Master 1: Biologie Humaine Lyon

*Master 2 M2R : **Immunologie** Paris VI*

Thèse de Médecine

Equipe de recherche coordonnée par **Jérôme Devaux** (DR) à l'INM

2007 *2014* *2019* *2020* *2021*

Show must go on…

Etudiant en médecine (Lyon Sud)

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Carrière Hospitalo-Universitaire (Montpellier)

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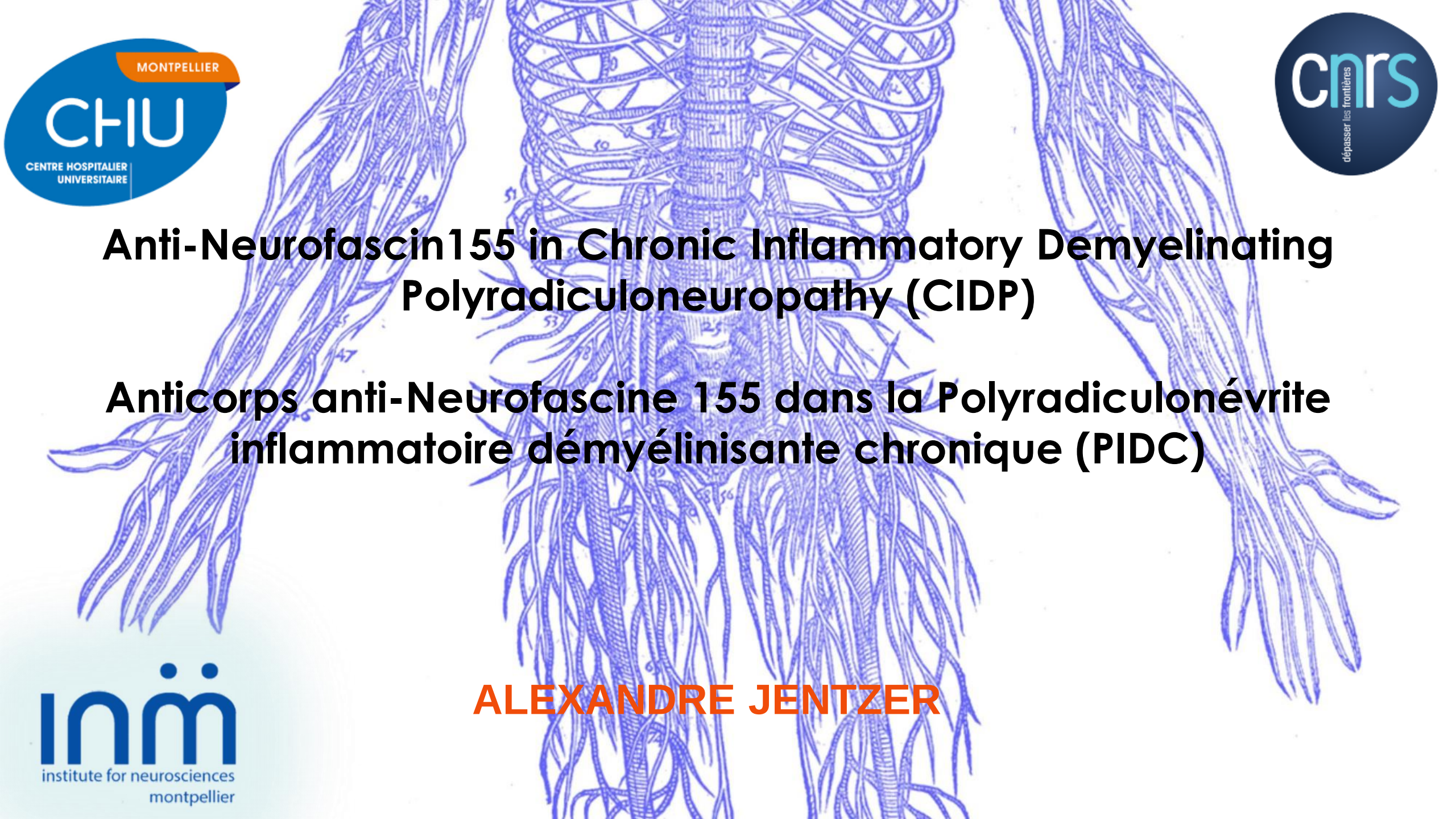
1 (Montpellier)

<u>Hospitalier</u> :
Auto-immunité
Allergologie

<u>Universitaire</u> :
Neuro-immunologie

Thèse de Science Juin 2021

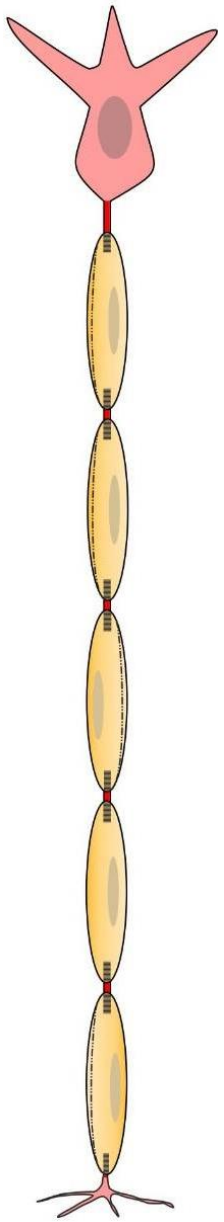


Anti-Neurofascin155 in Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

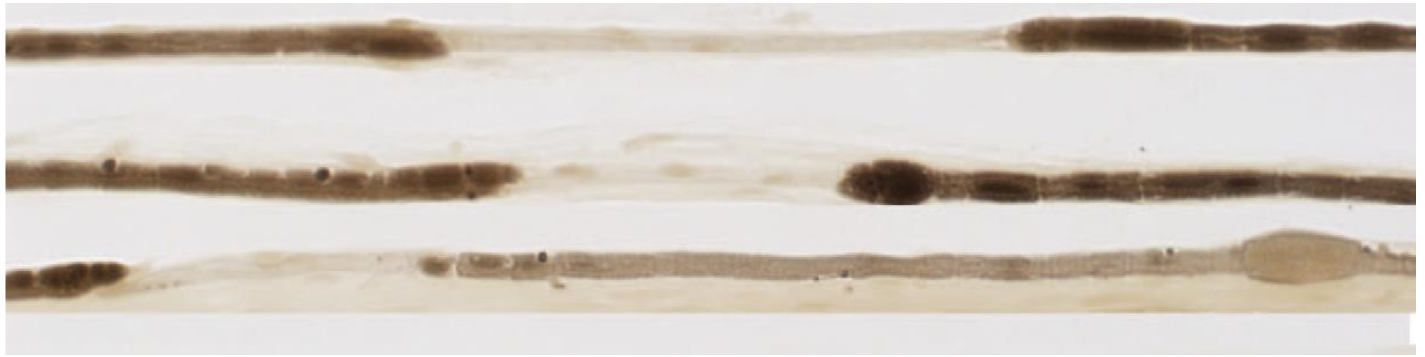
Anticorps anti-Neurofascine 155 dans la Polyradiculonévrite inflammatoire démyélinisante chronique (PIDC)

ALEXANDRE JENTZER

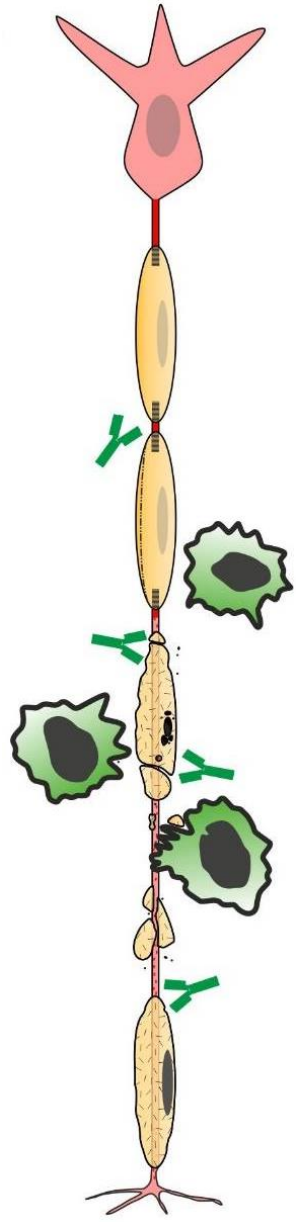
CIDP: Chronic Inflammatory Demyelinating Polyradiculoneuropathy



