Symposium partenaire

Les auto-anticorps dans les maladies neuromusculaires chroniques rares

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Symposium partenaire

Rôle des autoanticorps dans les maladies neuromusculaires rares et intérêt de leur ciblage

J.P. CAMDESSANCHE
L MAGY

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Liens d'intérêt

Je soussigné, Jean-Philippe Camdessanché déclare recevoir ou avoir reçu ponctuellement des rémunérations des laboratoires Akcea, Alnylam, Argenx, Biogen, Bristol Myers Squibb, CSL-Behring, Genzyme, Laboratoire Français des Biotechnologies, Merck-Serono, Novartis, Pfizer, Pharmalliance, Teva et des sociétés Editions Scientifiques L&C, Edimark, Expression Santé, Natus, Scien, SNF-Floerger en contrepartie de ma participation à des conférences, des réunions de formation, la rédaction d'articles de formation médicale continue ou d'activités de conseil.

Aucun lien d'intérêt dans le cadre de cette présentation.

21 janvier 2022

Liens d'intérêt

- À peu près tous les labos travaillant dans le domaine de la SEP et des neuropathies (boards, consulting, invitation congrès, symposia). La liste est très longue et donc j'ai peur d'en oublier

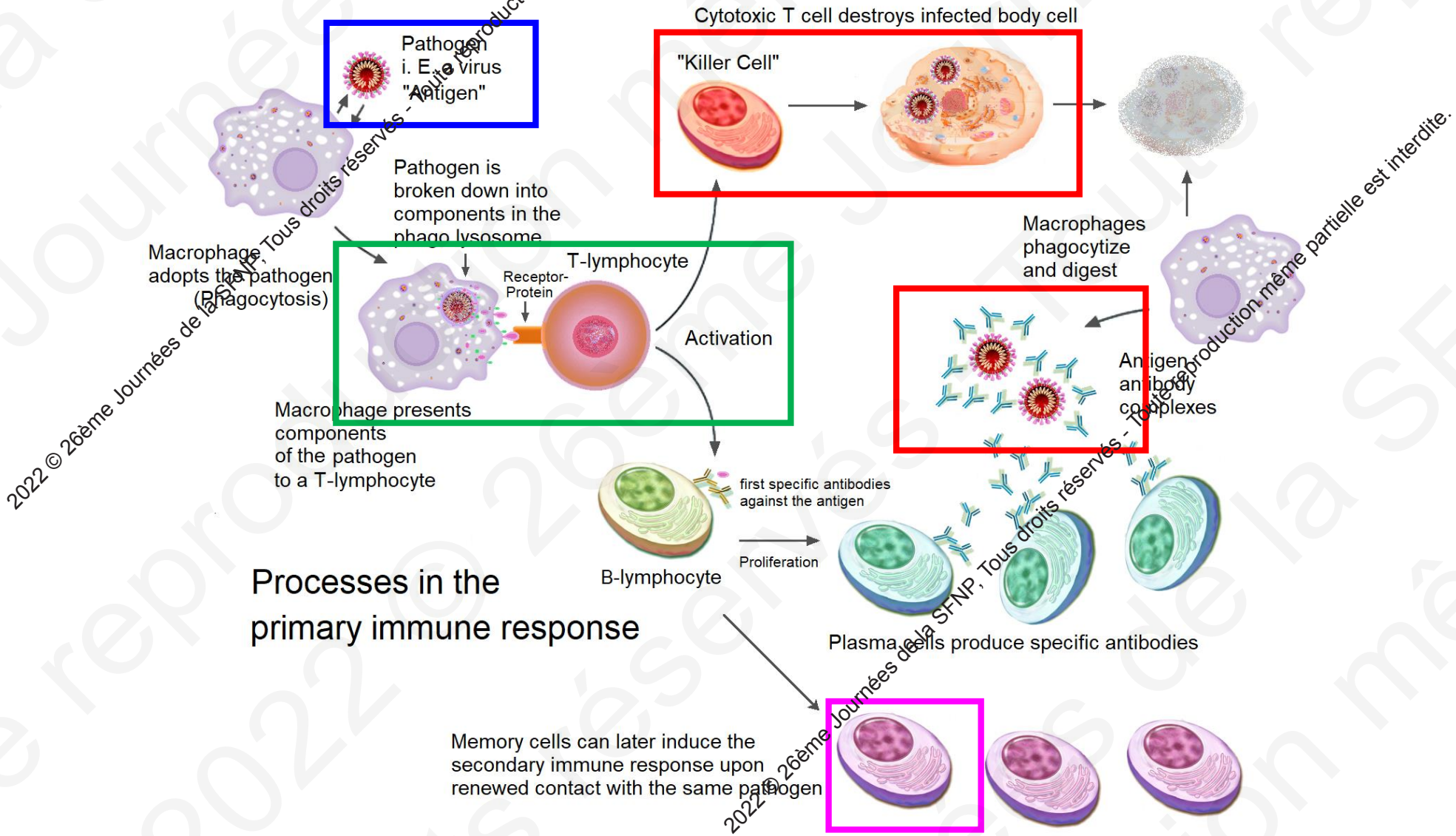
- Pour plus de précision : https://www.transparence.sante.gouv.fr

  https://www.eurosfordocs.fr/

21/01/2022

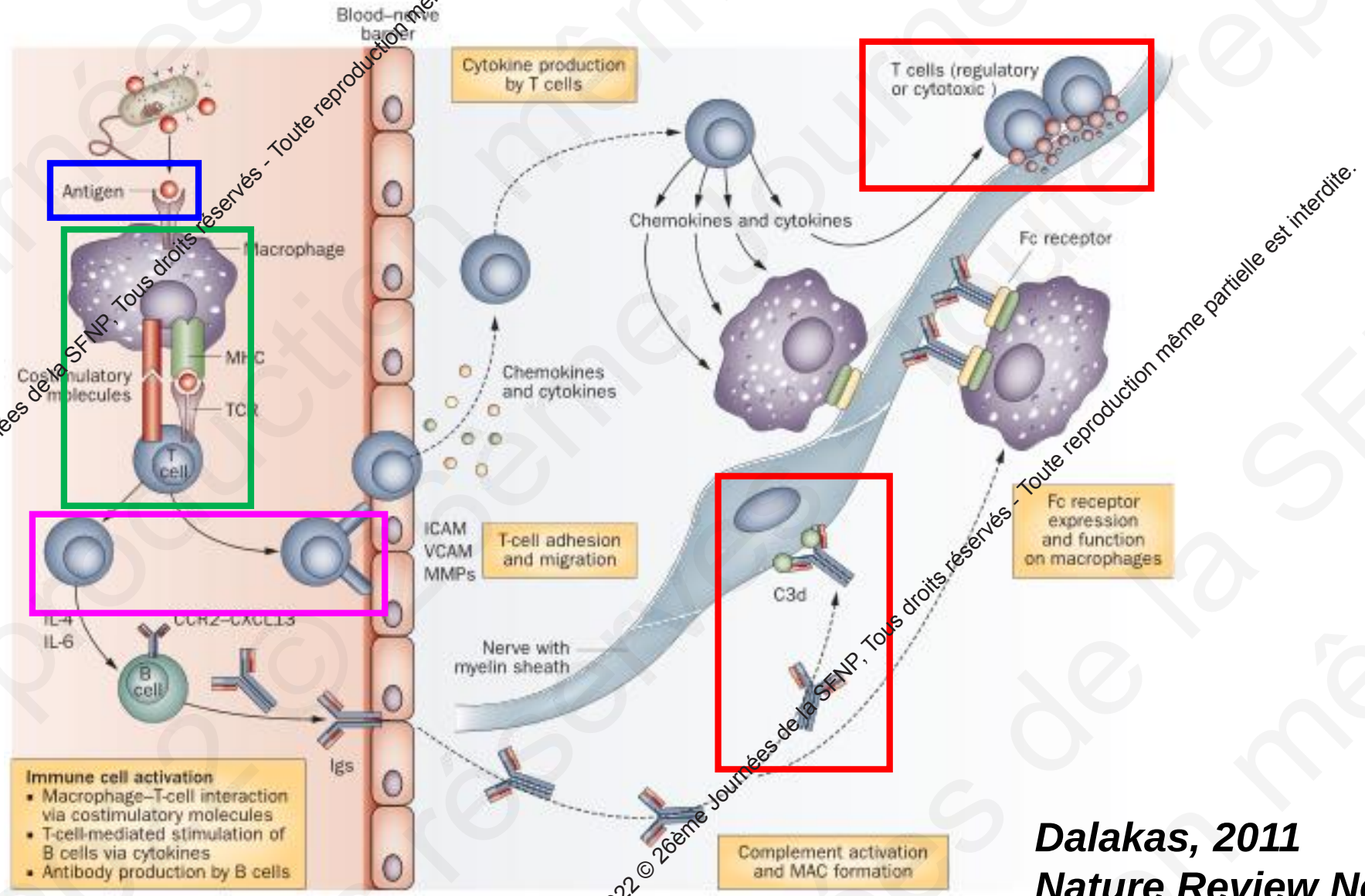
C.H.U. LIMOGES
Pr L. MAGY
10002940327

Notion d'immunité



Processes in the primary immune response

Notion d'auto-immunité : l'exemple de la PIDC

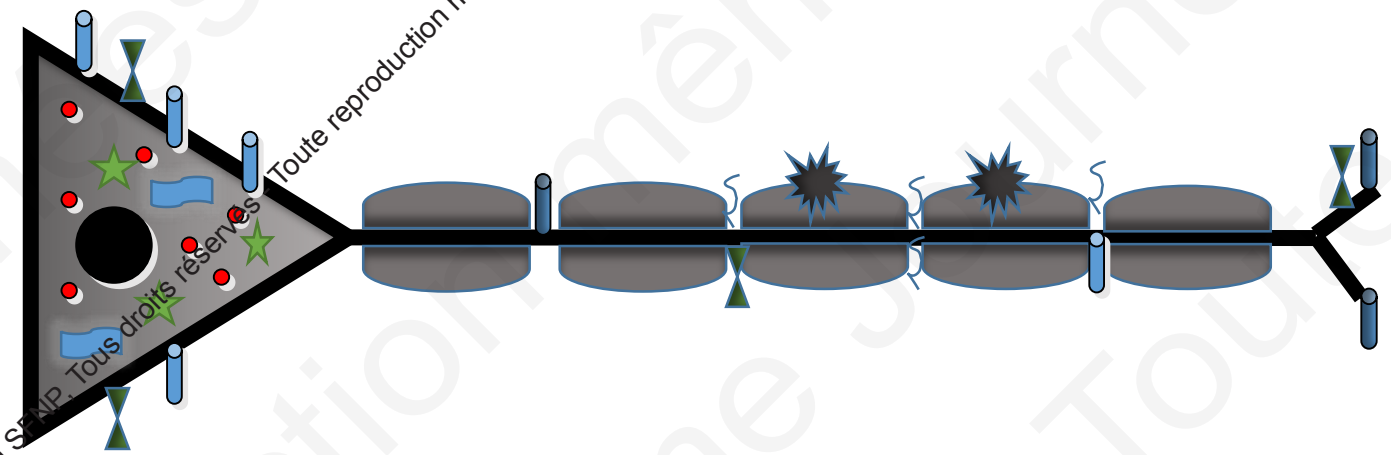


Dalakas, 2011
Nature Review Neurology

Anticorps et maladies neuromusculaires dysimmunes

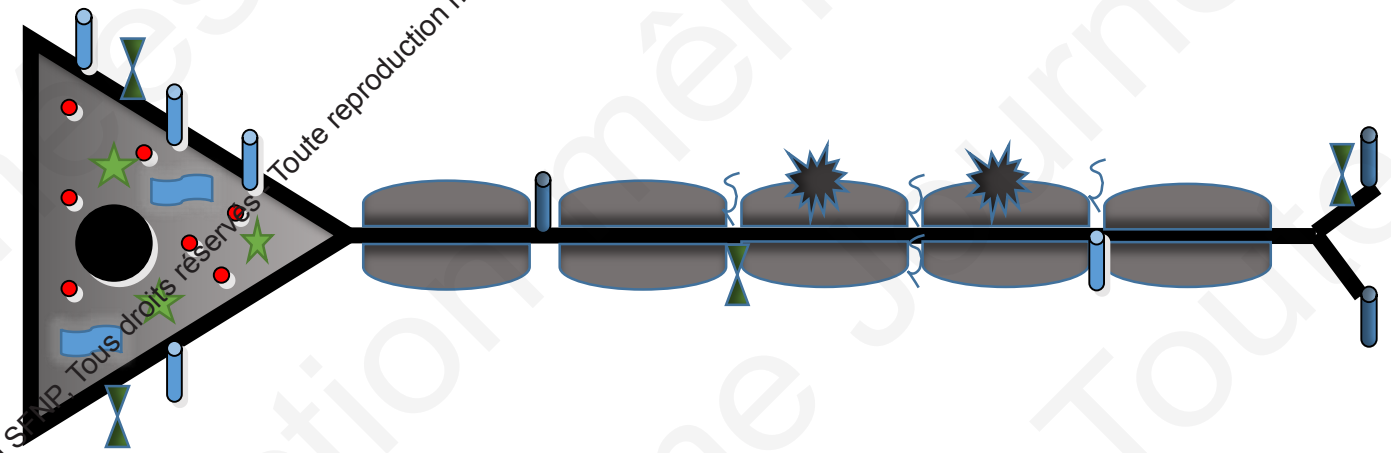
Neuropathy	Antibody	Frequency
AMAN	Gangliosides (monosialosyl - IgG)	60%
Miller-Fisher	Gangliosides (disialosyl - IgG)	#100%
CIDP	Contactin, Caspr 1, NF-155 (IgG)	5-6%
MMN	Gangliosides GM1 (IgM)	50-60%
CANOMAD	Gangliosides disiolsyl (M-IgM)	100%
SM neuropathy with M-IgM	MAG	50%
Sensory neuronopathy (paraneoplastic)	Hu, CRMP5	90%
Lambert-Eaton	VGCC	90%
Neuromyotonia	Caspr 2, LGI1	60-80% (?)
Acute autonomic neuropathy	Ganglionic AChR AB	15%
Sensory neuronopathy	Non organ specific AB (SSA-SSB)	10%
MNM and systemic vasculitis	Non organ specific AB (cANCA-pANCA)	90%
Myastnenia gravis	Acetylcholine receptor	80%

Auto-anticorps : 2 situations différentes



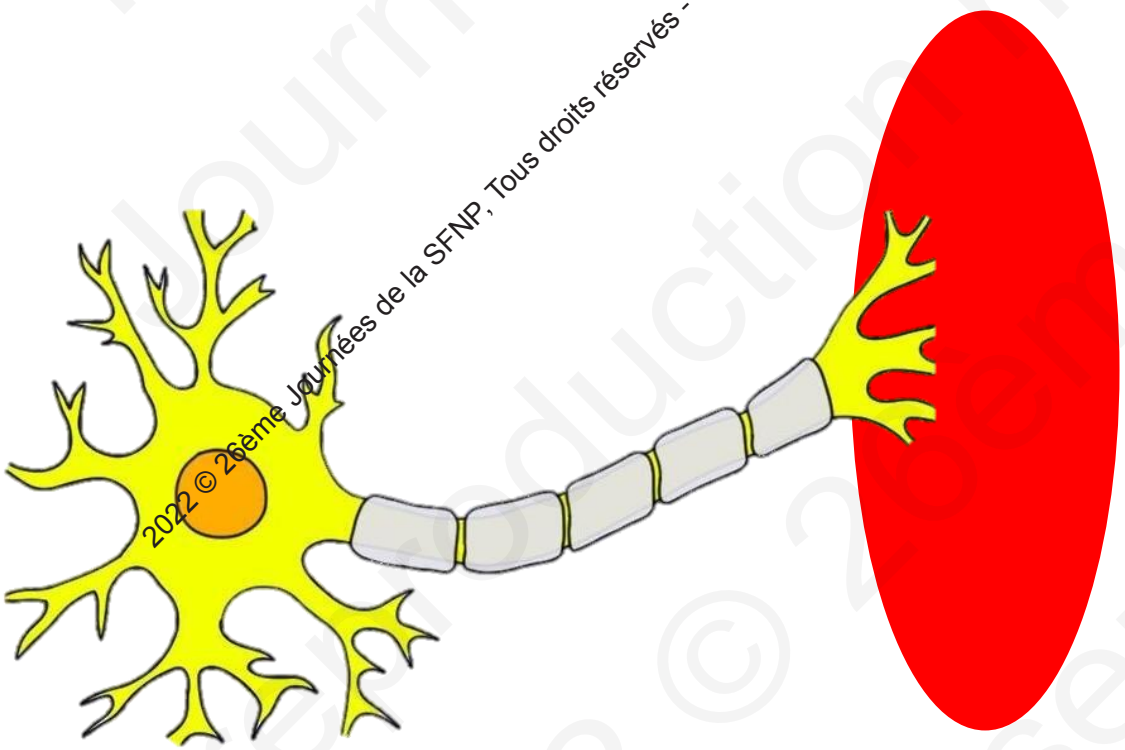
Intracellular antigens	Membrane/cell surface antigens
HuD	Ion channels: *CCVD CASPR2-LGI1*
CRMP5/CV2	Gangliosides: *GM1, GD1a….*
Other onconeural	Node of Ranvier: *contactin, CASPR1,NF155*
	Glycoproteins of myelin: *MAG*
High cancer frequency	**Low cancer frequency**

Auto-anticorps : 2 situations différentes



Intracellular antigens	Membrane/cell surface antigens
HuD	Ion channels: *CCVD CASPR2-LGI1*
CRMP5/CV2	Gangliosides: *GM1, GD1a….*
Other onconeural	Node of Ranvier: *contactin, CASPR1,NF155*
	Glycoproteins of myelin: *MAG*
Biomarkers	**Effectors**

Rôle des auto-anticorps



- **Myasthénie**
- **Polyradiculoneuropathie Inflammatoire Démyélinisante Chronique**
- **Neuropathie Motrice Multifocale**
- **Neuropathie MAG**

Comment cibler les auto-anticorps ?

