Y a-t-il un Ac dans la SEP ??

T. VINCENT
GEAI Marseille
14.09.2012

Ann Neurol. 2000 Jun;47(6):707-17.

Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination.

Lucchinetti C, Brück W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H.
Department of Neurology, Mayo Clinic, Rochester, MN, USA

➔ **grande hétérogénéité des patients**

➔ **4 groupes définis par leurs lésions anatomopath.**

➔ **groupe II = dépôt Ig + C'**

➔ **rôle des Ac (?)**

➔ **efficacité des plasmaϕ**

doi:10.1093/brain/aws105 Brain 2012: 135; 1819–1833 | 1819

BRAIN
A JOURNAL OF NEUROLOGY

Functional identification of pathogenic autoantibody responses in patients with multiple sclerosis

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Modèle de myélinisation *in vitro* (rat)

- **30 % des patients ont des IgG à activité « démyélinisante »**
- **Cible antigénique = sur les oligodendrocytes** (≠ MOG)
- **Mécanisme C' - dépendant**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Potassium Channel KIR4.1 as an Immune Target in Multiple Sclerosis

Rajneesh Srivastava, M.Sc., Muhammad Aslam, Ph.D., Sudhakar Reddy Kalluri, M.Sc., Lucas Schirmer, M.D., Dorothea Buck, M.D., Björn Tackenberg, M.D., Veit Rothhammer, M.D., Andrew Chan, M.D., Ralf Gold, M.D., Achim Berthele, M.D., Jeffrey L. Bennett, M.D., Thomas Korn, M.D., and Bernhard Hemmer, M.D.

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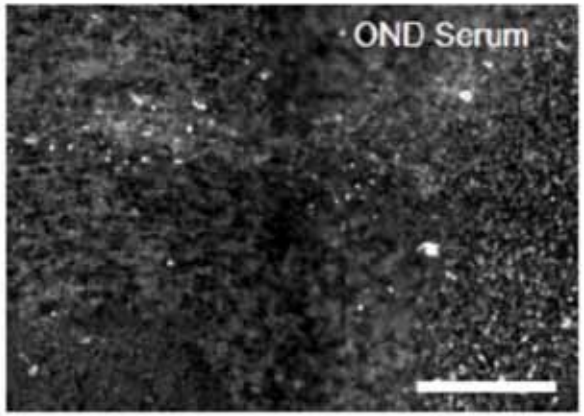
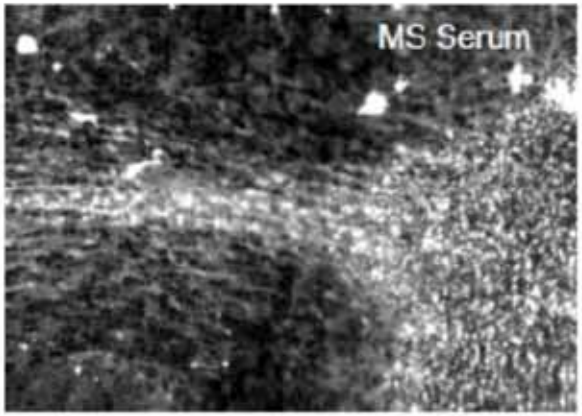
N Engl J Med. 2012 july 12; 367(2): 115-123

IFI avec IgG purifiées:

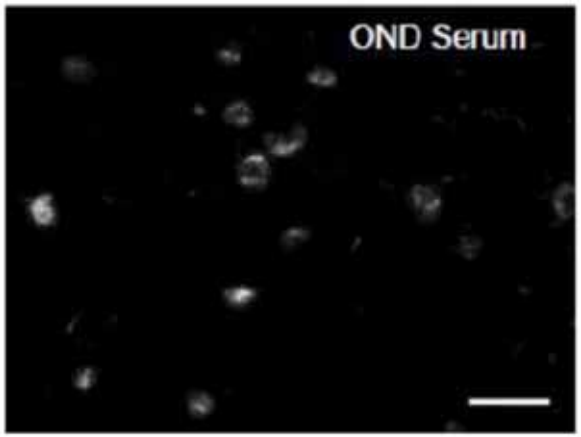
SEP (n=19) vs autres pathologies neurologiques (n=24)