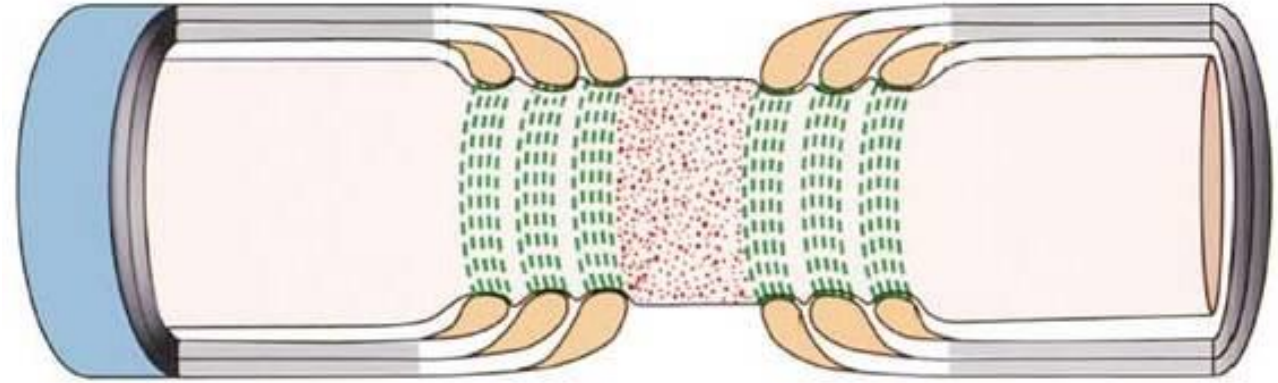
- *Symmetric proximal and distal weakness and sensory dysfunction of all extremities*
- *Absent or reduced tendon reflexes in all extremities*
- *Electrodiagnostic criteria (Reduced motor conduction velocity, prolonged F-wave latencies, conduction block,…)*
- *Nerve biopsies (demyelination and/or remyelination, endoneurial oedema,...)*
- *Elevated CSF protein*



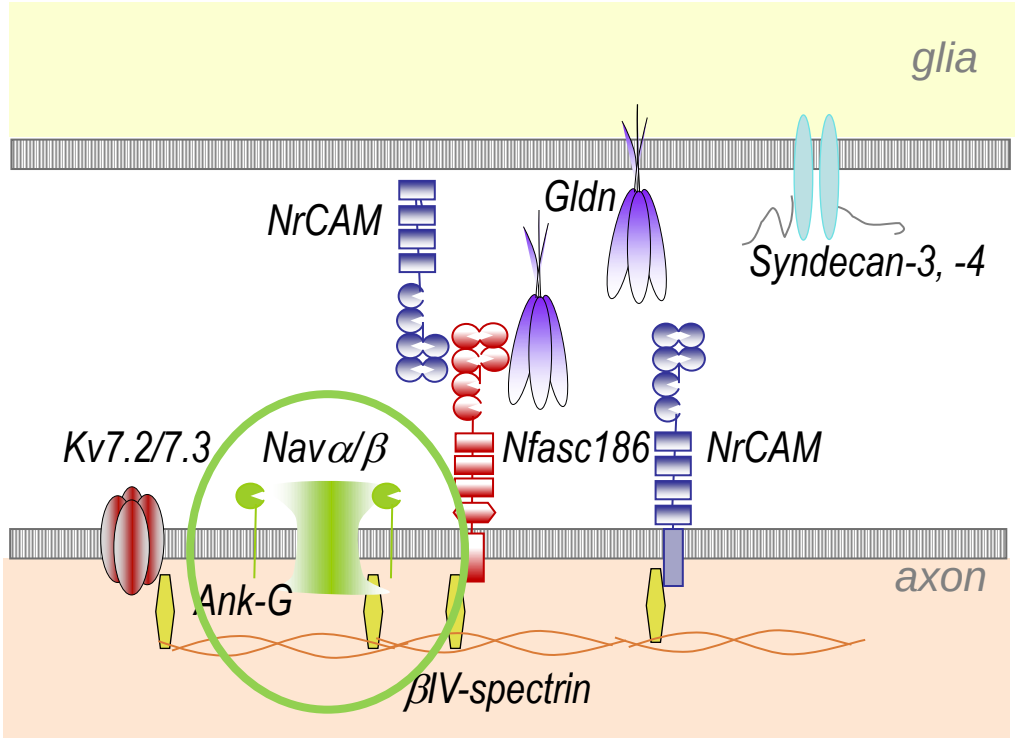
Laughlin et al., 2009



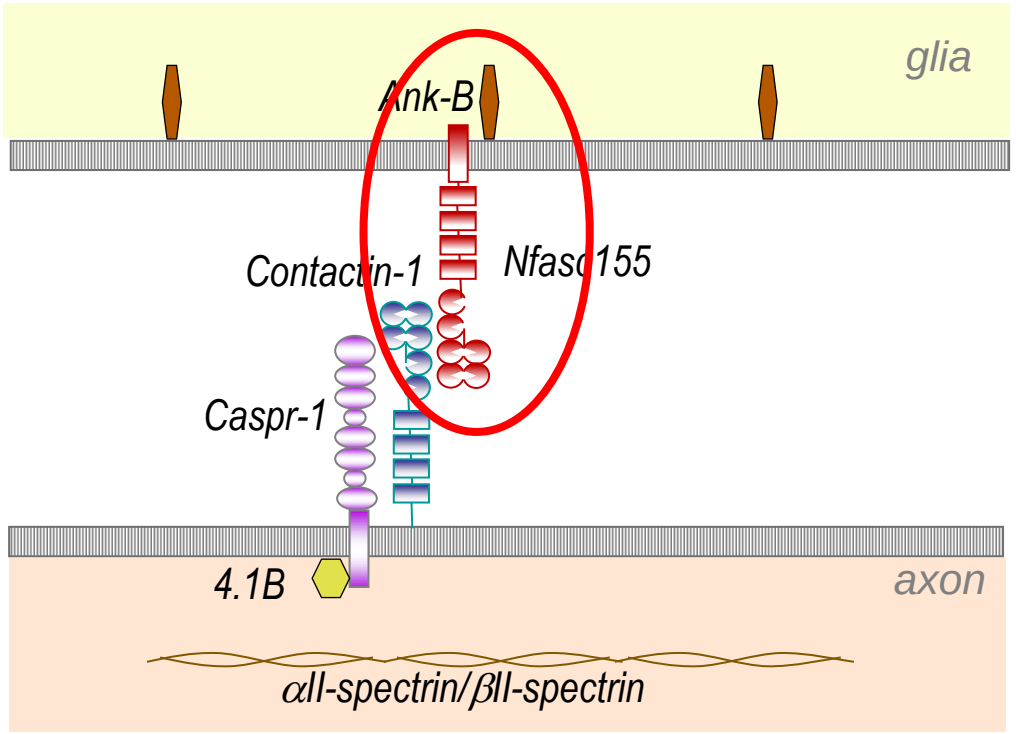
Structure of the node of Ranvier



Node



Paranode



Sarrailh et Devaux, 2013

Querol et al, 2017

Clinical relevance of autoantibodies in CIDP

Isotypes	Prevalence	Clinical presentation
Anti-CNTN1		
IgG4	1-2,4 %	Sensory ataxia Sub-acute onset Poor response to IVIg Good response to steroids
Anti-Nfasc155		
IgG4	4-7 %	Sensory ataxia, Tremors Sub-acute onset CNS demyelination Poor response to IVIg Good response to steroids
Anti-Caspr1		
IgG4/IgG3	1 %	Sensory ataxia Poor response to IVIg
Anti-Nfasc186		
IgG4/IgG3	2 %	Sensory ataxia Sub-acute onset Severe onset

