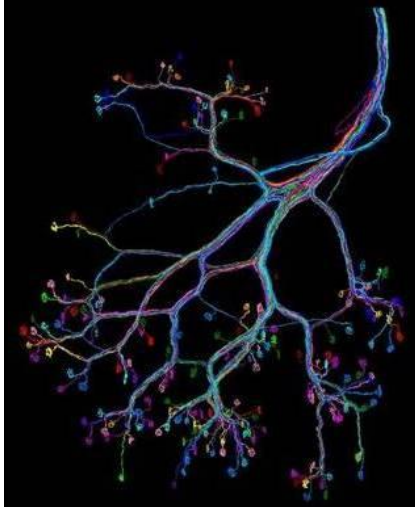
LEIDEN UNIVERSITY MEDICAL CENTER

XXI World Congress of Neurology

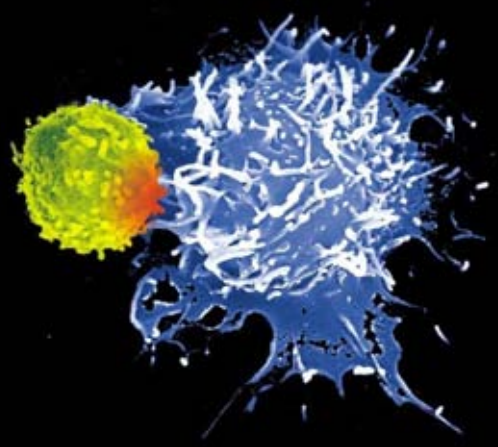
Autoimmune synaptic disorders of the PNS: Myasthenia Gravis and LEMS