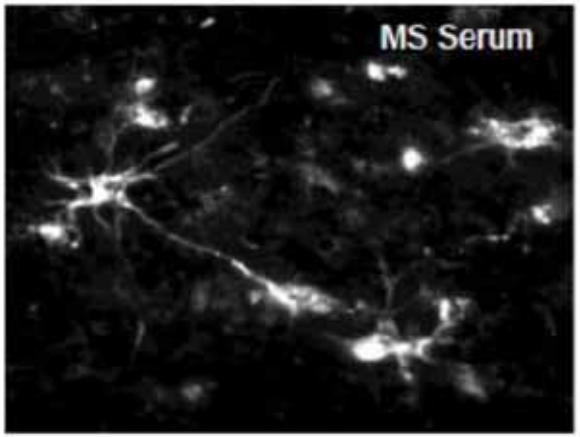
Rat Cerebellum





Human brain



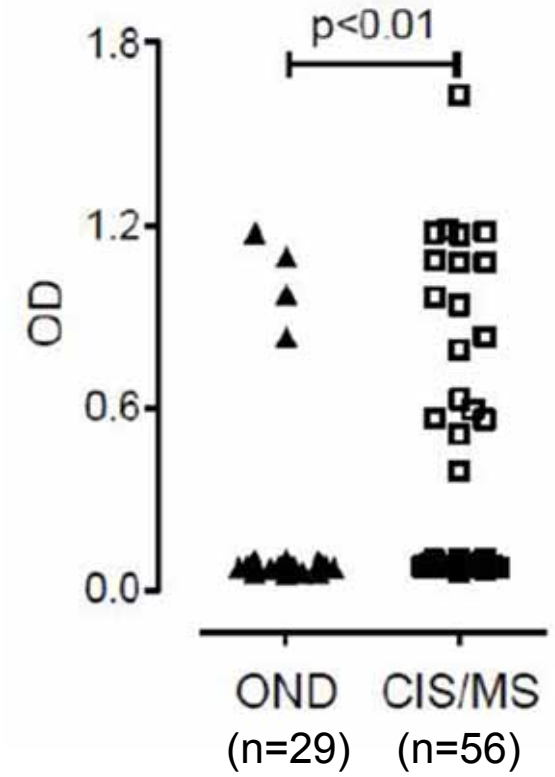


➡ **« glia specific immunoreactivity » (?)**

OND = 0%

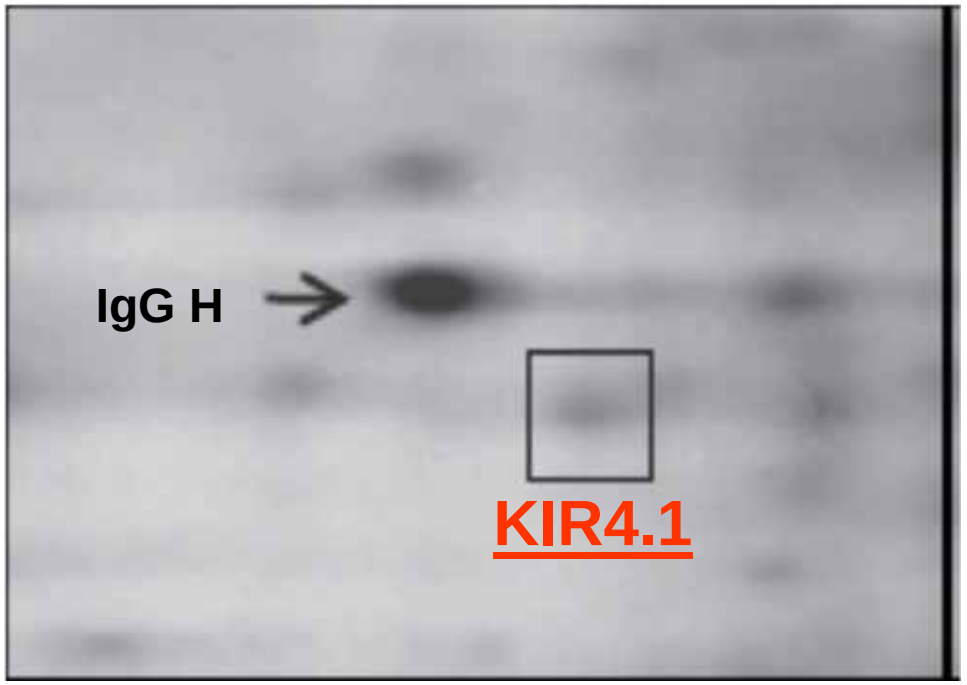
SEP = 58% (11/19) sur T humain
= 37% (7/19) sur rat

ELISA with membrane protein fractions prepared from rat (or human ?) brain tissue.



(pas de différence si protéines cytoplasmiques)

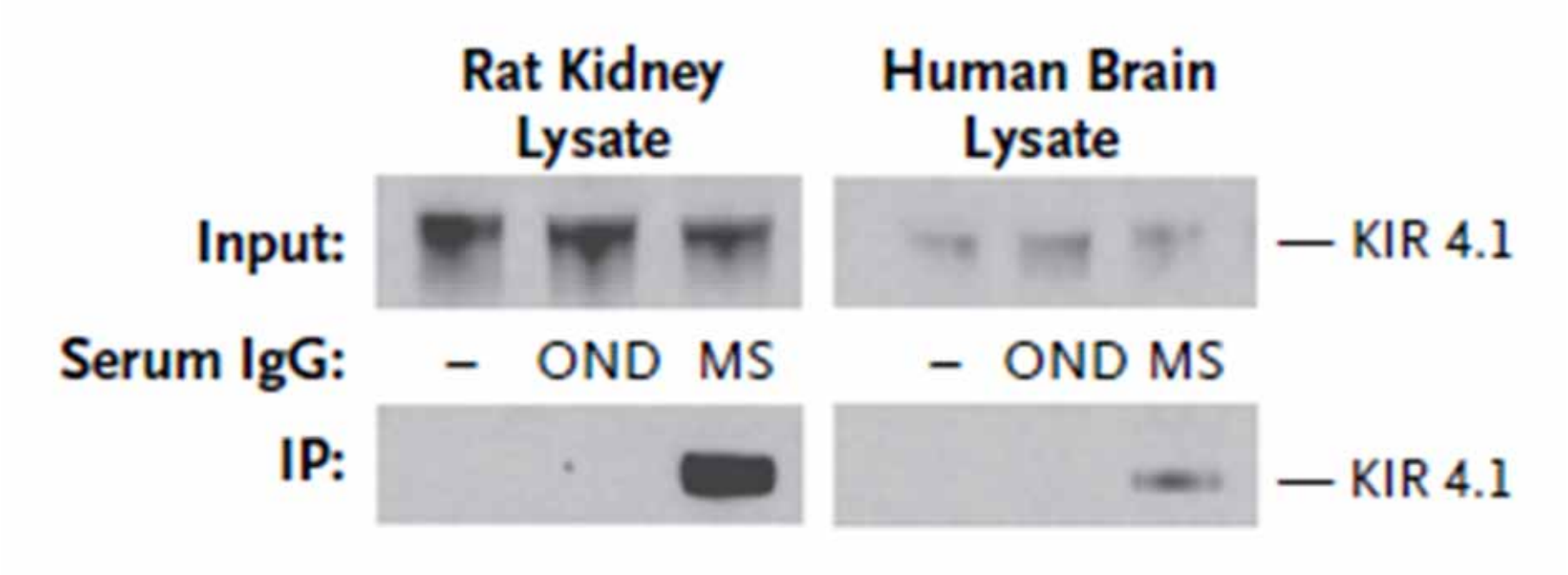
- **IP avec lysat de cerveau humain + IgG purifiées**
- **gel 2D**
- **spectrométrie de masse**