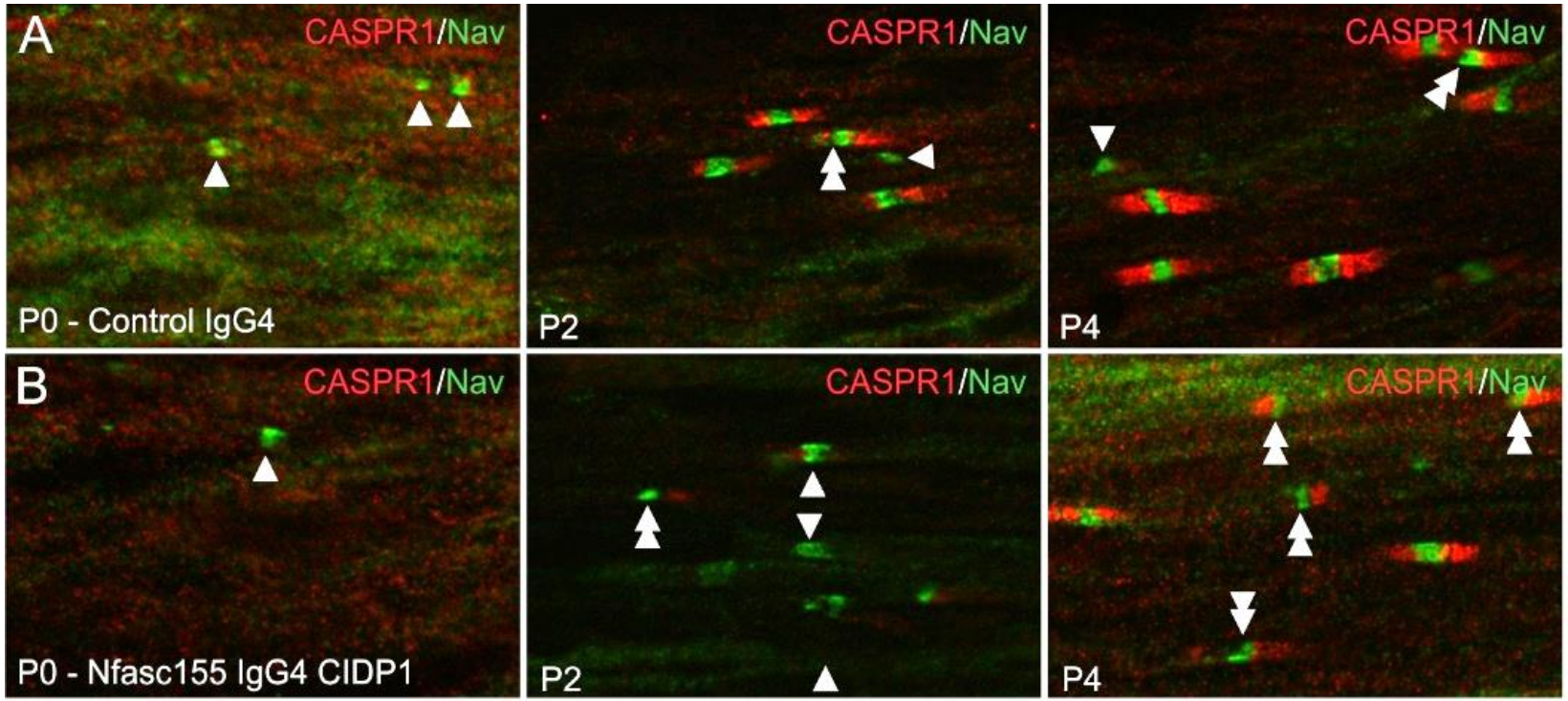
→ Specific of sub-groups of CIDP patients

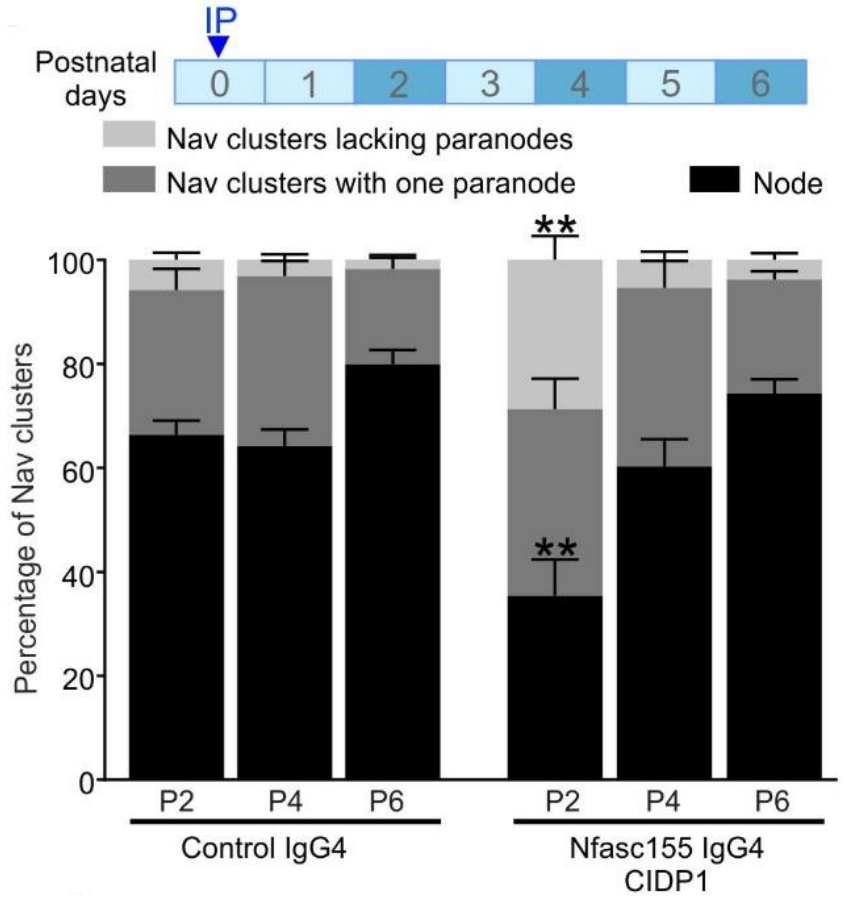
→ Prognosis and diagnosis

→ Help therapeutic choice: Rituximab

Miura *et al*, 2015 Devaux *et al*, 2016 Delmont *et al*, 2017 Cortese *et al*, 2019