Jan Verschuuren
Leiden University Medical Center
Leiden, the Netherlands

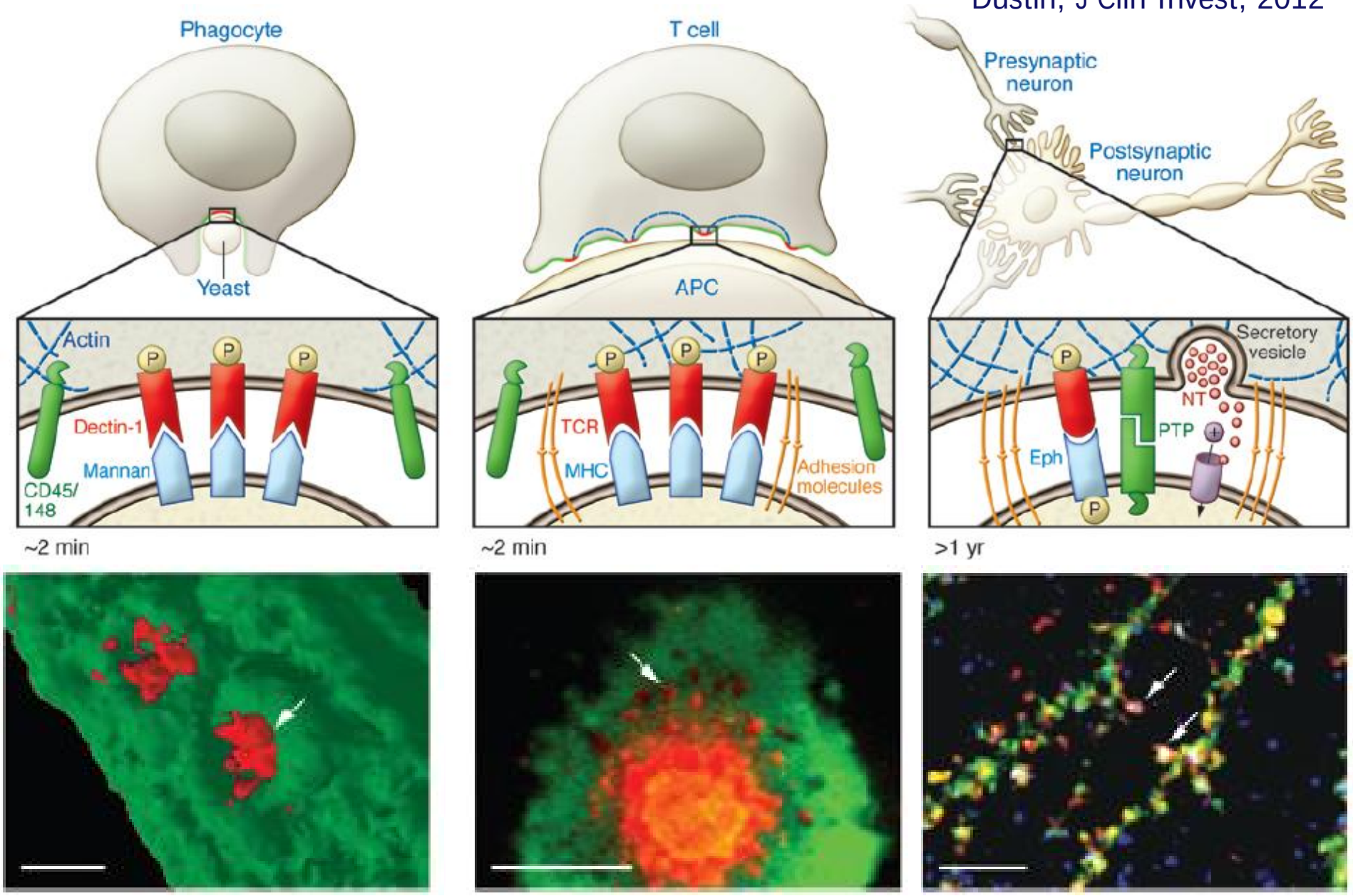
Inside

Inside

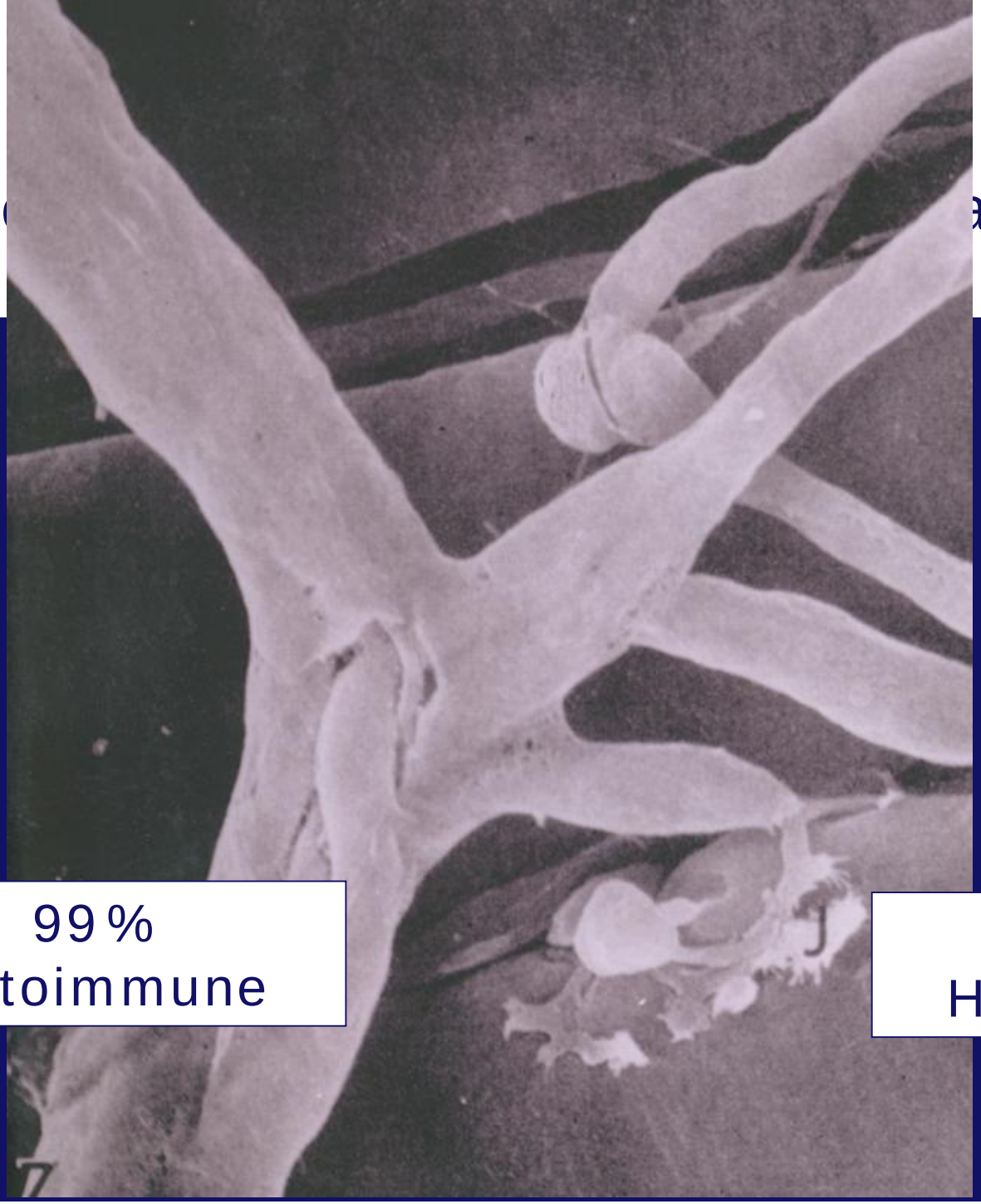


Communication by neuron, muscle or immune cells

Dustin, J Clin Invest, 2012



