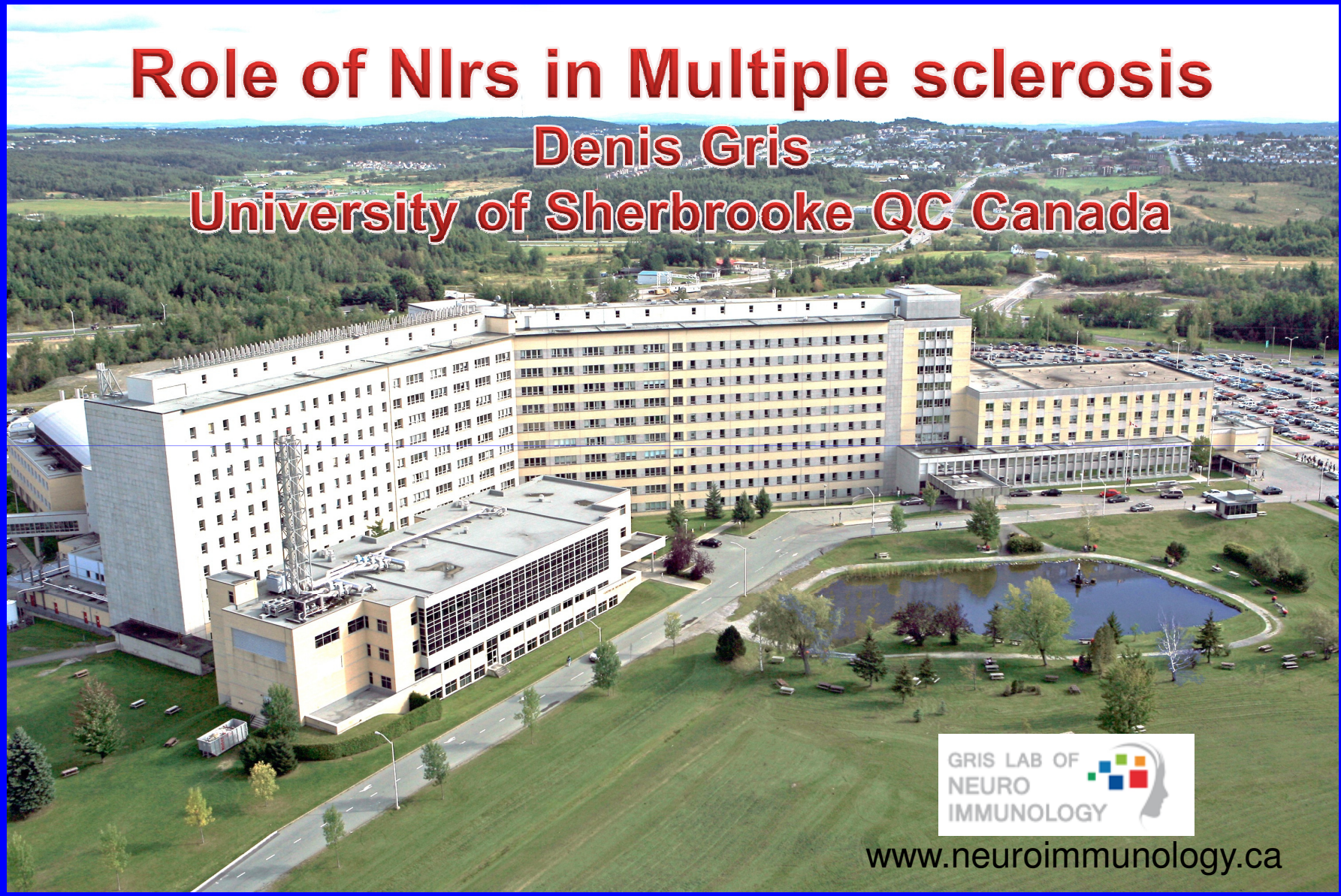
3rd International Conference on Neurology & Therapeutics

Role of Nlrs in Multiple sclerosis

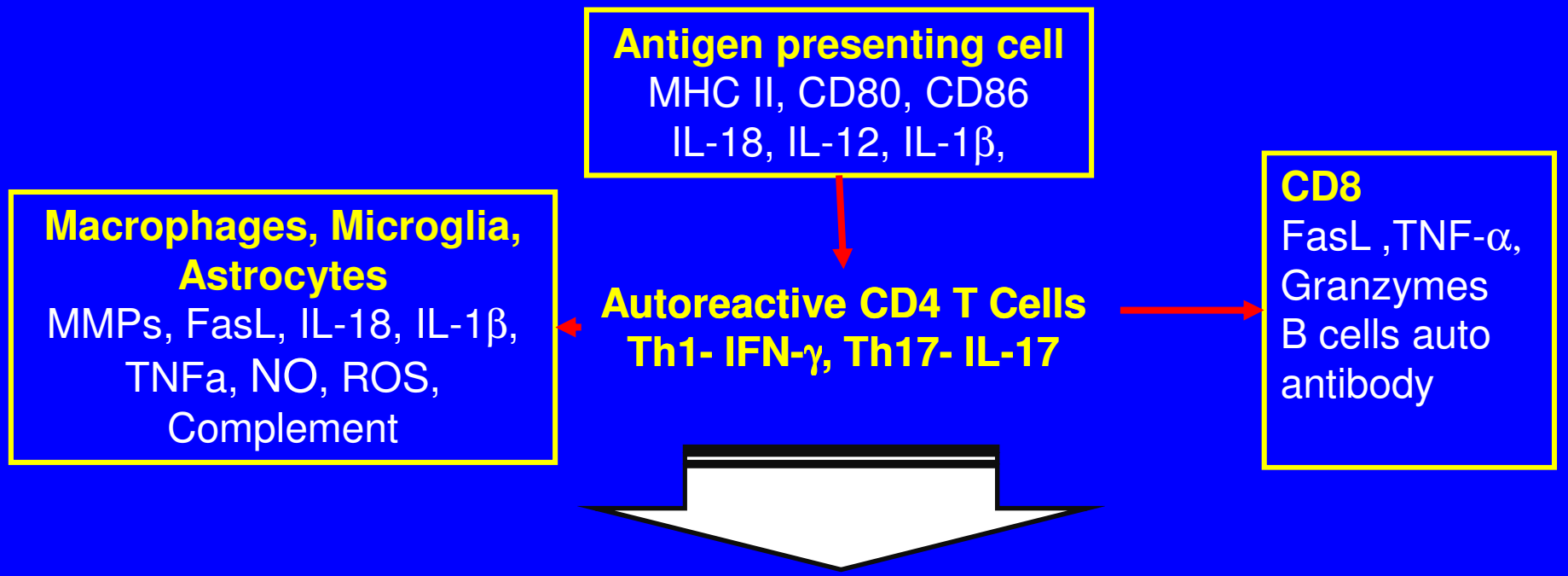
Denis Gris
University of Sherbrooke QC Canada