KIR4.1 = ATP-sensitive Inward Rectifying potassium channel

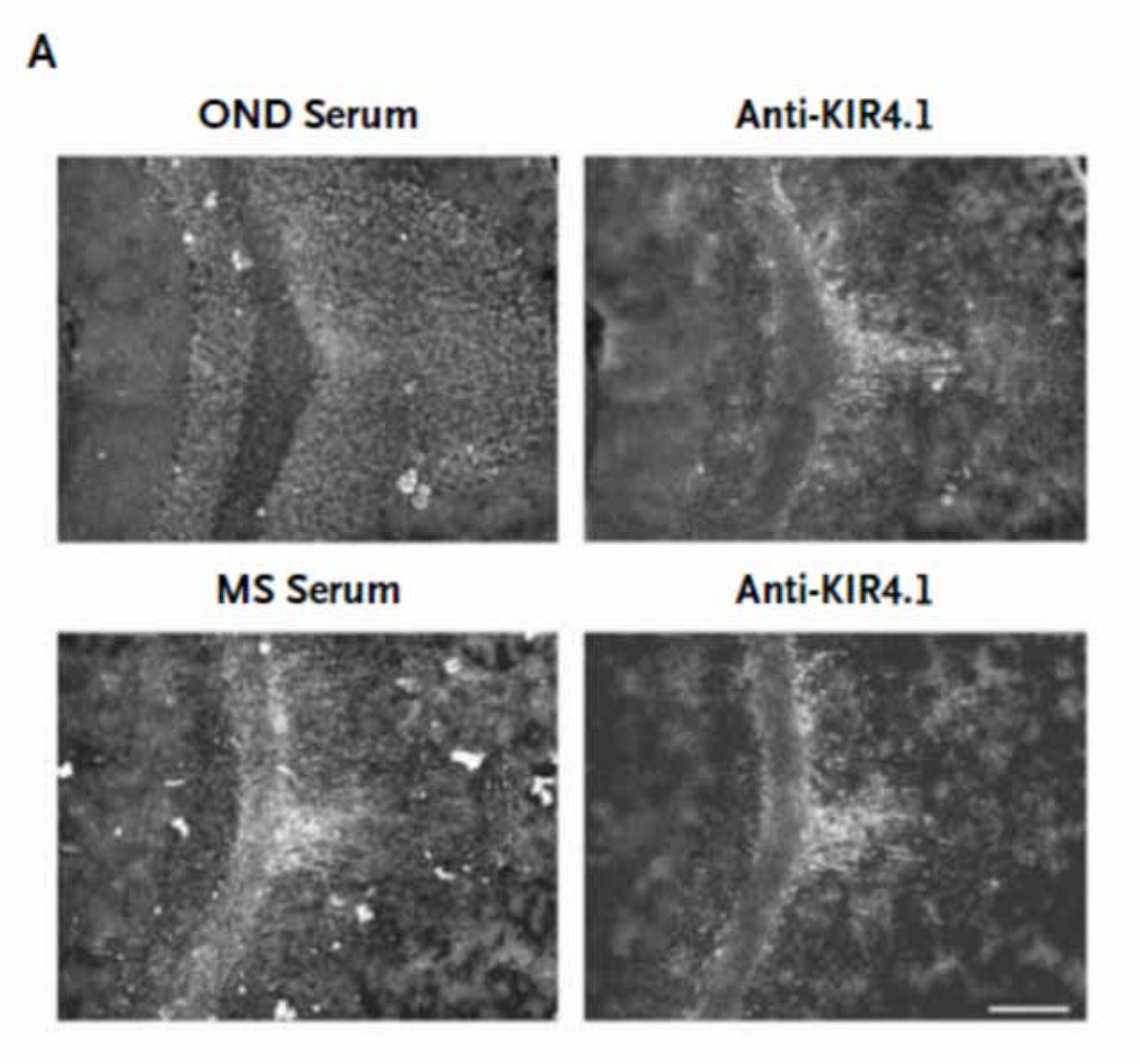
IP + WB :