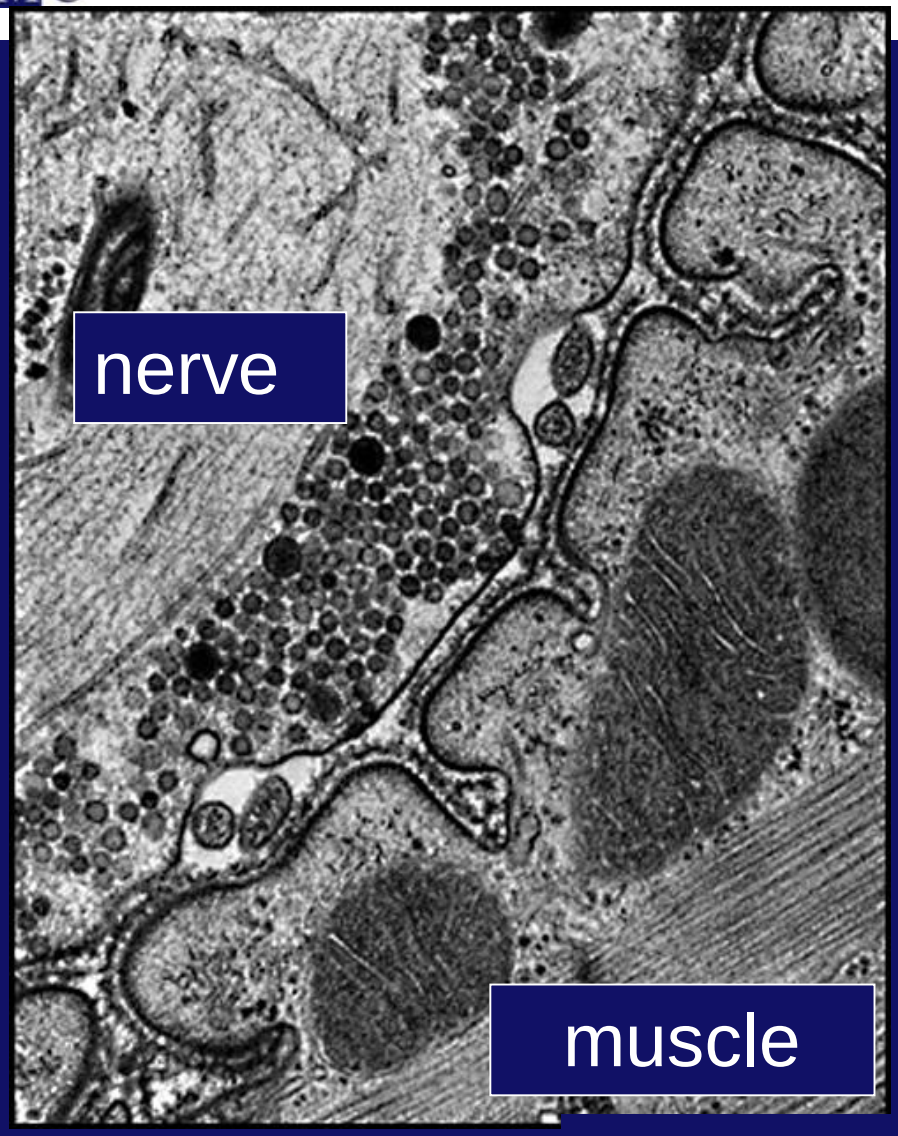
Diseas and muscle

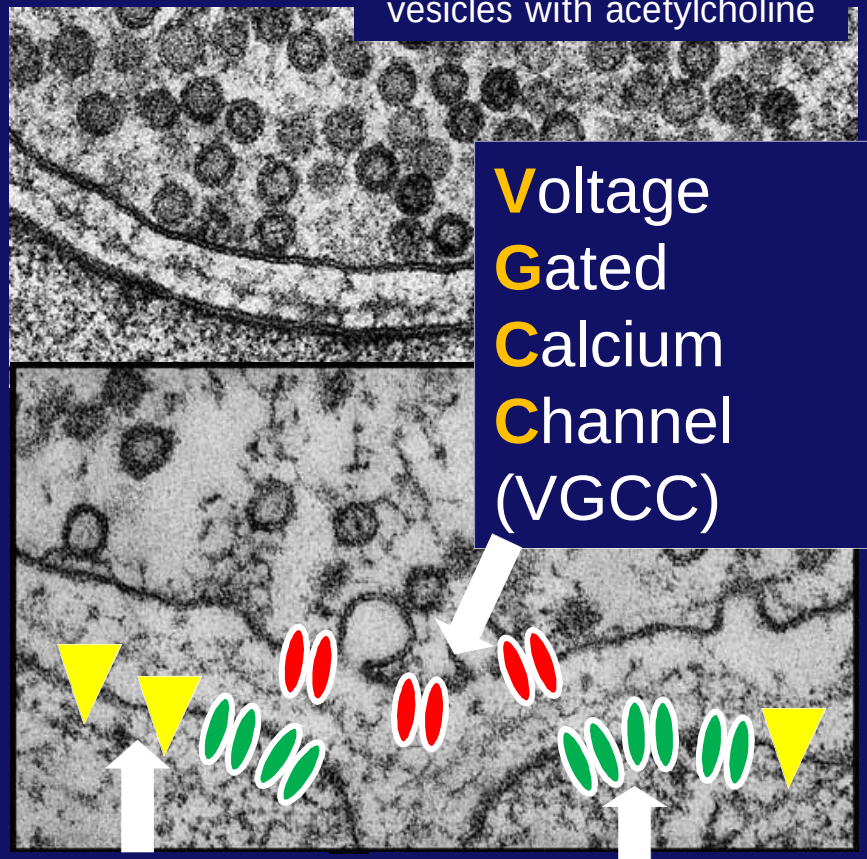


99%
Autoimmune

1%
Hereditary

Communication between nerve and muscle



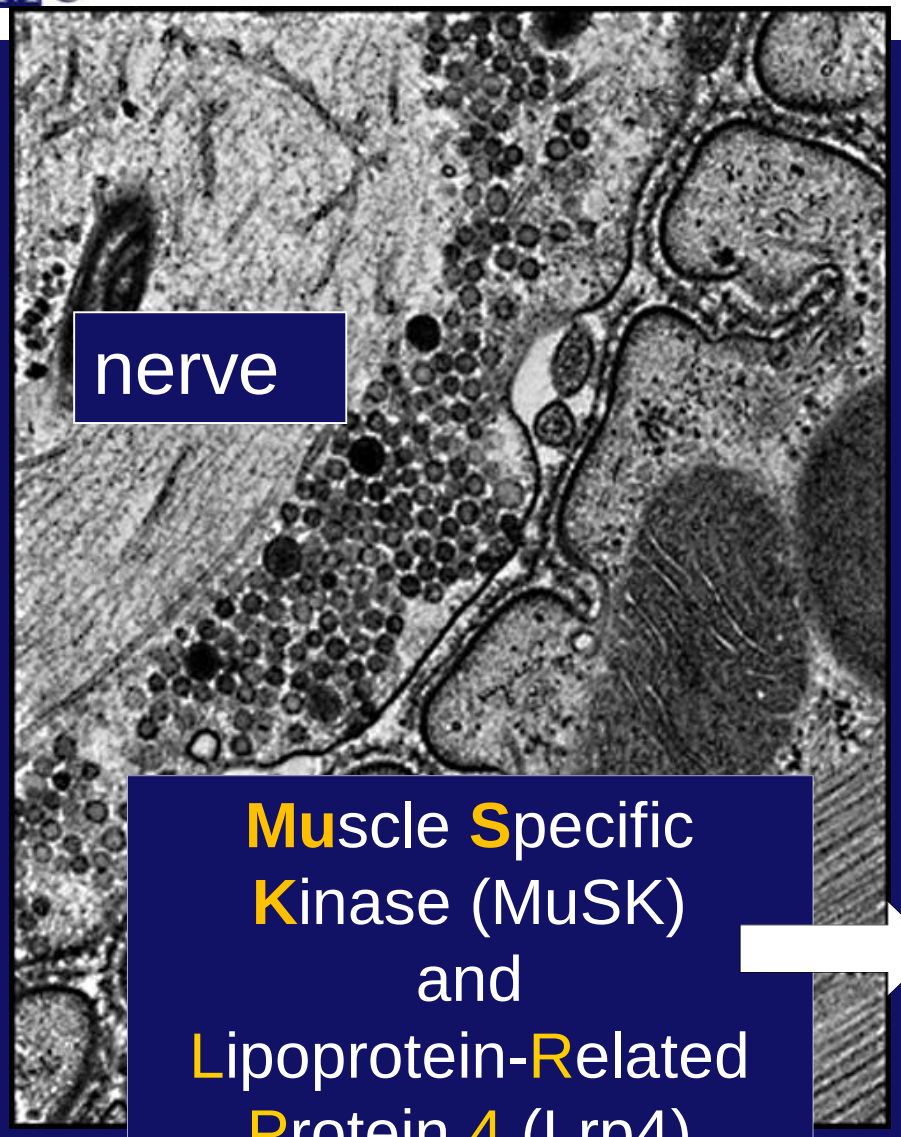


Voltage
Gated
Calcium
Channel