Multiple sclerosis is a devastating disease

- The first description of the disease was mentioned in 14th century
- In 1838 Dr. Charcot connected the symptoms to the pathology of the central nervous system (CNS)
- MS is characterized by appearance of demyelinating plaques throughout the brain and spinal cord
- Approximately **400,000 North Americans** acknowledge having MS, and every week about 200 people are diagnosed. Worldwide, MS may affect 2.5 million
- MS follows geographical gradient with the risk increasing further from equator. Canada and northern Europe have the highest risk of acquiring MS
- Genetic predisposition among twins is 30%
- Sex ration is 2 to 1, females to males
- MS is an autoimmune disorder
- MS is a progressive disease

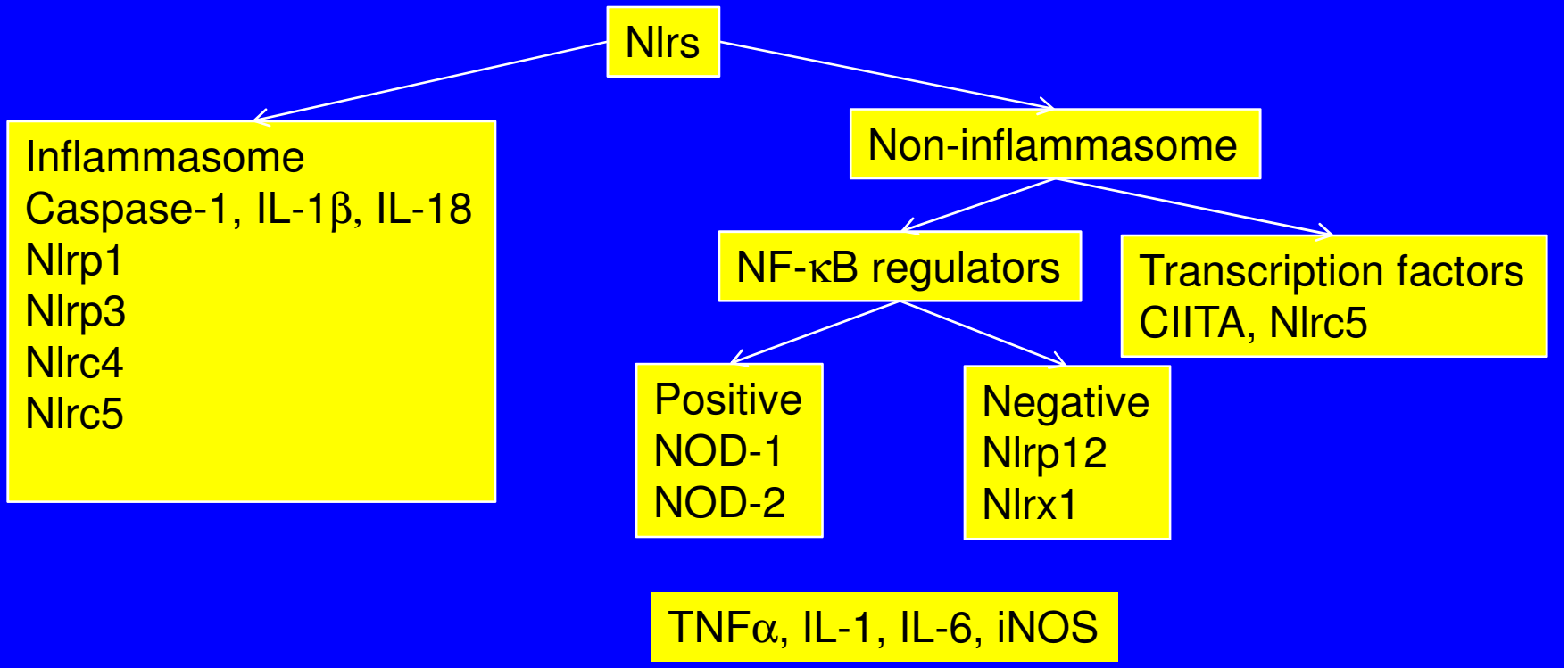
Mechanism of MS



Neurological symptoms

NLRS
Nucleotide-binding Leucine-rich repeat - containing proteins NOD-like receptors