- **Traiter la production des auto-anticorps**
- **Éliminer**

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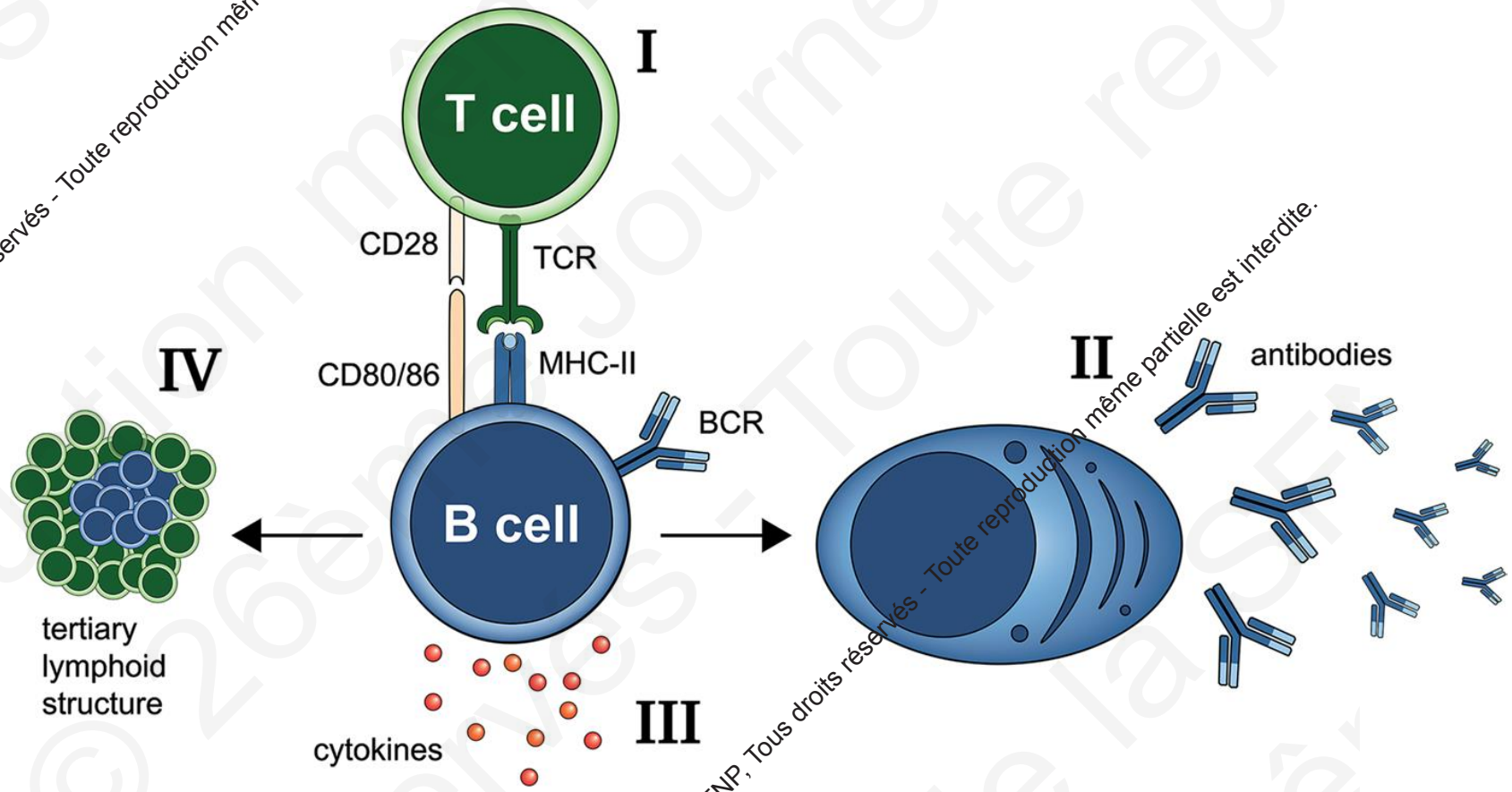
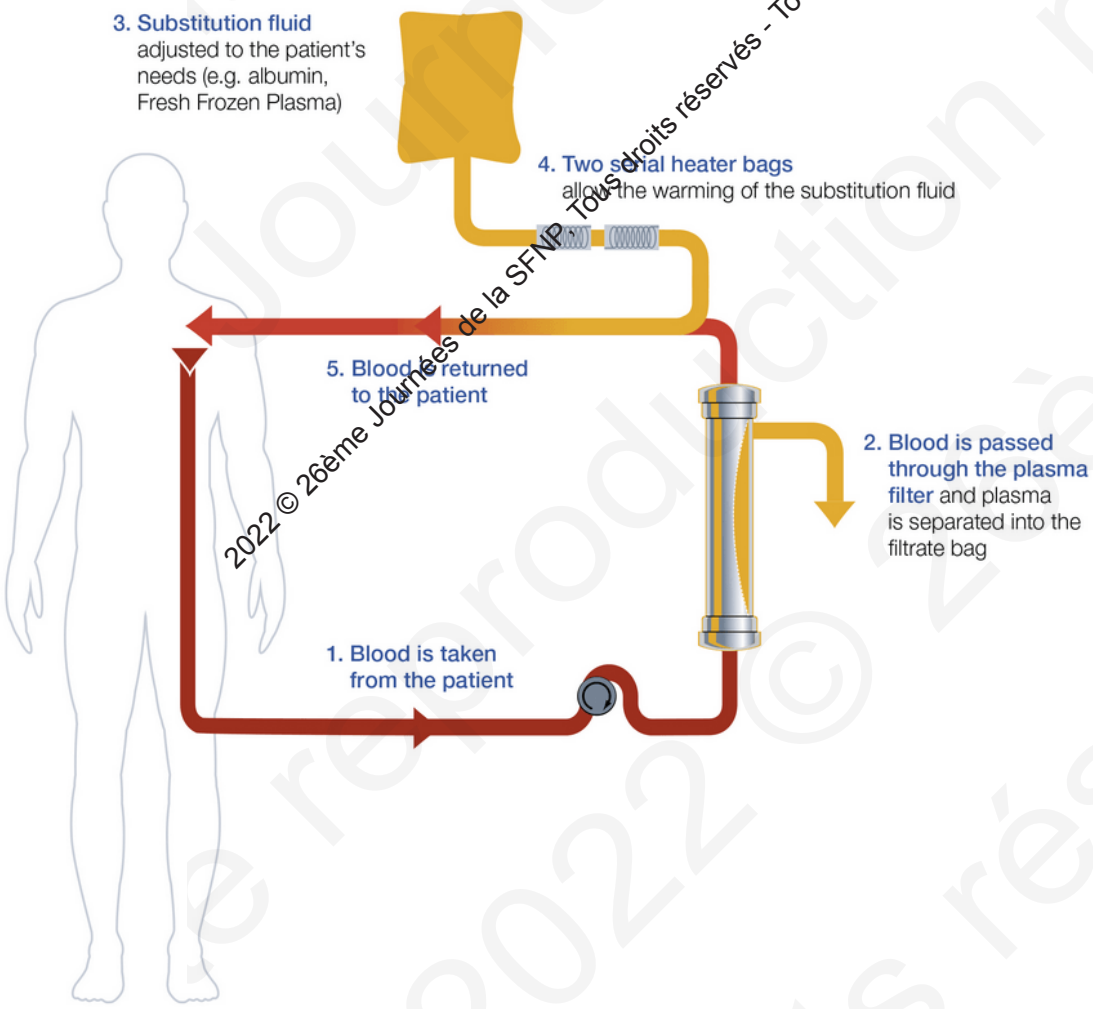
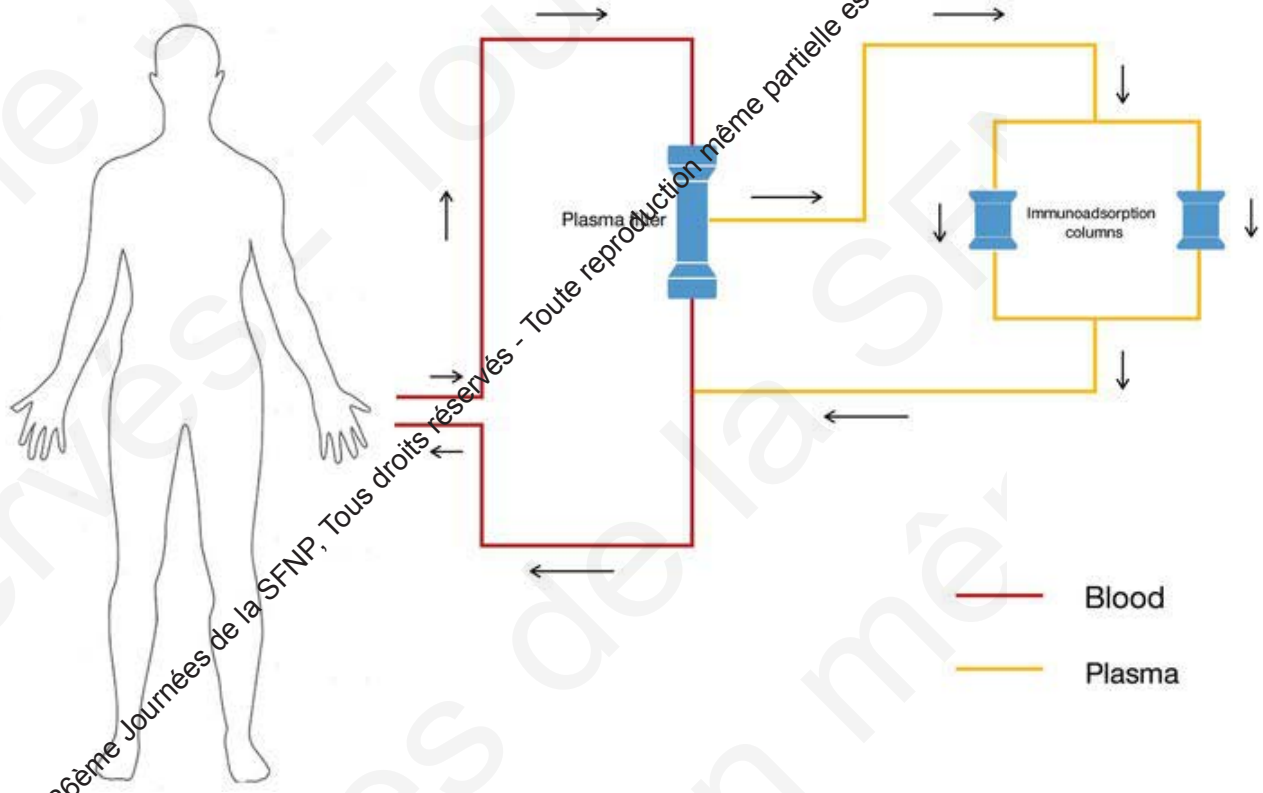


Fig. 2 The four main pathogenic roles of B cells in the context of systemic autoimmune disease. (I) Initiation or enhancement of autoimmune responses by presenting auto-antigens to T cells and concomitantly providing co-stimulatory signals. (II) B cells can differentiate into autoantibody-producing plasma cells. (III) B cells can produce pro-inflammatory cytokines. (IV) B cells are involved in stimulating the development and maintenance of these tertiary lymphoid structures

Neys et al. Drugs 2021

Échanges plasmatiques et immunoadsorption





Clinical Implications of Basic Research

The New England Journal of Medicine

ZHIYA YU, M.D., PH.D.
VANDA A. LENNON, M.D., PH.D.

Mayo Clinic
Rochester, MN 55905

1999

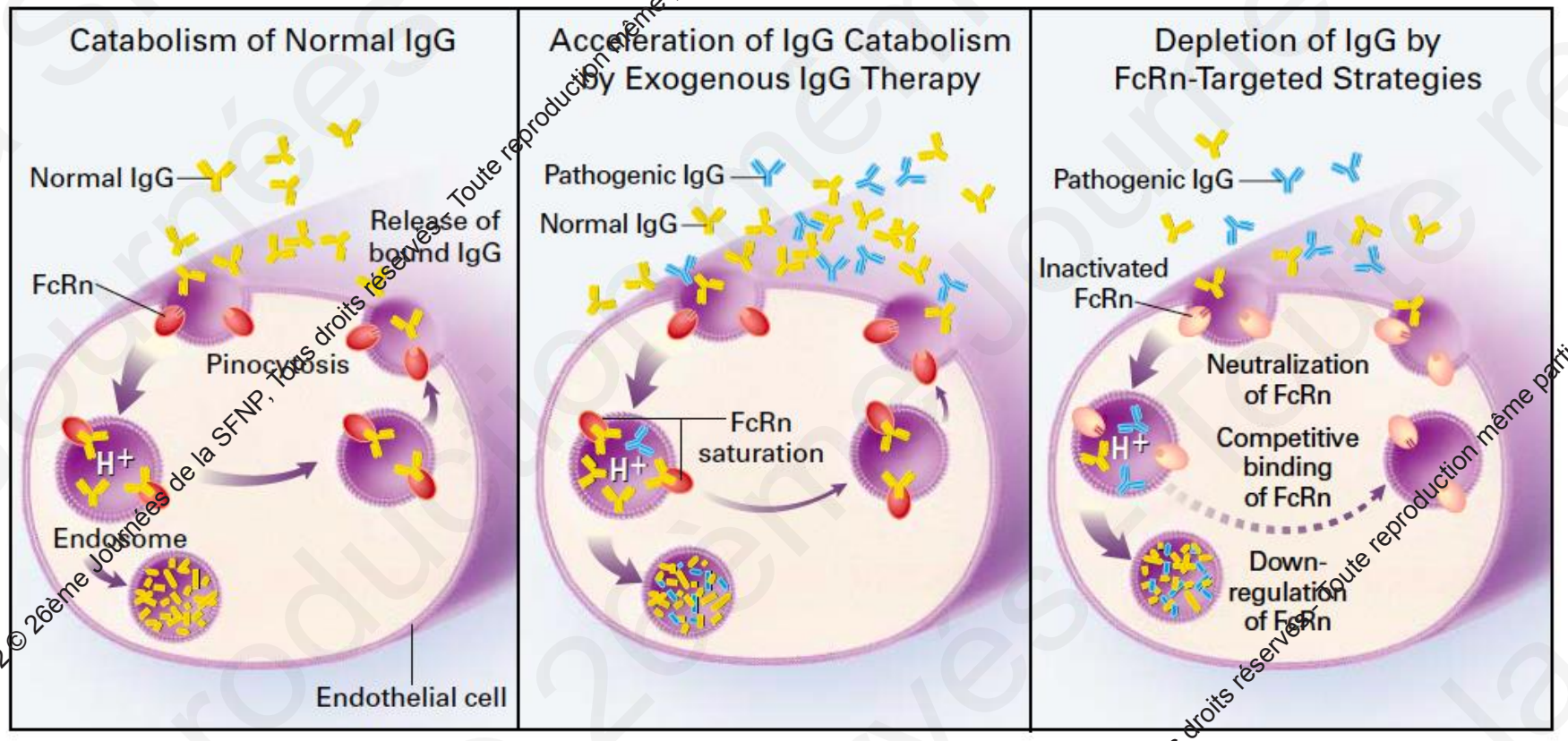
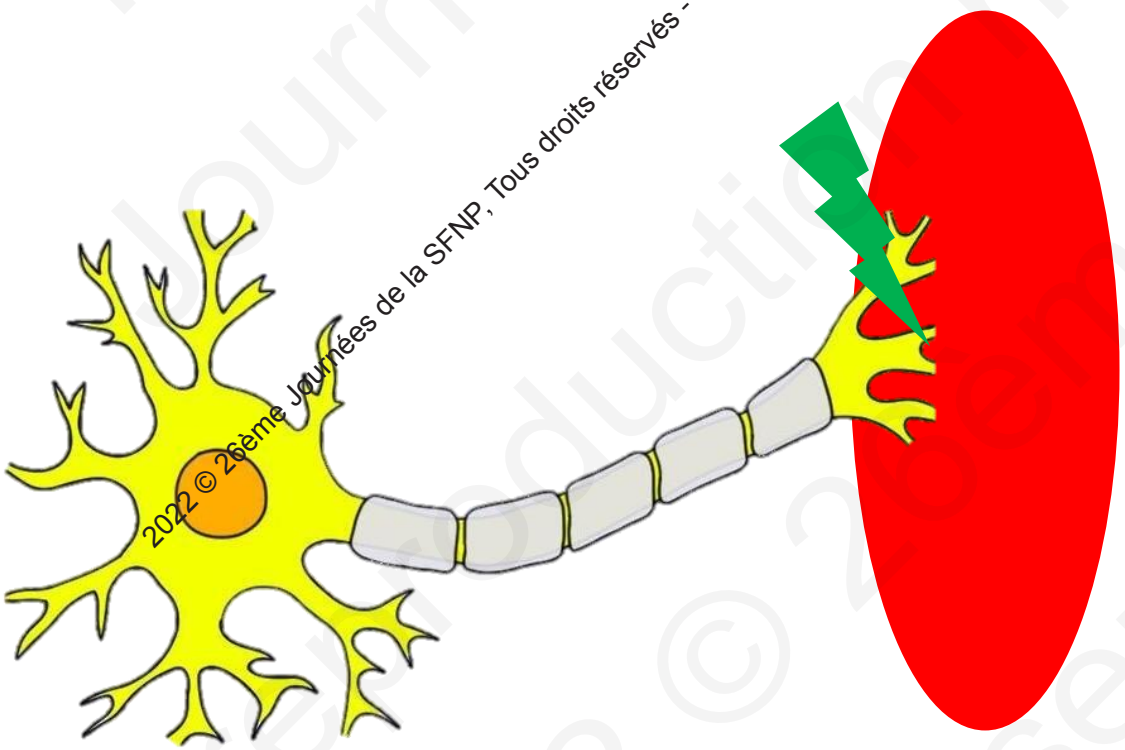


Figure 1. Regulation of the Catabolism of IgG by FcRn.

A specialized intracellular Fc receptor — FcRn — that is abundant in endothelial cells binds pinocytosed IgG only in the acidic environment of the endosome. It releases intact IgG when its transport vesicle is redirected to the neutral pH of the cell surface. Unbound IgG is transferred to lysosomes for degradation.[6] The saturation of FcRn in states of hypergammaglobulinemia accelerates the catabolism of IgG. This IgG-depleting mechanism plausibly explains the temporary benefit of intravenous therapy with high doses of normal IgG in autoimmune diseases mediated by pathogenic IgG. Alternative therapeutic strategies that inactivate the FcRn receptor would be effective for longer periods than immune globulin therapy, would be more economical, and would be devoid of the risk of infection. For example, one might design neutralizing monoclonal antibodies to modify FcRn covalently, synthetic ligands with a higher affinity than IgG for the receptor and that would thus saturate FcRn, or antisense nucleotides to down-regulate the expression of FcRn. With the use of such strategies, levels of IgG would not rebound because the synthesis of IgG is driven by immunogenic stimulation and is not affected by the rate of catabolism.

Rôle des auto-anticorps



- **Myasthénie**
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Auto-anticorps & Myasthénie

Les pathologies de la jonction neuromusculaire (JNM) se caractérisent par une faiblesse de la musculature striée, focalisée ou généralisée, le plus souvent fluctuante.

Leur étiologie peut être génétique (syndromes myasthéniques congénitaux), toxique (curares, botulisme) ou liée à des auto-anticorps (myasthénie autoimmune [MAI] et néonatale, syndrome de Lambert-Eaton).

La <u>myasthénie auto-immune (MAI)</u> est de loin la plus fréquente de ces entités.

Nguyen-Cao et al., 2019

Auto-anticorps & Myasthénie

- **Premiers cas décrits au 17ème siècle,**
- **Hypothèse d'une attaque auto-immune émise à la fin des années 1950 : modèles animaux, myasthénie néonatale.**
- **Identification des récepteurs à l'acétylcholine (RACh) comme antigène cible,**
- **Début de la thérapeutique : corticothérapie et échanges plasmatiques dans les années 1970, puis immunoglobulines intraveineuses la décennie suivante.**

Nguyen-Cao et al., 2019

Auto-anticorps & Myasthénie

2 sous-groupes de myasthénie anti- RAch :

- **Myasthénie à début précoce (< 45–50 ans) : sex-ratio = 3 F / 1 H ; titre AC anti-RACh habituellement élevé ; hyperplasie thymique fréquente et plus souvent retrouvée chez les femmes (80 %) ; association groupes HLA DR3 et B8 avec risque de maladies auto-immunes associées. Formes pédiatriques = idem.**
- **Myasthénie à début tardif (> 45–50 ans) : sex-ratio = légère prédominance masculine ; hyperplasie thymique plus rare mais thymome plus fréquent.**

Gilhus et al., 2015
Gilhus et al., 2016

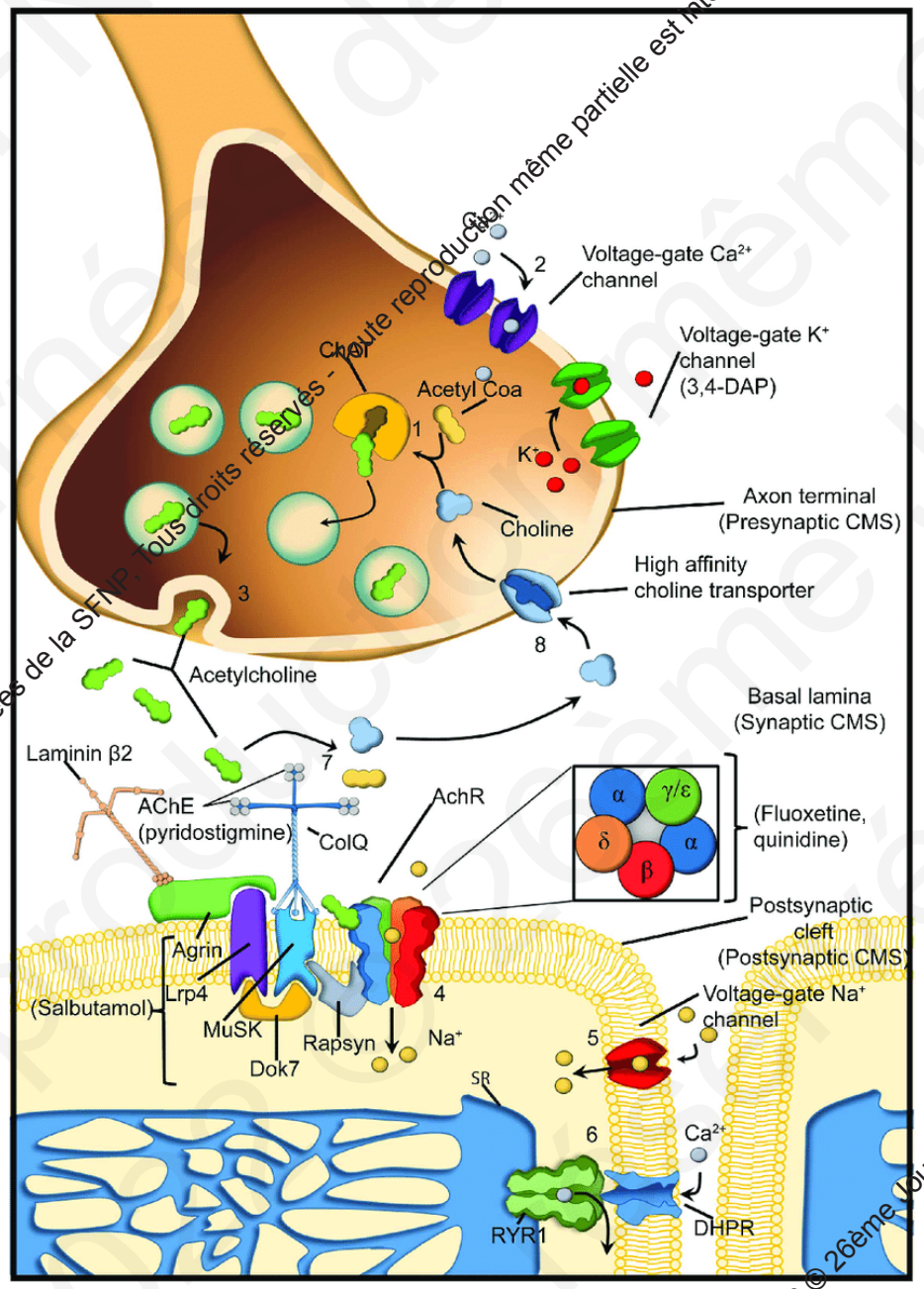
Auto-anticorps & Myasthénie

- La prévalence MAI : entre 40 et 180 par million,
- Incidence annuelle : 4 à 12 par million,
- Pas de variations géographiques significatives à l'exception d'une incidence élevée de cas pédiatriques en Asie où 50 % des cas débutent avant 15 ans,

- AC anti-RACh : 80 % des patients présentant une myasthénie généralisée,
- AC anti-MuSK : 1-10%, prévalence 2-9 & incidence annuelle de 3 par million,
- AC anti-LRP4 : 1-33%, 2 fois moins fréquentes que formes anti-MuSK.

