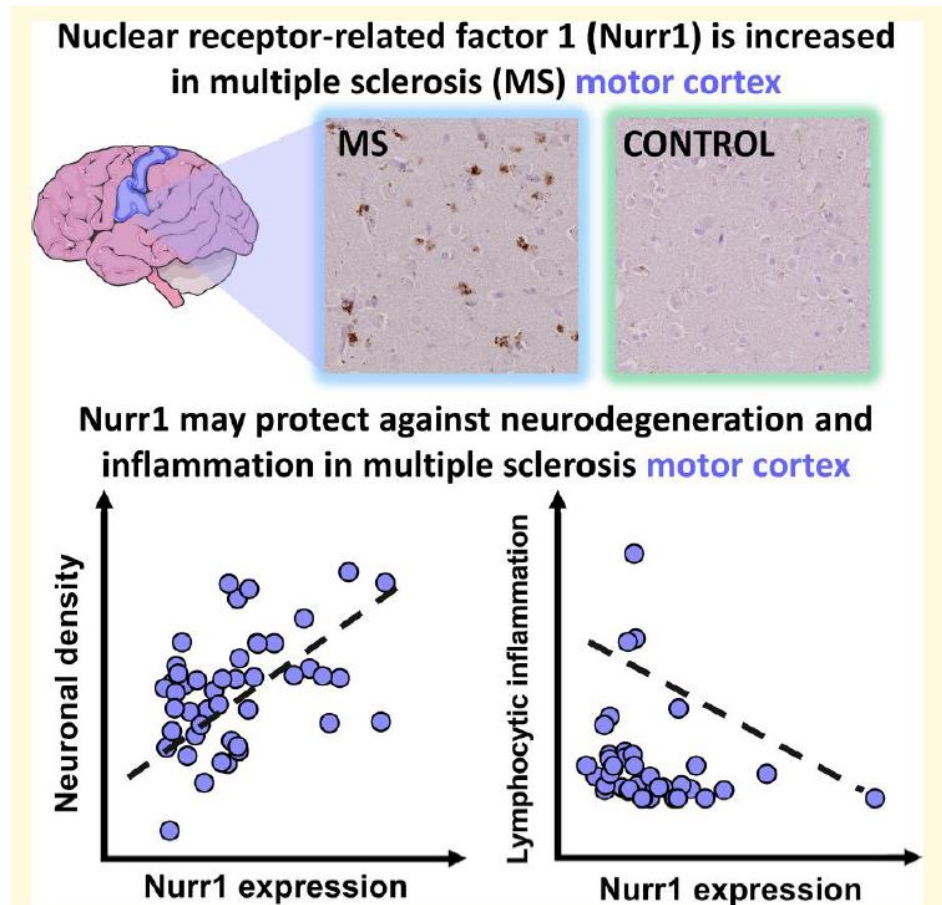
Learning from Nature: Pregnancy Changes the Expression of Inflammation-Related Genes in Patients with Multiple Sclerosis

Francesca Gilli^{1*}, Raija L. P. Lindberg², Paola Valentino¹, Fabiana Marnetto¹, Simona Malucchi¹, Arianna Sala¹, Marco Capobianco¹, Alessia di Sapio¹, Francesca Sperli¹, Ludwig Kappos², Raffaele A. Calogero³, Antonio Bertolotto¹

Gilli et al., 2010, 2011, Navone et al., 2014, Montarolo et al., 2019

NURR1 is expressed human MS brain tissue, and its expression correlates with neuronal cell density ==

== Higher expression of NURR1 found in the high neuronal density area === **Neuro-protective role**



<https://doi.org/10.1093/braincomms/fcad072>

BRAIN COMMUNICATIONS 2023, Page 1 of 11 | 1

BRAIN COMMUNICATIONS

A potential protective role of the nuclear receptor-related factor 1 (Nurr1) in multiple sclerosis motor cortex: a neuropathological study

©Jonathan Pansieri, ©Marco Pisa, Richard L. Yates, Margaret M. Esiri and Gabriele C. DeLuca