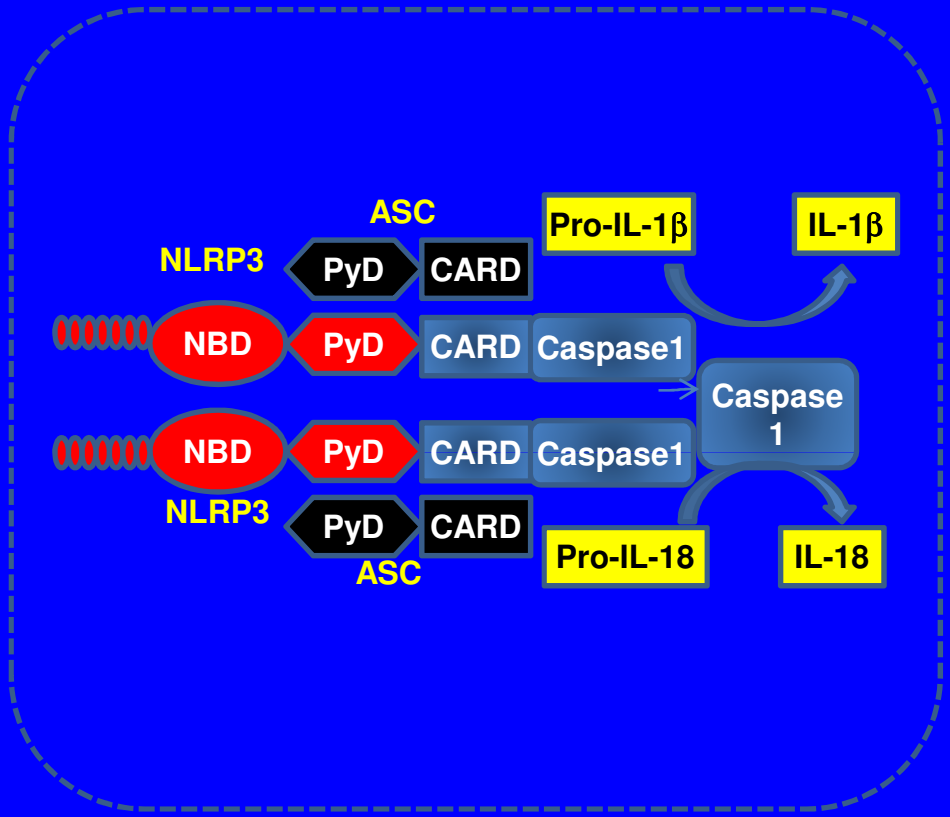




NLRs are sensing and redirecting multiple molecular pathways

Inflammasome in MS

Stimulation
ATP
Poreforming toxins
Nigiricine
MSU
Asbestos
Silica
Bacterial RNA

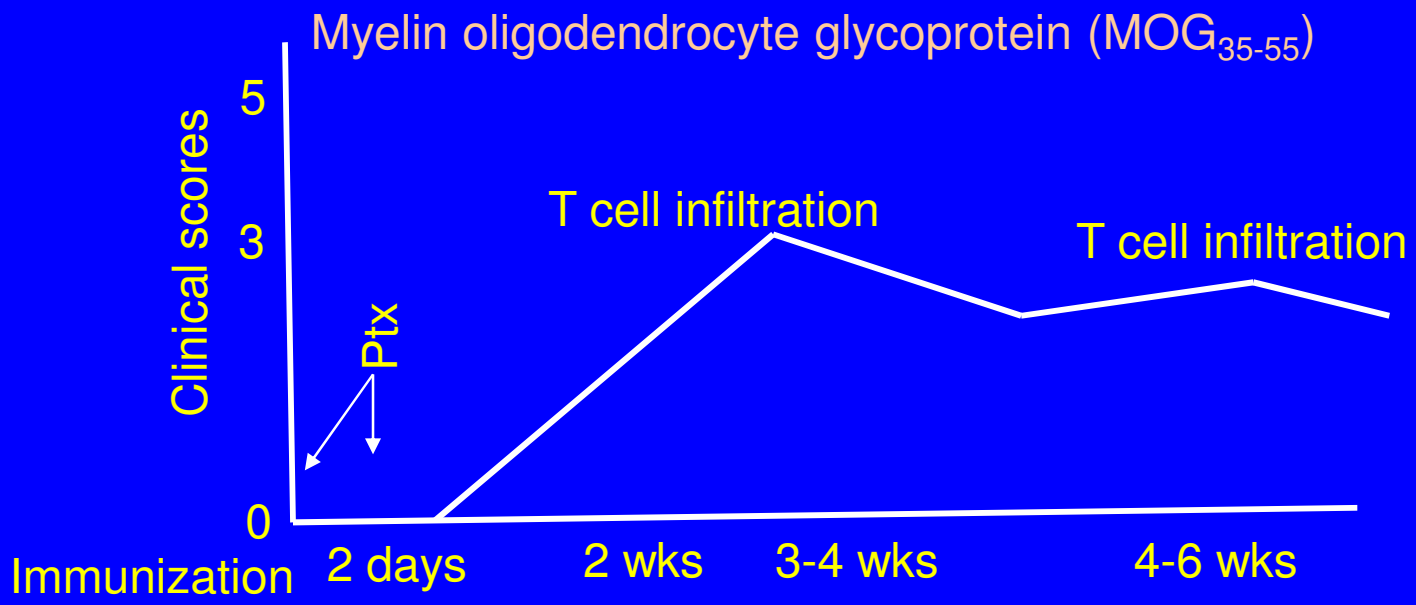


Inflammasome

Hypothesis
Inflammasome exacerbates MS

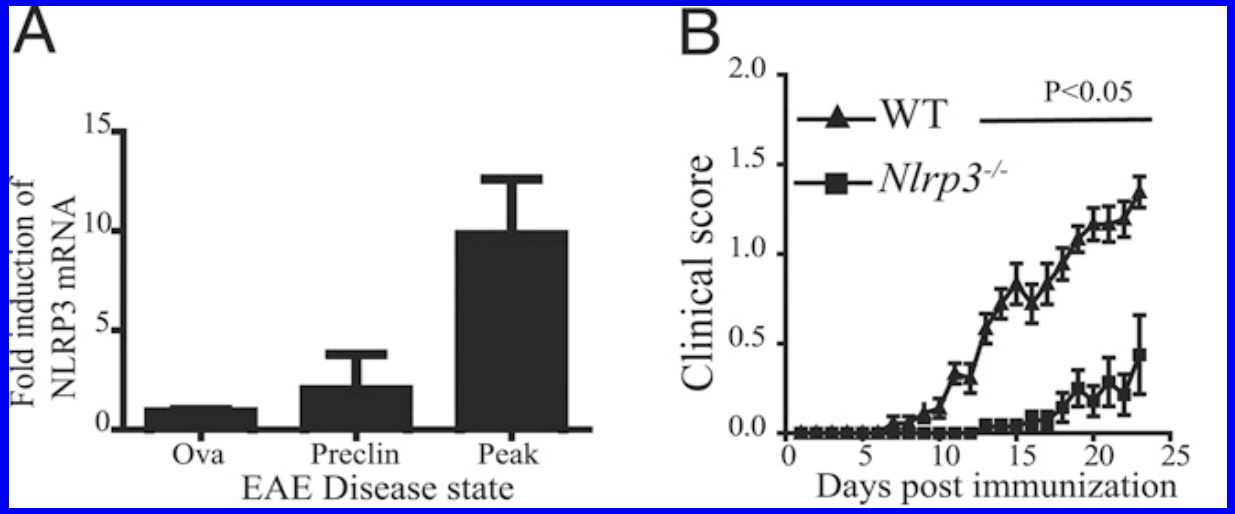
EAE model of MS

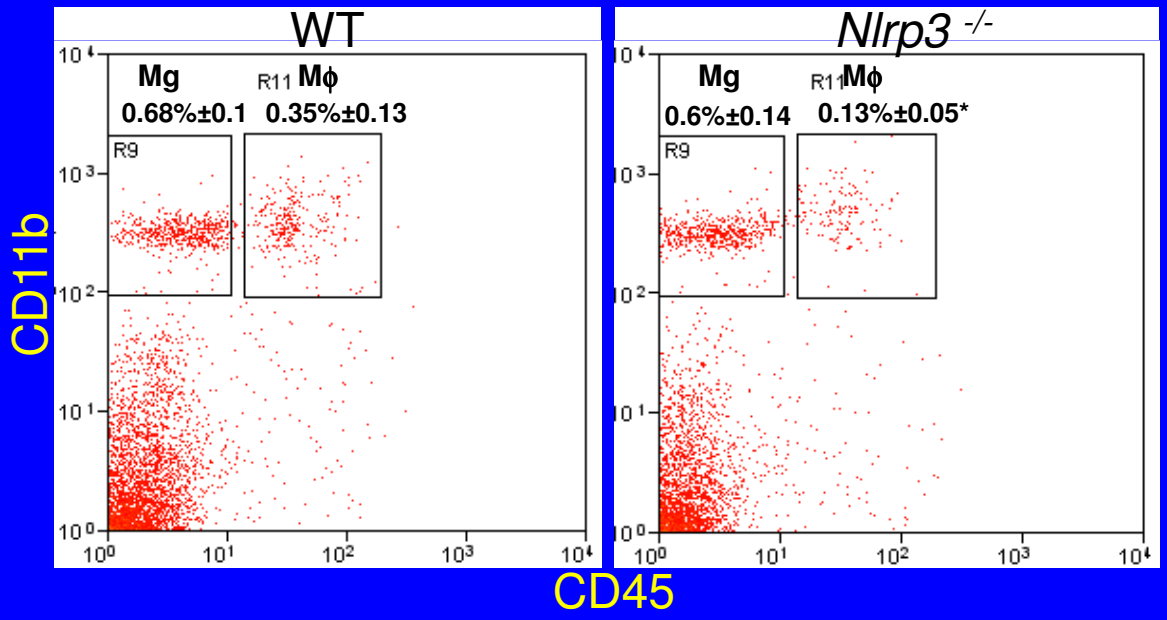
Experimental Autoimmune Encephalomyelitis