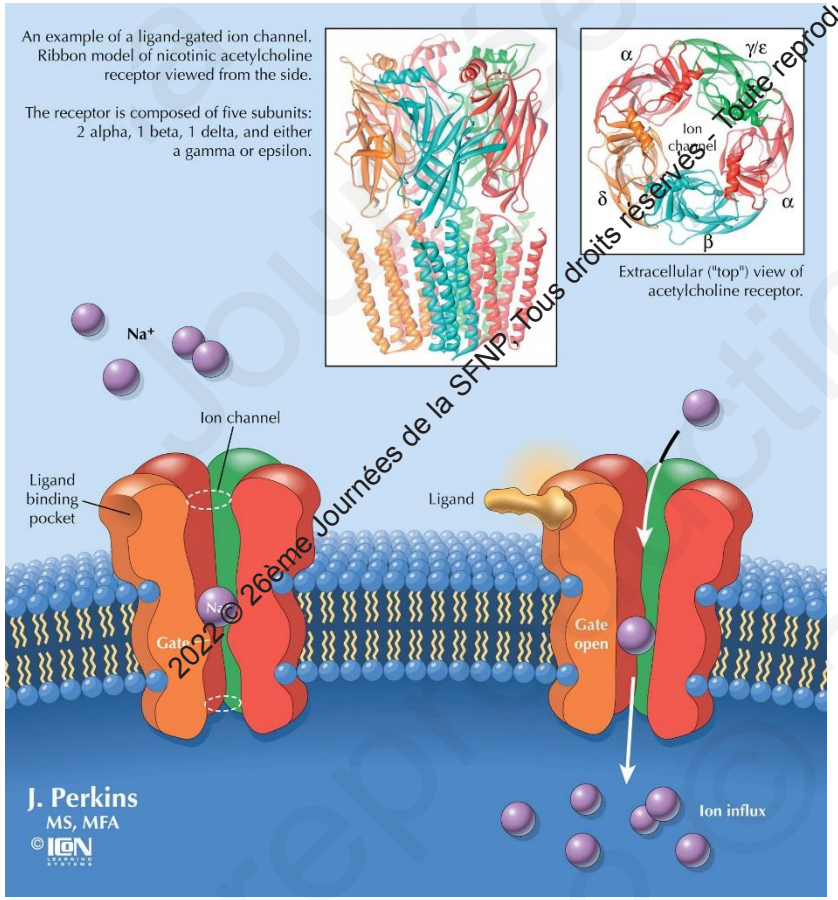
Gilhus et al., 2015
Mantegazza et al., 2018
Nguyen-Cao et al., 2019

Auto-anticorps & Myasthénie



Dowling et al., 2017

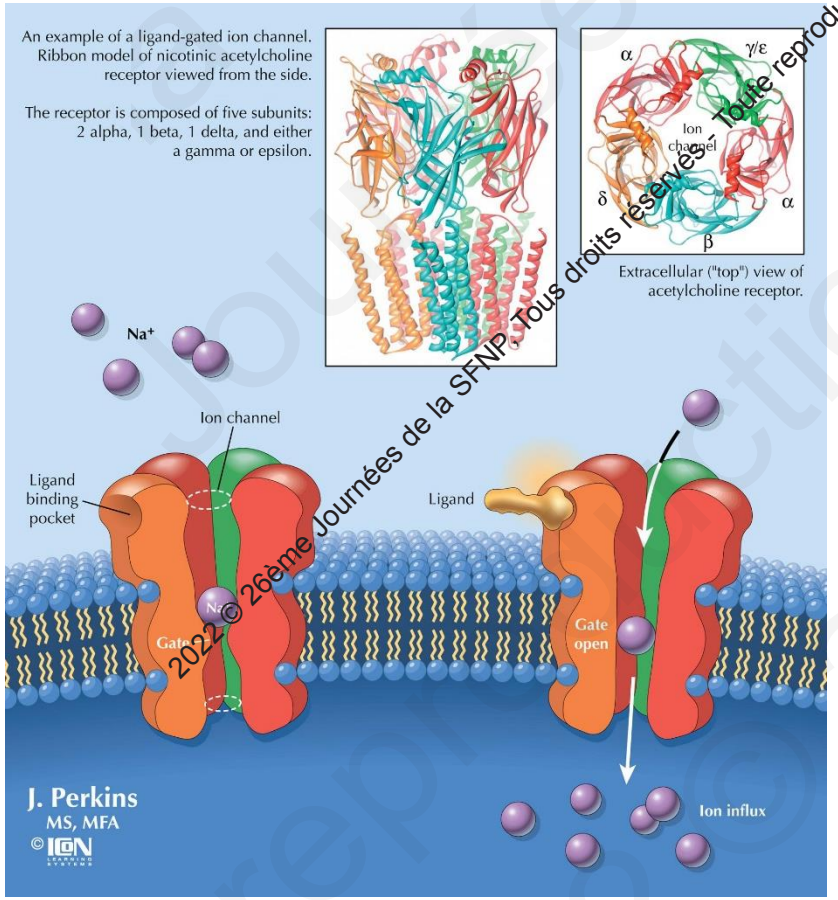
Auto-anticorps & Myasthénie



- **Récepteur à l'acétylcholine = 5 sous-unités,**
- **AC le plus souvent dirigés contre épitope extracellulaire des 2 sous unités α,**
- **AC dirigés contre la sous-unité β moins pathogènes,**
- **AC = IgG1 et IgG3 → activation voie du complément → formation complexe d'attaque membranaire → lyse membrane post-synaptique → déplétion en RACh.**

Béhin et al., 2018
Koneczny et Herbst, 2019

Auto-anticorps & Myasthénie



- **Lésions structurelles responsables de symptômes fixés non améliorés par les traitements,**
- **Internalisation des RACh ou la fixation de l'anticorps sur le site de liaison à l'acétylcholine sont d'autres mécanismes pathogènes possibles des anti-RAch.**

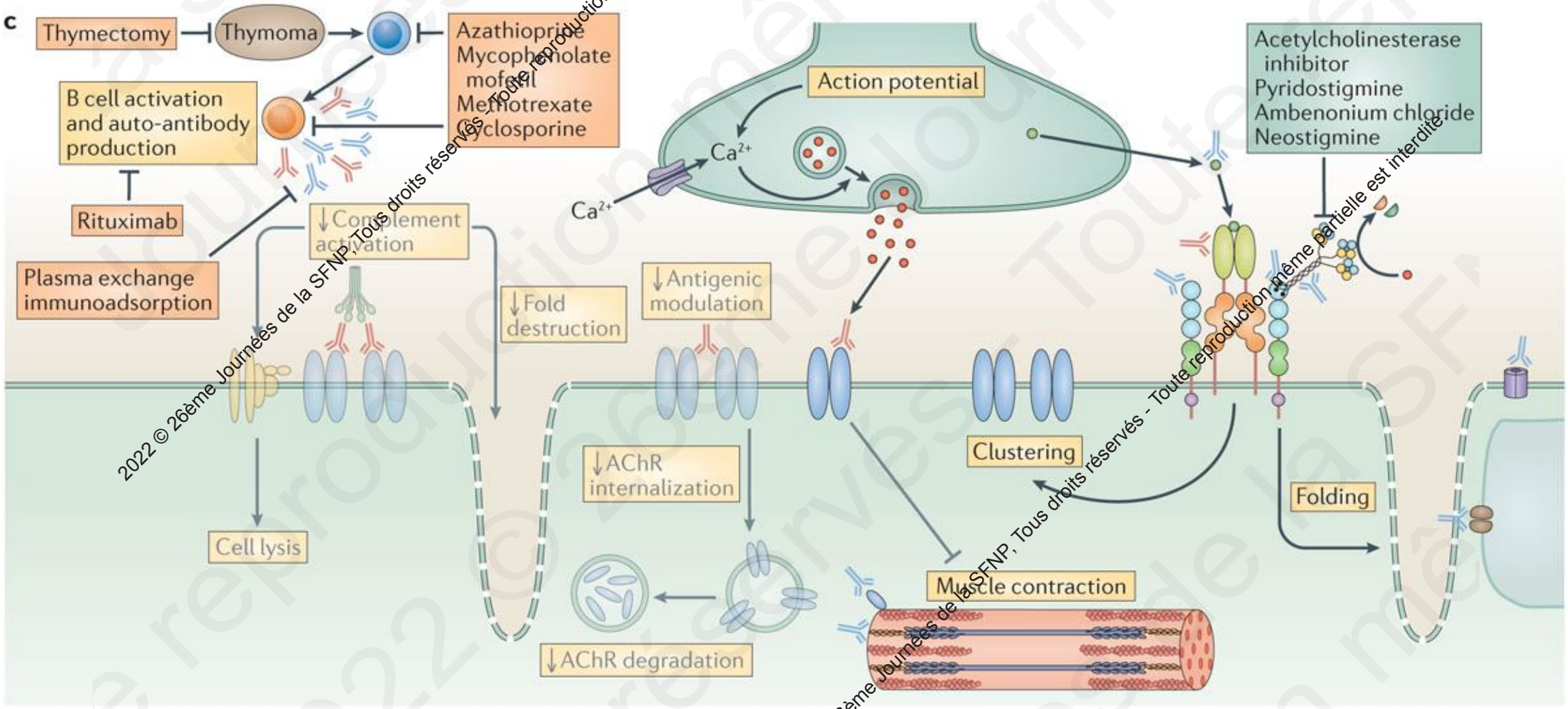
Béhin et al., 2018
Souto et al., 2019

Auto-anticorps & Myasthénie

Gilhus et al., 2016
Catar et al., 2017

- **Pas de corrélation titre AC anti-RACh & sévérité myasthénie,**
- **Parallélisme titre & évolutivité,**
- **Chez 16 à 38 % des patients séronégatifs en technique usuelle (immunoprécipitation), des anti-RACh dits à faible affinité peuvent être détectés par des méthodes plus sensibles (transfection cellulaire). Ces anticorps reconnaissent les RACh agrégés.**

Auto-anticorps & Myasthénie



Nature Reviews | Neurology 2016

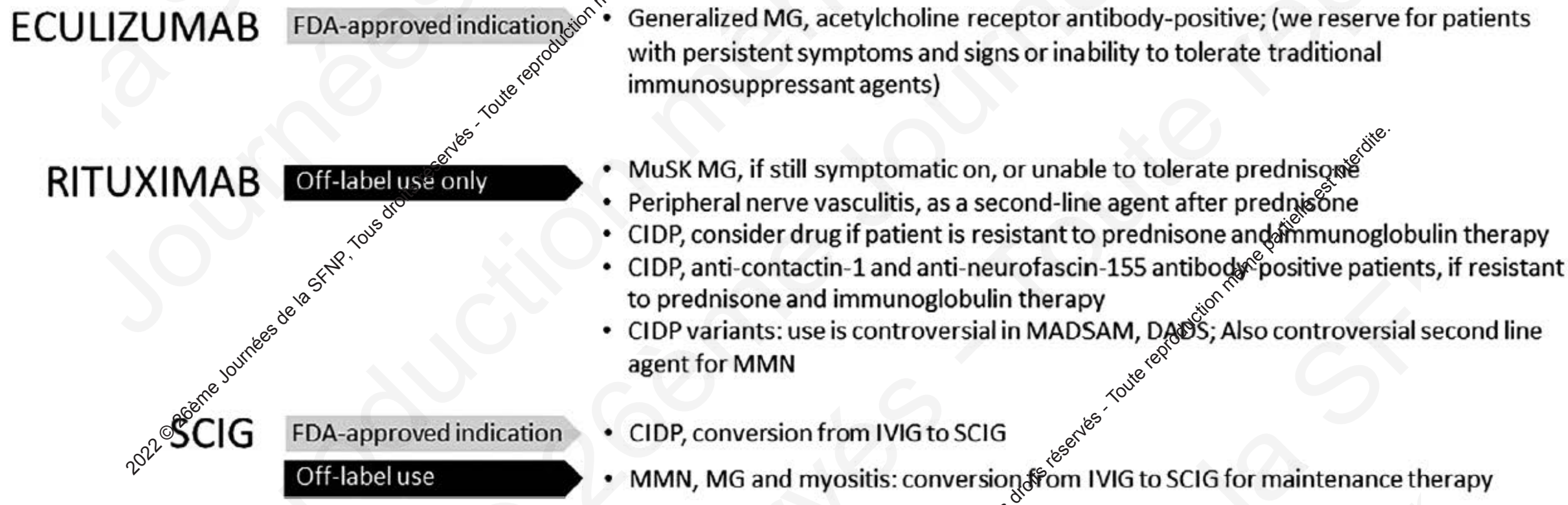


FIGURE 1 FDA-approved and off-label uses of new immune-based agents in neuromuscular diseases. DADS, distal acquired demyelinating symmetric neuropathy; MADSAM, multifocal acquired demyelinating sensory and motor neuropathy

Farmakidis et al. Muscle Nerve 2019

Myasthénie

Table 2. Drugs Used Most Frequently for the Treatment of Myasthenia Gravis.

Drug	Mode of Action	Dose	Side Effects	Risks and Contraindications
Pyridostigmine	Symptomatic; acetylcholinesterase inhibition	Single dose: 10–120 mg; daily dose: 240–600 mg	Cholinergic autonomic effects	Cholinergic crisis
Prednisone or prednisolone	Immunomodulation	Induction dose: 40–80 mg daily; stable dose: 5–20 mg daily; alternate-day treatment is an alternative	Widespread dose-dependent glucocorticoid effects	Gastrointestinal bleeding, cushingoid appearance
Azathioprine	Suppression of B and T cells	50–250 mg daily	Nausea, vomiting, tiredness, infections, night sweats	Leukopenia, liver toxicity
Mycophenolate mofetil	Suppression of B and T cells	1.5–2 g daily	Nausea, vomiting, diarrhea, joint pain, infections, tiredness	Leukopenia, progressive multifocal leukoencephalopathy; contraindicated during pregnancy
Rituximab	Suppression of B cells	0.5–1 g, repeated after 2 wk; can be repeated at 6-mo intervals	Nausea, infections, infusion-related problems	Progressive multifocal leukoencephalopathy
Methotrexate	Inhibition of folate metabolism	Gradual increase to 20 mg/wk	Nausea, infections, lung disease	Leukopenia, liver toxicity; contraindicated during pregnancy
Cyclosporine	Suppression of T cells and natural killer cells	2.5–5 mg/kg of body weight daily	Nausea, hypertension, infections, hypertrichosis	Kidney toxicity
Tacrolimus	Suppression of T cells and natural killer cells	3 mg daily	Nausea, infections, lung disease, hypertension, neuropsychiatric problems	Liver and kidney toxicity
Cyclophosphamide	Suppression of B and T cells	1–5 mg per kg administered by intravenous infusion every 4 wk for a limited period	Nausea, vomiting, alopecia, discoloration of nails and skin, infections	Leukopenia
Intravenous immune globulin	Suppression of B and T cells, neutralization of autoantibodies	2 g per kg administered over a period of 2 to 5 days	Nausea, headache, fever, hypotension or hypertension, local skin reactions	IgA deficiency, allergic reactions

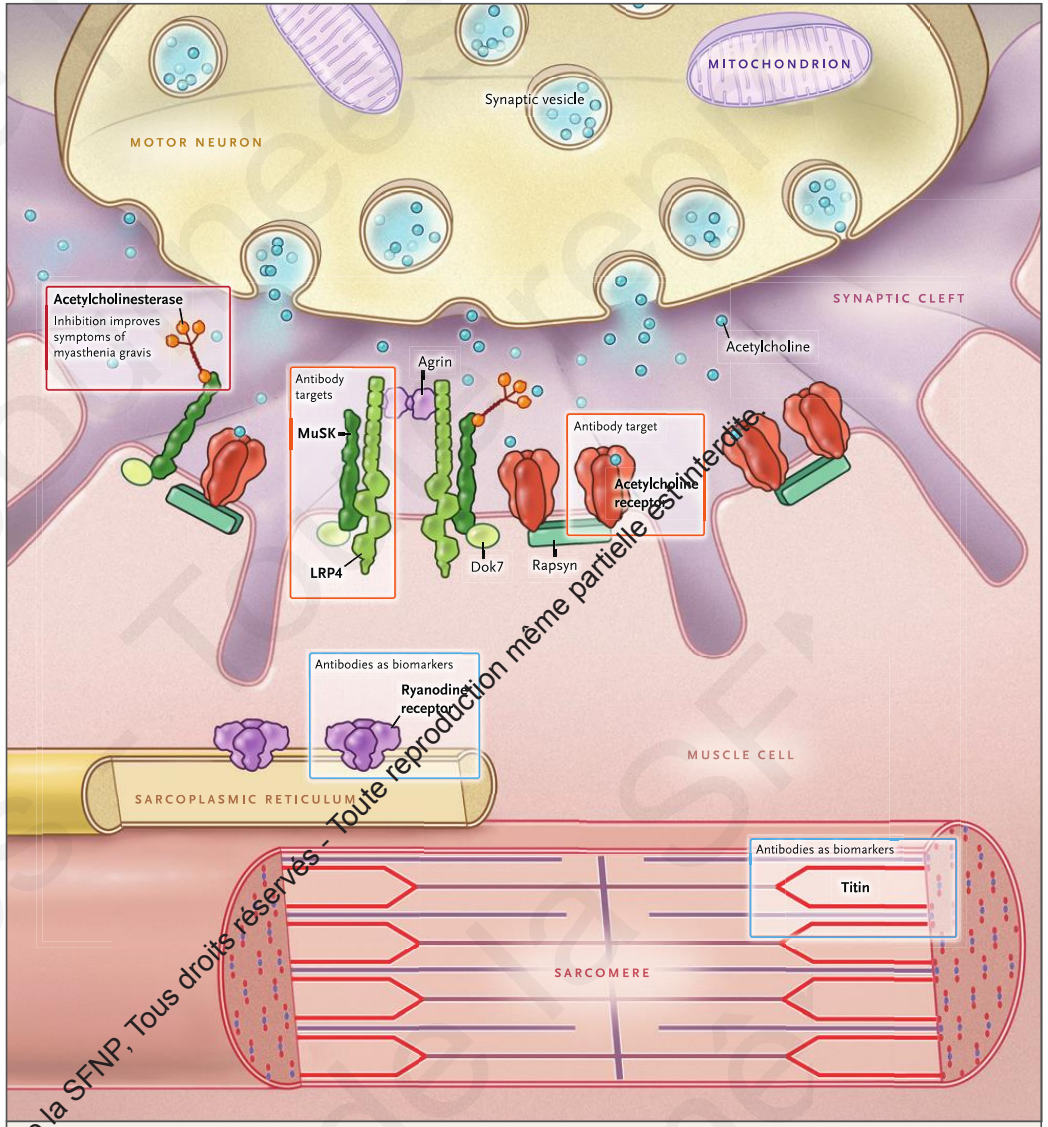


Figure 1. Neuromuscular Junction and Key Elements for the Pathogenesis of Myasthenia Gravis.
Neuromuscular transmission involves release of presynaptic acetylcholine, which binds to acetylcholine receptors in the postsynaptic membrane. The receptors interact with several other proteins in the membrane, including Dok7 and rapsyn. Mutant Dok7 and rapsyn are important in the development of congenital myasthenia. Antibodies against acetylcholine receptors, as well as antibodies against muscle-specific kinase (MuSK) and lipoprotein receptor–related peptide 4 (LRP4), induce myasthenic weakness. Antibodies against the intramuscular proteins titin and ryanodine receptor are relevant biomarkers in some subgroups of myasthenia gravis. Acetylcholine is degraded by local acetylcholinesterase, and acetylcholinesterase inhibition leads to symptomatic improvement in patients with myasthenia gravis.