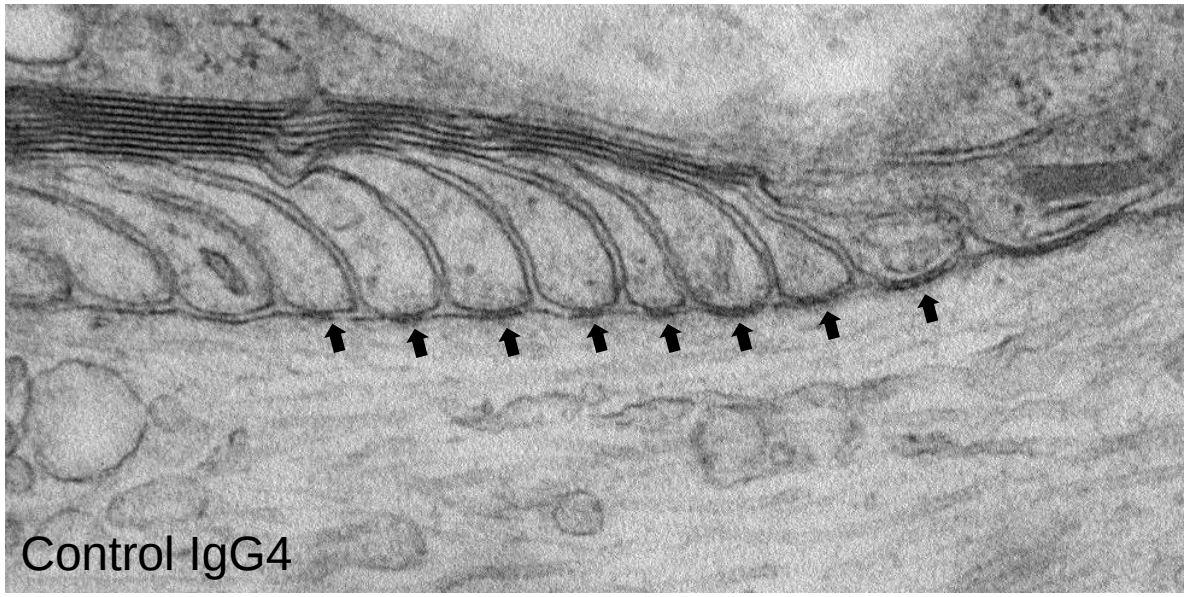
Passive transfer of anti-Nfasc155 IgG4 delays paranode formation