0 healthy animal
1 tail dragging on ground constantly
2 tail dragging and locomotor disturbance of at least one hind leg
3 severe hind body paralysis
4 severe locomotor deficiency of front limbs
5 conditions to terminate experiment

Progression of EAE in *Nlrp3*$^{-/-}$ mice





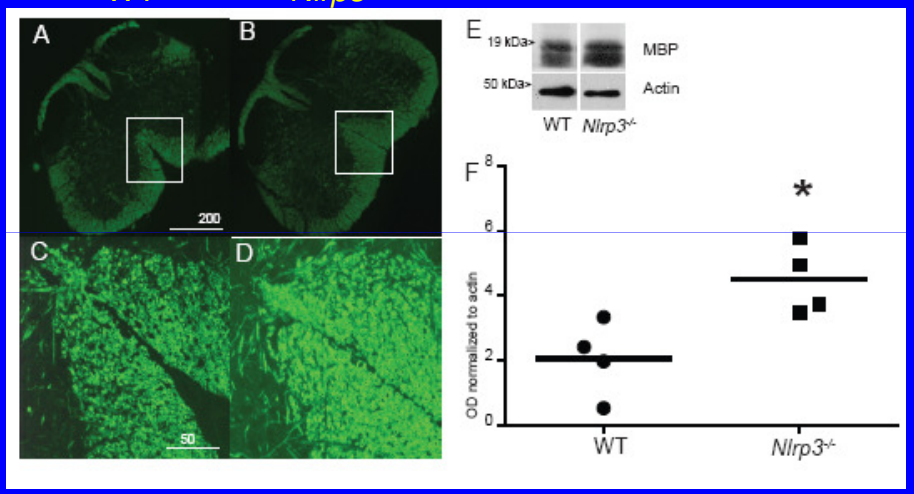
Expression of Nlrp3 drives inflammation within the spinal cord

Demyelination and gliosis are reduced in Nlrp3-/- mice

Three weeks after immunization spinal cords were prepared for immunohistochemistry