Gilhus N Engl J Med 2016

Molécules candidates développées pour la déplétion des auto-anticorps

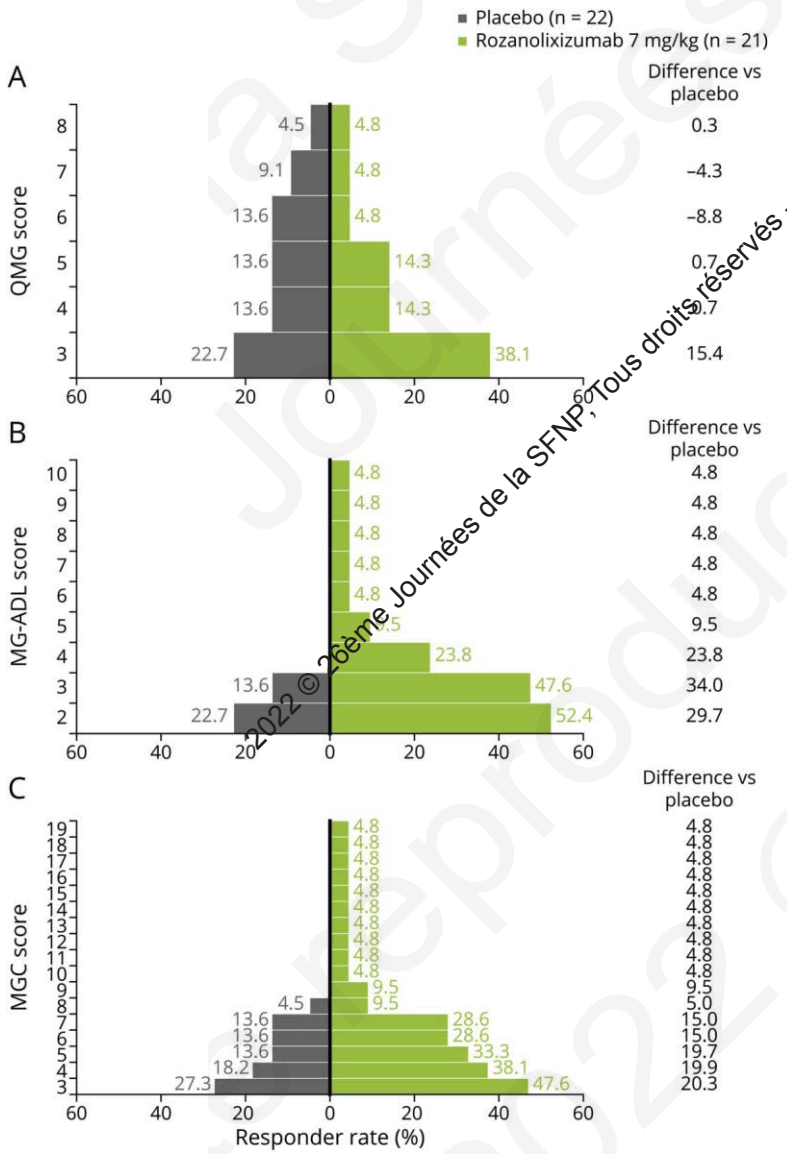
Molécule	Type	Voie d'administration	Stade de développement dans la myasthénie
Molécules de déplétion des lymphocytes B			
Inébilizumab (Viela Bio)[1]	 Anticorps IgG4 monoclonal humanisé	IV	Phase 3 (en cours)
TAK-079 (Takeda)[2,3]	 Anticorps IgG1 monoclonal entièrement humain	SC	Phase 2 (en cours)
Inhibiteurs du FcRn			
Efgartigimod (argenx)[1,4]	 Fragment Fc d'anticorps IgG1 humain	IV ou SC	Phase 3 IV (publiée)[11]
Rozanolixizumab (UCB)[5,6]	 Anticorps IgG4P monoclonal humanisé anti-FcRn humain	IV ou SC	Phase 3 (recruitment terminé)
Nipocalimab (Momenta)[7,8]	 Anticorps IgG1 monoclonal anti-FcRn entièrement humain	IV	Phase 2 (terminée)
Orilanolimab (Alexion)[9]	 Anticorps IgG4 monoclonal humanisé, purifié par chromatographie d'affinité et désimmunisé	IV	Phase 2 (en attente de lancement)
IMVT-1401 (Immunovant)[8,10]	 Anticorps IgG1 monoclonal entièrement humain	IV ou SC	Phase 2 (terminée)

FcRn, récepteur Fc néonatal ; IgG, immunoglobulines G ; IV, intraveineux ; SC, sous-cutané.

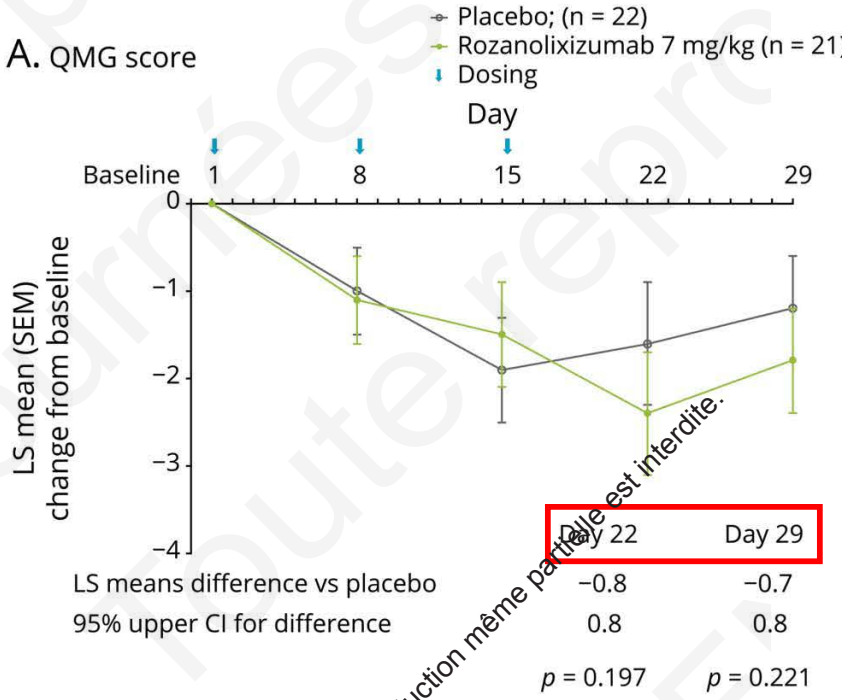
1. Huda R. *Front Immunol.* 2020;11:240. doi: 10.3389/fimmu.2020.00240. **2.** Smithson G, et al. *J Immun*. 2017;198(1 Suppl). 3. ClinicalTrials.gov. Consulté le 26 février 2021. https://clinicaltrials.gov/ct2/show/NCT04159805. **4.** Vaccaro C, et al. *Nat Biotechnol.* 2005;23:1283-1288. **5.** ClinicalTrials.gov. Consulté le 26 février 2021. https://clinicaltrials.gov/ct2/show/NCT03971422. **6.** Kiessling P, et al. *Sci Transl Med.* 2017;9:eaan1208. **7.** Ling LE, et al. *Clin Pharmacol Ther.* 2019;105:1031-1039. 8. Habib AA. Neurol Rev.2020:34-36.(Supplément). 9. Blumberg L, et al. Sci Adv. 2019;5:eaax9586. 10. Collins J, et al. Neurology. 2019;92(15 Supplément). **11**. Howard J.F Jr. *Lancet Neurol*. 2021 Jul;20(7):526-536.

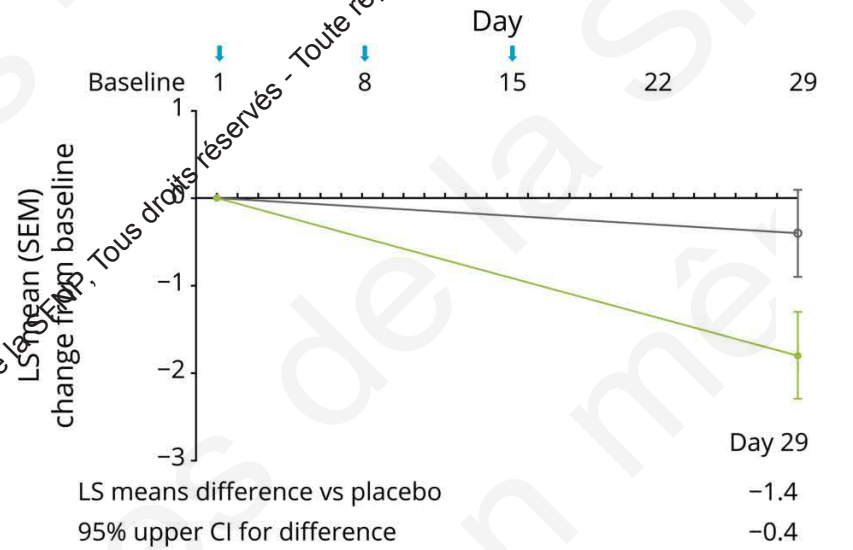
Rozanolixizumab

Figure 3 Responder Rate Analysis (Full Analysis Set) at Day 29 for Measures of Clinical Effect



Day 29 responder rates (≥3.0-point improvement from baseline) for (A) Quantitative Myasthenia Gravis (QMG) score, (B) Myasthenia Gravis–Activities of Daily Living (MG-ADL) score, and (C) Myasthenia Gravis–Composite (MGC) score.





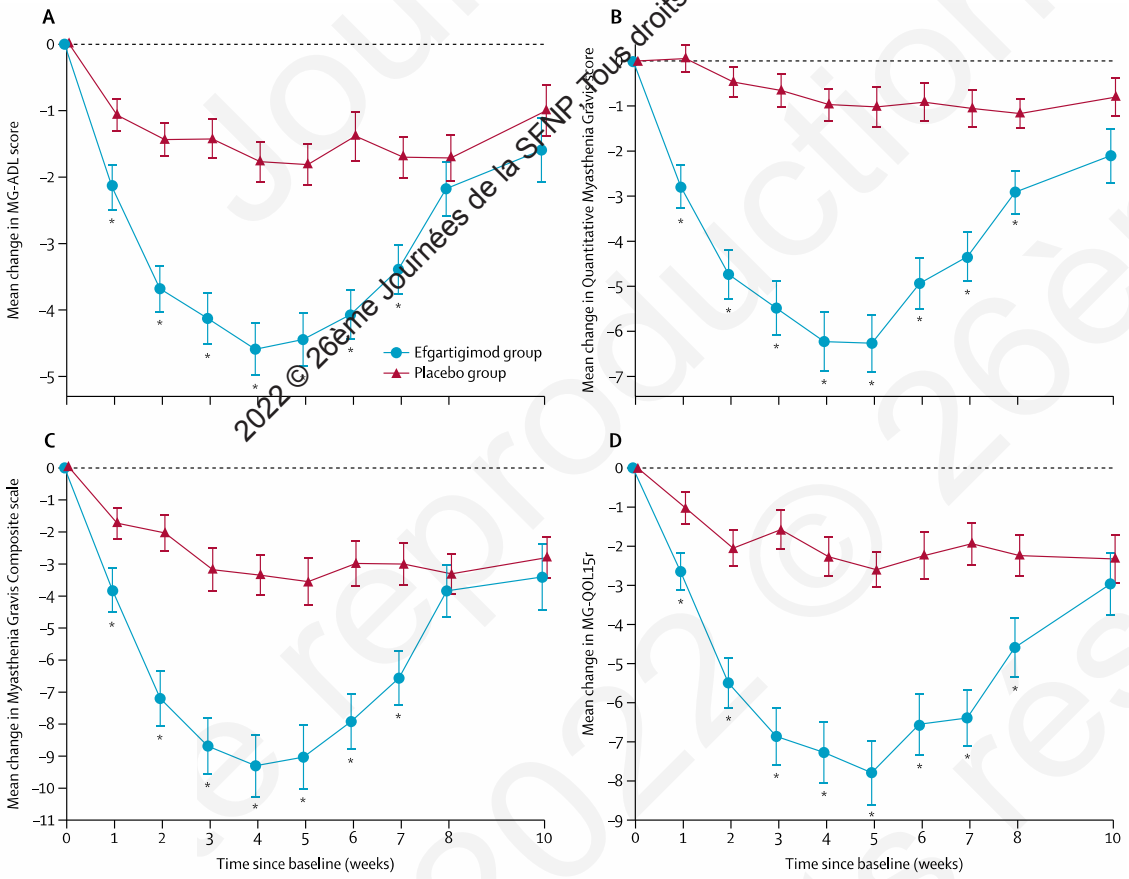
Bril et al. Neurology 2021

Efgartigimod

	Efgartigimod group	Placebo group	OR (95% CI)	p value
MG-ADL responder in cycle 1 (primary endpoint)	44/65 (68%)	19/64 (30%)	4·95 (2·21–11·53)	<0·0001
Quantitative Myasthenia Gravis responder in cycle 1	41/65 (63%)	9/64 (14%)	10·44 (4·18–31·20)	<0·0001
MG-ADL responder in cycle 1 (all patients)	57/84 (68%)	31/83 (37%)	3·70 (1·85–7·58)	<0·0001
Percentage of time with ≥2-point improvement in MG-ADL up to day 126	48·7%	26·6%	..	0·0001
Median time from day 28 until no clinically meaningful improvement, days	35 (18–71)	8 (1–57)	..	0·26
Early MG-ADL responder (cycle 1)	37/65 (57%)	16/64 (25%)	..	Not assessed*

Data are n/N (%), or median (IQR), unless stated otherwise. Analyses were done in acetylcholine receptor antibody-positive patients unless otherwise stated. MG-ADL=Myasthenia Gravis Activities of Daily Living. *Secondary endpoints were tested in hierarchical order. The fifth secondary endpoint was not assessed because the fourth secondary endpoint was not significant.

***Table 2*: Summary of primary and secondary endpoints**



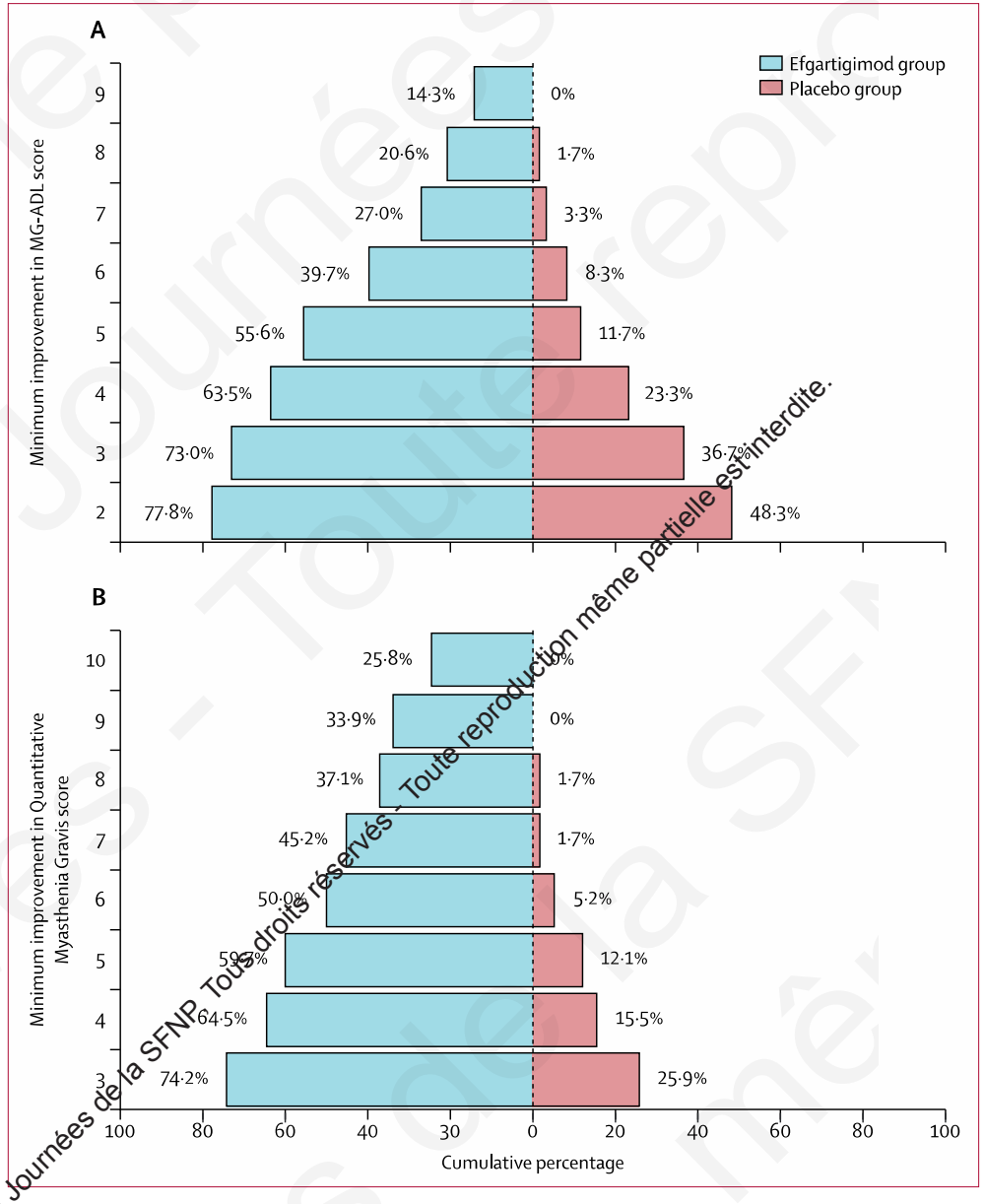
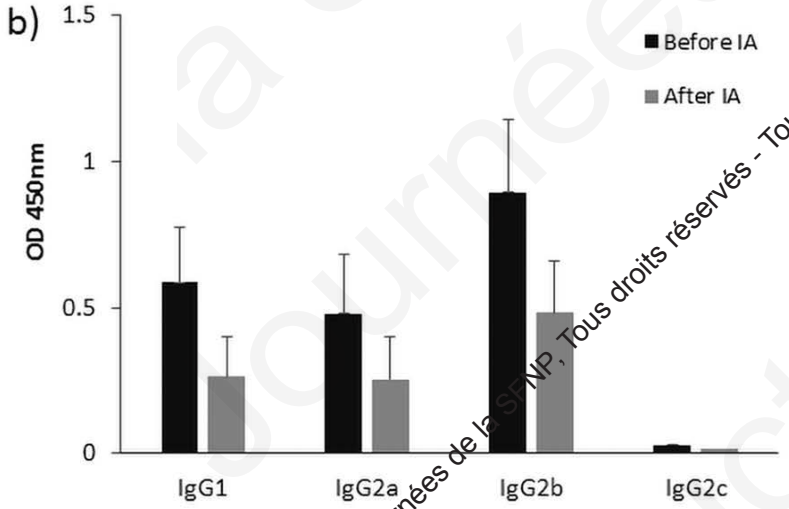
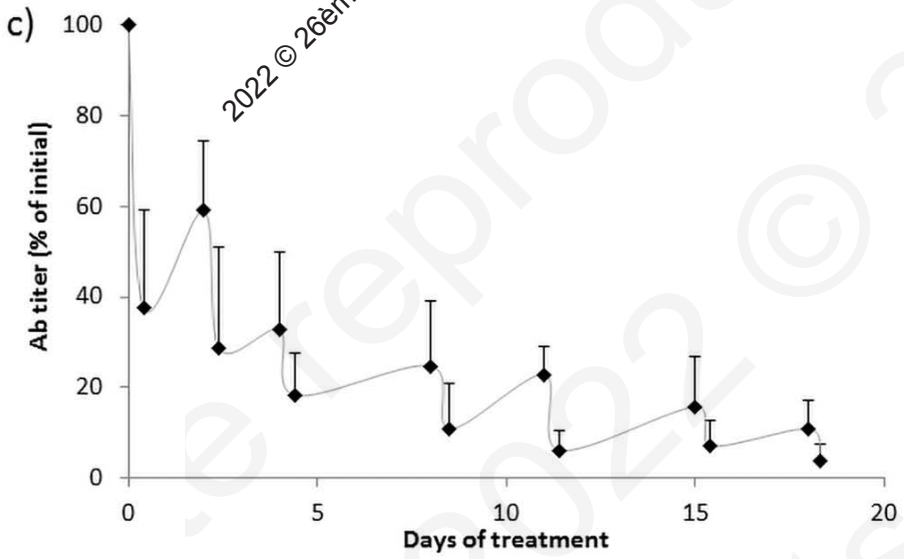


***Figure 3*: Minimum point improvement in MG-ADL (A) and Quantitative Myasthenia Gravis (B) score in cycle 1, in acetylcholine receptor antibody-positive patients**
Minimum improvements 1 week after the last infusion of cycle 1 (week 4). MG-ADL=Myasthenia Gravis Activities of Daily Living.