(VGCC)

Muscle **S**pecific
Kinase (MuSK)

Acetyl**Ch**oline
Receptor (AChR)

Communication between nerve and muscle



nerve

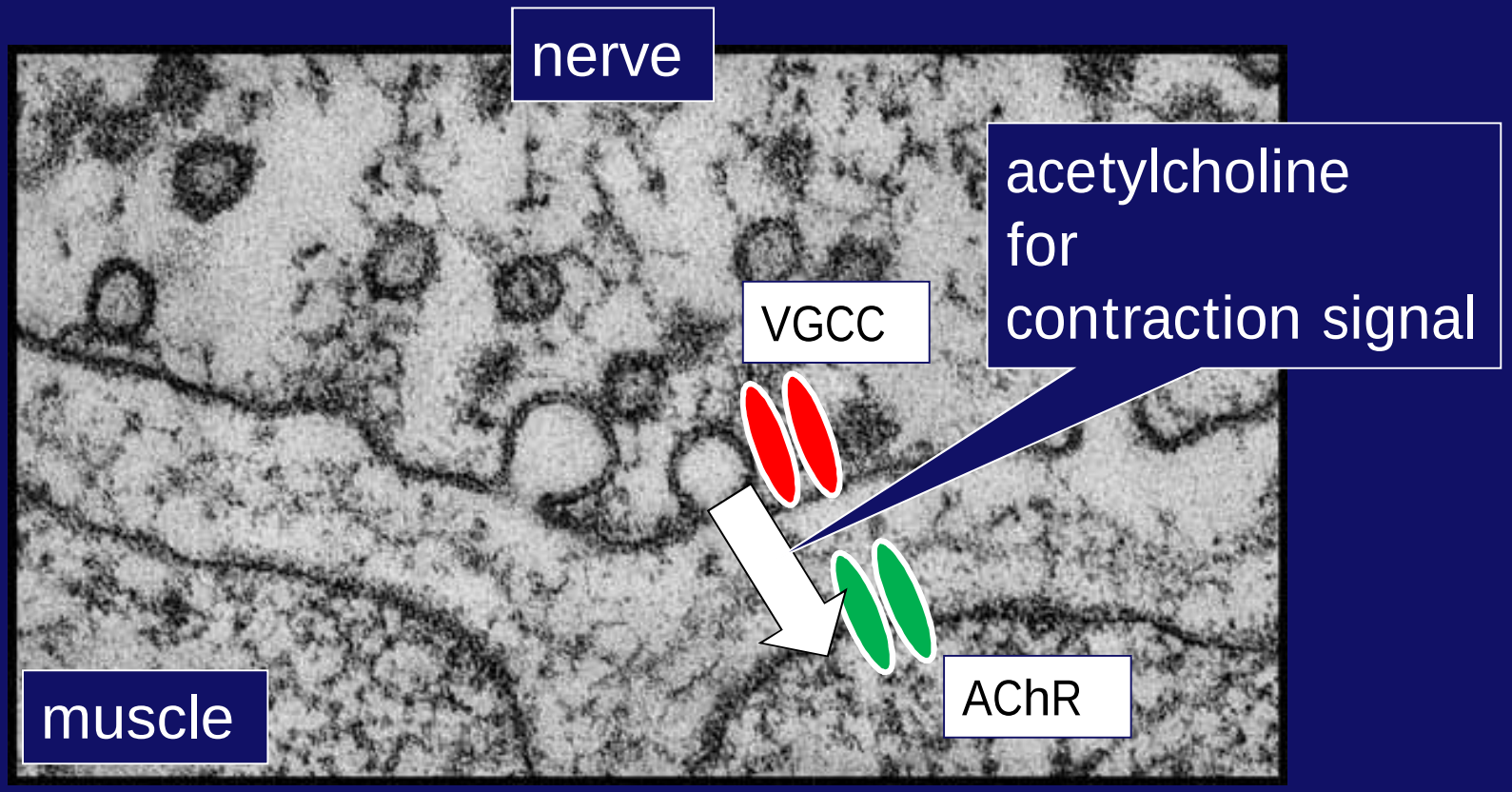
Muscle **S**pecific
Kinase (MuSK)
and
Lipoprotein-**R**elated
Protein 4 (Lrp4)