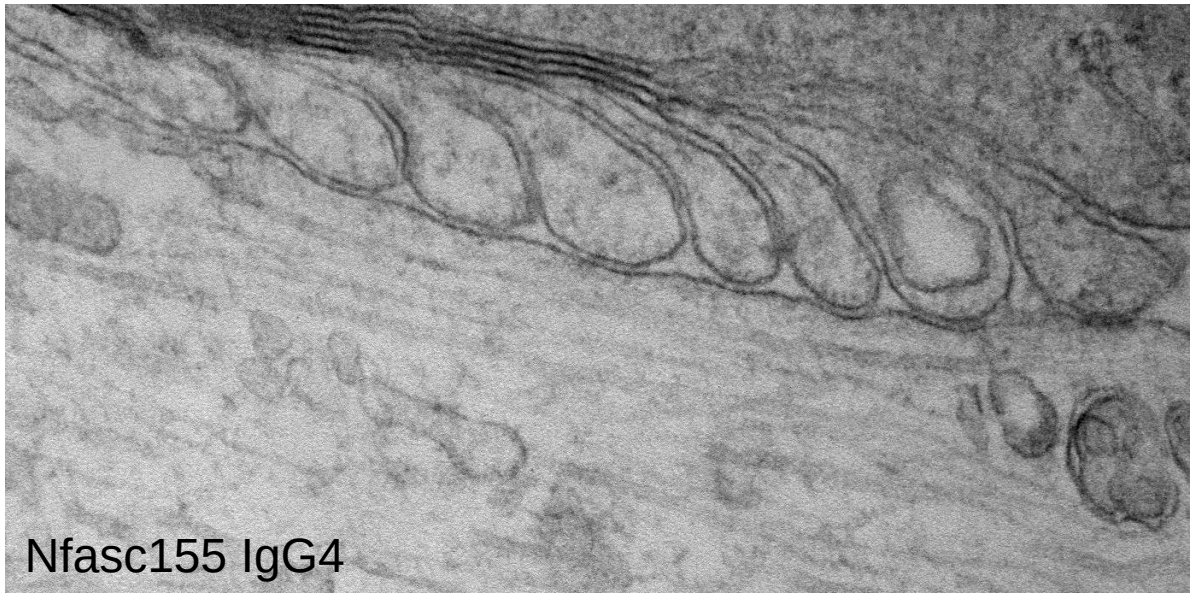


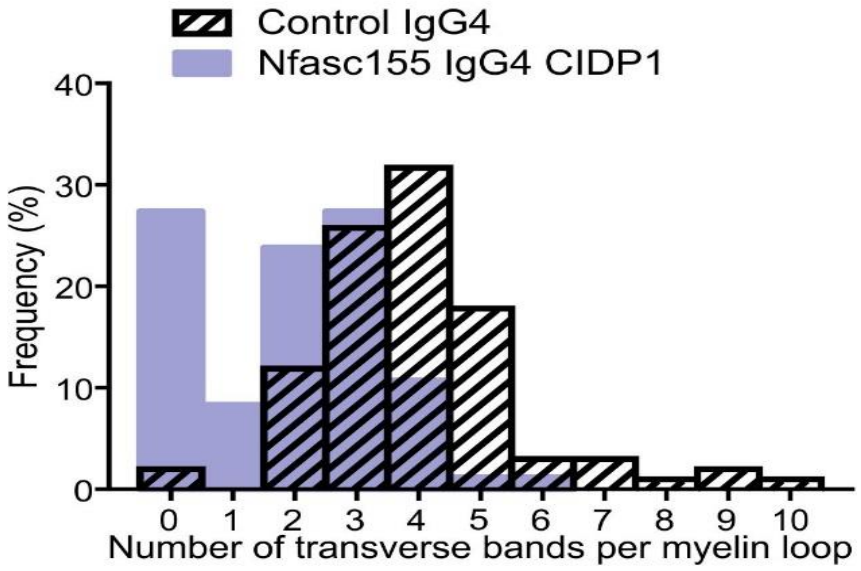


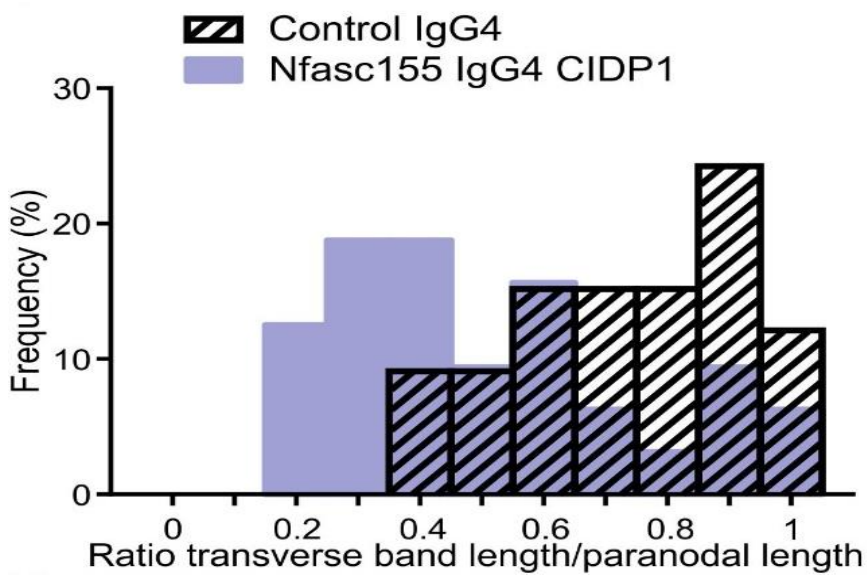
Manso *et al.*, 2019

Nfasc155 depletion associates with a loss of septate-like junctions

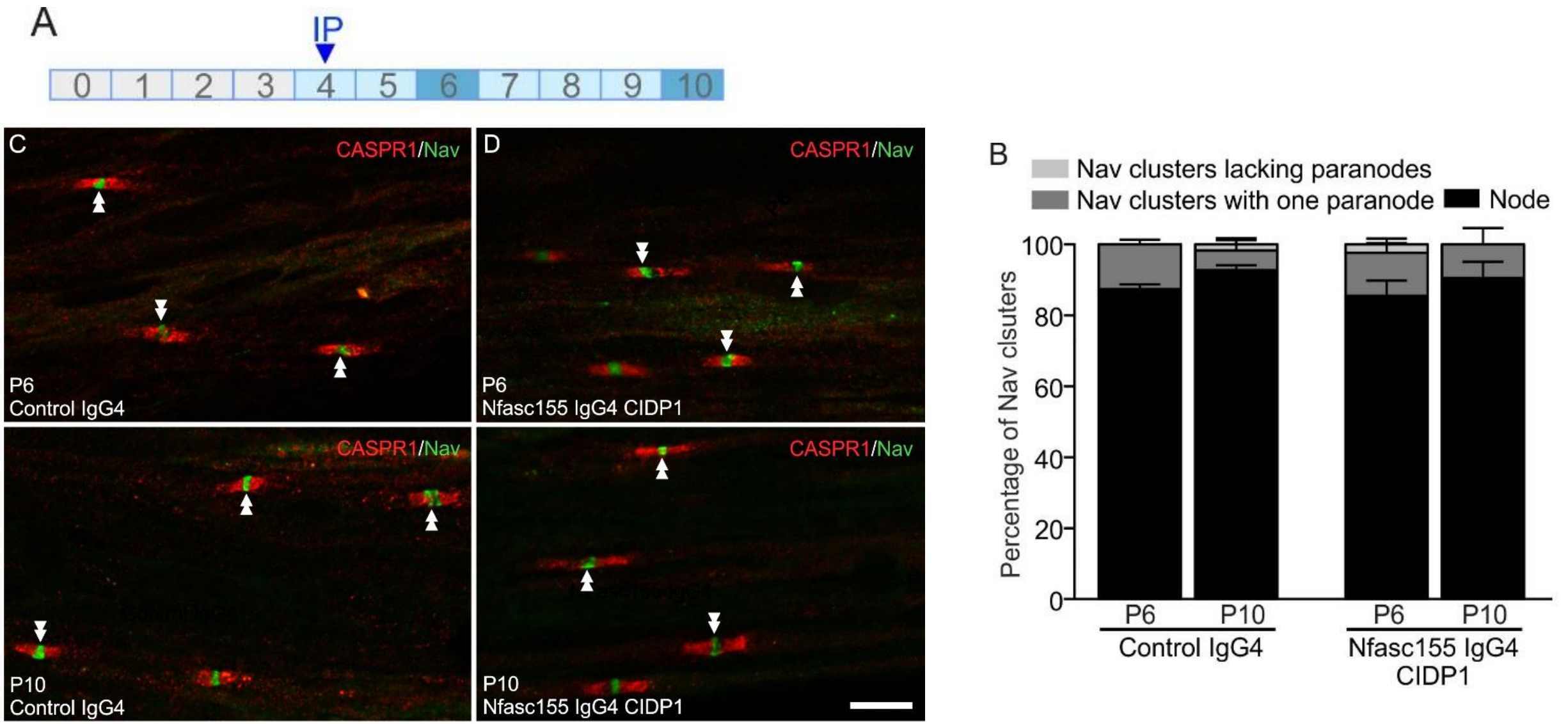






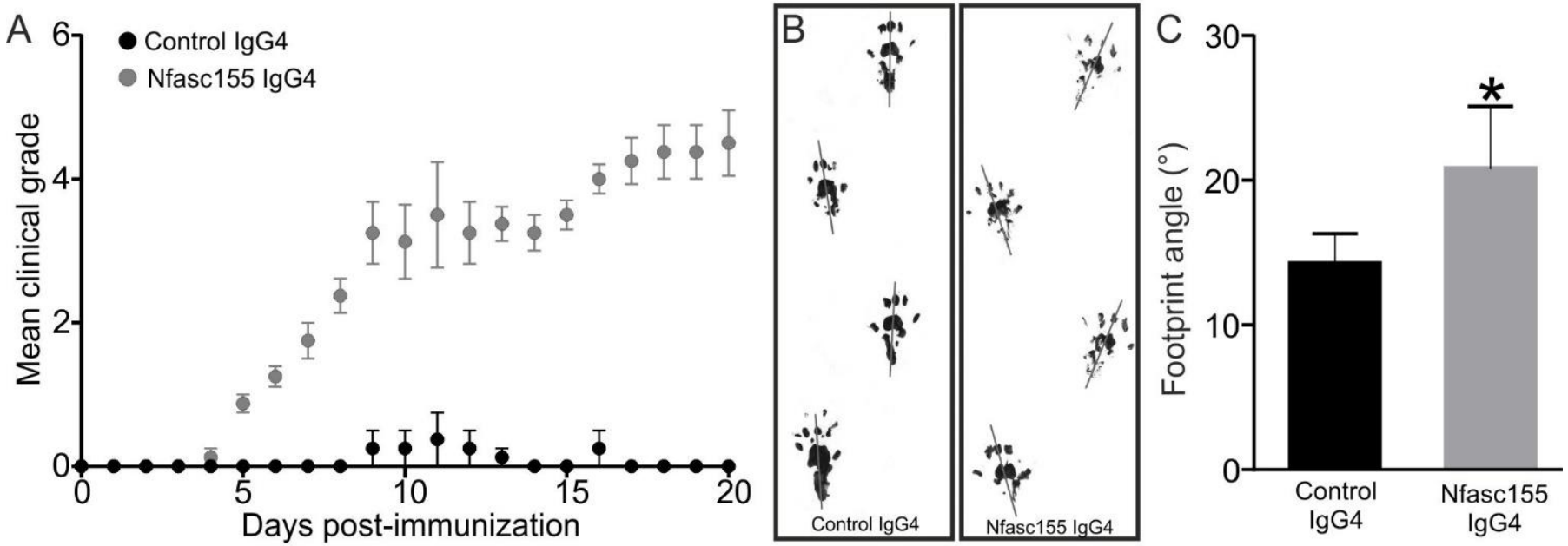


Acute injection of anti-Nfasc155 IgG4 does not affect mature paranode

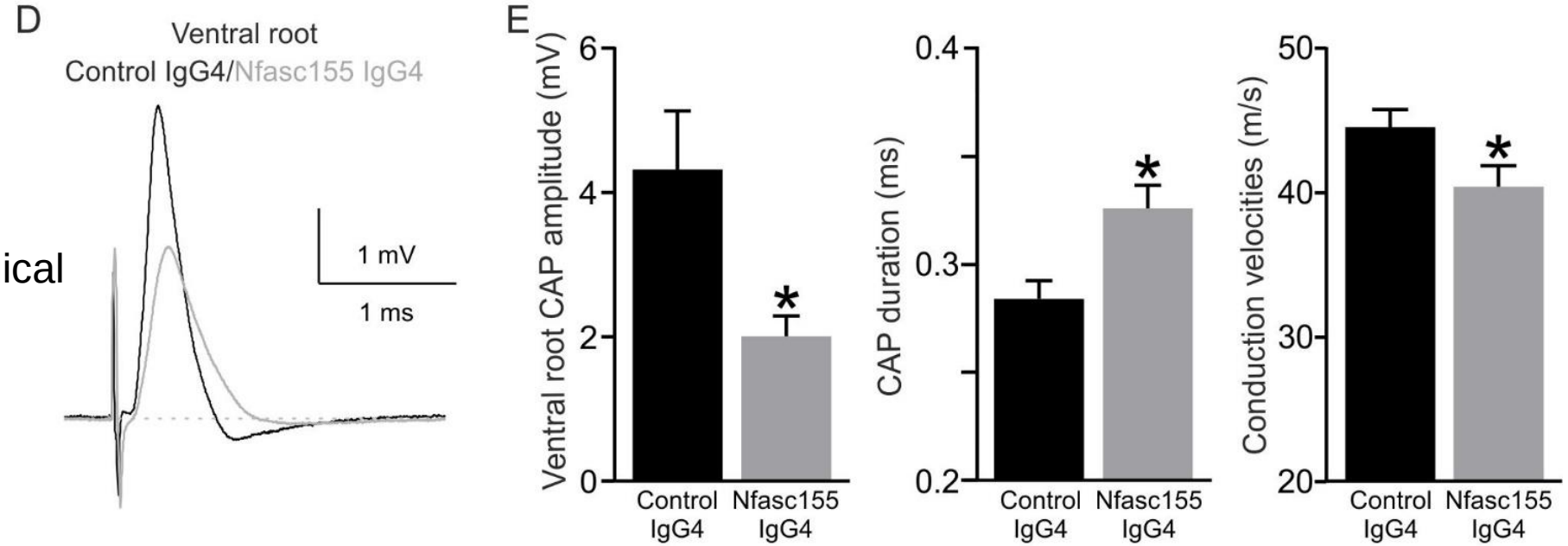


Manso *et al.*, 2019

Passive transfer of anti-Nfasc155 IgG4 induces a demyelinating polyneuropathy



Electrophysiological examination



Manso *et al.*, 2019

What is the pathophysiological mechanism?