Howard et al. Lancet Neurol 2021

Nouveaux développements d'une vieille méthode





Antigen-specific immunoadsorption of MuSK autoantibodies as a treatment of MuSK-induced experimental autoimmune myasthenia gravis

Konstantinos Lazaridis[a,*], Vasiliki Baltatzidou[a], Nikolaos Tektonidis[a], Socrates J. Tzartos[a,b,*]

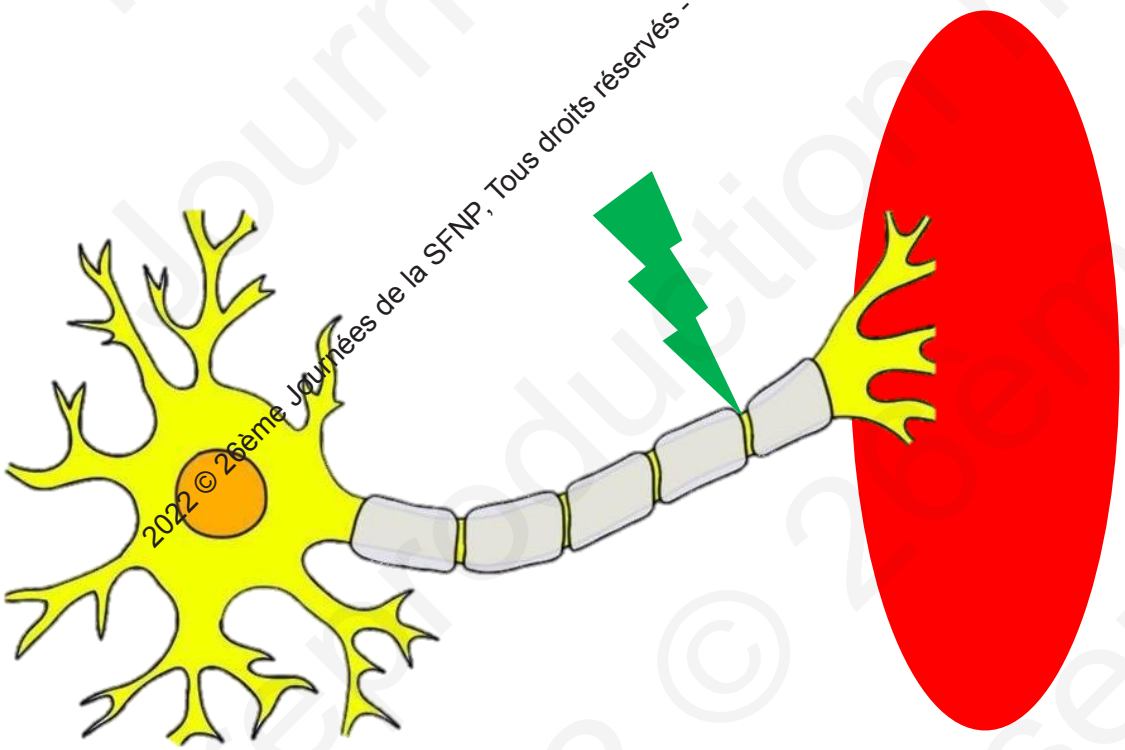
Immunoadsorption:
Retirer IgG, IgM…

Antigen specific immunoadsorption:
Retirer sélectivement un anticorps

Théoriquement applicable à n'importe quelle maladie à auto-anticorps

Lazaridis et al. J Neuroimmunol 2020

Rôle des auto-anticorps

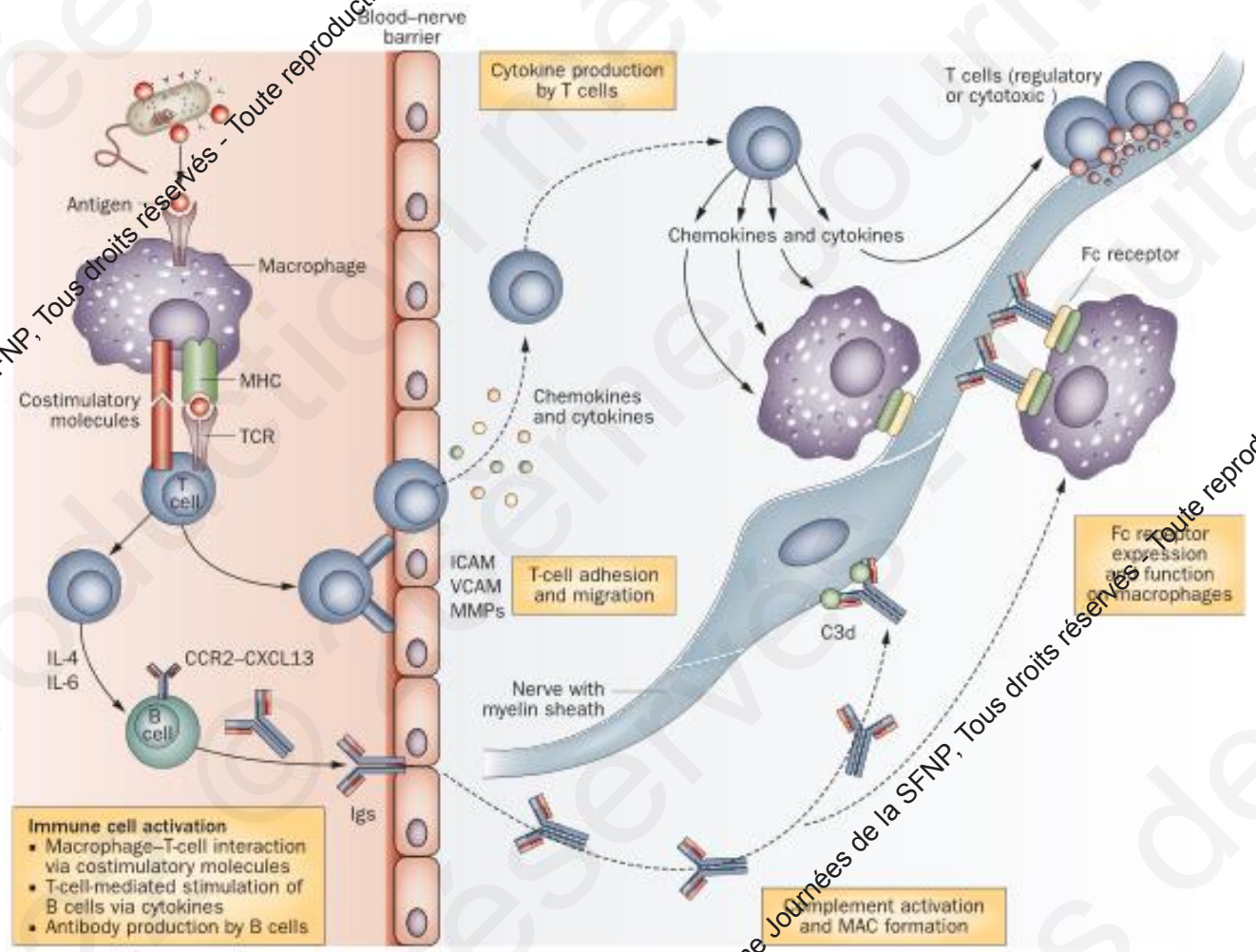


- **Myasthénie**
- **Polyradiculoneuropathie Inflammatoire Démyélinisante Chronique**
- **Neuropathie Motrice Multifocale**
- **Neuropathie MAG**

Auto-anticorps & PIDC

- **Historique : polyneuropathies cortico-sensibles, entité distincte entre 1975-1976,**
- **Neuropathies sensitivomotrices, démyélinisantes, segmentaires multifocales, auto-immunes, à rechutes (30 à 40%) ou progressives ; grande hétérogénéité clinique, pronostique et de réponse thérapeutique,**
- **La plus fréquente des neuropathies auto immunes chroniques ; affection rare (prévalence 1-7/100 000 ; incidence 0,5/100 000), terrain : 40-60 ans, hommes > femmes (ratio 1,5),**
- **Invalidante : Bouchard et al. (1999) : 83 patients, 9 décès (10,8%). Lunn et al. (1999) : mRS moyen au nadir 3,5 et 54% des patients 4 ou 5 durant leur maladie.**

Auto-anticorps & PIDC



Dalakas, Nature Review Neurology, 2011

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(Auto-anticorps & PIDC)

Le concept de neuropathie démyélinisante est-il suffisant et satisfaisant ?

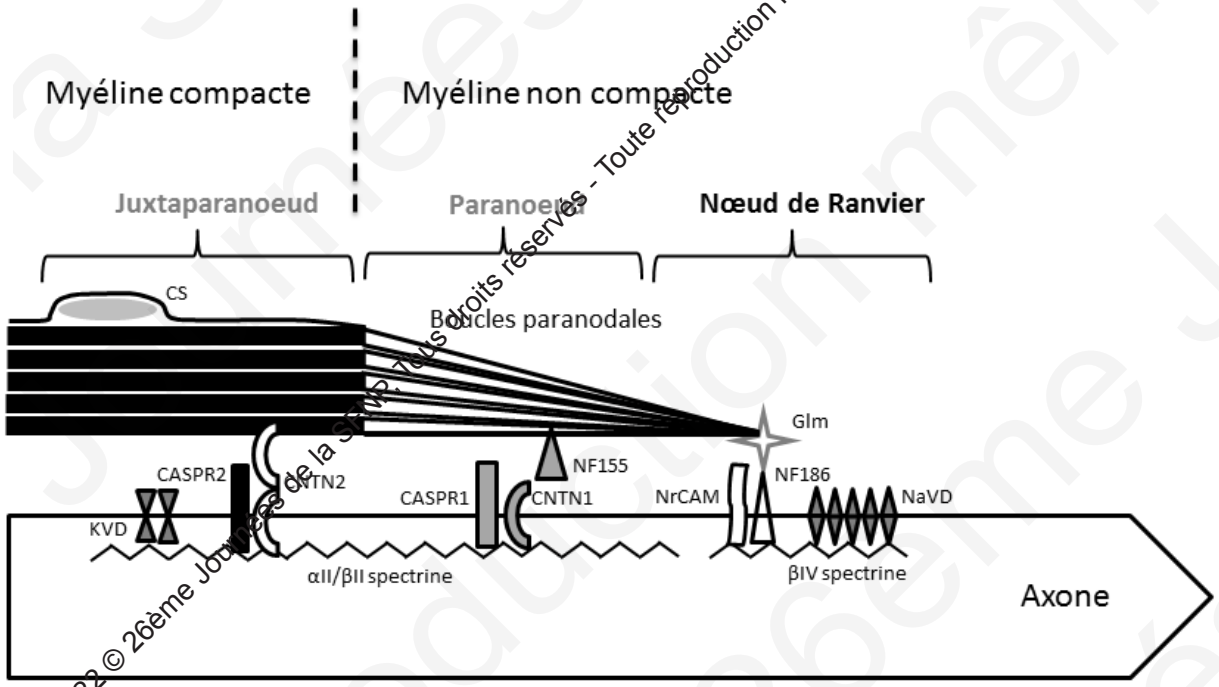
Comment expliquer qu'un Guillain-Barré s'améliore si vite sous IgIV ?

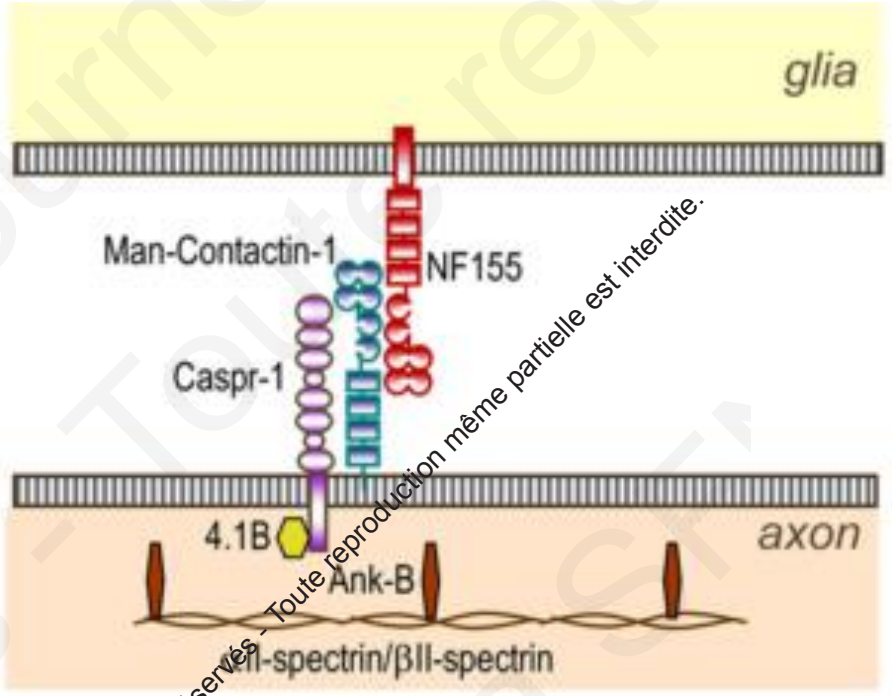
Comment expliquer qu'une neuropathie motrice à bloc de conduction s'améliore si vite sous IgIV ?

A l'inverse comment expliquer qu'un Guillain-Barré démyélinisant ne s'améliore finalement pas si bien ?

De quoi parle-t-on quand on dit neuropathie démyélinisante ???

Auto-anticorps & PIDC





- **Contactin 1 (Querol et al., 2013 ; Doppler et al., 2016),**
- **Neurofascin 155 (Ng et al., 2012 ; Querol et al., 2014 ; Devaux et al., 2016),**
- **Caspr 1 (Doppler et al., 2016).**
- **Neurofascin 140 & 186 (Delmont et al., 2017)**

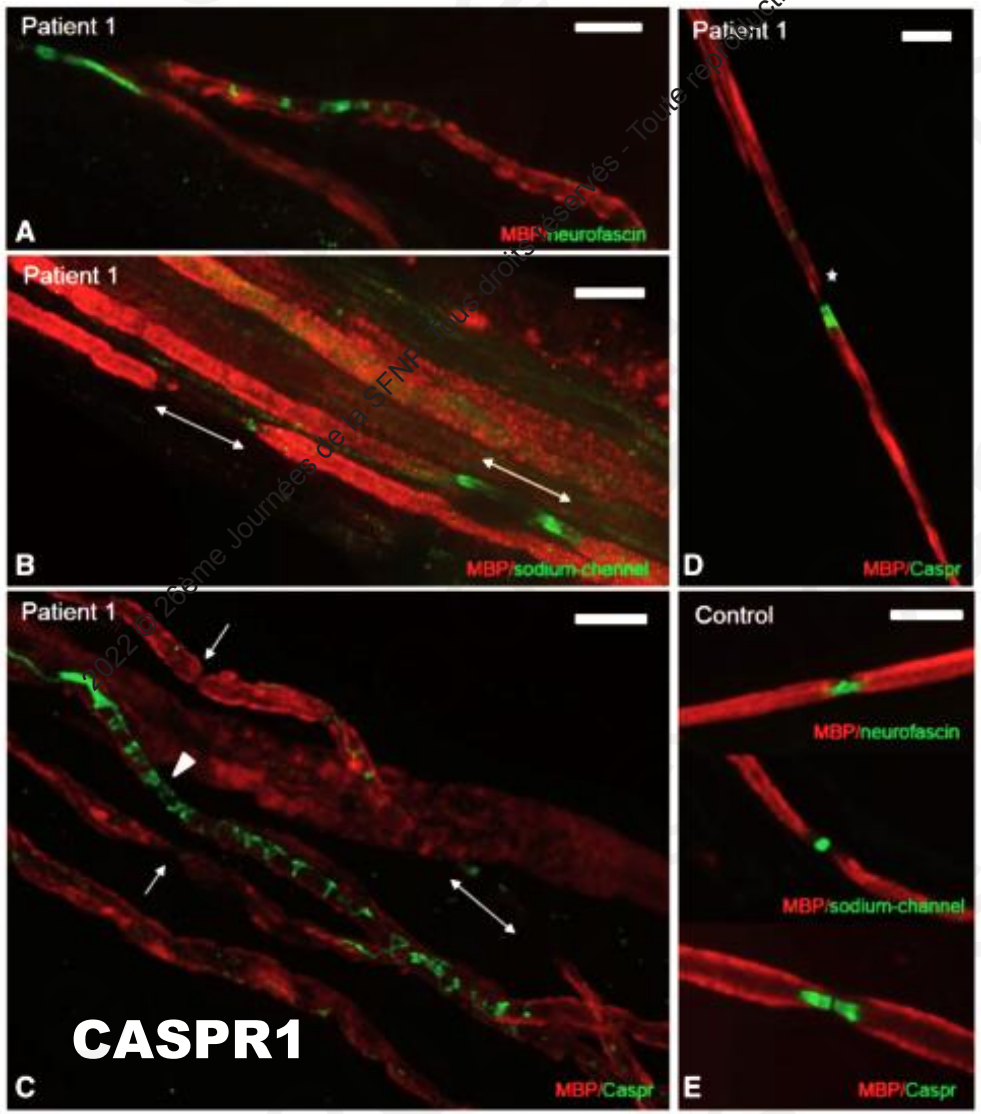
< 10% des PIDC

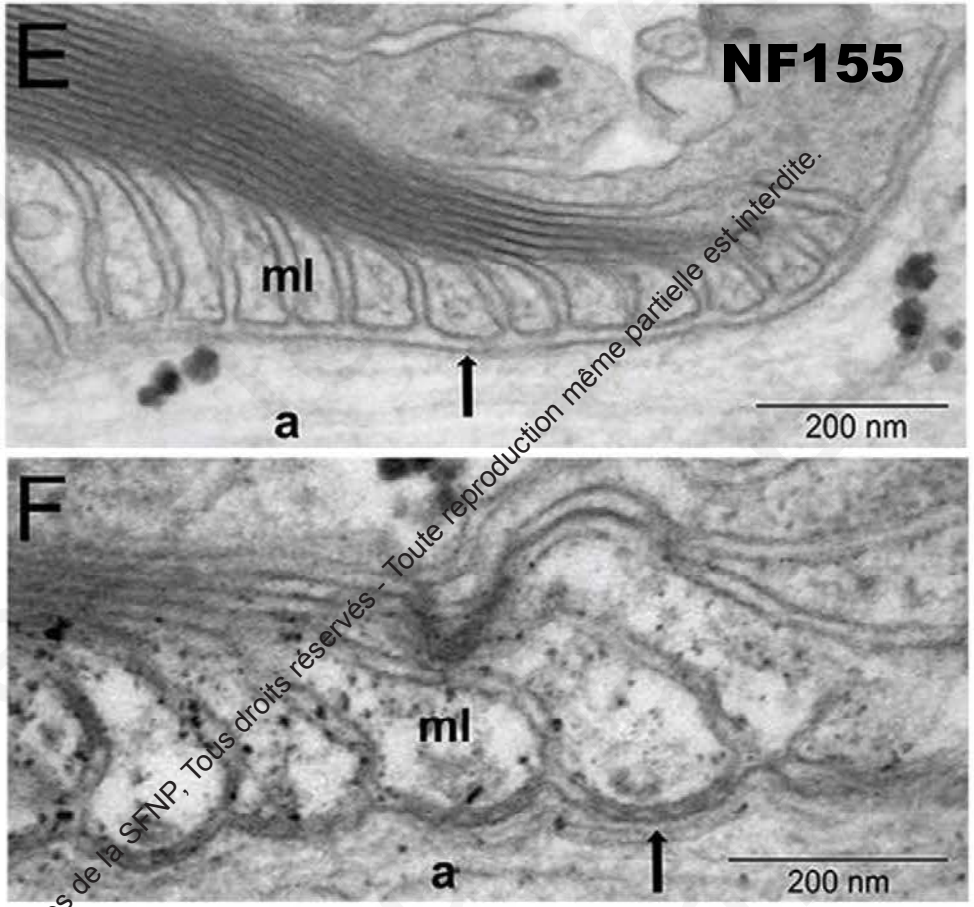
Auto-anticorps & PIDC

▪ Contactin 1	▪ NF 155
▪ Patients âgés ▪ Ataxie ▪ Installation Subaiguë ▪ Tremblements ▪ **Réfractaire aux IgIV** ▪ **Bonne réponse aux CC**	▪ Patients plus jeunes ▪ **Tremblement invalidant** de fréquence lente, postural et intentionnel ▪ Neuropathie sévère distale motrice avec ataxie ▪ Installation/évolution subaigue ▪ Démyélinisation centrale ▪ **Réfractaire aux IgIV**

- **Mauvaise réponse aux IgIV,**
- **IgG4,**
- **Pas d'activation du complément.**