vesicles with acetylcholine

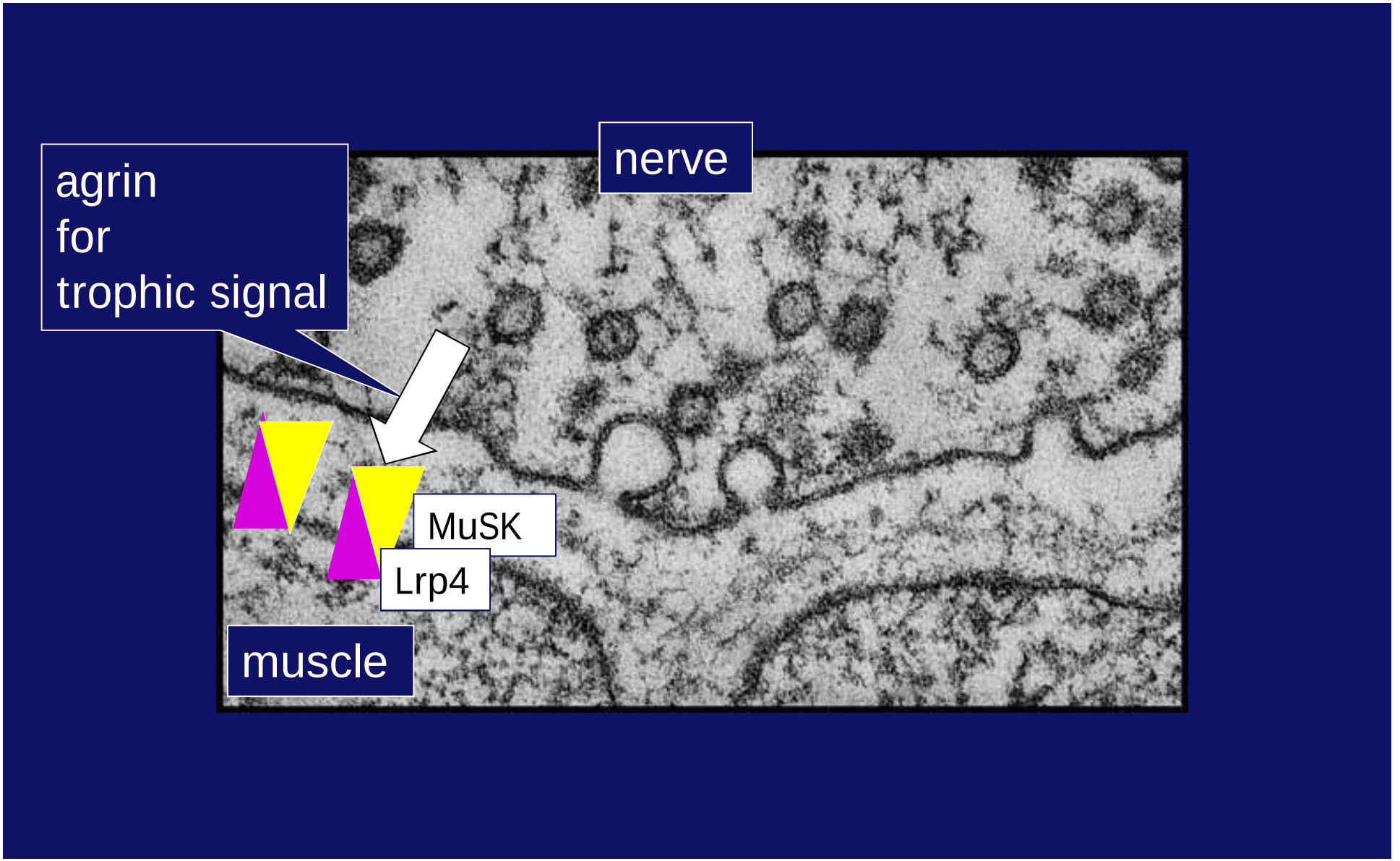
Voltage
Gated
Calcium
Channel
(VGCC)

Acetyl**Ch**oline
Receptor (AChR)