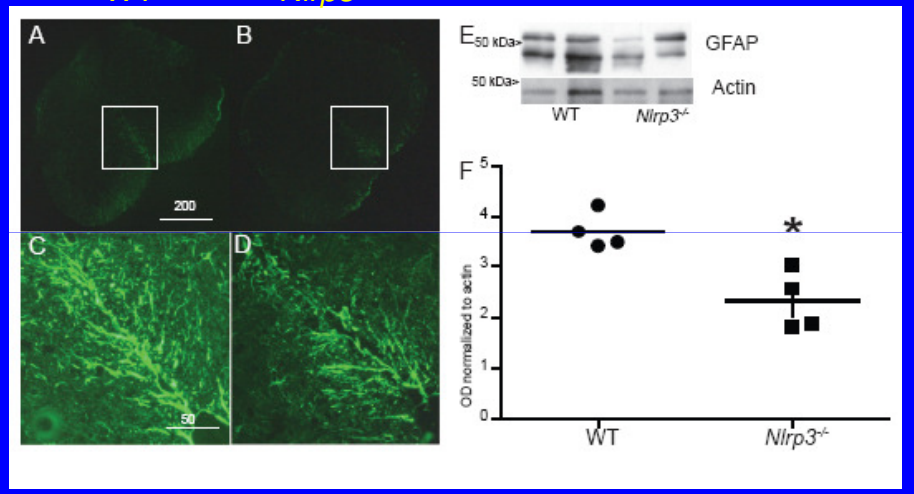
Myelin

WT *Nlrp3*$^{-/-}$



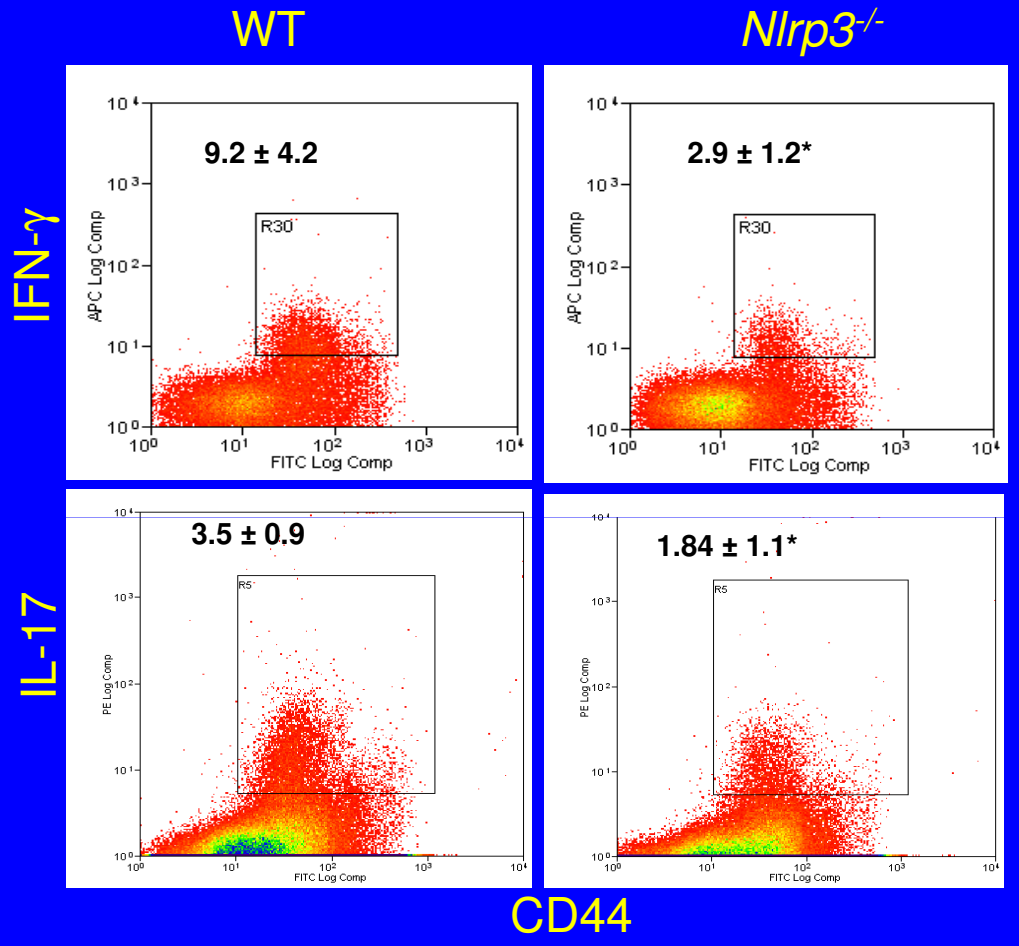
Astrocytes

WT *Nlrp3*$^{-/-}$



Spinal cords from *Nlrp3*$^{-/-}$ mice had significantly more myelin and reduced gliosis

Th1 and Th17 responses after *ex vivo* recall



Th1 and Th17 responses are reduced in *Nlrp3*$^{-/-}$ mice

NLRP3 plays detrimental role in MS

Gris et al J Immunology 2011
Inoue and Shinohara Autoimmune Dis. 2013
Cuprizone model
The inflammasome sensor, NLRP3, regulates CNS inflammation and demyelination via caspse-1 and IL-18. Jha et al J Neurosci. 2010 Nov
Caspase 1 KO has improved course of EAE
ASC KO Shaw et al J Immunol. 2010 May

NOD1 and NOD 2 enhance pro-infammatory role of dendritic cells and augment CNS inflammation in mice. Immunity 2011 Jan 28

Nlrx1 and Nlrp12
Negative regulators of NFkB

Nlrx1



Localized to mitochondria
Inhibits NFkB and Type I interferon signaling during viral infections
Plays role in cell death (autophagy and apoptosis)
Augments ROS production

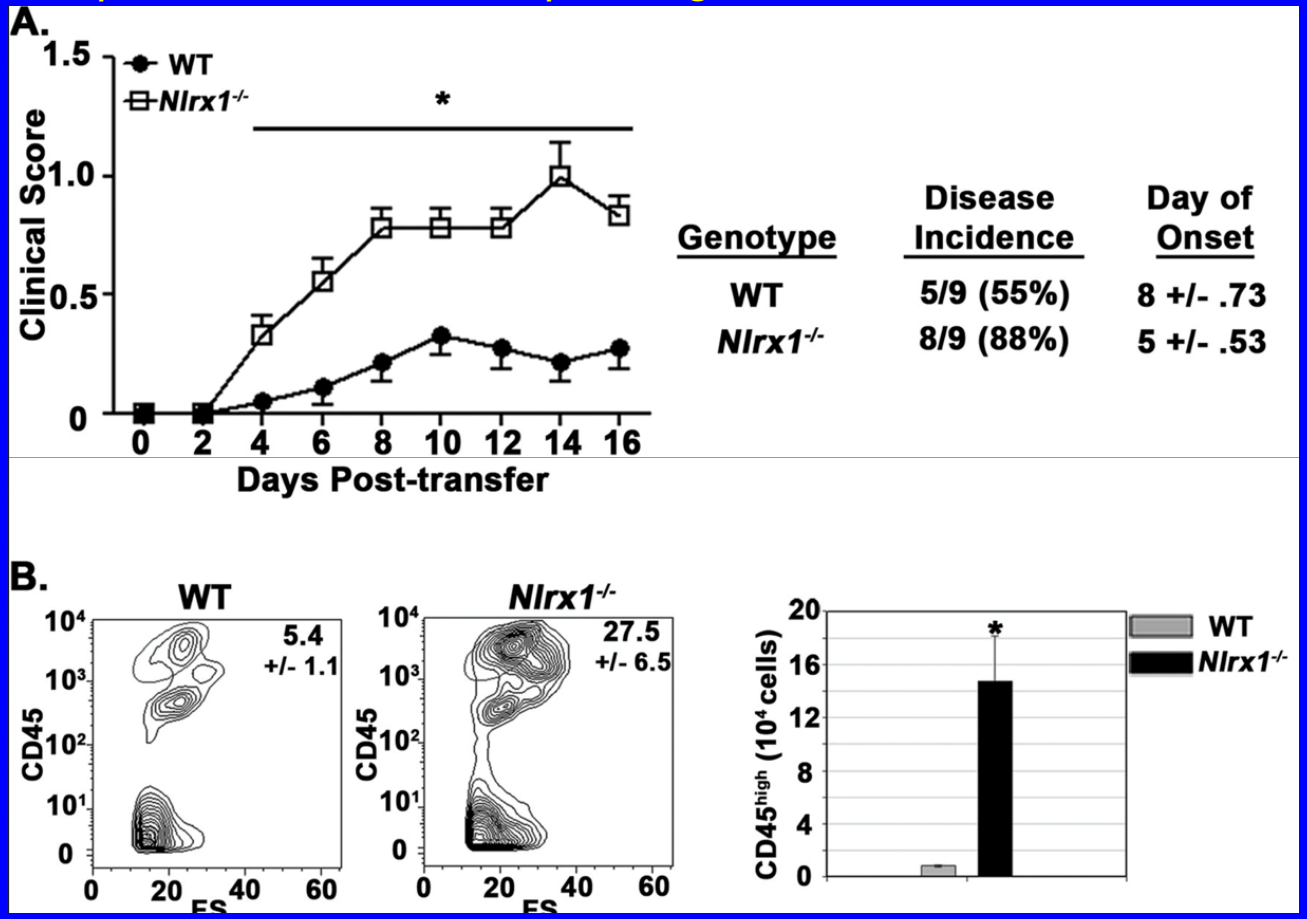
Nlrp12



Inhibits NFkB pathway
Plays role in intestinal tumorogenesis
Forms an inflammasome
Associates with human diseases