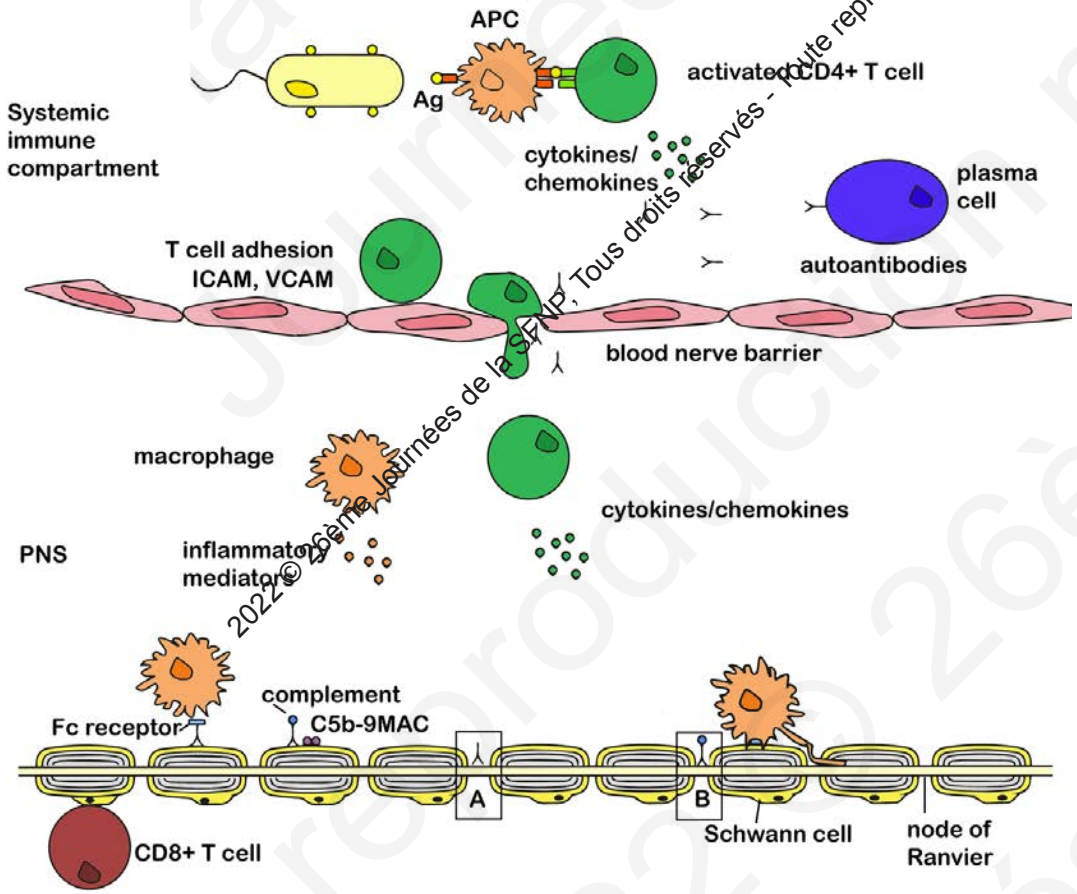
Auto-anticorps & PIDC



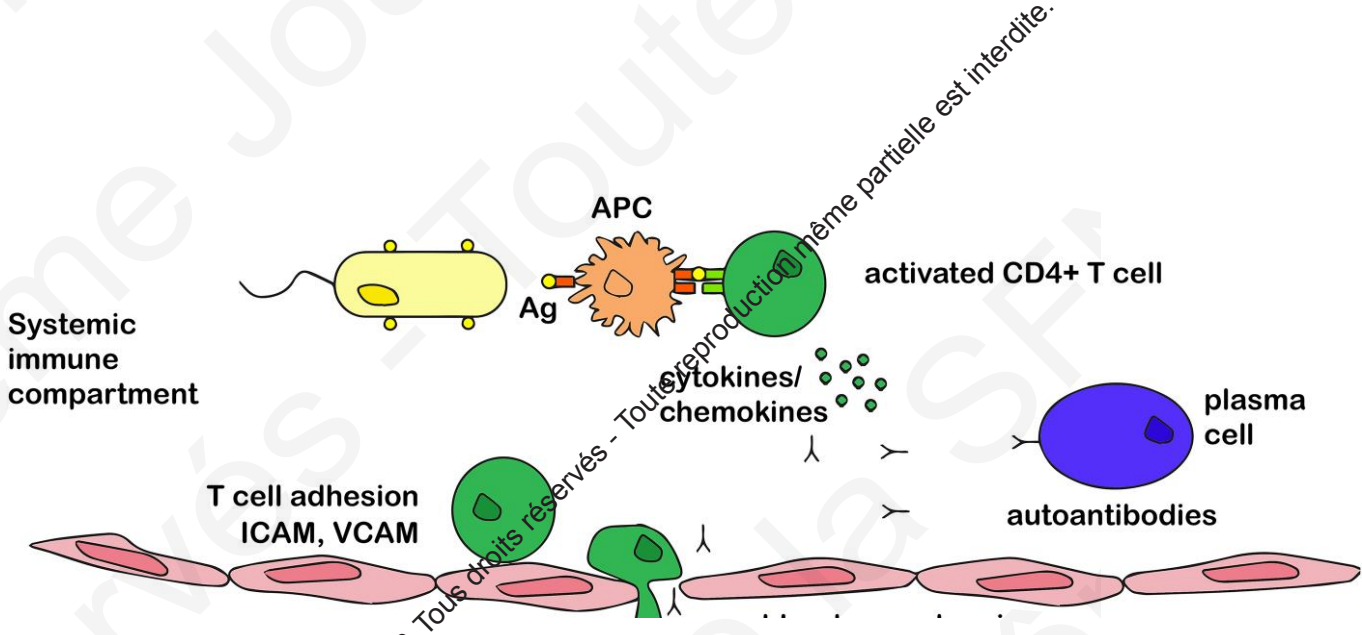


Doppler et al., 2016
Vallat et al., 2016

Ciblage des auto-anticorps: SGB / PIDC



Cibles : myéline / cellules de Schwann



Nodopathies autoimmunes

Cibles : composants du nœud de Ranvier

Mathey et al. J Neuro Neurosurg Psychiatry 2015

A Plasma Exchange Versus Immune Globulin Infusion Trial in Chronic Inflammatory Demyelinating Polyradiculoneuropathy

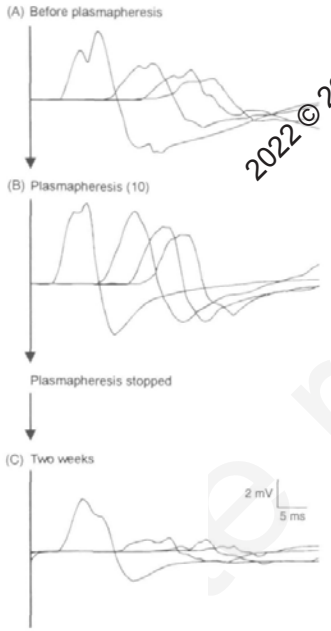
Peter James Dyck, MD,* William J. Litchy, MD,* Kay M. Kratz,* Guillermo A. Suarez, MD,*
Phillip A. Low, MD,* Alvaro A. Pineda, MD,† Anthony J. Windebank, MD,*
Jeannine L. Karnes, MSc,* and Peter C. O'Brien, PhD‡

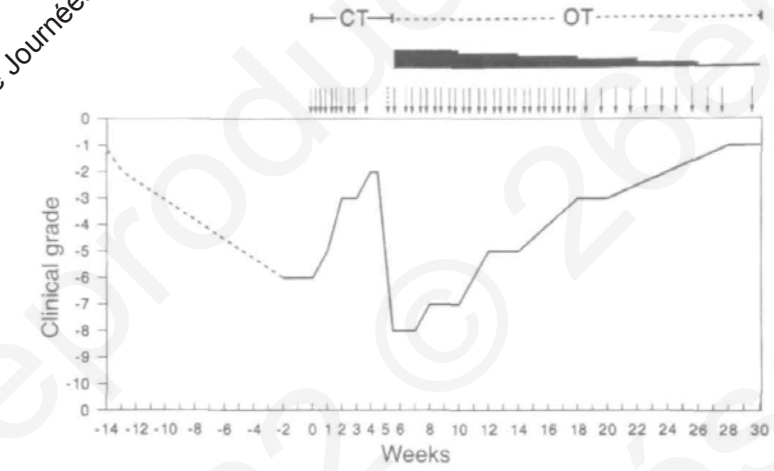
Brain (1996), **119**, 1055–1066

Plasma-exchange therapy in chronic inflammatory demyelinating polyneuropathy

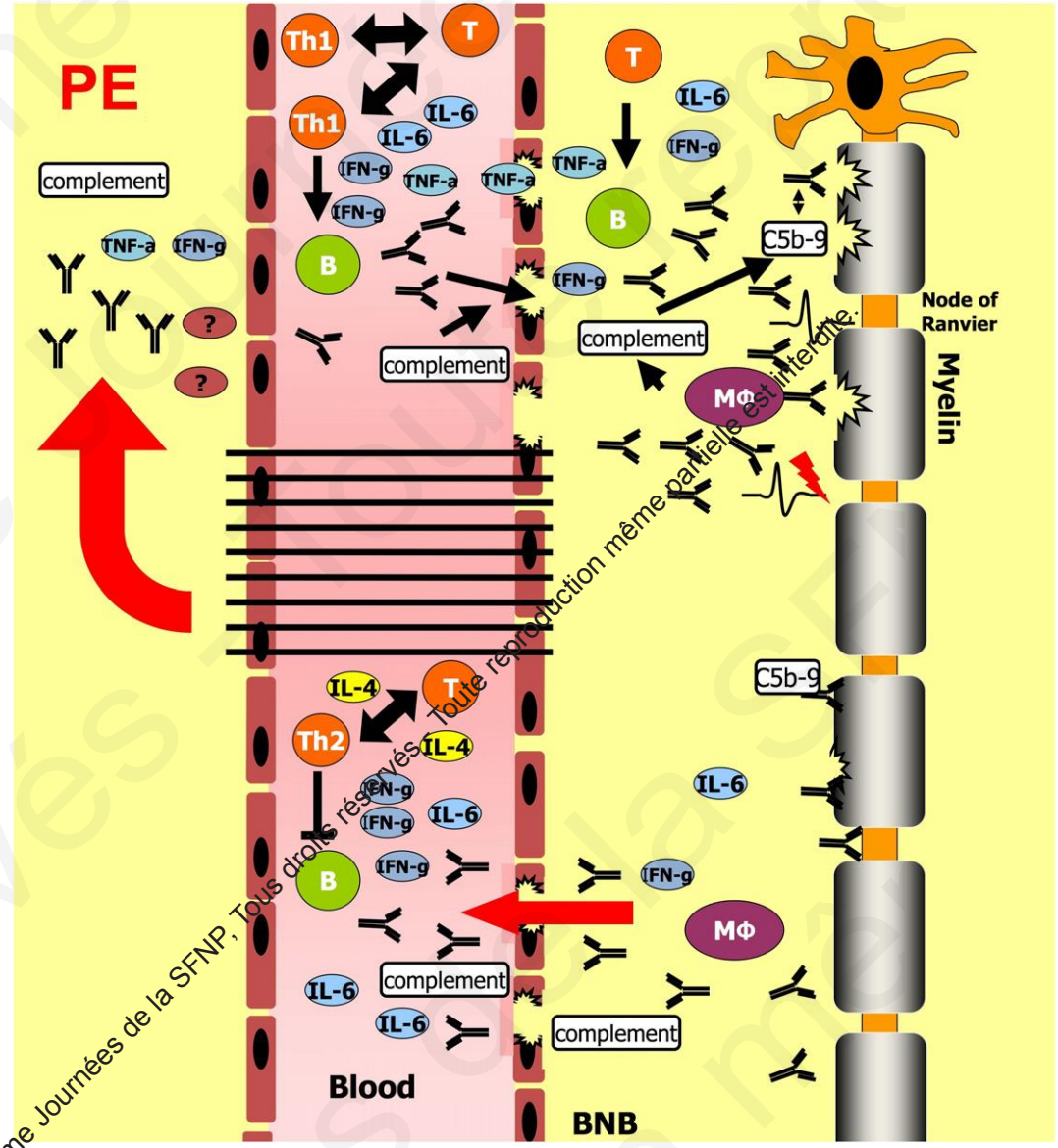
A double-blind, sham-controlled, cross-over study

A. F. Hahn,[1] C. F. Bolton,[1] N. Pillay,[2] C. Chalk,[3] T. Benstead,[4] V. Bril,[5] K. Shumak,[5]
M. K. Vandervoort[1] and T. E. Feasby[6]





- The TF **strongly recommended treatment with plasma exchange**.
- The initial treatment may start with 5 exchanges over 2 weeks; thereafter, the plasma exchange interval should be individually adapted. If possible, peripheral veins should be used.



Lehmann & Hartung J Neuroimmunol 2011, Vand den Bergh et al. JPNS 2021

TABLE 2 Drugs under continued investigation or drug development in neuromuscular diseases

	Drug Category	Route of Administration	Disease	Study Status
Efgartigimod	Neonatal Fc receptor inhibitor	IV	Generalized MG CIDP	Phase 2 complete; phase 3 underway
Rozanolixizumab	Neonatal Fc receptor inhibitor	IV	Generalized MG CIDP	Phase 2 complete. Phase 3 ongoing Phase 2 ongoing
M281	Neonatal Fc receptor inhibitor	IV	Generalized MG	Phase 2 ongoing
Ravulizumab	Terminal complement inhibitor	IV	Generalized MG	Phase 2 complete; phase 3 underway
Zilucoplan	Terminal complement inhibitor	SQ	Generalized MG Immune-mediated necrotyzing myopathy	Phase 2 complete; phase 3 in planning stage Phase 2 study in planning stage

Farmakidis et al. Muscle Nerve 2019

7	☐	Recruiting	A Study to Assess the Long-term Safety and Efficacy of a Subcutaneous Formulation of **Efgartigimod** in Adults With Chronic Inflammatory Demyelinating Polyneuropathy (CIDP, an Autoimmune Disorder That Affects the Peripheral Nerves)	• Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	• Biological: **Efgartigimod** PH20 SC	• Investigator site 34 Phoenix, Arizona, United States • Investigator site 15 Scottsdale, Arizona, United States • Investigator site 42 Carlsbad, California, United States • (and 59 more...)
3	☐	Completed	A Study to Assess Long-term Safety, Tolerability and Efficacy of **Rozanolixizumab** in Subjects With Chronic Inflammatory Demyelinating Polyradiculoneuropathy	• Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)	• Drug: **Rozanolixizumab**	• Cidp04 50082 Scottsdale, Arizona, United States • Cidp04 50075 Augusta, Georgia, United States • Cidp04 50117 Charlotte, North Carolina, United States • (and 11 more...)

1. A Study to Assess the Long-term Safety and Efficacy of a Subcutaneous Formulation of Efgartigimod in Adults With Chronic Inflammatory Demyelinating Polyneuropathy (CIDP, an Autoimmune Disorder That Affects the Peripheral Nerves) - Full Text View - ClinicalTrials.gov
2. A Study to Assess Long-term Safety, Tolerability and Efficacy of Rozanolixizumab in Subjects With Chronic Inflammatory Demyelinating Polyradiculoneuropathy - Full Text View - ClinicalTrials.gov

Table 2 Treatment and Clinical Response

Treatment	No. of patients (n, %)	Response (n, %)	Dose/Protocol
IVIg	38 (95%)	Yes: 5 (13.1%) Partial: 9 (23.7%) No: 24 (63.2%)	2g/kg per course
Steroids	36 (90%)	Yes: 10 (27.8%) Partial: 16 (44.4%) No: 10 (27.8%)	1 mg/kg/d: 23 (63.9%) MP iv pulse: 4 (11.1%) MP iv pulse + mg/kg/d: 5 (13.9%) Others: 4 (11.1%)
PLEX	18 (46.2%)	Yes: 7 (38.9%) Partial: 6 (33.3%) No: 5 (27.8%)	No of sessions (median, IQR): 6 (5–9)
Rituximab[a],[b]	23 (57.5%)	Yes: 17 (77.3%) Partial: 3 (13.6%) No: 2 (9.1%)	4 + 2: 8 (36.4%) 4: 6 (27.3%) 1 + 1: 6 (27.3%) Others: 2 (9.1%)
Azathioprine	9 (22.5%)	Yes: 1 (11.1%) Partial: 4 (44.4%) No: 4 (44.4%)	—
Mycophenolate	3 (7.5%)	Partial: 1 (33.3%) No: 2 (66.7%)	—
Methotrexate	3 (7.5%)	Partial: 1 (33.3%) No: 2 (66.7%)	—
Cyclosporine	1 (2.5%)	No: 1 (100%)	—
Interferon beta 1a	1 (2.5%)	No: 1 (100%)	—

Nodopathies autoimmunes

Treatment with IVIg was not effective in CIDP with antibodies against the node of Ranvier (Table 1 and Fig. 2). One patient with IgG4 antibodies anti Nfasc155 had a 1 year remission after receiving a combination of steroids and plasma exchanges. Efficacy of plasma exchanges and steroids was initially good, but usually transient in all treated patients.

Martin-Aguilar et al. Neurol Neuroimmunol Neuroinflamm 2021, Delmont et al. J Neurol 2020

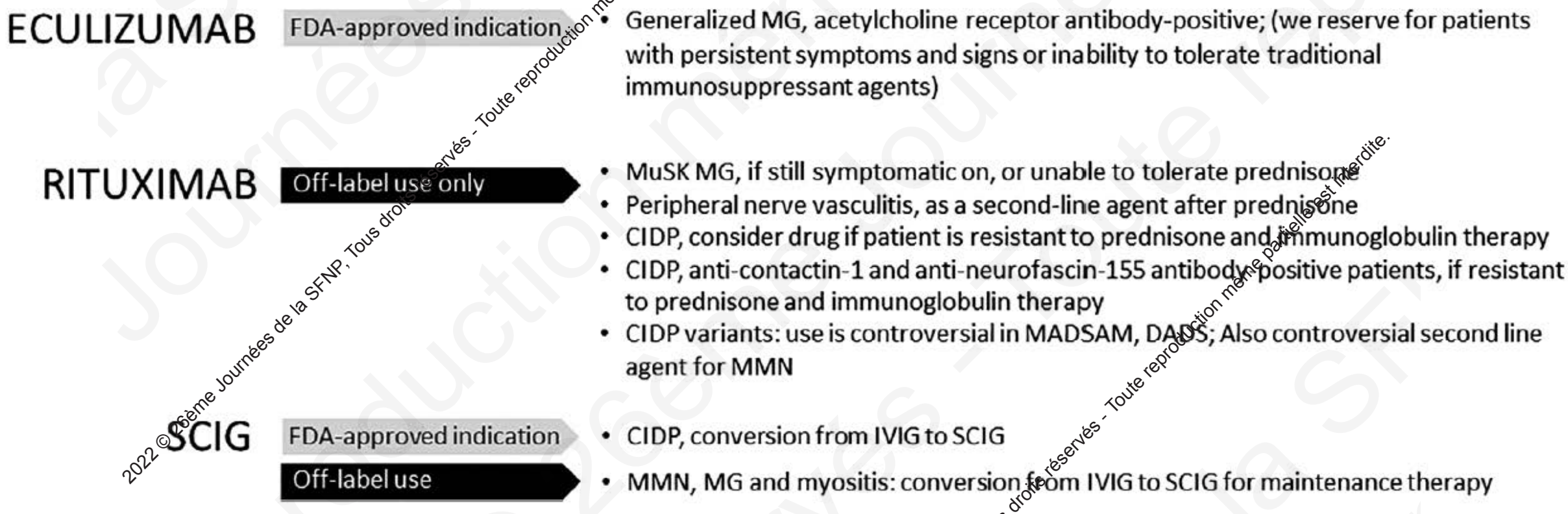
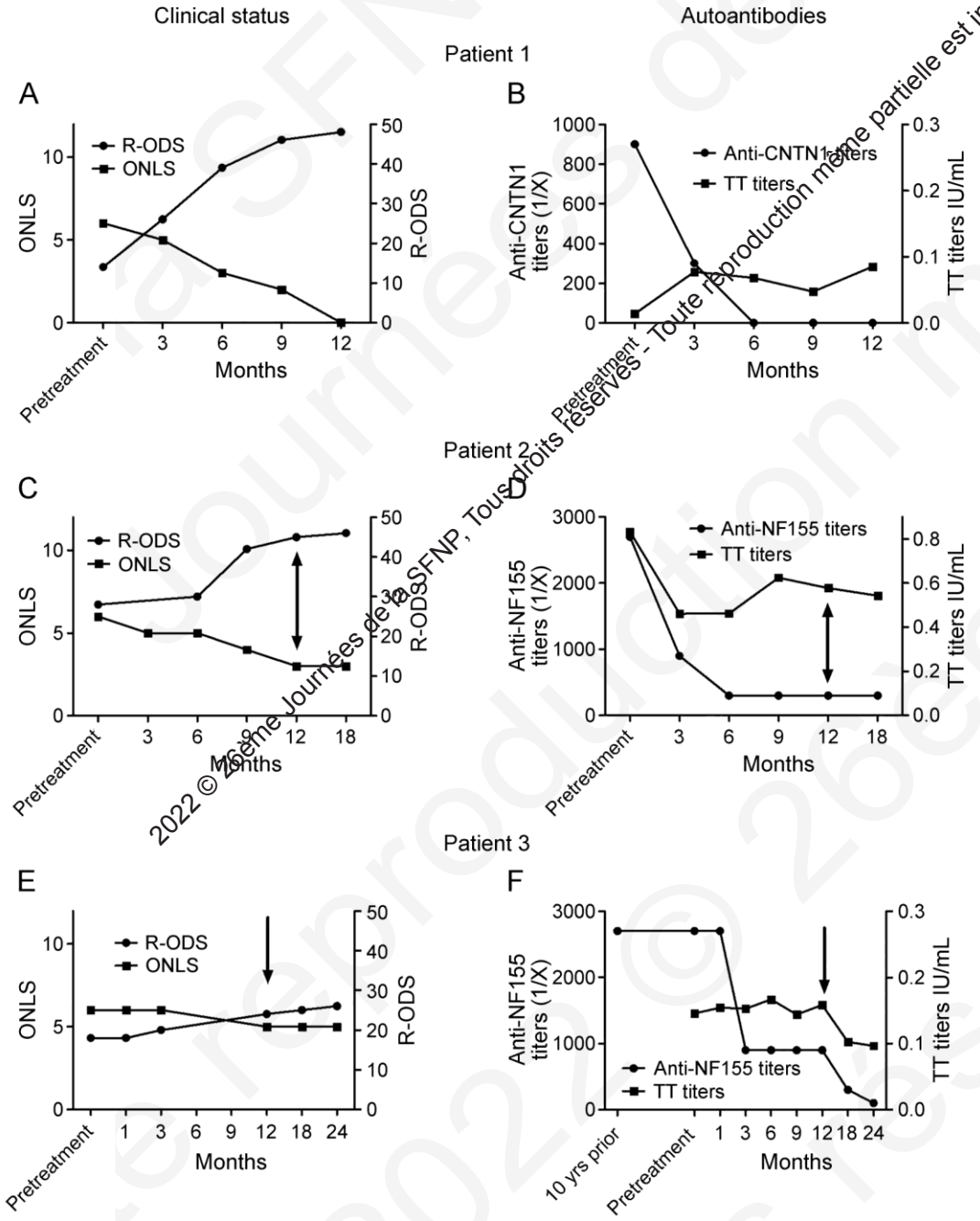