Identification of KIR4.1 as a Target of Serum IgG in Multiple Sclerosis



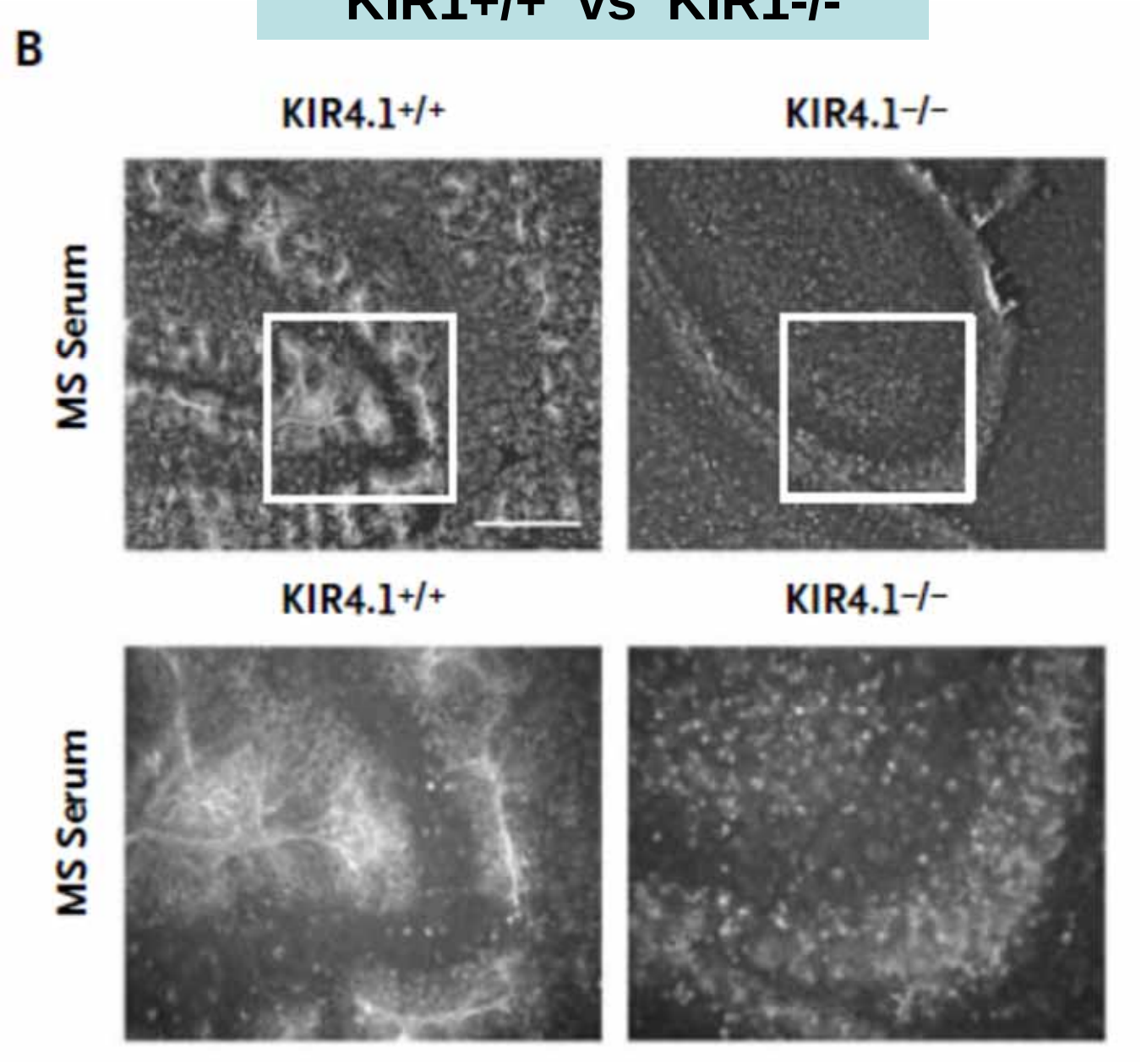
IFI on rat cerebellum (purified IgG)