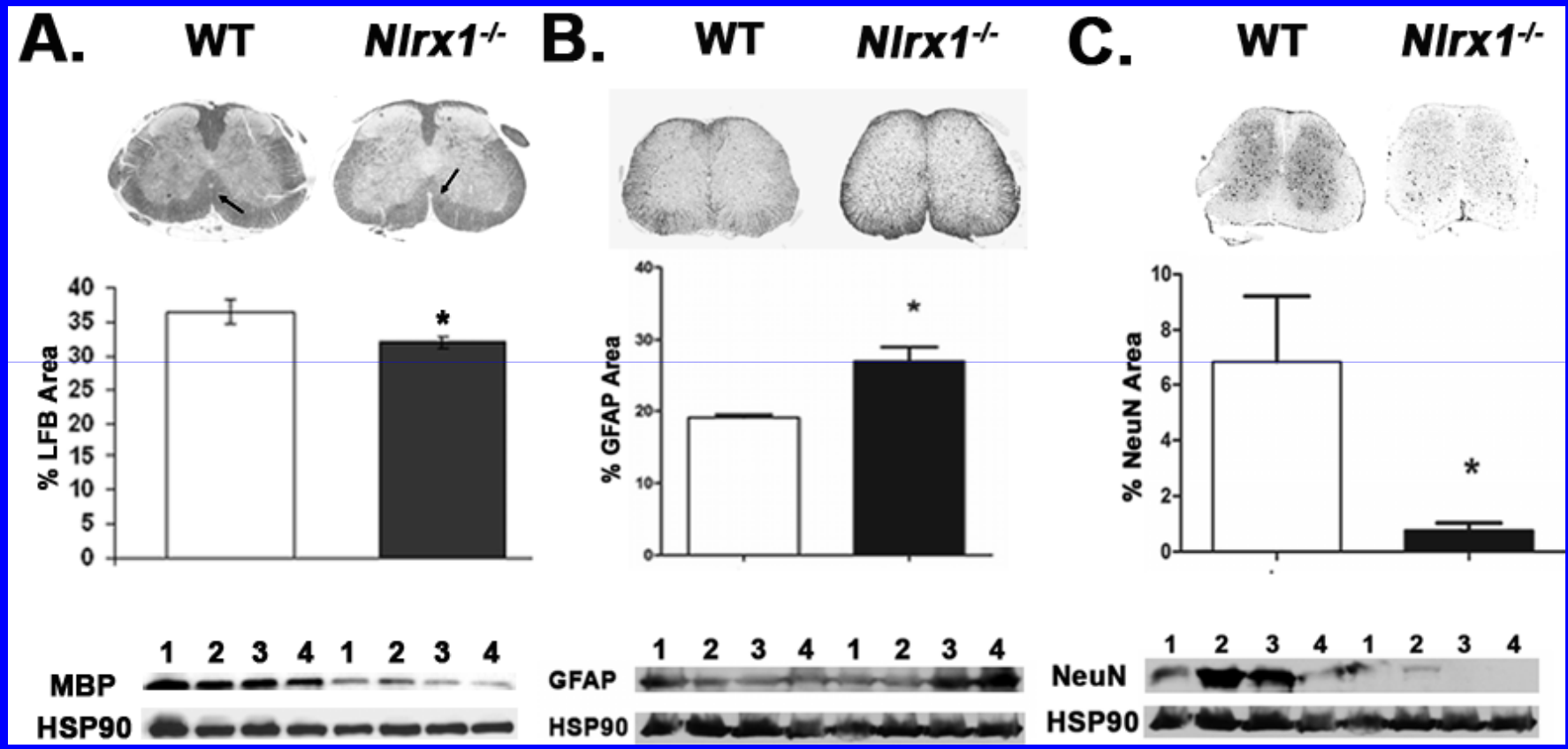
Nlrx1 controls inflammation within the CNS

Adoptive transfer of encephalitogenic T cells from 2D2 mice

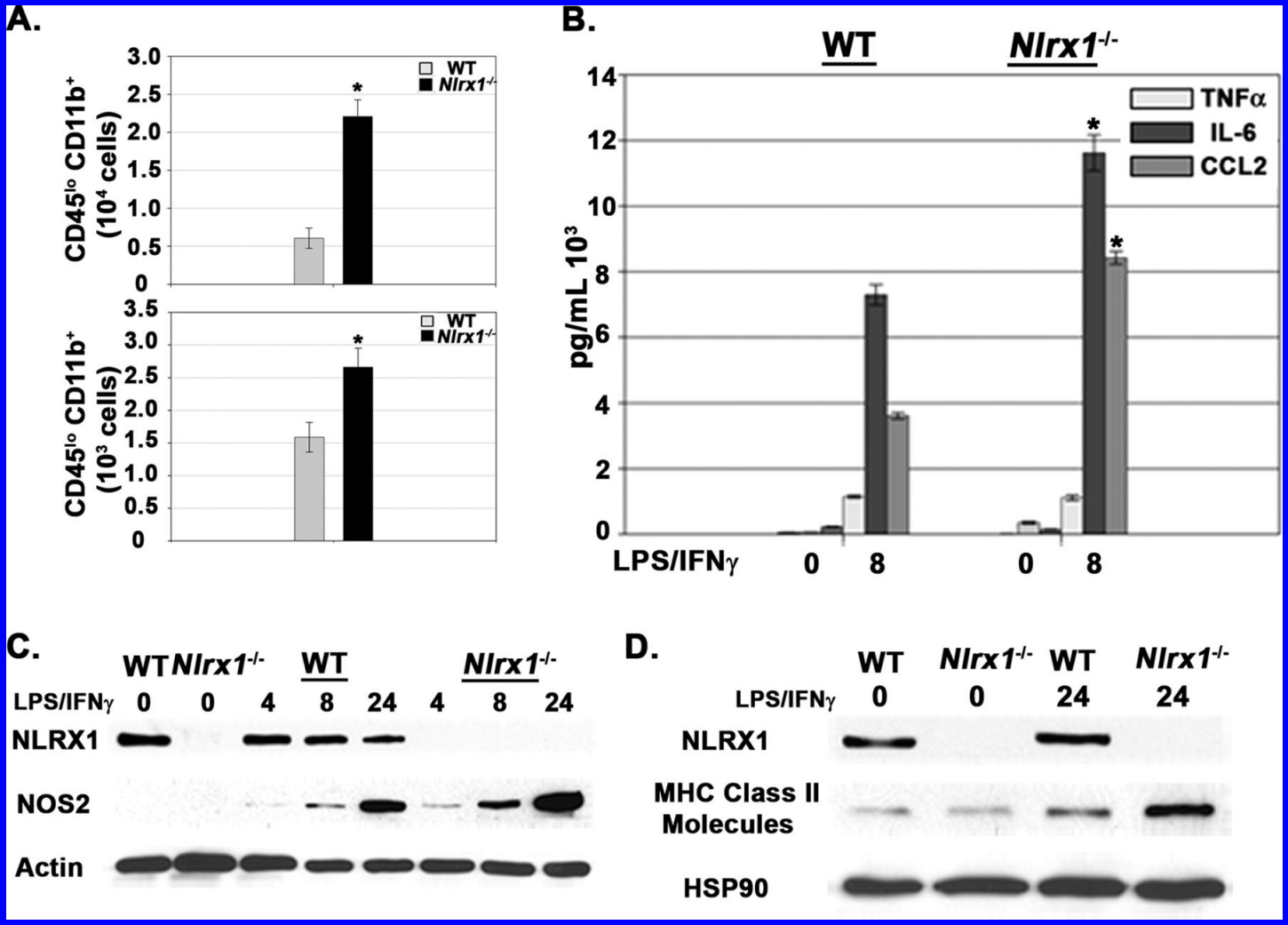


Nlrx1$^{-/-}$ mice have exacerbated EAE

Myelin Astrocytes Neurons



Nlrx1$^{-/-}$ microglia have enhanced inflammatory responses.