→ Autoantibodies to CNTN1, Caspr1, Nfasc186, and Nfasc155 are specific to CIDP sub-groups.

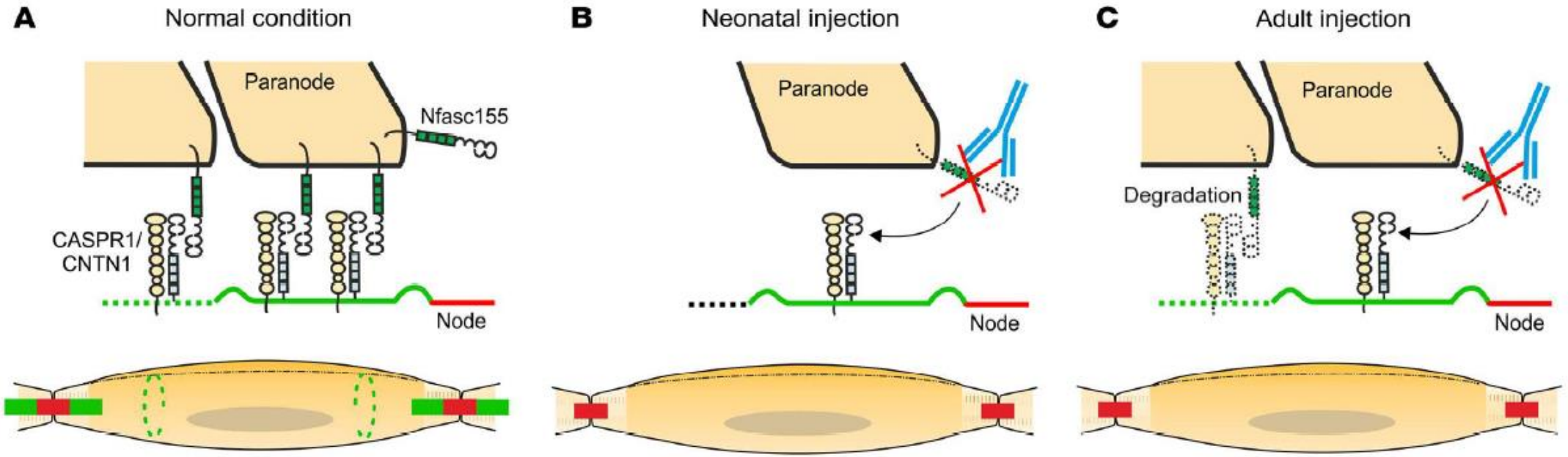
→ Rituximab is a therapeutic option in those patients not responding to conventional therapies.

→ Why patients are poorly responsive to IVIg, but responsive to steroids?

→ IgG4 are pathogenic

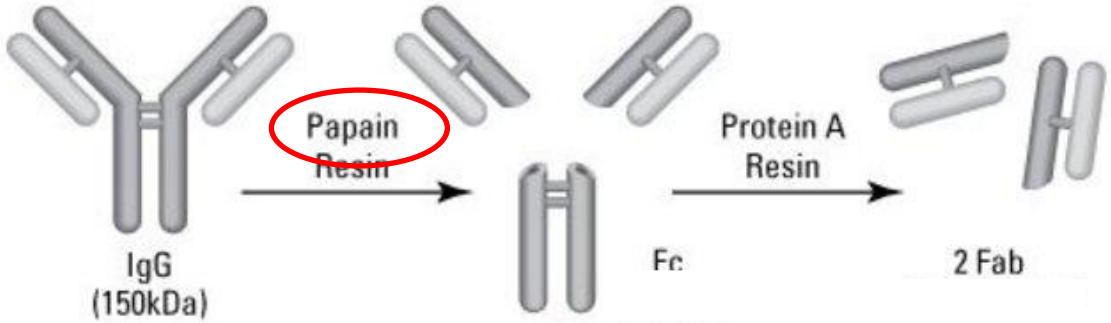
→ Anti-Nfasc155 IgG4 induce the depletion of Nfasc155 and preclude paranode formation.

→ How do anti-Nfasc155 IgG4 induce Nfasc155 depletion? Clustering?