colocalization anti-Kir4.1 / MS sera

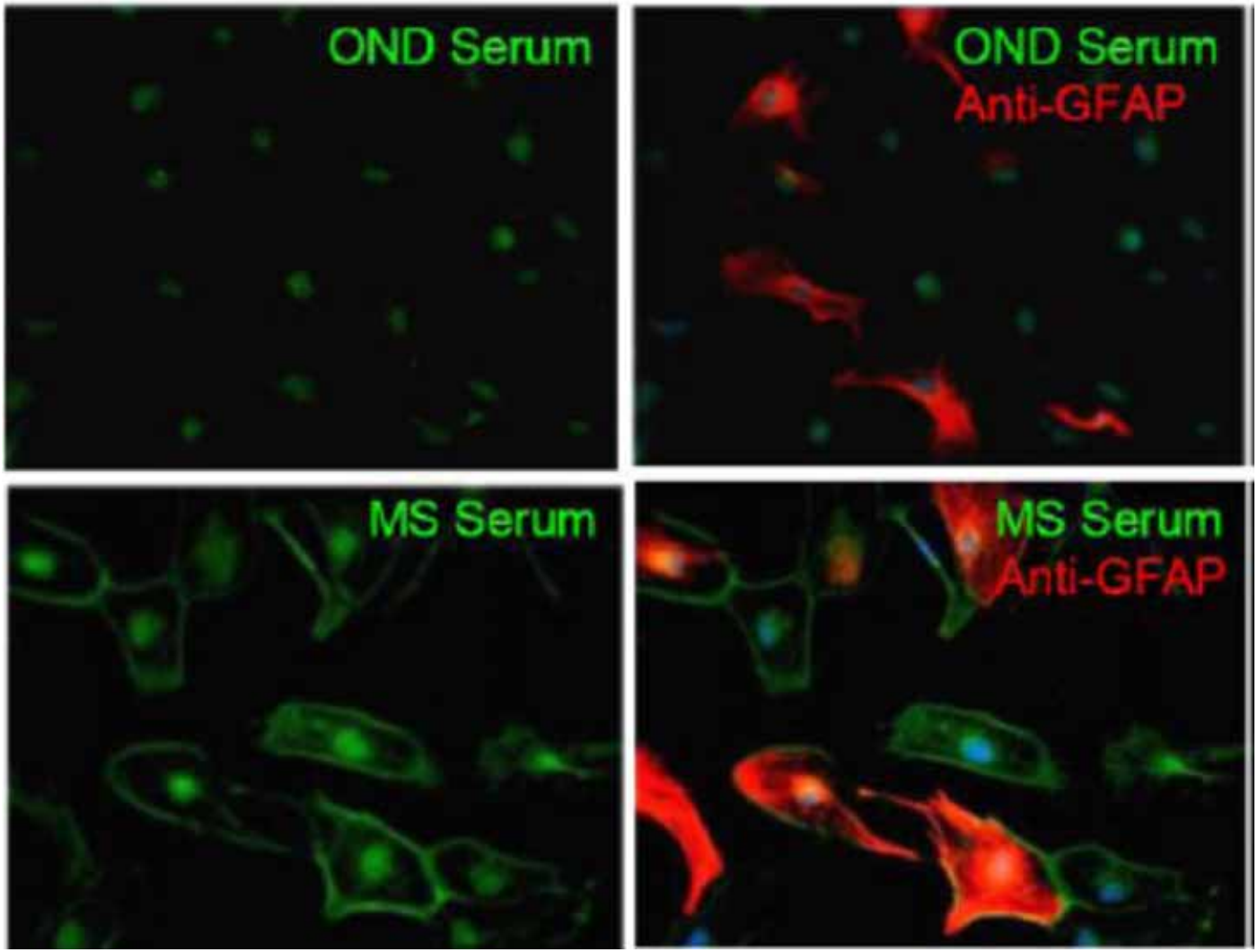


IFI on rat cerebellum:

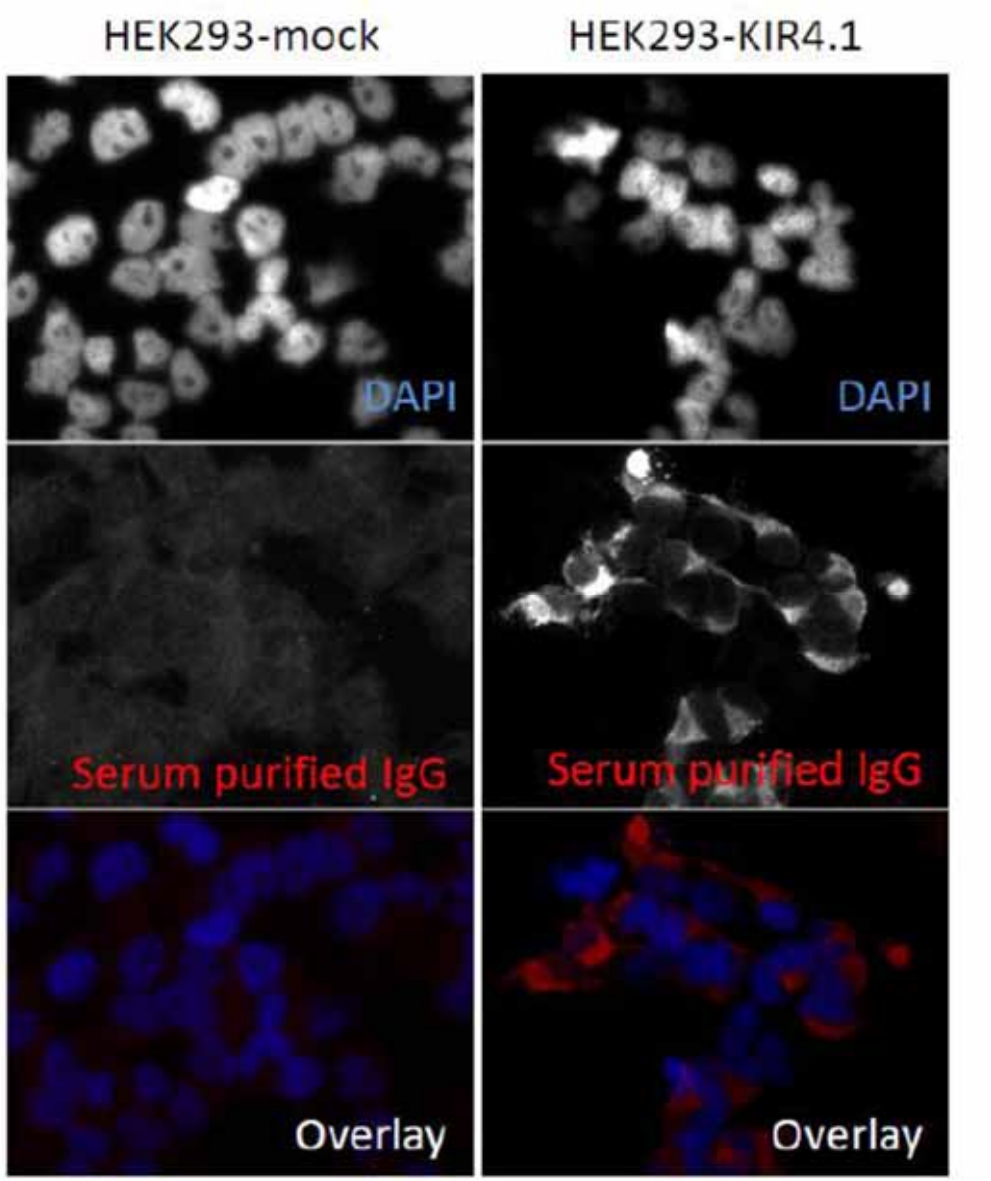
KIR1+/+ vs KIR1-/-



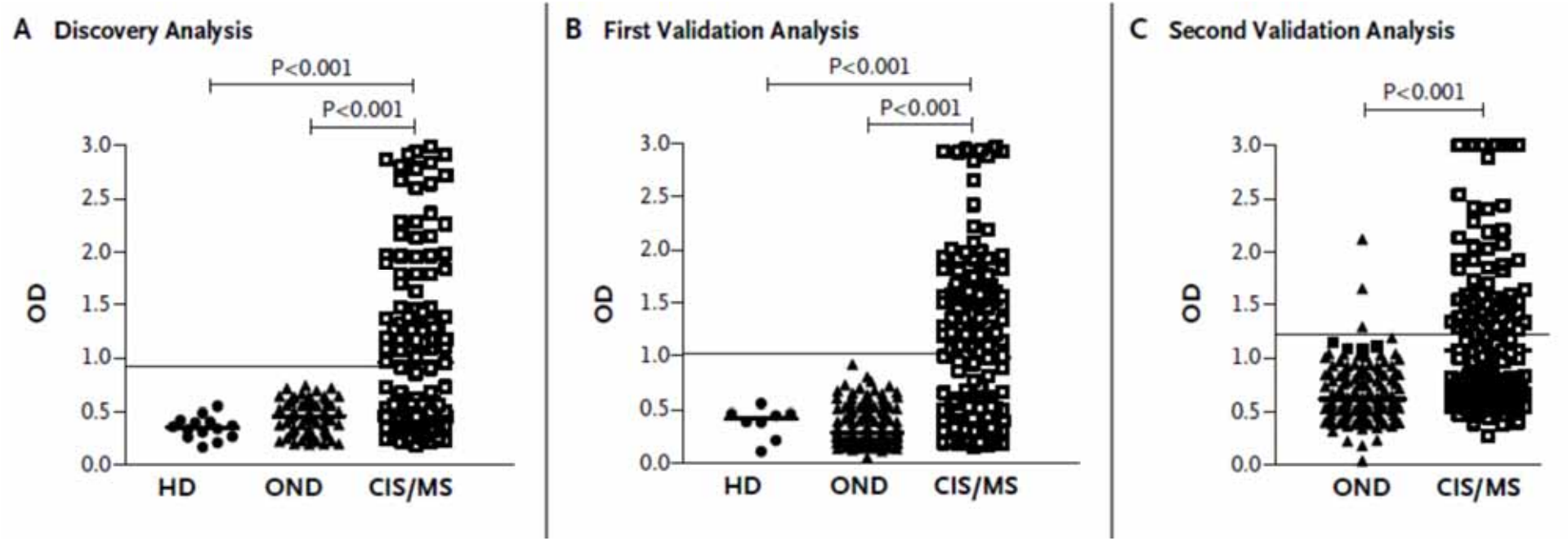
IFI on mouse primary mixed glial culture