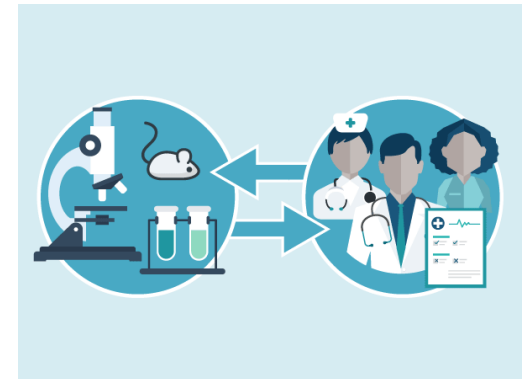
NICO
Neuroscience Institute Cavalieri Ottolenghi



UNIVERSITÀ
DI TORINO

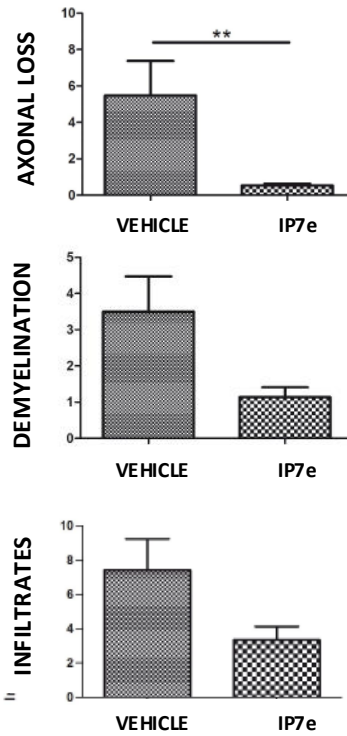
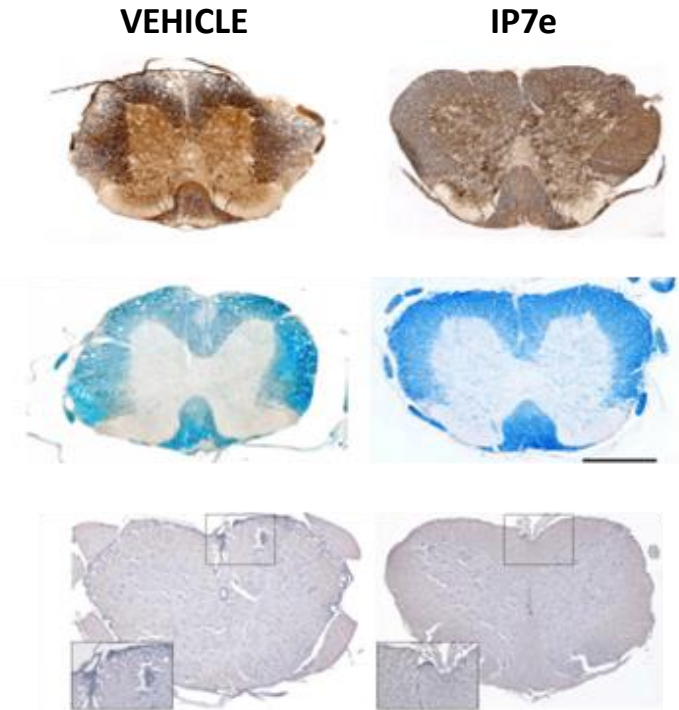
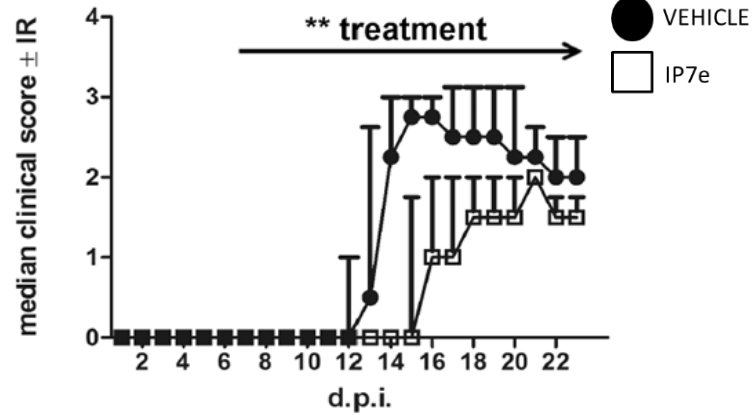
AGENDA