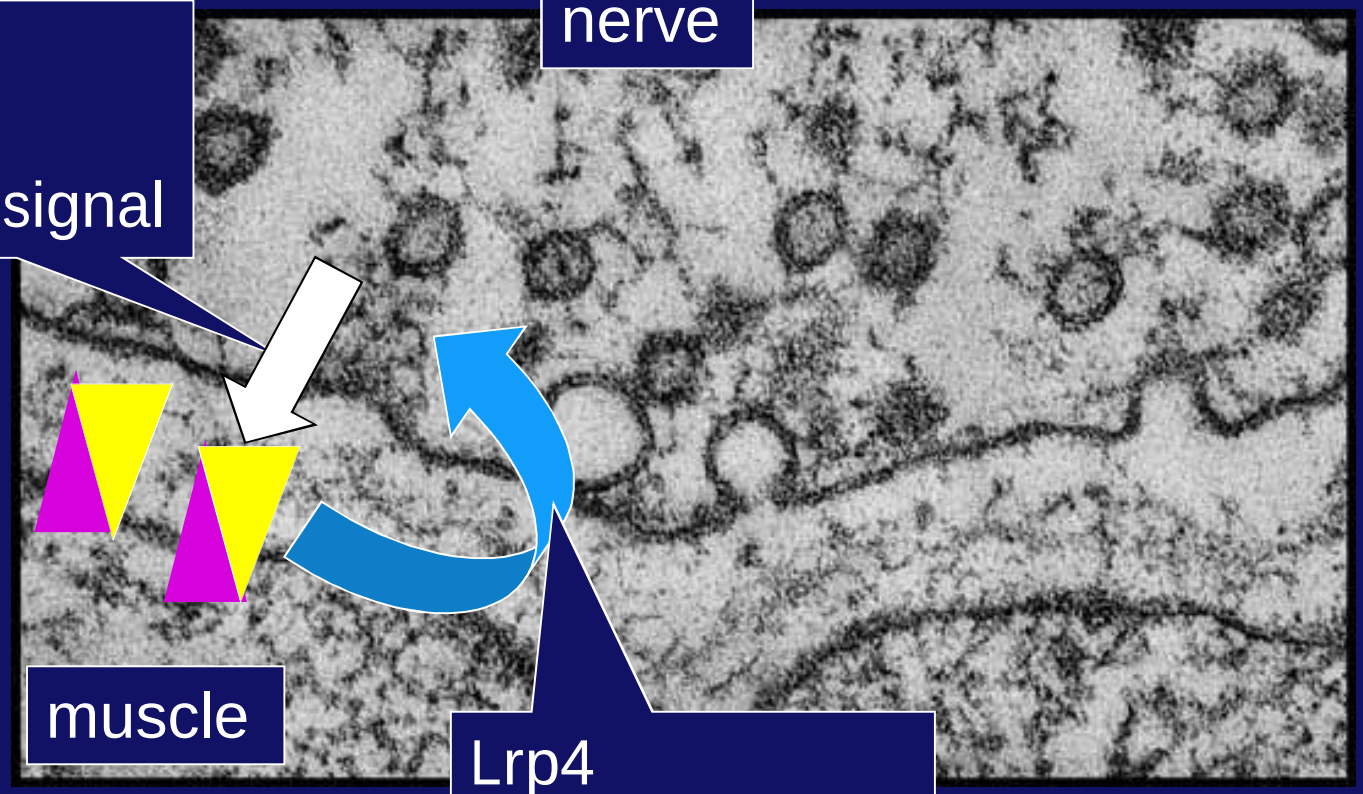
Communication between nerve and muscle



Communication between nerve and muscle

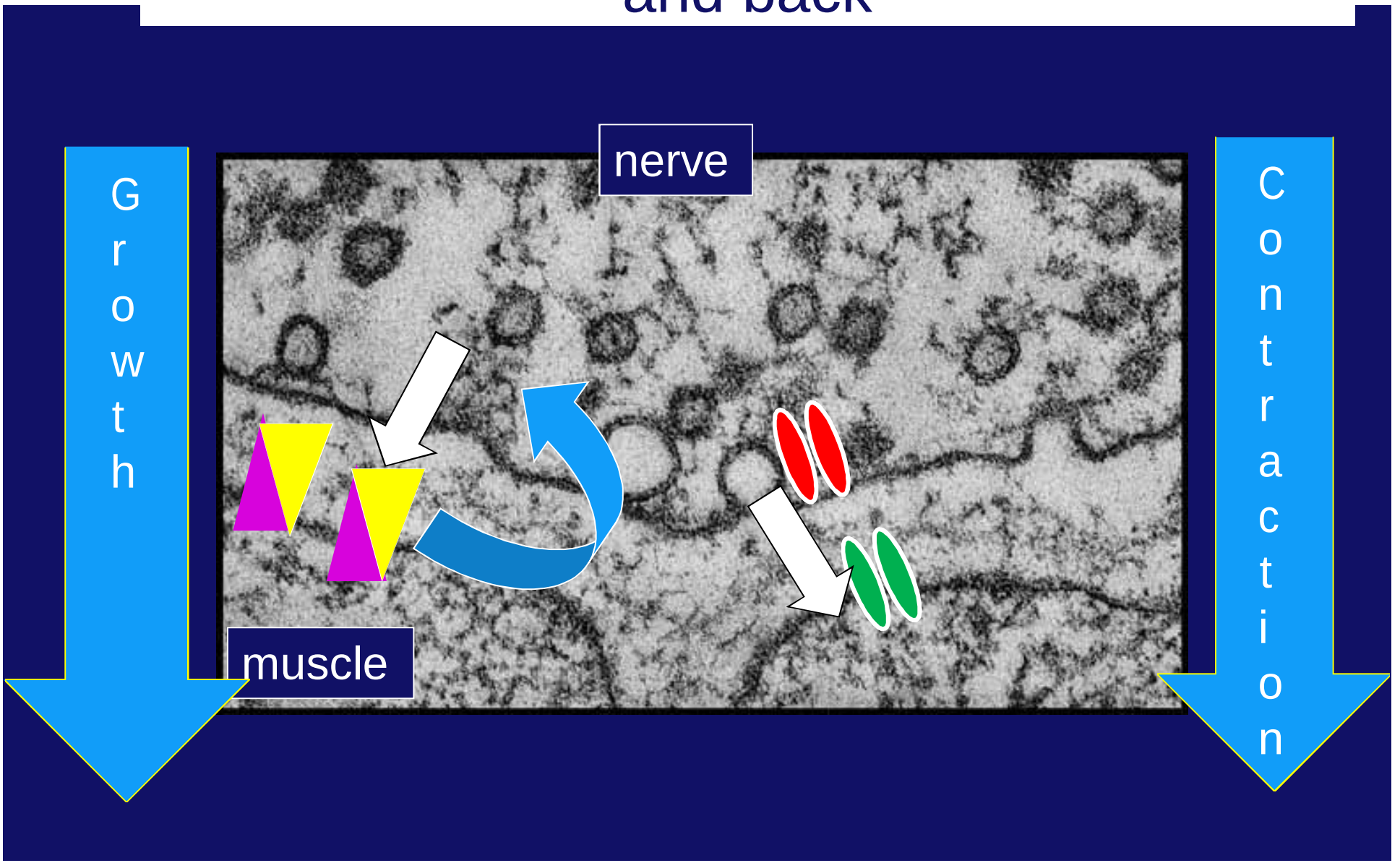


Communication between nerve and muscle and back



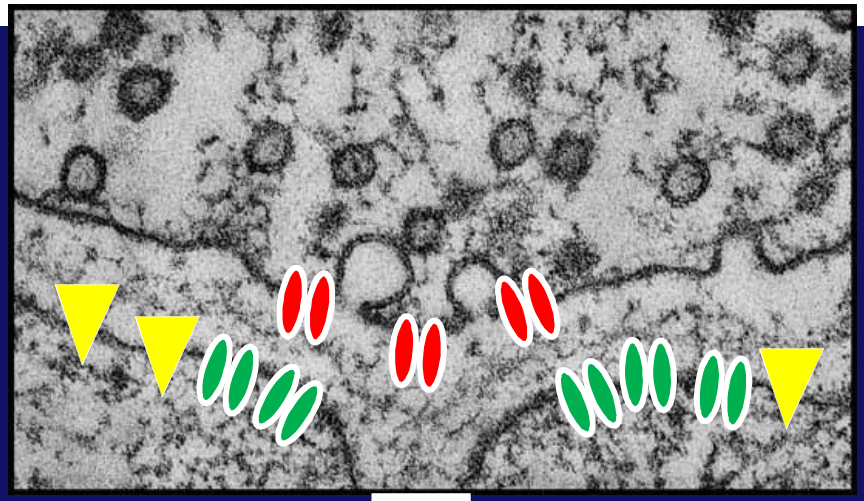
Yumoto, Kim, Burden. Nature Aug 2012

Communication between nerve and muscle and back



Yumoto, Kim, Burden. Nature Aug 2012

Clinical features of myasthenia