IFI on HEK-293 transfected cells



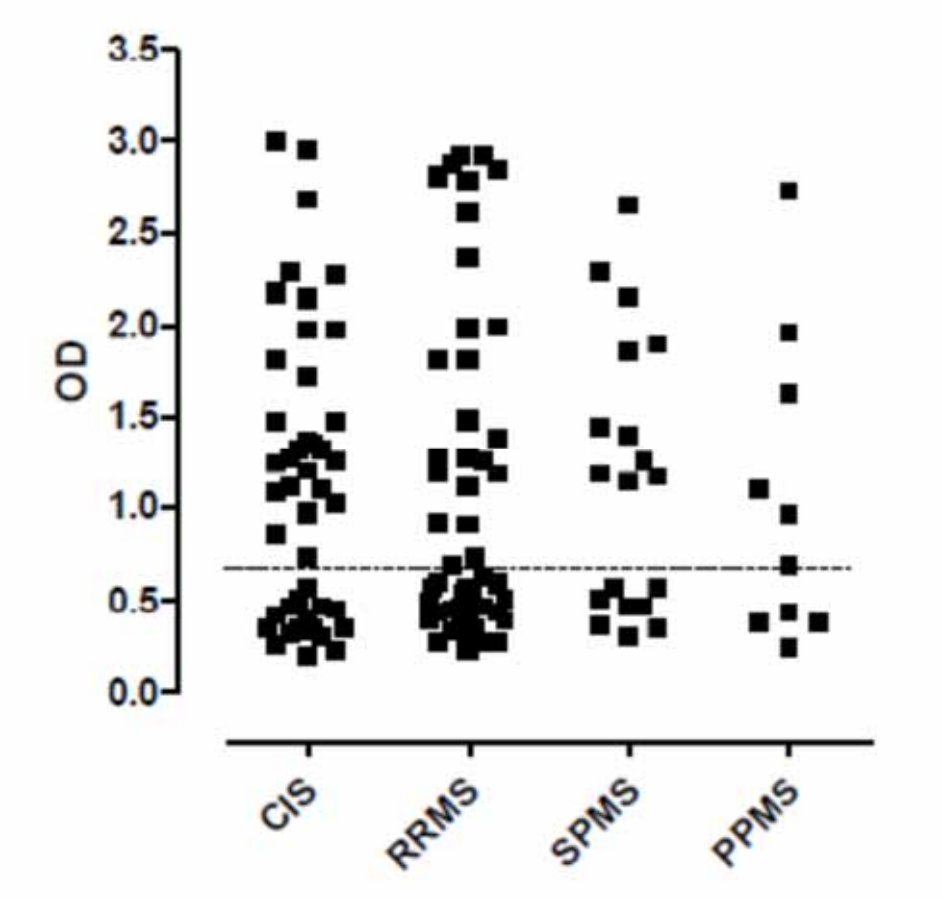
ELISA avec rKIR4.1



Seuil de positivité = DO des contrôles sains + 5 SD

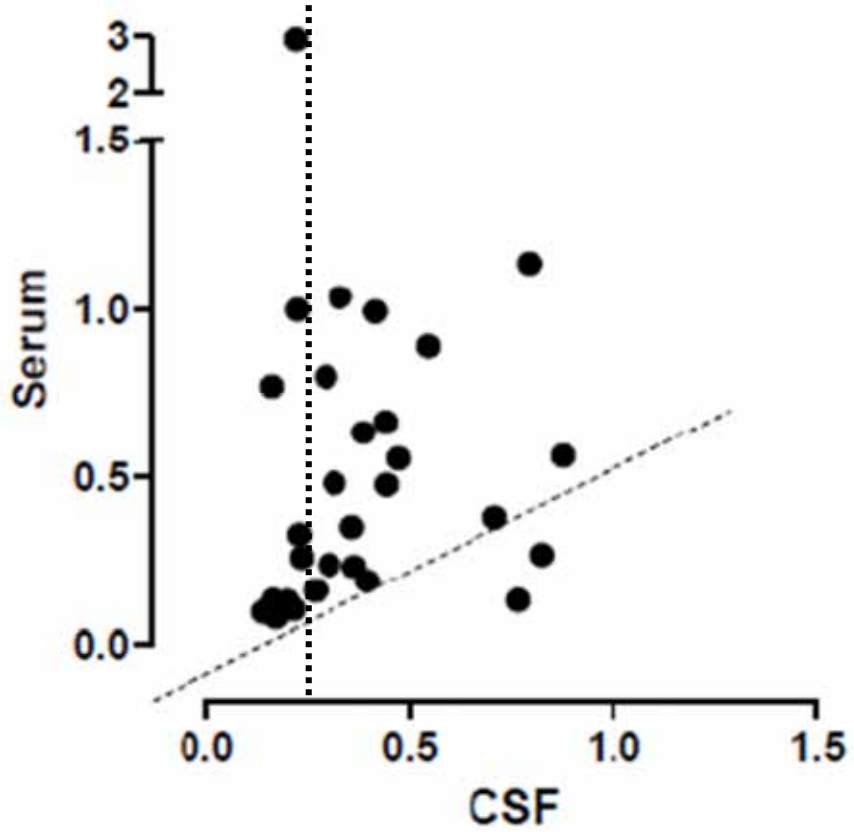
- **CIS/SEP: 186 / 397 = 46.9%**
- **OND: 3 / 329 = 0.9%**
- **HC 0 / 59 = 0%**

ELISA avec rKIR4.1



- pas de différence entre CIS / RRMS / SPMS / PPMS
- pas de corrélation avec âge ou caractéristiques cliniques