- Role of NURR1 – neuro-protective and anti-inflammatory
 - **NURR1 in Multiple Sclerosis (MS)**
Human data / pregnancy
Murine model data
 - NURR1: a target for DMTs



Effects of Isoxazolo-Pyridinone 7e, a Potent Activator of the Nurr1 Signaling Pathway, on Experimental Autoimmune Encephalomyelitis in Mice

Francesca Montarolo^{1*}, Chiara Raffaele², Simona Perga¹, Serena Martire¹, Annamaria Finardi², Roberto Furlan², Samuel Hintermann³, Antonio Bertolotto¹



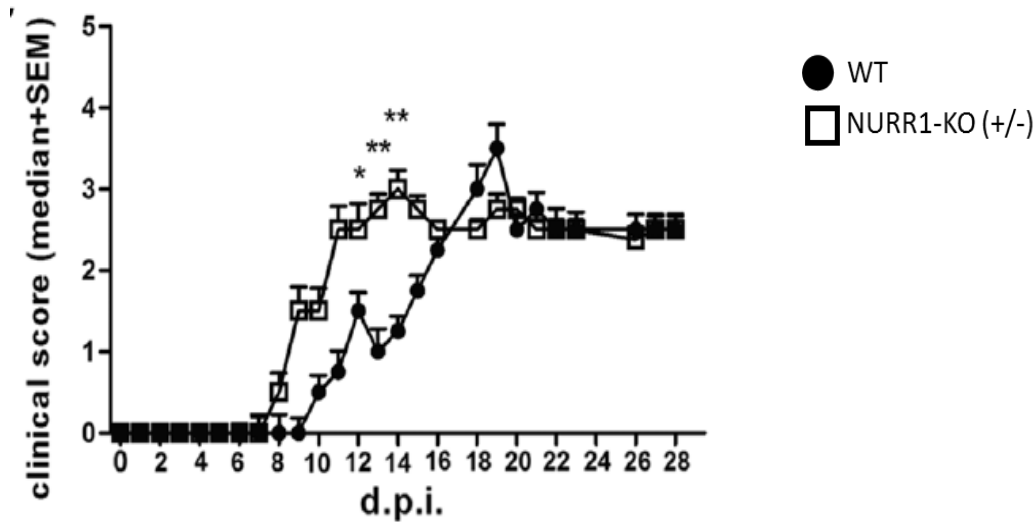
Induced Experimental Autoimmune Encephalomyelitis (EAE) model of inflammatory demyelination in C57Bl/6 female mice

The activation of NURR1 delays the onset of the EAE (MOG₃₅₋₅₅-chronic MS model)

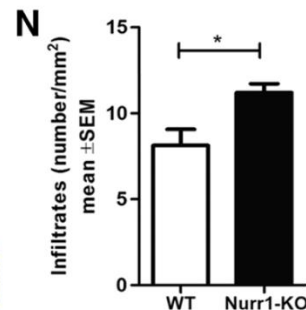
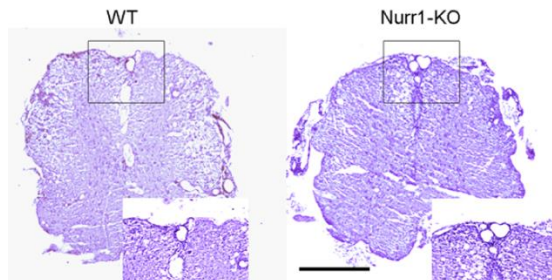


Nurr1 reduction influences the onset of chronic EAE in mice

Francesca Montarolo¹ · Simona Perga¹ · Serena Martire¹ · Antonio Bertolotto¹



Induced Experimental Autoimmune Encephalomyelitis (EAE) model of inflammatory demyelination in heterozygous NURR1-KO female mice