FIGURE 1 FDA-approved and off-label uses of new immune-based agents in neuromuscular diseases. DADS, distal acquired demyelinating symmetric neuropathy; MADSAM, multifocal acquired demyelinating sensory and motor neuropathy

Farmakidis et al. Muscle Nerve 2019



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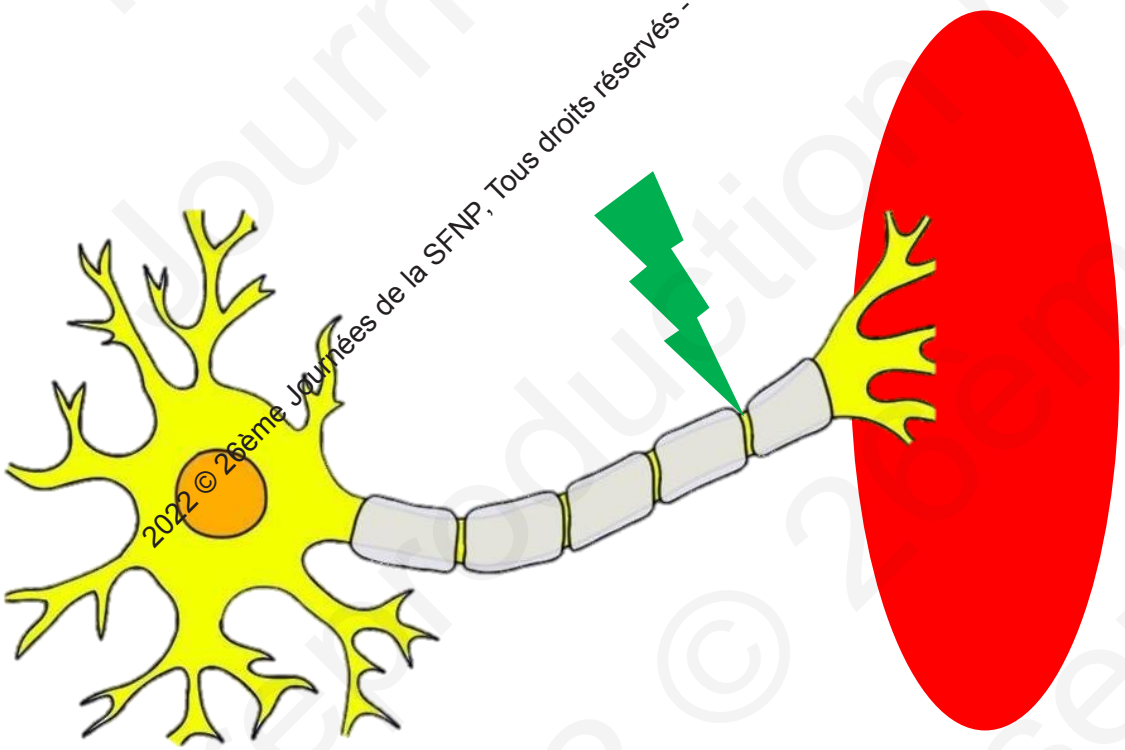
Querol et al. Neurol Neuroimmunol Neuroinflamm 2015, Martin-Aguilar et al. Neurol Neuroimmunol Neuroinflamm 2021

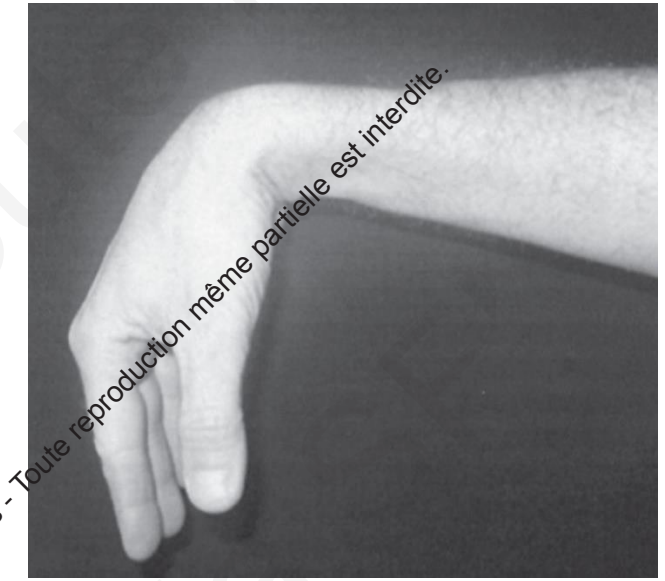
Rôle des auto-anticorps



- **Myasthénie**
- **Polyradiculoneuropathie Inflammatoire Démyélinisante Chronique**
- **Neuropathie Motrice Multifocale**
- **Neuropathie MAG**

Auto-anticorps & NMM

- Neuropathie rare (très rare ?),
- Atteinte motrice pure des membres supérieurs de l'homme (sex ratio 2,7) jeune (40 ans),
- Respect des fléchisseurs,
- 1/3 de pieds tombants comme premier symptômes puis atteinte MS,
- Crampes & fasciculations 40%, parfois hypertrophie musculaire,
- Aggravation au froid > 80%.



Yeh et al., 2020

Auto-anticorps & NMM

REVIEW

Multifocal motor neuropathy: controversies and priorities

Wei Zhen Yeh ,[1,2] P James Dyck,[3] Leonard H van den Berg,[4] Matthew C Kiernan,[5,6] Bruce V Taylor[1,7]

JNNP 2020

- Is MMN an axonal or demyelinating neuropathy?
- Is MMN a nodo-paranodopathy?
- Are anti-GM1 IgM antibodies pathogenic or a bystander?
- Are there other relevant antibodies when anti-GM1 is negative?

Table 1 Controversies and priorities in multifocal motor neuropathy (MMN)

Diagnosis	► What is the role for nerve MRI and ultrasound? ► Can a patient have MMN despite the lack of conduction block identified on comprehensive routine neurophysiological testing?
Pathophysiology	► Is MMN an axonal or demyelinating neuropathy? ► Is MMN a nodo-paranodopathy? ► Are anti-GM1 IgM antibodies pathogenic or a bystander? ► Are there other relevant antibodies when anti-GM1 is negative?
Treatment	► What are other treatment options apart from intravenous immunoglobulin? ► What are current treatment recommendations based on the available evidence?

Auto-anticorps & NMM

Une démyélinisation segmentaire : non,

- **Une lésion de la myéline au niveau du nœud de Ranvier exposant le paranœud à une attaque immunitaire = oui,**
- **Une lésion segmentaire avec démyélinisation focale interrompant la conduction du signal = non,**
- **D'ailleurs, comment expliquer une récupération rapide rapidement après un traitement par IgIV ≠ remyélinisation,**
- **Au moins en début de maladie, VCM normales.**

Yeh et al., 2020

Auto-anticorps & NMM

Une modification de l'excitabilité nerveuse : oui,

- Dépolarisation sur le site du bloc = blocage des pompes Na^+/K^+,
- Hyperexcitabilité d'aval → crampes + fasciculations,
- Blocs modifiés par l'activité nerveuse (amélioration) via les pompes Na/K (controversé),
- Paralysie au froid = aggravation symptômes = « blocage » des pompes Na^+/K^+ thermosensibles.

Yeh et al., 2020

Auto-anticorps & NMM

Les anticorps anti-GM1 (IgM) : oui,

- Présents chez 40% des patients,
- Présents hors MMN mais taux plus faibles,
- GM1 présent au niveau du nœud de Ranvier,
- GM1 = maintien des tight junctions + regroupement des canaux ioniques (K^+, paranoeud ; Na^+, nœud),
- Homéostasie calcium cellulaire,
- « Toxicité » directe = augmentation courants K^+ ; Ca^{++}
- Activation complément.

Yeh et al., 2020

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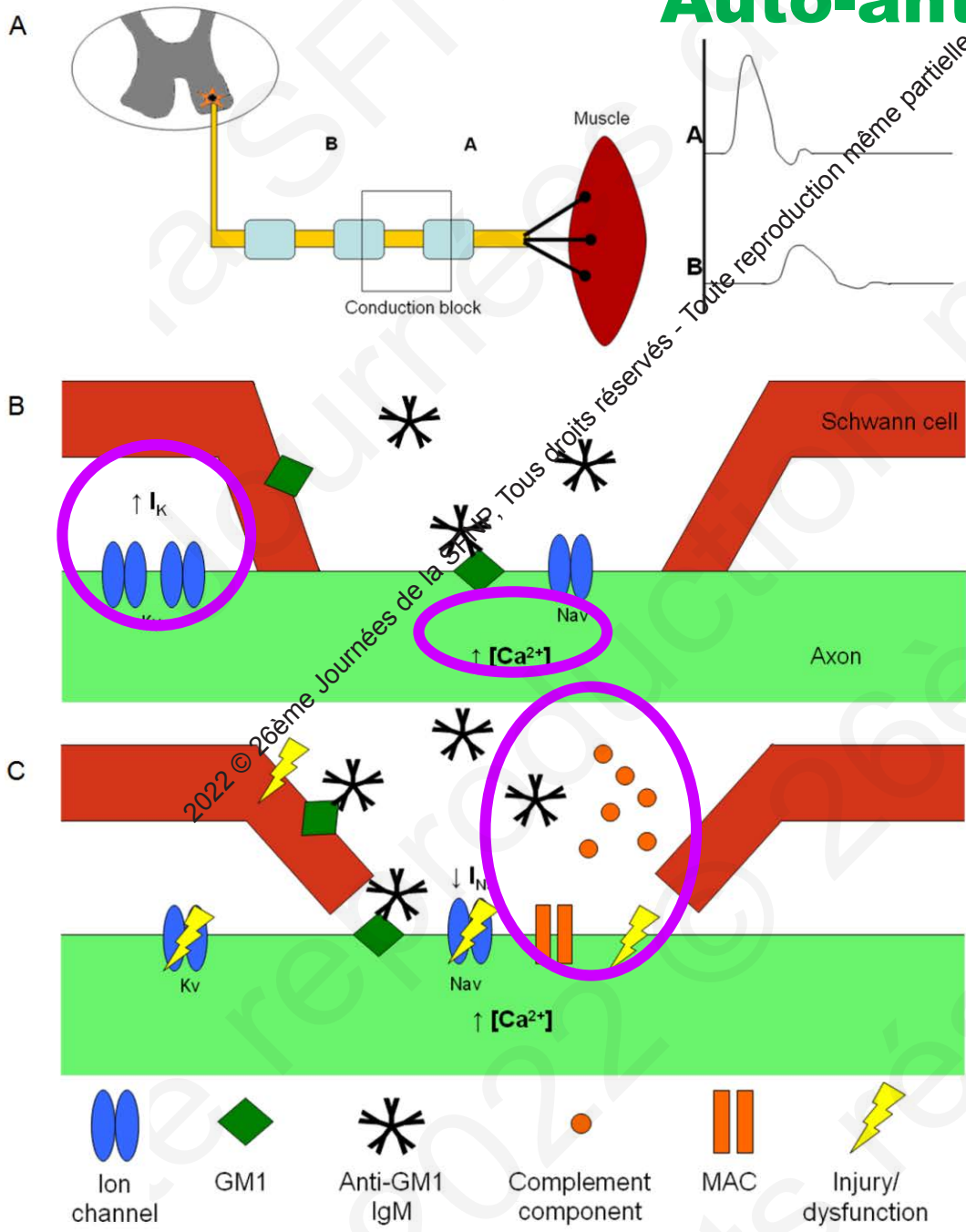
Auto-anticorps & NMM



NMM = nodopathie ?

- **Action directe :** perturbation homéostasie Ca (▲ intracellulaire), ▲ courant potassique.
- **Action indirecte :** complément et complexe d'attaque,
- **Conséquences :** perturbation canaux Na, canaux K, défaut de regroupement des canaux Na,
- **A la phase ultime → dégénérescence axonale.**

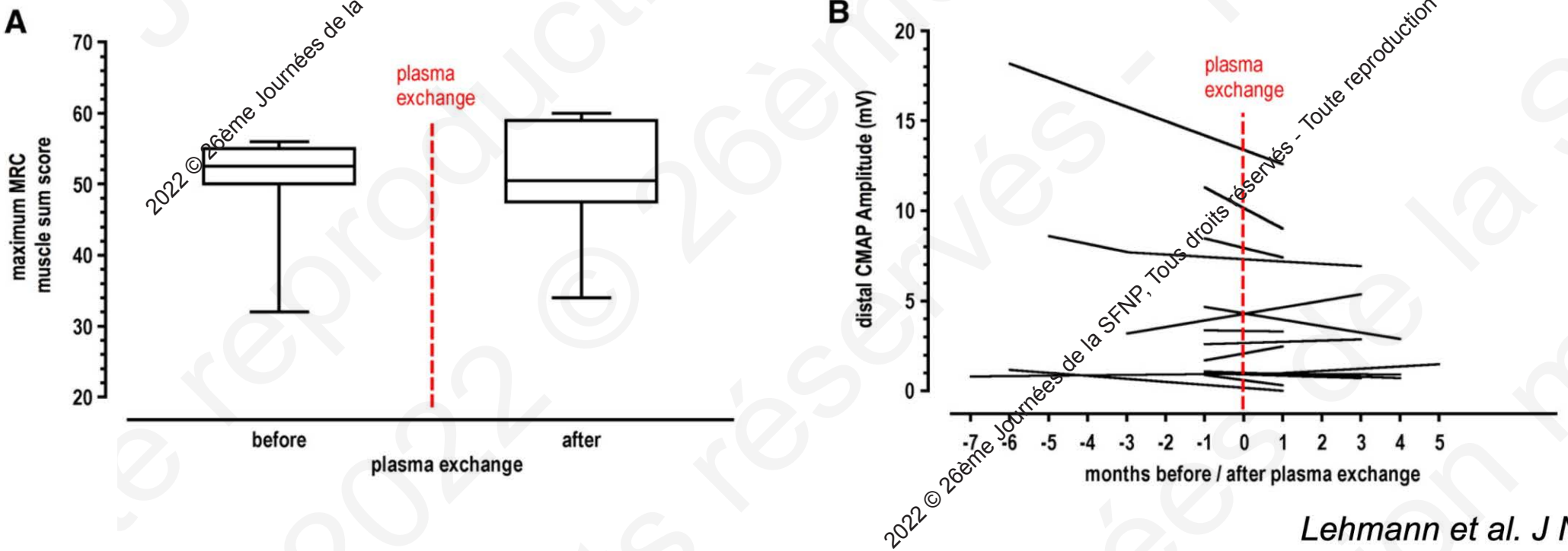
Yeh et al., 2020

Deterioration of multifocal motor neuropathy after plasma exchange

Article abstract—We report a patient with motor neuropathy in whom plasma exchange (PE) was followed by a pronounced clinical worsening with the appearance of conduction blocks in previously clinically unaffected motor nerves, leading to the diagnosis of multifocal motor neuropathy (MMN). This report highlights the different response to therapy of MMN and chronic inflammatory demyelinating polyneuropathy (CIDP) because not only steroids but also PE, which is often effective in CIDP, do not improve and at times may even worsen MMN.

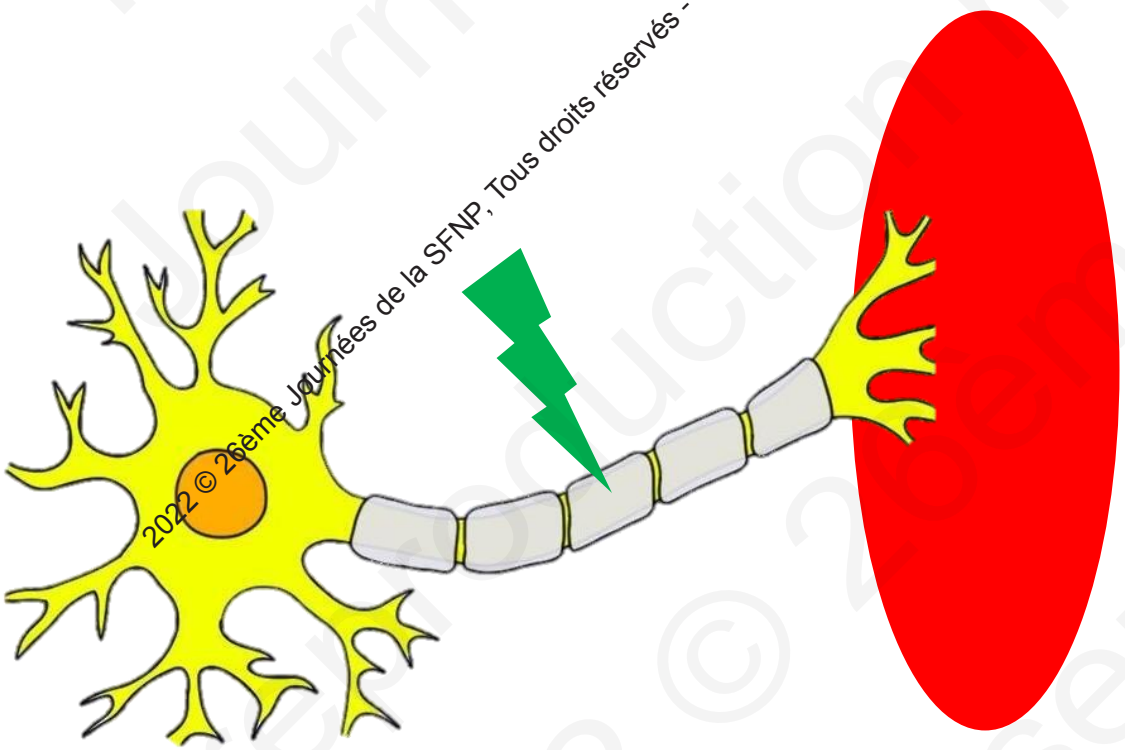
NEUROLOGY 1998;50:1480–1482

M. Carpo, MD, PhD; A. Cappellari, MD; G. Mora, MD; R. Pedotti, MD; S. Barbieri, MD, PhD; G. Scarlato, MD; and E. Nobile-Orazio, MD, PhD



Lehmann et al. J Neurol Sci 2008

Rôle des auto-anticorps



- **Myasthénie**
- **Polyradiculoneuropathie Inflammatoire Démyélinisante Chronique**
- **Neuropathie Motrice Multifocale**
- **Neuropathie MAG**

Auto-anticorps & MAG

Qu’est-ce qu’une neuropathie MAG typique ?

- IgM,
- Activité anti-MAG,
- Chronique,
- Progressive,
- Neuropathie sensitive,
- Atteinte motrice distale des membres inférieurs tardive,
- Ataxie,
- Tremblement.

Nobile-Orazio E, 1994
Ellie E et al., 1996

Auto-anticorps & MAG

COFRAMAG - Svahn et al., 2018	Patients (n=202)
"Typical" clinical phenotype	**135 (66.8)**
Sensory ataxic distal PNP	51 (25.2)
Sensory ataxic distal PNP with tremor	31 (15.3)
Sensory ataxic distal PNP with progressive distal motor deficit	53 (26.2)
"Variant" clinical phenotype	**33 (16.3)**
Sensory non-ataxic PNP	20 (9.9)
Asymptomatic/paucisymptomatic sensory PNP	11 (5.4)
Sensorimotor non-ataxic PNP	2 (1)
"Atypical" clinical phenotype	**34 (16.8)**
Chronic sensorimotor PRN	22 (10.9)
Asymmetric and/or multifocal NP	6 (3)
Acute sensory/sensorimotor PRN	4 (2)
Suggestive of small fibre NP	1 (0.5)
Amyotrophic lateral sclerosis and sensory PNP	1 (0.5)

Auto-anticorps & MAG

COFRAMAG – Svahn et al., 2018

AC anti-MAG : Pas de différence selon les groupes cliniques

Taux faible (<10 000 BTU) : 11% (n=22),
Taux moyen (10 000-70 000) : 51% (n=104),
High (≥70 000) : 38% (n=76).