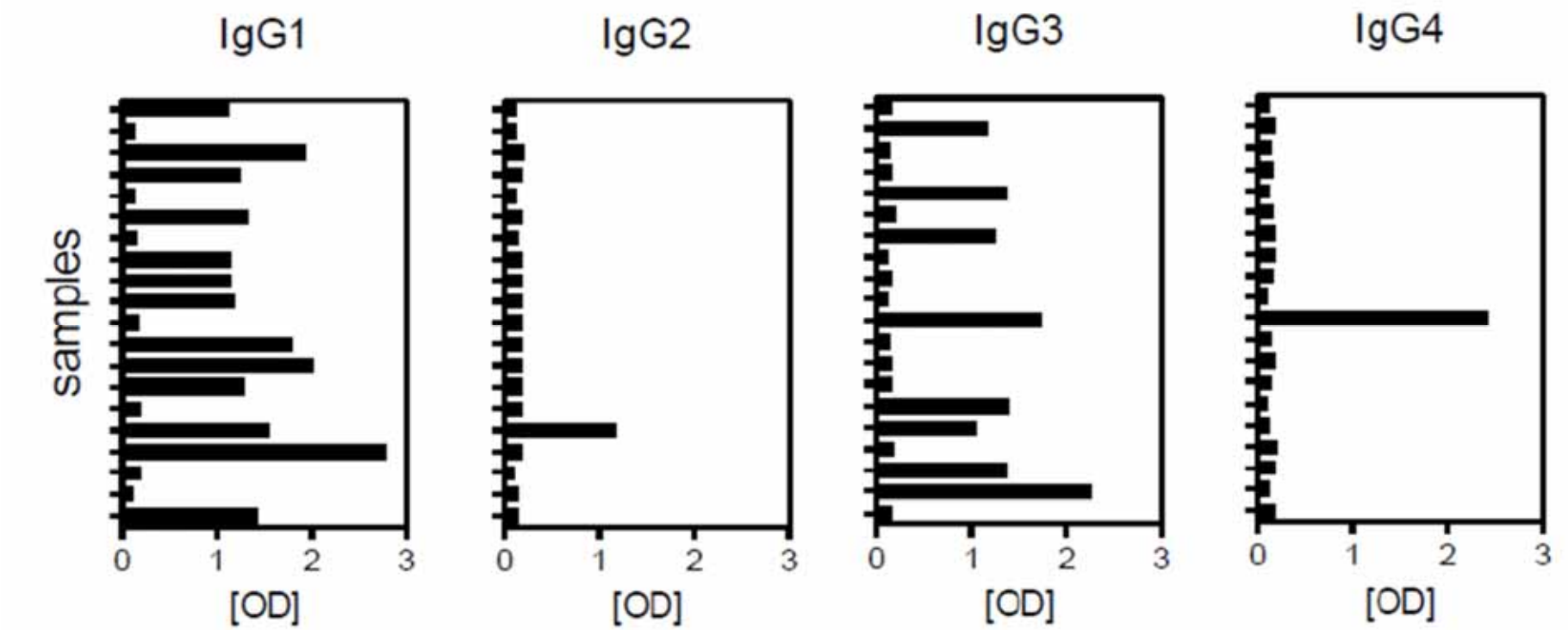
ELISA avec rKIR4.1



Présence d'Ac dans le LCR: 19/30

2 patients (seulement) avec sécrétion intra-thécale (index > 2)

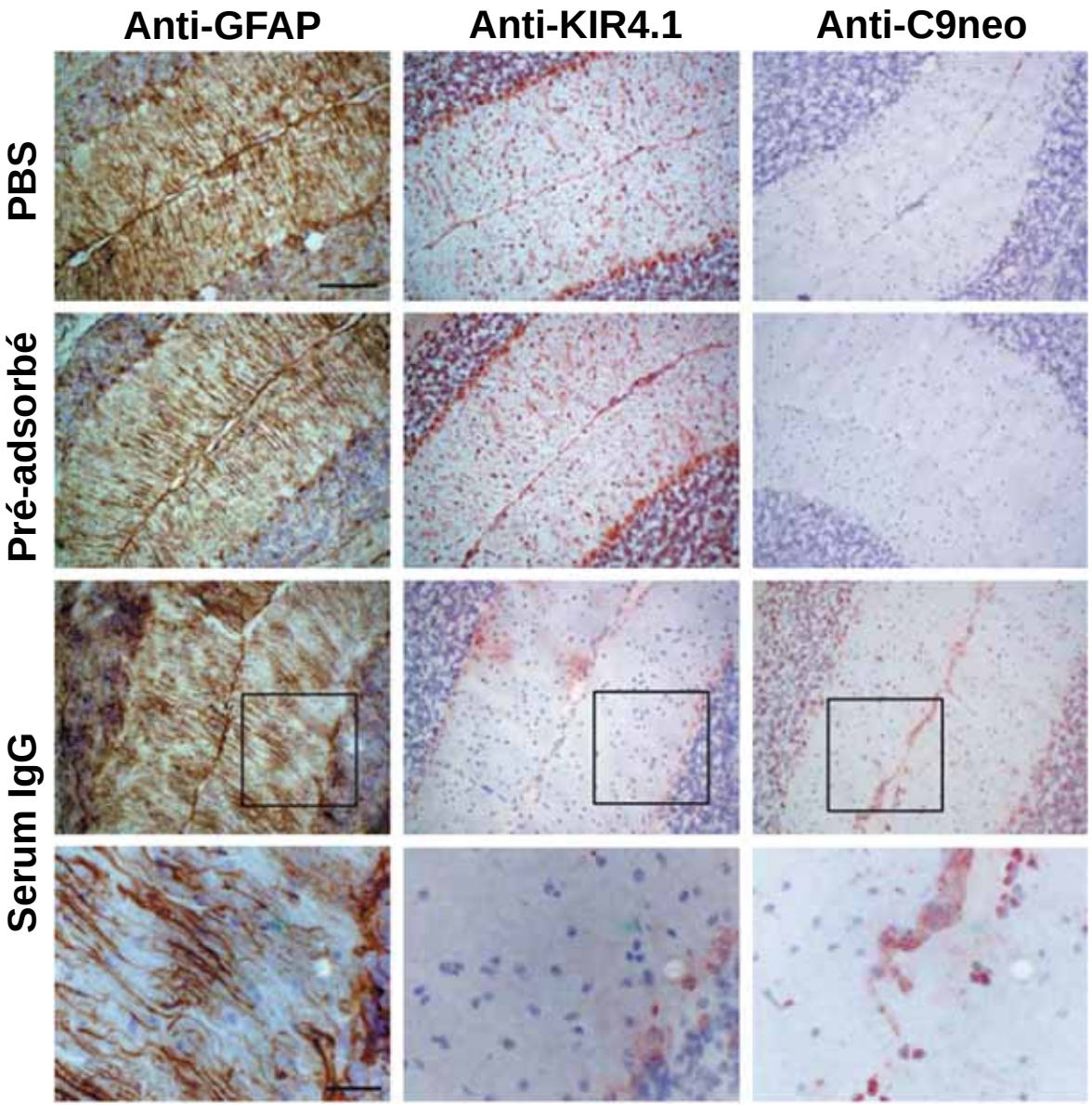
ELISA avec rKIR4.1



Tous les patients = IgG1 et/ou IgG3

➔ Capables d'activer le C'

Injection in vivo (grande citerne): IgG purifiées + C’



À 24h:

- **↘ expression GFAP**
- **perte expression KIR4.1**
- **dépôt C9neo**

conclusion

Présence d'Ac anti-KIR4.1 chez 46.9% des patients

KIR4.1: - homéostasie H_20 / K^+ (couplage AQP4)
- recapture glutamate
- développt des oligodendrocytes et myélinisation

- Perturbation homéostasie H_20 / K^+
- excitotoxicité
- lésions directes oligoD et/ou astrocytes (CDC – ADCC)
- inflammation (activation C')

???