The deficiency of NURR1 anticipates the onset of the EAE (MOG₃₅₋₅₅-chronic model)



NICO
Neuroscience Institute Cavalieri Ottolenghi



UNIVERSITÀ
DI TORINO

TAKE HOME MESSAGE (I)

- NURR1 expression level is down-regulated in the immune cells of RRMS compared to HC (i.e. female and male - whole blood, PBMCs, CD4+ T cells, monocytes)
- Lower levels of NURR1 expression are present in the most active and aggressive MS forms
 - NURR1 activation delays the onset of the MS murine model, while NURR1 deficiency anticipates its onset

NURR1 functionality is protective for MS



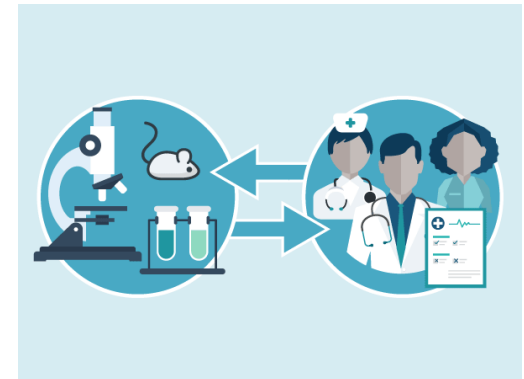
NICO
Neuroscience Institute Cavalieri Ottolenghi



**UNIVERSITÀ
DI TORINO**

AGENDA

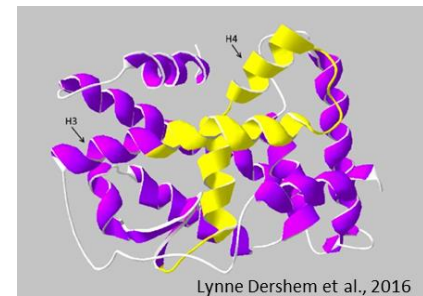
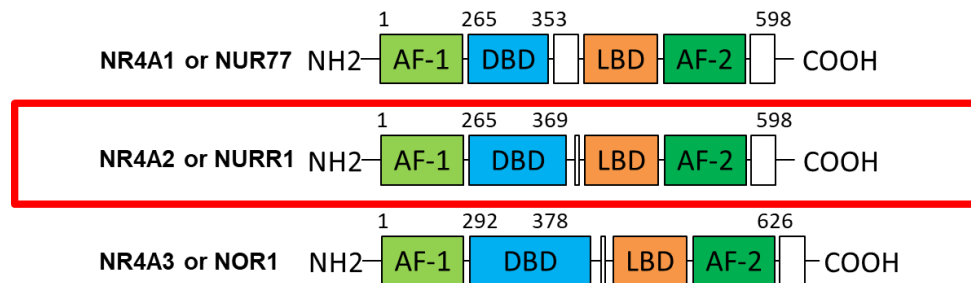
- Role of NURR1 – neuro-protective and anti-inflammatory
 - NURR1 in Multiple Sclerosis (MS)
 - Human data / pregnancy
 - Murine model data
 - **NURR1: a target for DMTs**