Fab anti-NF155 production

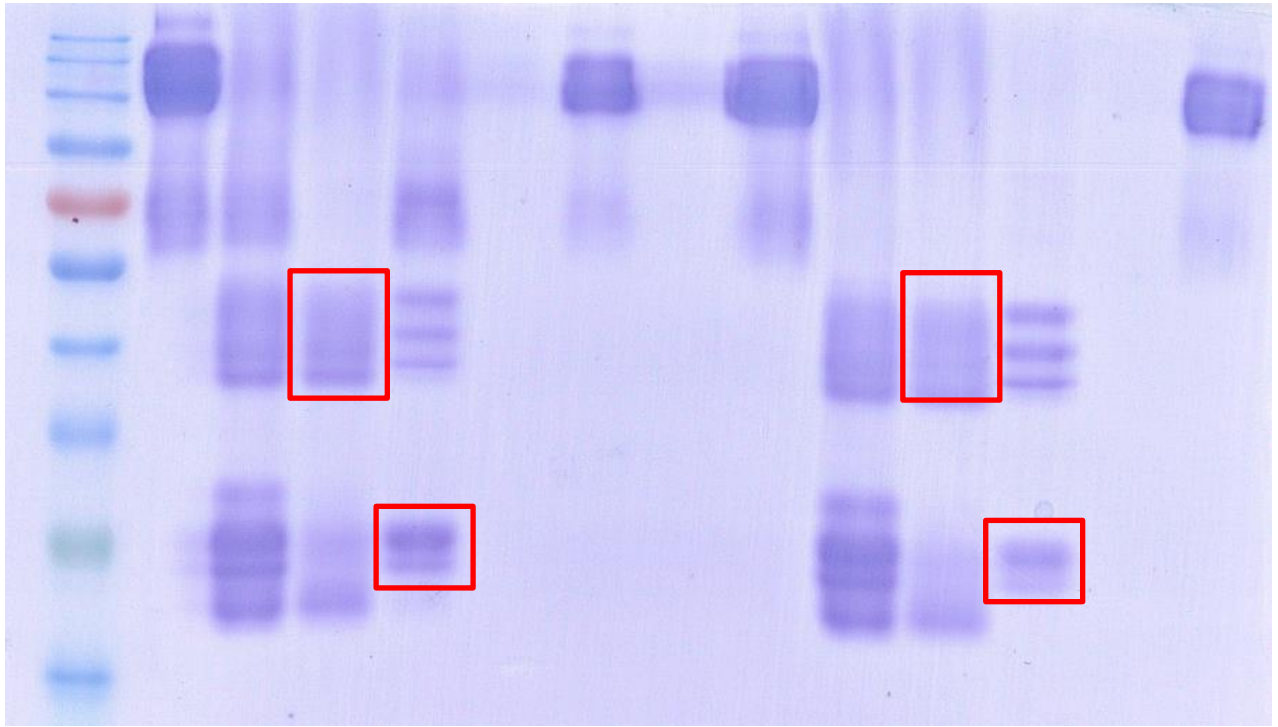
CIDP
patient's serum



Anti-NF155 IgG4
Digested by papain

Ct Dig Fab Fc

Ct Dig Fab Fc



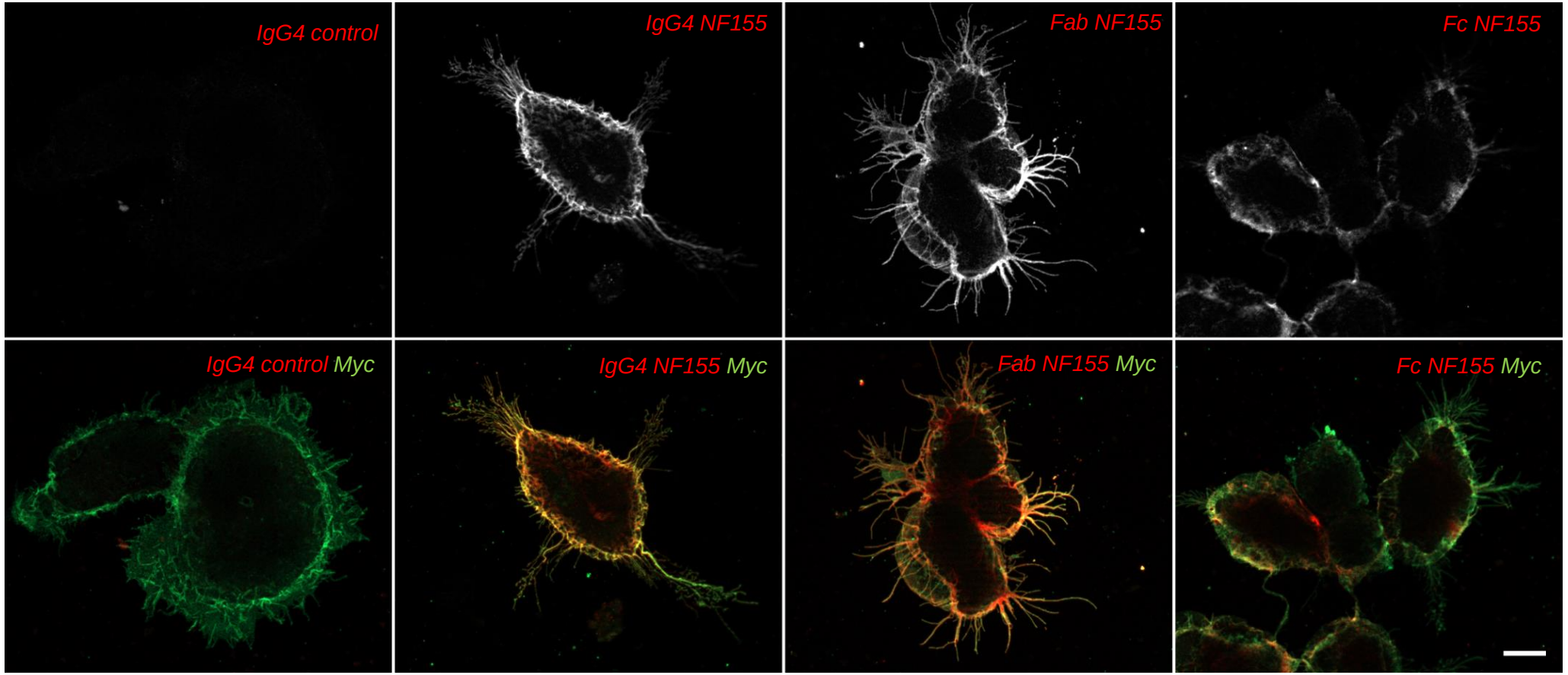
Fab
45kDa

Fc
30kDa

Fab anti-NF155 production: cellular test

→ HEK cells transfected by NF155 tagged with Myc

→ Fab anti-NF155 recognizes NF155 protein



Fab anti-NF155 production: cellular test

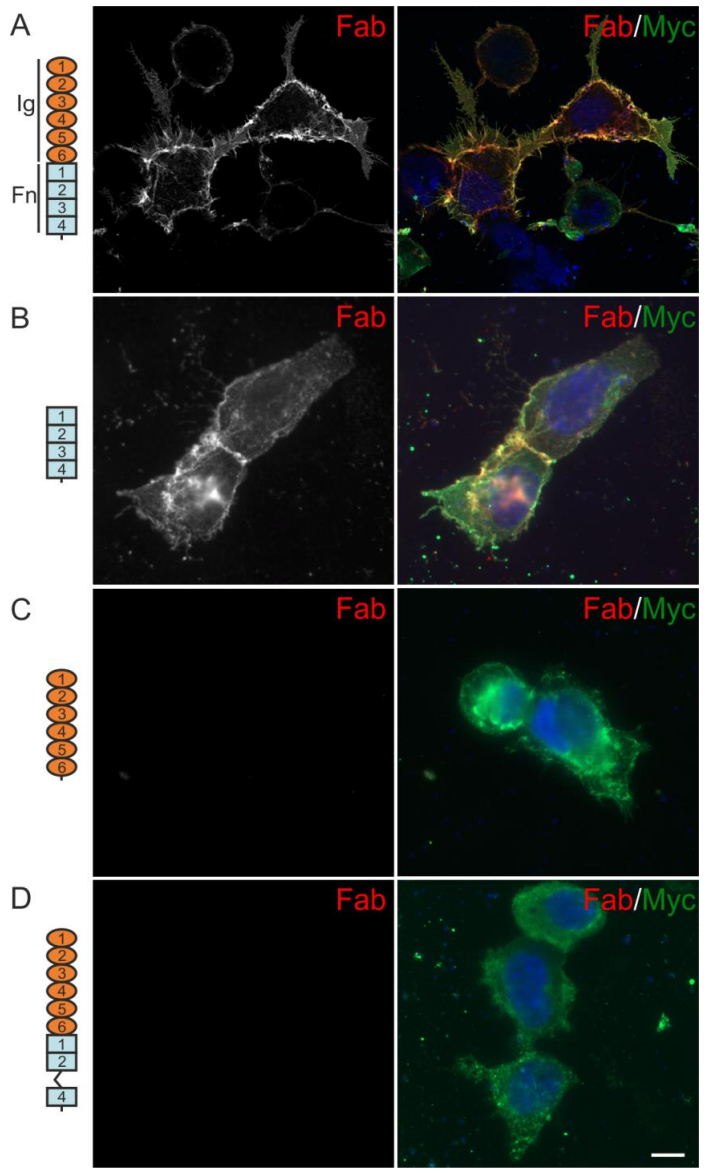
HEK cells Transfected by:

Full NF155

NF155 without Ig domains

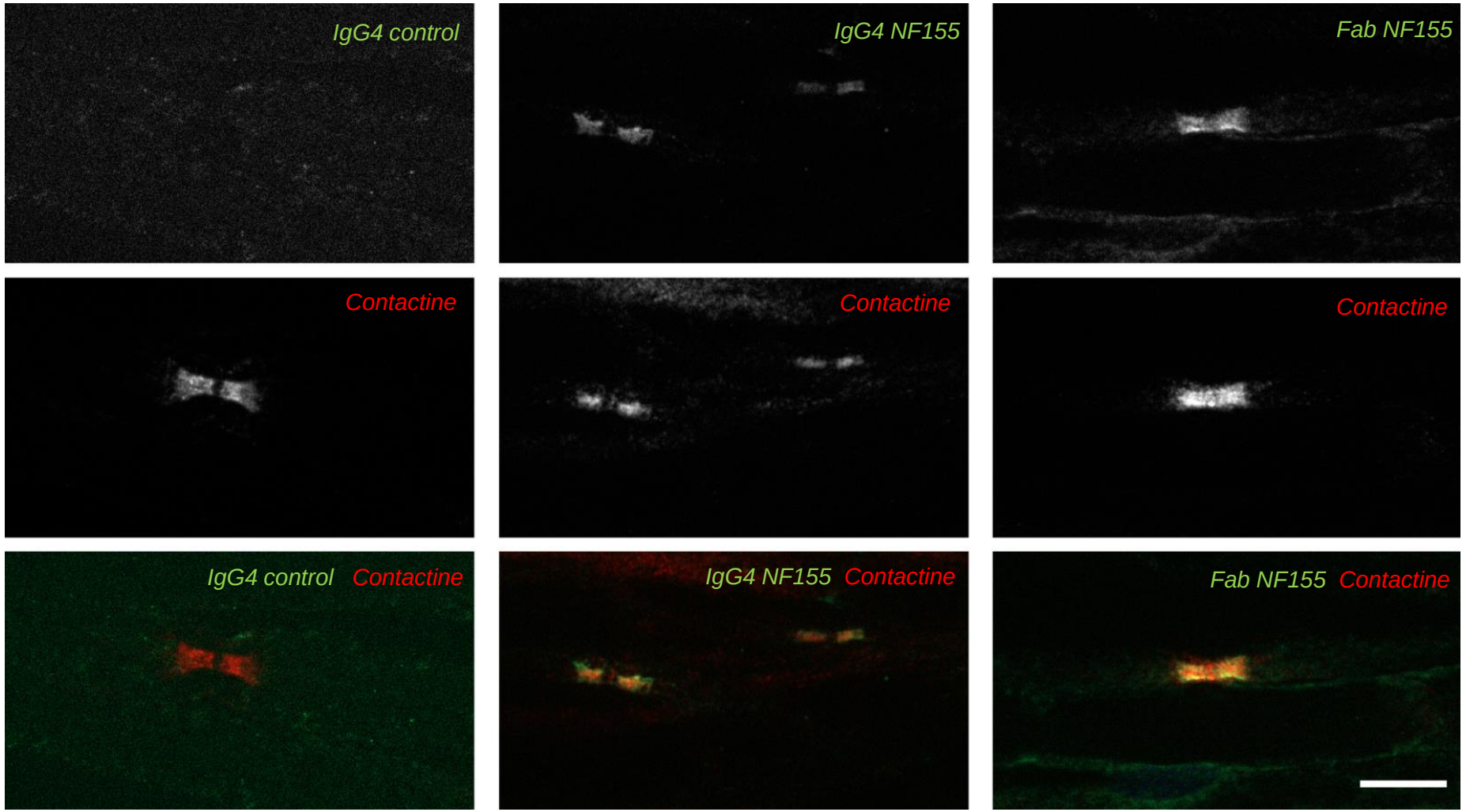
NF155 without Fn domains

NF155 3rd Fn domain deleted



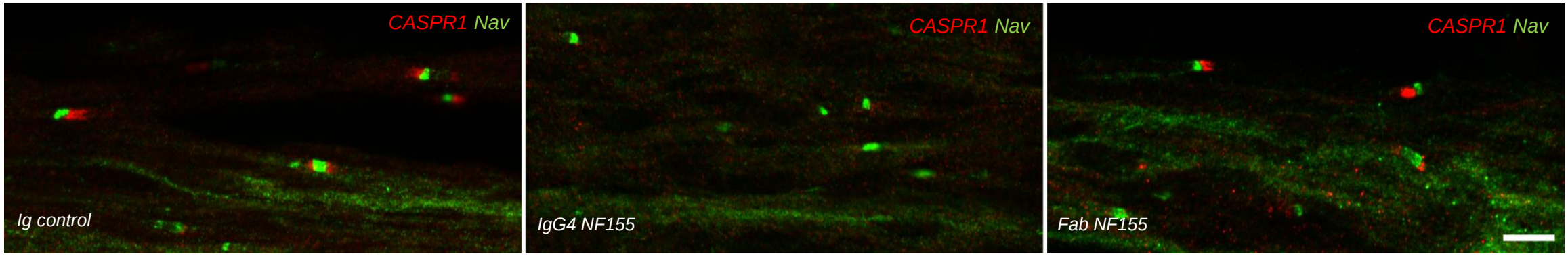
Fab anti-NF155 is directed against the 3rd Fn NF155 domain

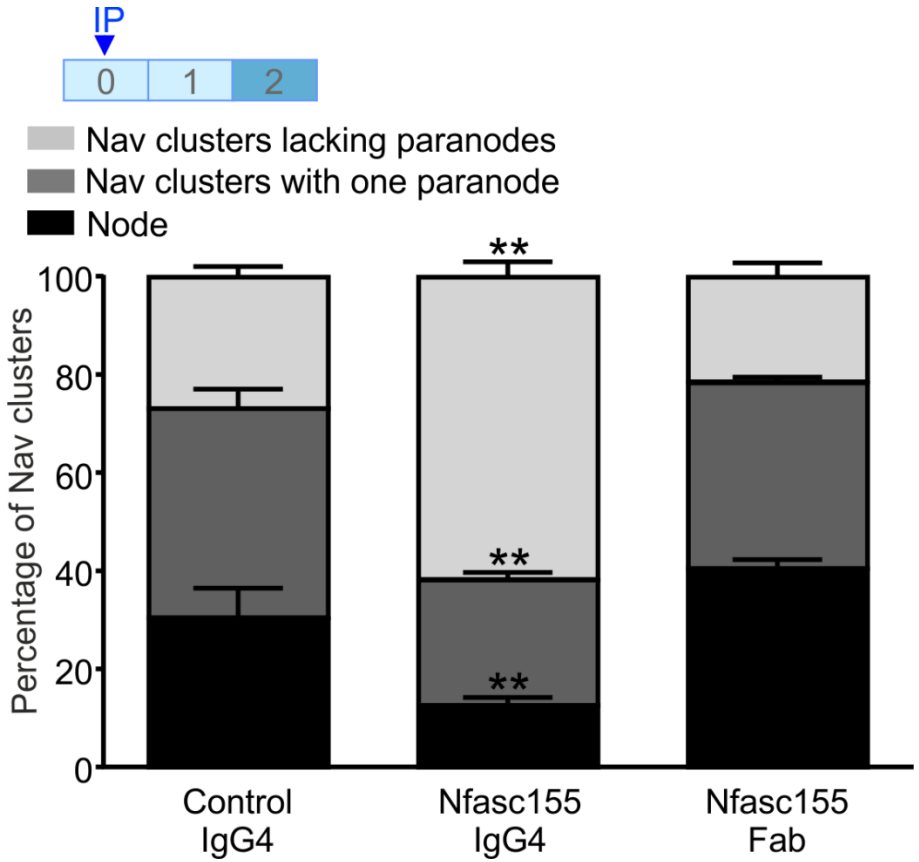
Fab anti-Nfasc155 bind paranode



Does Fab anti-Nfasc155 affect paranode formation like full NF155 IgG4?

Passive transfer of Fab anti-Nfasc155 does not affect paranode formation





What is the pathophysiological mechanism?

→ IgG4 are bispecific and pathogenic

→ IgG4 anti-Nfasc155 affects paranode formation

→ Fab anti-Nfasc155 does not affect paranode formation

→ What is the pathophysiological mechanism?

→ Does it induce internalization and degradation ?

→ Is it a blockade of protein renewal ?

→ Does the antibodies anti-NF155 stabilize NF155 on the surface of the plasma membrane ?

→ Test internalization inhibitors

→ Validate the results with Fab from other patients

→ Demonstrate the bispecificity of IgG4 (monoclonal antibodies generation)

Thank you for your attention