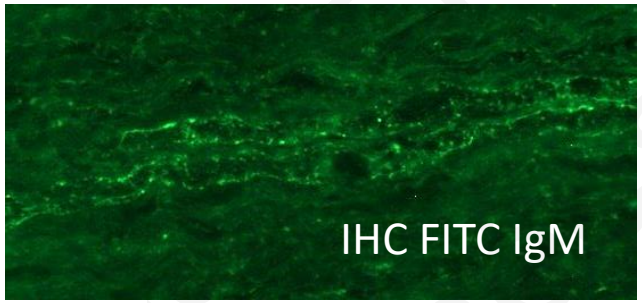
	> 10000 BTU (n=180)	< 10000 BTU (n=22)
MGUS	120 (66,6%)	17 (77,3%)
Waldenström	54 (30%)	5 (22,7%)
Autre maladie hématologique	6 (3%)	0

Auto-anticorps & MAG

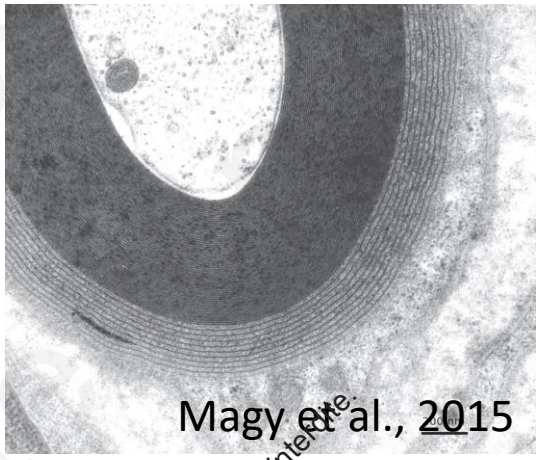
Les preuves de la pathogénicité :

- Latov et al., 1981 : IgM reconnaissant la MAG du SNP et du SNC ; perte de la réactivité en cas de déglycosilation,
- Co-réaction avec SGPG présente uniquement dans le SNP,
- Co-réaction avec l'épitope HNK-1,
- Réactivité MAG > SGPG,
- ELISA > Western blot (sensibilité & facilité).

Dalakas, 2018



Auto-anticorps & MAG

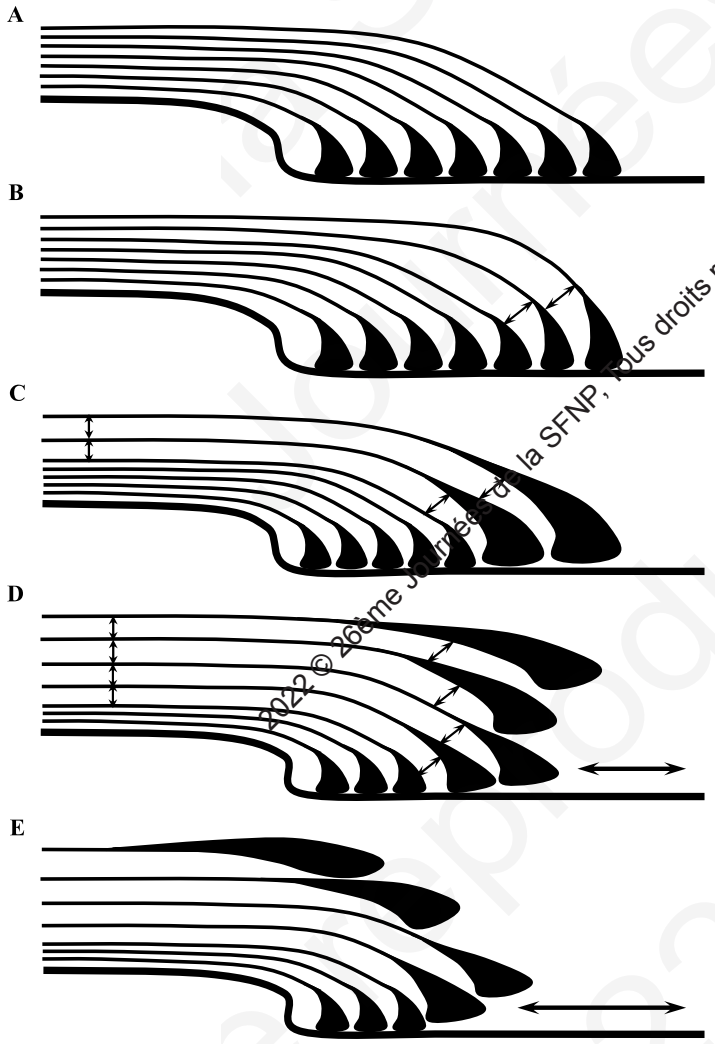


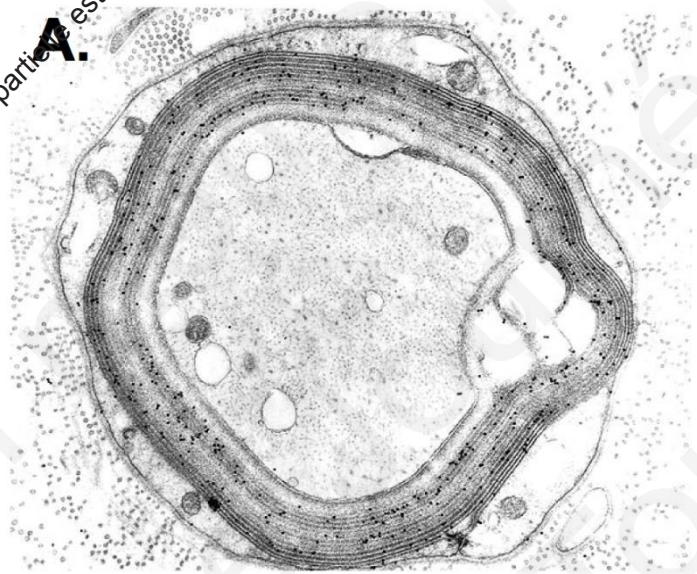
Les preuves de la pathogénicité :

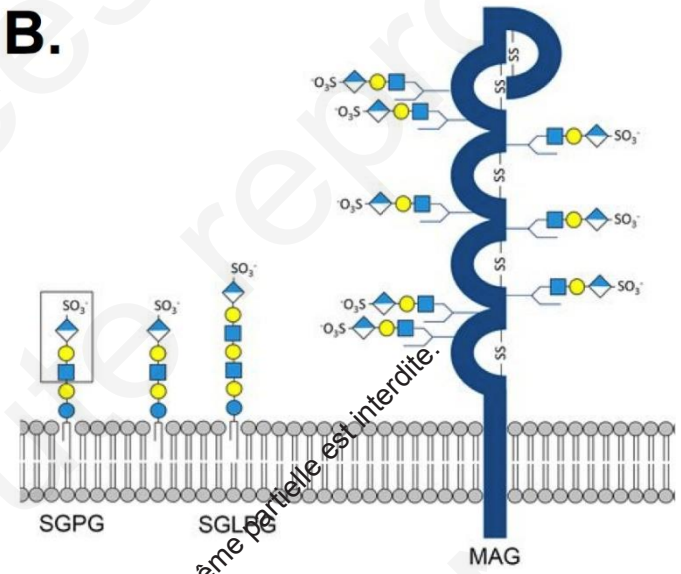
- IgM et complément dans le nerf,
- Co-localisation IgM & MAG lamelles myéline décompactées,
- IgM + complément + MAG derme → perte en fibre chez patients,
- Sérum anti-MAG + complément dans nerf chat → démyélinisation et BC en qq jours,
- Injection systémique IgM anti-MAG poulet → démyélinisation, dépôt IgM nerf, widening,
- Immunisation chats avec SGPG → neuropathie ataxique.

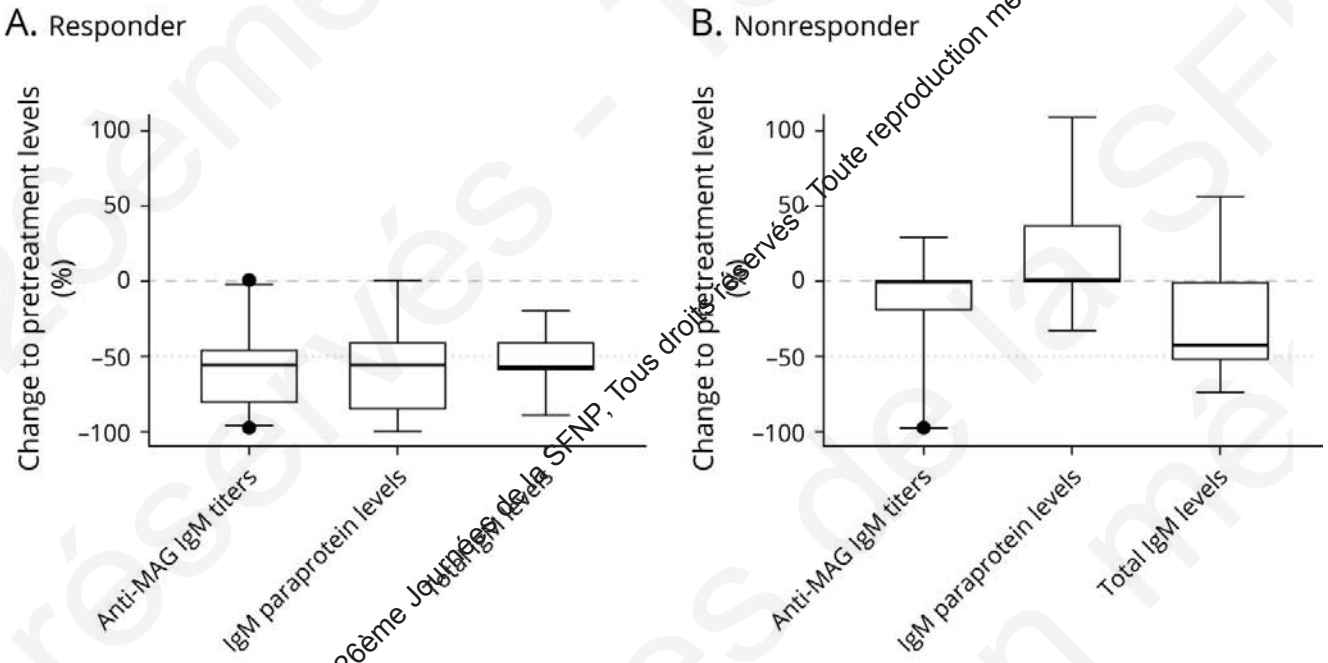
Dalakas, 2018

Ciblage des auto-anticorps : neuropathies anti-MAG









IgM MGUS ou Waldenström

Kawagashira et al. J Neuropathol Exp Neurol 2010, Matamala J Neurol Neurosurg Psychiatry 2018, Hänggi et al. Neurol Neuroimmunol Neuroinflamm 2022

High-dose rituximab and anti-MAG–associated polyneuropathy

Abstract—Rituximab has been administered successfully in patients with polyneuropathy associated with antibodies to myelin-associated glycoprotein (anti-MAG). The authors present a follow-up study with high-dose rituximab. Increase of rituximab from 375 mg/m^2 to a dose of 750 mg/m^2 was well tolerated and led to clinical improvement in four of eight patients, along with improvement of nerve conduction velocities and a reduction of anti-MAG antibody titers.

NEUROLOGY 2006;66:742–744

S. Renaud, MD; P. Fuhr, MD; M. Gregor, MD; K. Schweikert, MD; D. Lorenz, MD; C. Daniels, MD; G. Deuschl, MD; A. Gratwohl, MD; and A.J. Steck, MD

Placebo-controlled trial of rituximab in IgM anti-myelin–associated glycoprotein neuropathy

Jean-Marc Léger, MD
Karine Viala, MD
Guillaume Nicolas, MD, PhD
Alain Créange, MD, PhD
Jean-Michel Vallat, MD
Jean Pouget, MD
Pierre Clavelou, MD
Christophe Vial, MD
Andreas Steck, MD
Lucile Musset, MD, PhD
Benoit Marin, MD, PhD
For the RIMAG Study Group (France and Switzerland)

Neurology® 2013;80:2217-2225

Anti-MAG antibodies in 202 patients: clinicopathological and therapeutic features

J Neurol Neurosurg Psychiatry 2017;**0**:1–7.

Juliette Svahn,[1] Philippe Petiot,[1] Jean-Christophe Antoine,[2] Christophe Vial,[1] Emilien Delmont,[3] Karine Viala,[4] Andreas J. Steck,[5] Armelle Magot,[6] Cecile Cauquil,[7] Aline Zarea,[8] Andoni Echaniz-Laguna,[9] Ruxandra Iancu Ferfoglia,[10] Antoine Gueguen,[11] Laurent Magy,[12] Jean-Marc Léger,[13] Thierry Kuntzer,[14] Karine Ferraud,[2] Arnaud Lacour,[2] Jean-Philippe Camdessanché,[2] The Francophone anti-MAG cohort Group

Obinutuzumab, a new anti-CD20 antibody, and chlorambucil are active and effective in anti-myelin-associated glycoprotein antibody polyneuropathy

European Journal of Neurology 2018, **26:** 371–375

C. Briani[a], A. Visentin[b], A. Salvalaggio[a], M. Cacciavillani[c] and L. Trentin[b]

[a]*Neurology Unit, Department of Neuroscience, University of Padova, Padova;* [b]*Hematology and Clinical Immunology Unit, Department of Medicine, University of Padova, Padova; and* [c]*CEMES, Data Medica Group, Padova, Italy*

Difficulté +++ de l'évaluation clinique de la réponse aux traitements dans les neuropathies anti-MAG

Effet bénéfique indiscutable des anti-CD20 surtout
- En phase précoce
- Si installation subaiguë
- Quand perte axonale non encore installée

Pas de consensus sur le traitement à long terme (dose/intervalle)

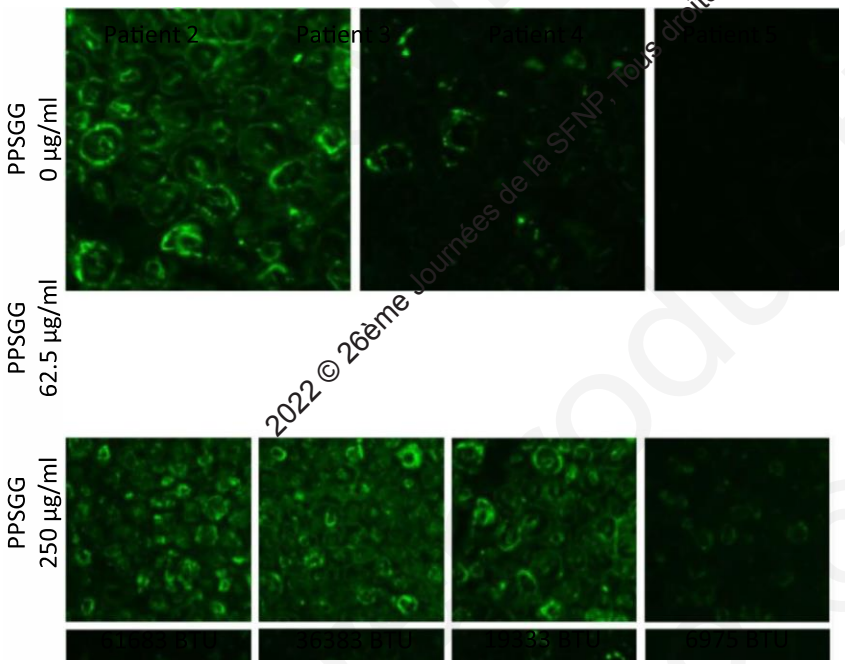
Risque inhérent aux anti-CD20 (infectieux, mauvaise réponse vaccinale…)

Selective inhibition of anti-MAG IgM autoantibody binding to myelin by an antigen-specific glycopolymer

Journal of Neurochemistry. 2020;154:486–501.

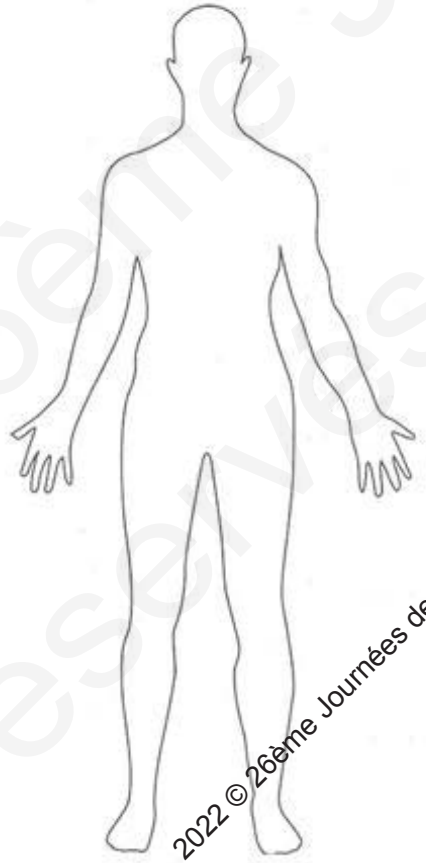
Butrint Aliu[1] | Delphine Demeestere[1] | Emilie Seydoux[2] | José Boucraut[3,4] | Emilien Delmont[5] | Alexandre Brodovitch[3,5] | Thomas Obenholzer[2] | Shahram Attarian[5] | Marie Théaudin[6] | Pinelopi Tsouni[6] | Thierry Kuntzer[6] | Tobias Derfuss[7] | Andreas J. Steck[7] | Beat Ernst[1] | Ruben Herrendorff[1,2] | Pascal Hänggi[1,2]

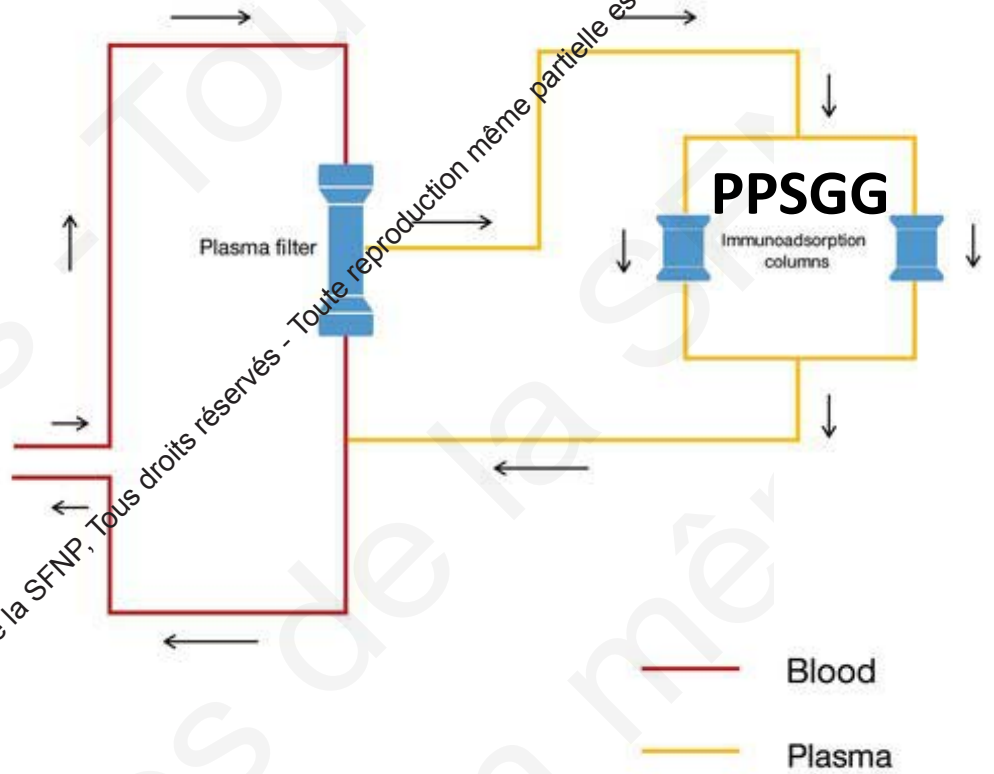
PPSGG



3.2 | Fast and efficient removal of circulating anti-HNK-1 IgM by PPSGG in BALB/c mice, while CD20$^+$ cell depletion showed no significant effect on the anti-MAG IgM titers in the immunological mouse model for anti-MAG neuropathy

Effets indésirables lors de la première administration à l'humain





Conclusion

- Rôle pathogène des auto-anticorps évident et prouvé dans certaines pathologies
- Rôle beaucoup moins démontré et/ou intriqué dans d'autres
  - Nécessité de développer de nouvelles approches
- De nouvelles options thérapeutiques en développement
  - Place dans la stratégie thérapeutique ?