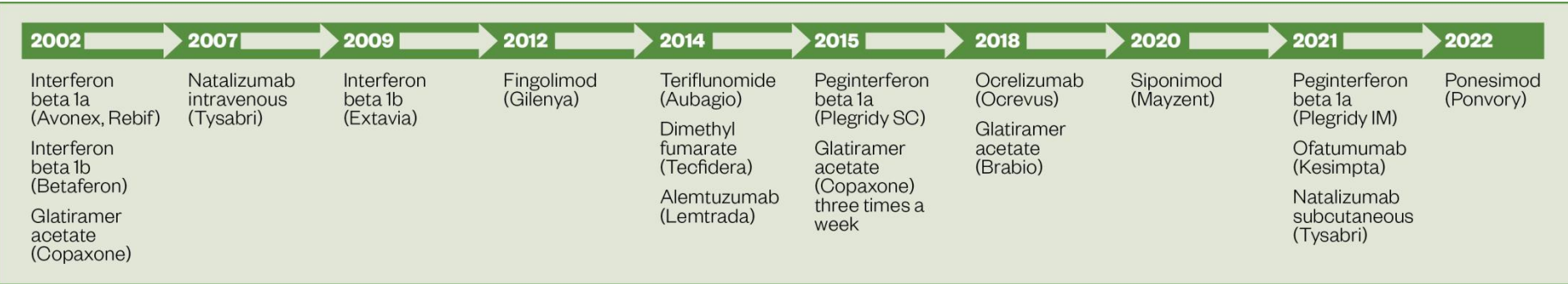
NURR1: a target for DMTs

Limitations in the search for NURR1 agonists:

- ✓ High homology with other NR;
- ✓ LBD with hydrophobic residues
- ✓ ...



NURR1: a target for DMTs



DMTs selected	
Interferon beta (Avonex)	ns
Interferon beta (Rebif)	ns
Interferon beta (Betaferon)	ns
Natalizumab	ns
Glatiramer acetate	ns

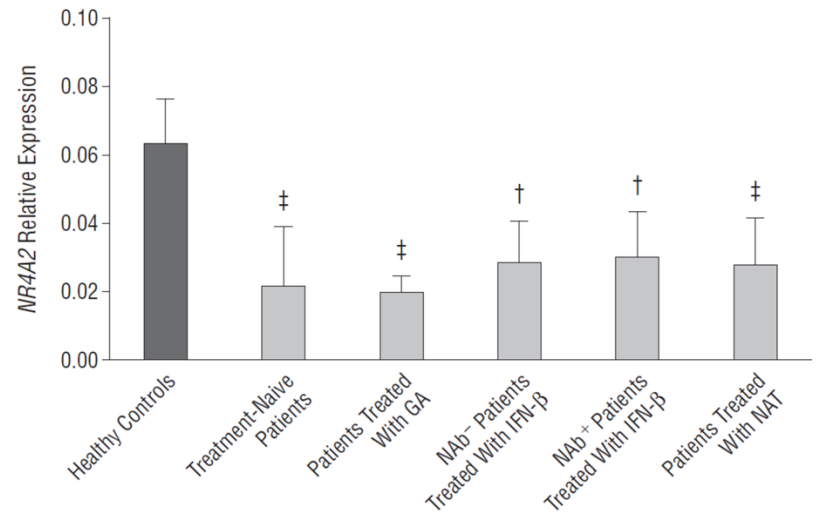
ONLINE FIRST

2011

Loss of Braking Signals During Inflammation

A Factor Affecting the Development and Disease Course of Multiple Sclerosis

Francesca Gilli, PhD; Nicole Désirée Navone, MSc; Simona Perga, PhD; Fabiana Marnetto, MSc; Marzia Caldano, PharmD; Marco Capobianco, MD; Annalisa Pulizzi, MD; Simona Malucchi, MD; Antonio Bertolotto, MD



NURR1: a target for DMTs

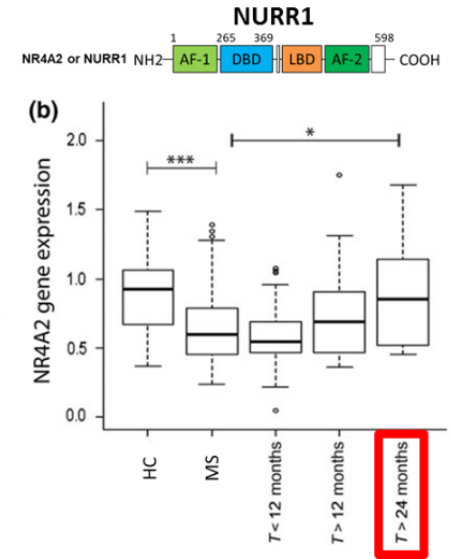
Study of the NR4A family gene expression in patients with multiple sclerosis treated with Fingolimod