Eitas T K et al. J. Biol. Chem. 2014;289:4173-4179

Conclusions

- NLRs play detrimental role in development of EAE by augmenting pro-inflammatory effect of T cells, dendritic cells, macrophages, and microglia.
  Inflammasome, Nlrp3, NOD1, and NOD2

- NLRS can play protective role by acting at the level of microglia and macrophages to control excessive inflammation.
  NLRX1 and NLRP12

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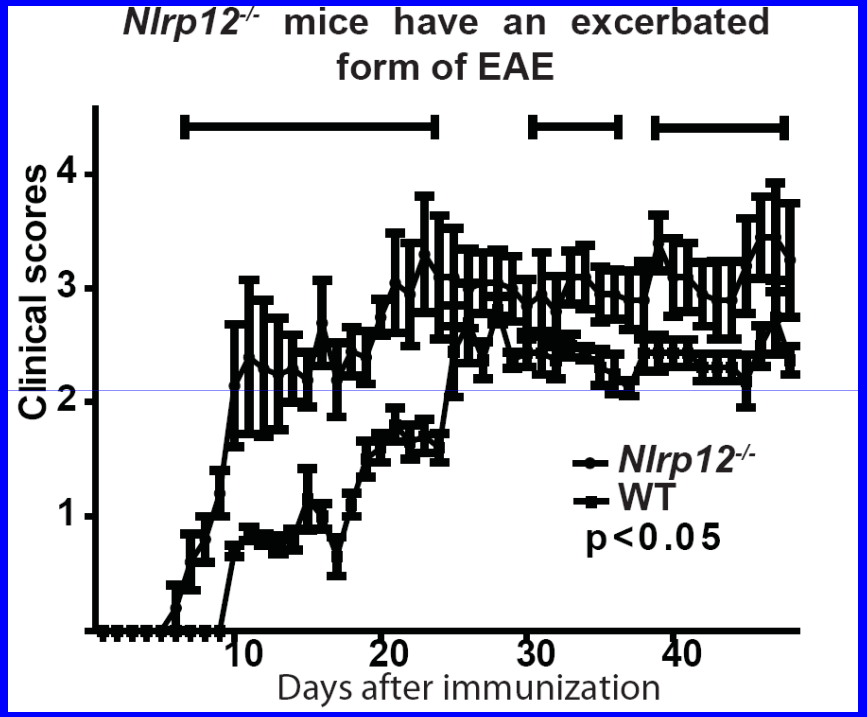
McGill University
Dr. Gris
Dr. Antel

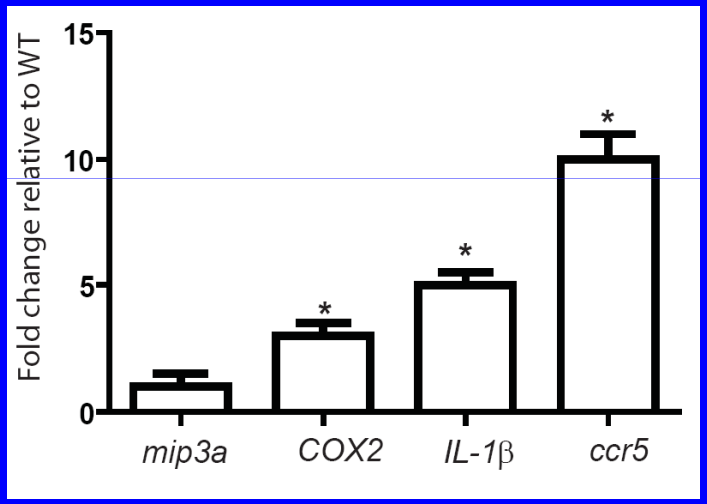
University of Bayreuth
Dr. Braun

University of Klien
Dr. Rosenstiel



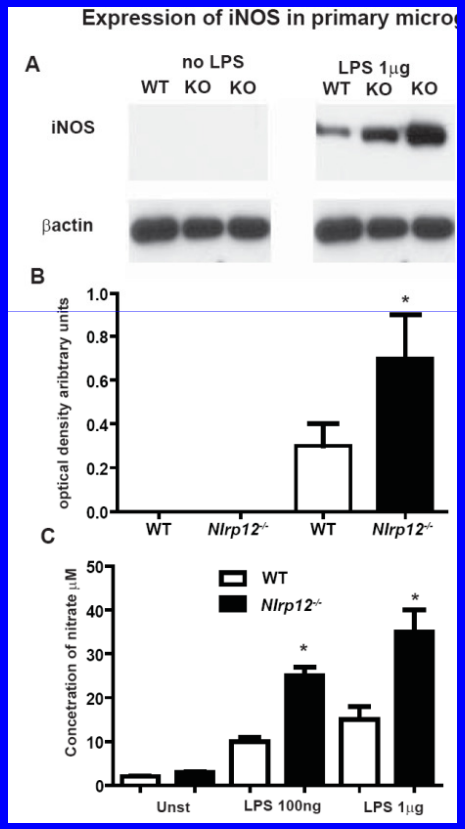
Nlrp12

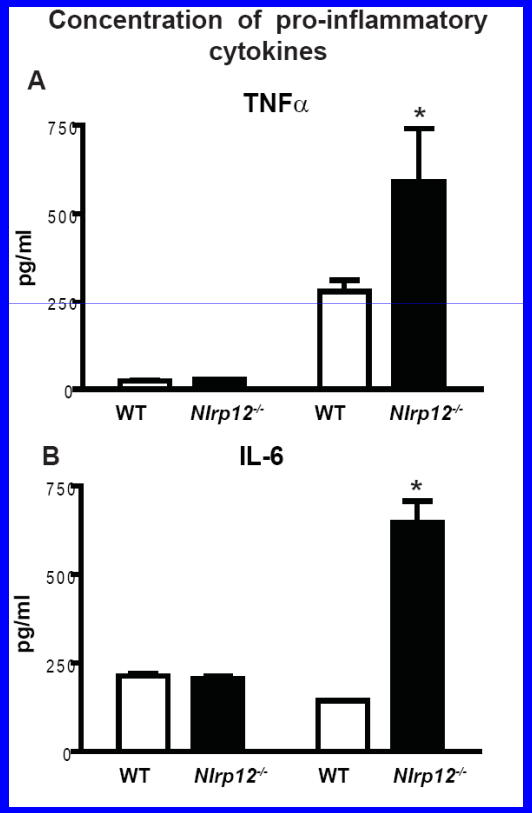




Nlrp12$^{-/-}$ mice have exacerbated form of EAE and elevated inflammatory response