F. Montarolo^{a,b,c} , S. Perga^{a,b,c} , S. Martire^{a,b} , F. Brescia^{a,b} , M. Caldano^{a,b} , M. Lo Re^b , G. Panzica^{a,c}  and A. Bertolotto^{a,b} 

^aNeuroscience Institute Cavalieri Ottolenghi, Orbassano, Turin; ^bNeurobiology Unit, Neurology – CReSM (Regional Referring Center of Multiple Sclerosis), AOU San Luigi Gonzaga, Orbassano, Turin; and ^cDepartment of Neuroscience ‘Rita Levi Montalcini’, University of Turin, Turin, Italy



European Journal of Neurology 2018, **0**: 1–6

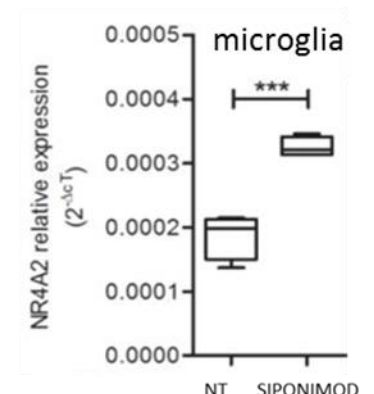
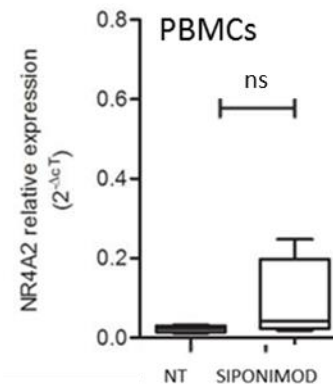
doi:10.1111/ene.13875



Article

The Selective Agonist for Sphingosine-1-Phosphate Receptors Siponimod Increases the Expression Level of NR4A Genes in Microglia Cell Line

Francesca Montarolo^{1,2,3} , Serena Martire^{1,2,4} , Fabiana Marnetto^{1,2}, Paola Valentino^{1,2,4}, Sabdi Valverde^{1,2}, Marco Alfonso Capobianco^{1,2} and Antonio Bertolotto^{1,*}



NURR1: a target for DMTs

Development of a Potent Nurr1 Agonist Tool for In Vivo Applications

Jan Vietor, Christian Gege, Tanja Stiller, Romy Busch, Espen Schallmayer, Hella Kohlhof, Georg Höfner, Jörg Pabel, Julian A. Marschner, and Daniel Merk*

Cite This: *J. Med. Chem.* 2023, 66, 6391–6402

Read Online

ACCESS |

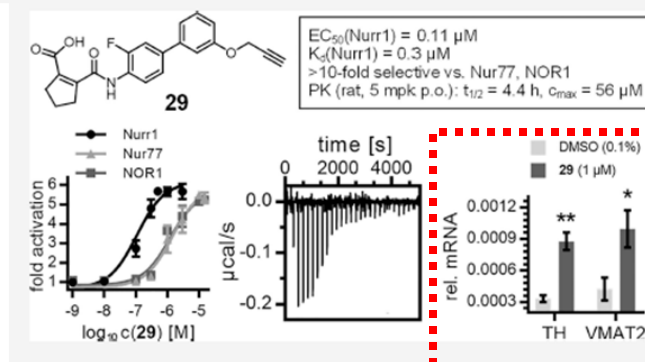
Metrics & More

Article Recommendations

Supporting Information

Optimized Nurr1 agonist with nM potency, strong activation efficacy, pronounced preference over the highly related receptors NR4.

Nurr1-regulated gene expression in astrocytes



Thanks

Regional referral MS center (CReSM) of AOU San Luigi Gonzaga, Orbassano, Turin, Italy

- Clinical activity to manage MS patients
- Clinical neurophysiology
- Neurobiology laboratory
- Secretary
- Psychology
- CReSM BioBank



UNIVERSITÀ
DI TORINO