Nlrp12 inhibitor of iNOS and cytokines expression



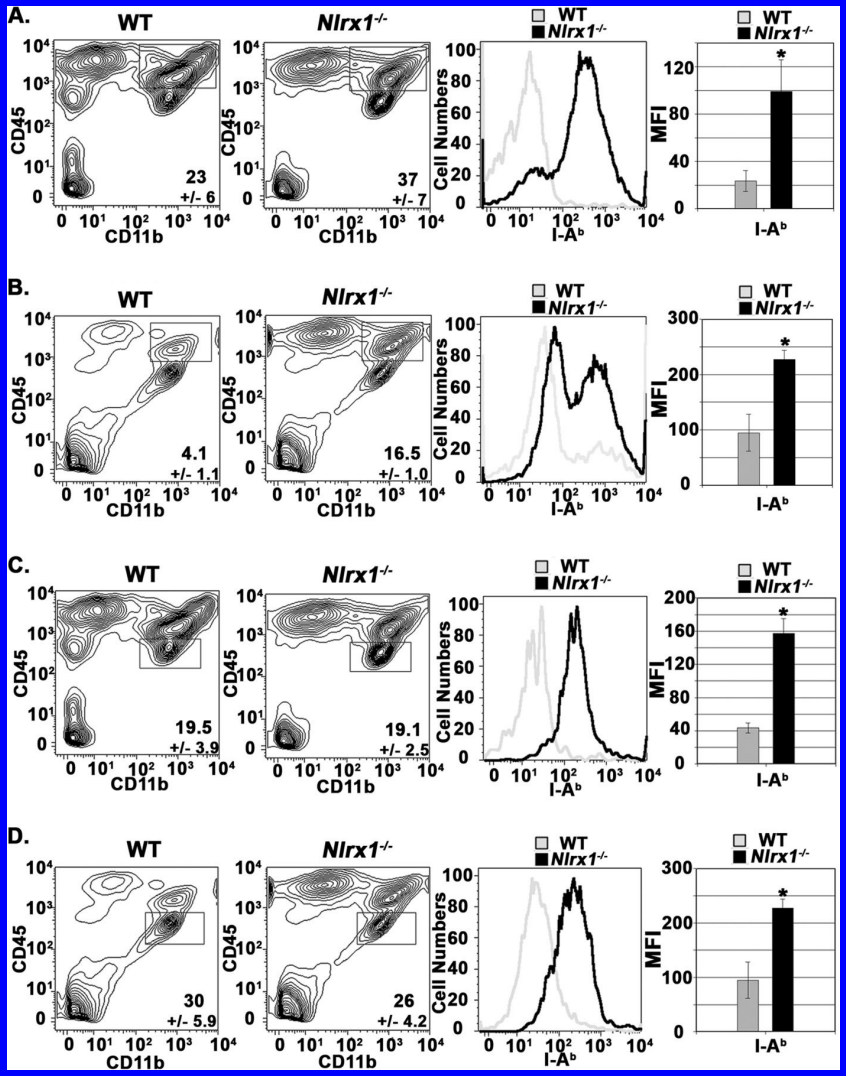


Significant increase in iNOS expression and TNFα and IL-6 production by *Nlrp12*$^{-/-}$ microglia

Microglia and macrophages are hyperactivated in *Nlrx1*$^{-/-}$ mice during EAE

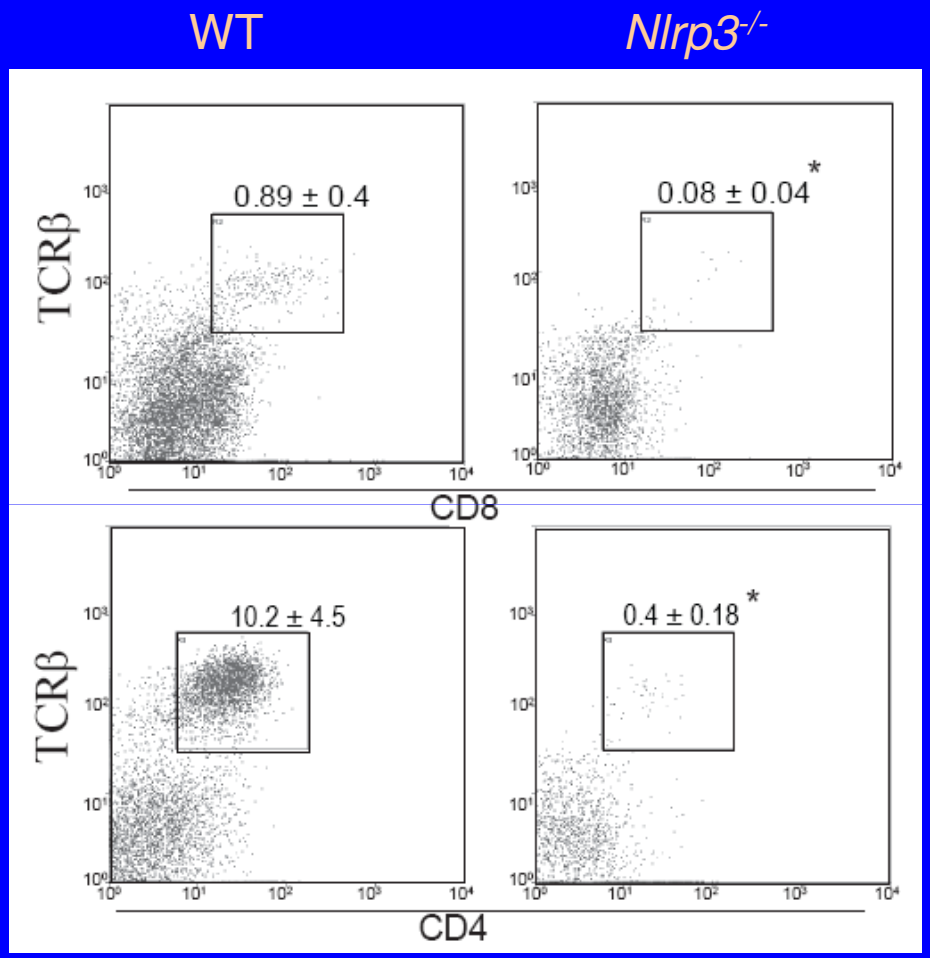
Macrophages

Microglia



Eitas T K et al. J. Biol. Chem. 2014;289:4173-4179

T cell infiltration 3 weeks after immunization



Spinal cords from *Nlrp3*$^{-/-}$ animals had fewer CD4 and CD8 T cells