Fluctuating muscle weakness,
which improves after rest

Myasthenia gravis with AChR antibodies

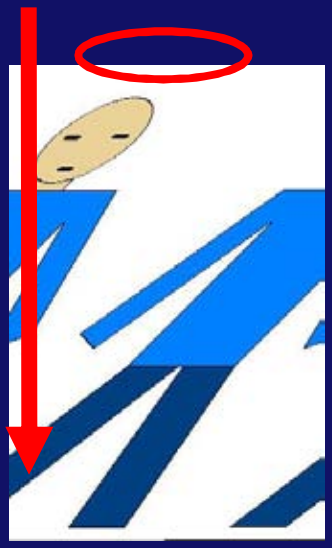
MG with AChR antibodies

Clinical Clues

Asymmetric,

Fluctuating ptosis

Ophthalmoplegia with diplopia



Descending weakness

Symmetric ptosis in Congenital Myasthenia Gravis

courtesy of prof. Hanns Lochmüller

Mitochondrial

PEO: Progressive External Ophthalmoplegia

Myotonic Dystrophy

Congenital MG

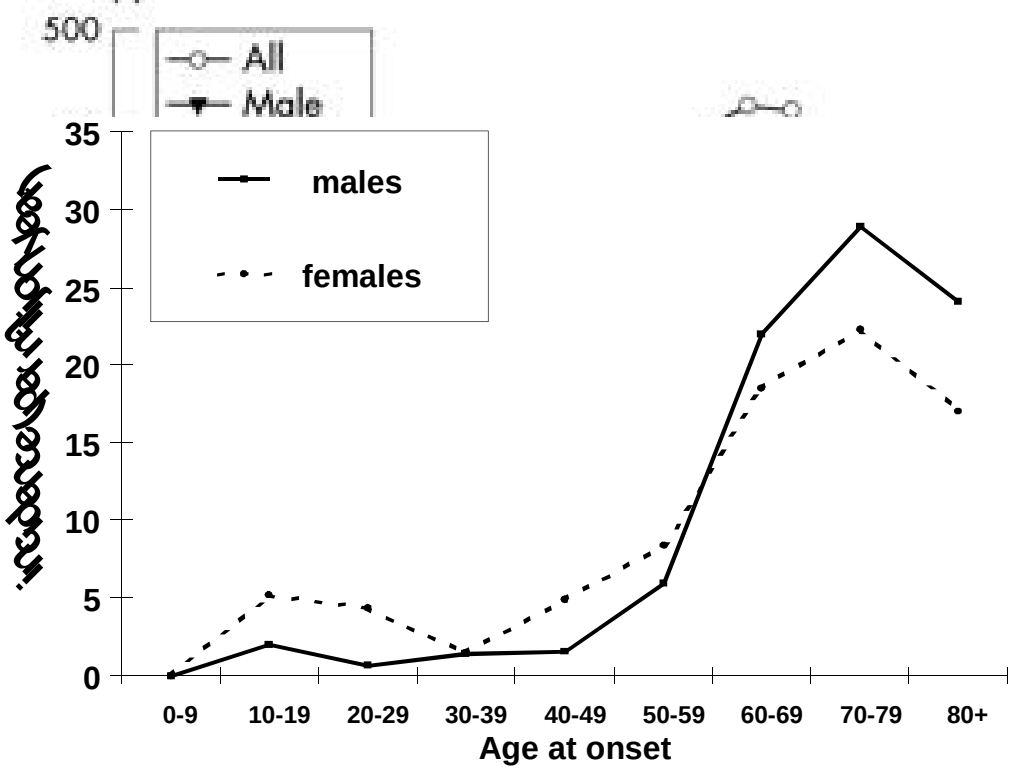
Autoimmune MG

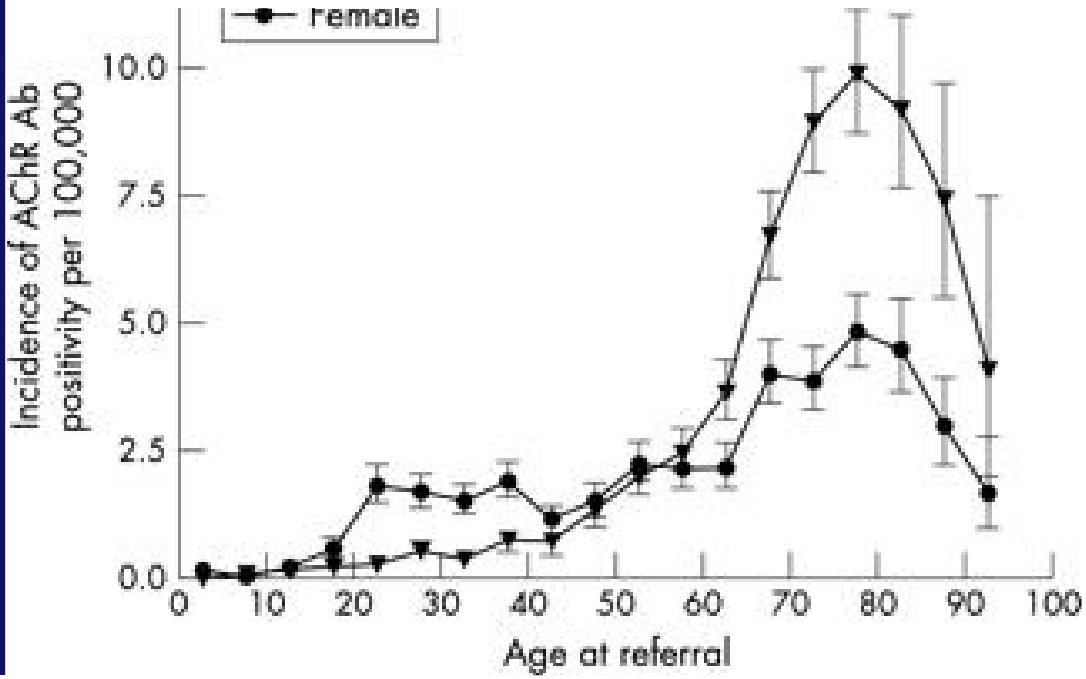
Incidence of AChR Myathenia Gravis

the Netherlands →

Highest incidence in young females and older males

Oxford →



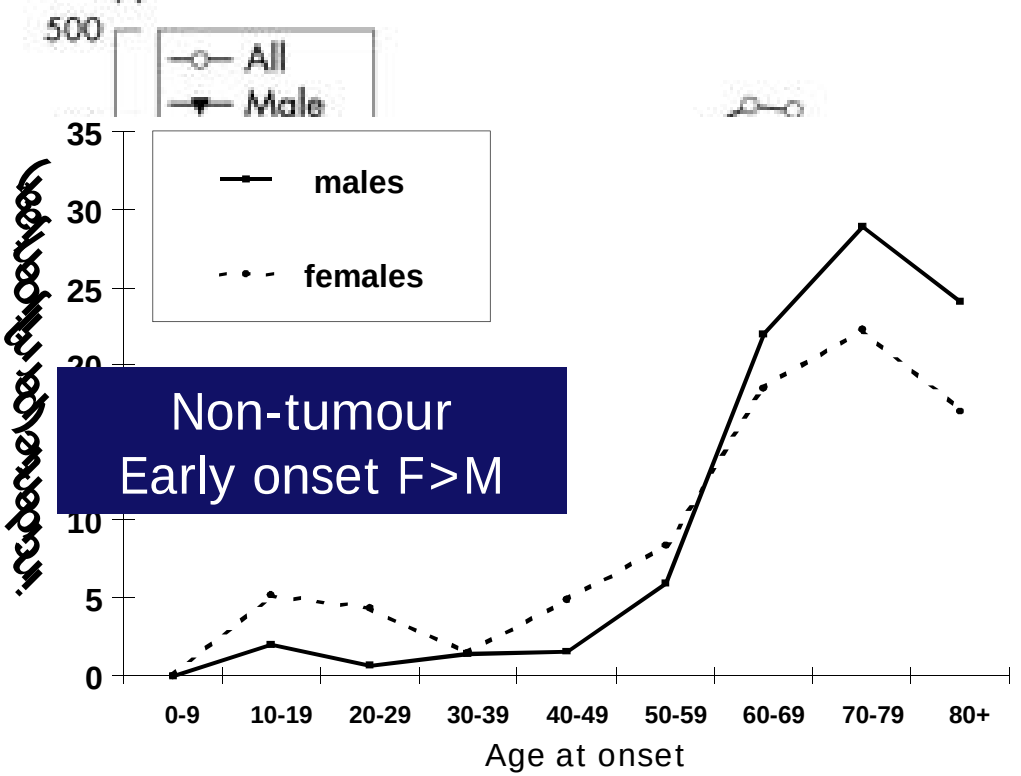


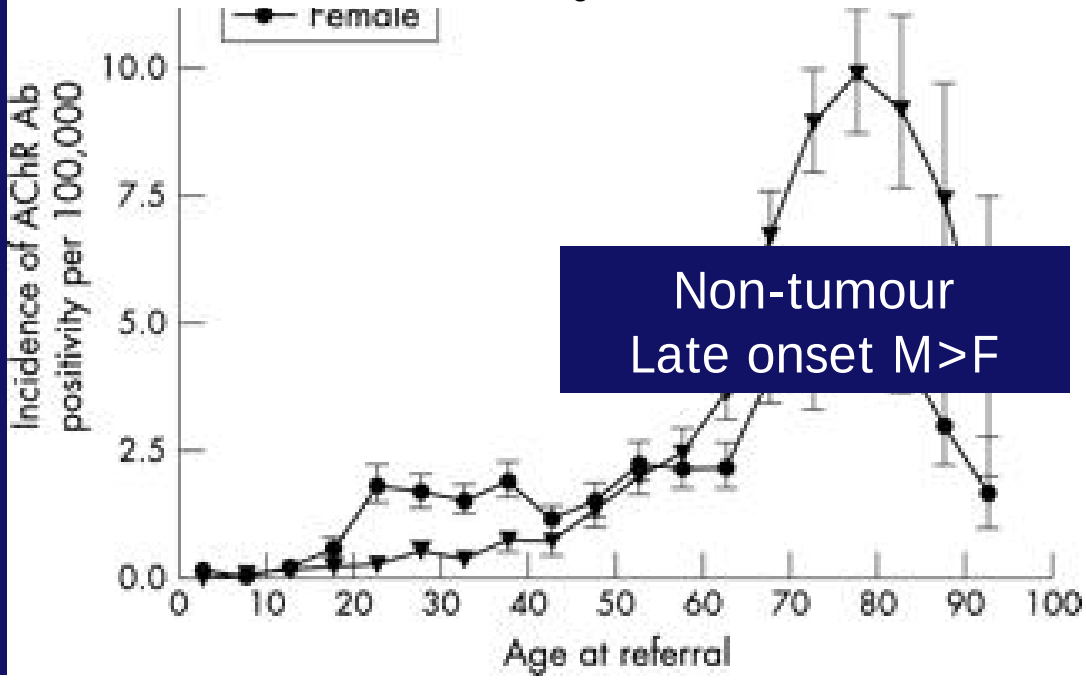
Incidence of AChR Myasthenia gravis

the Netherlands

Highest incidence in young females and older males

Oxford





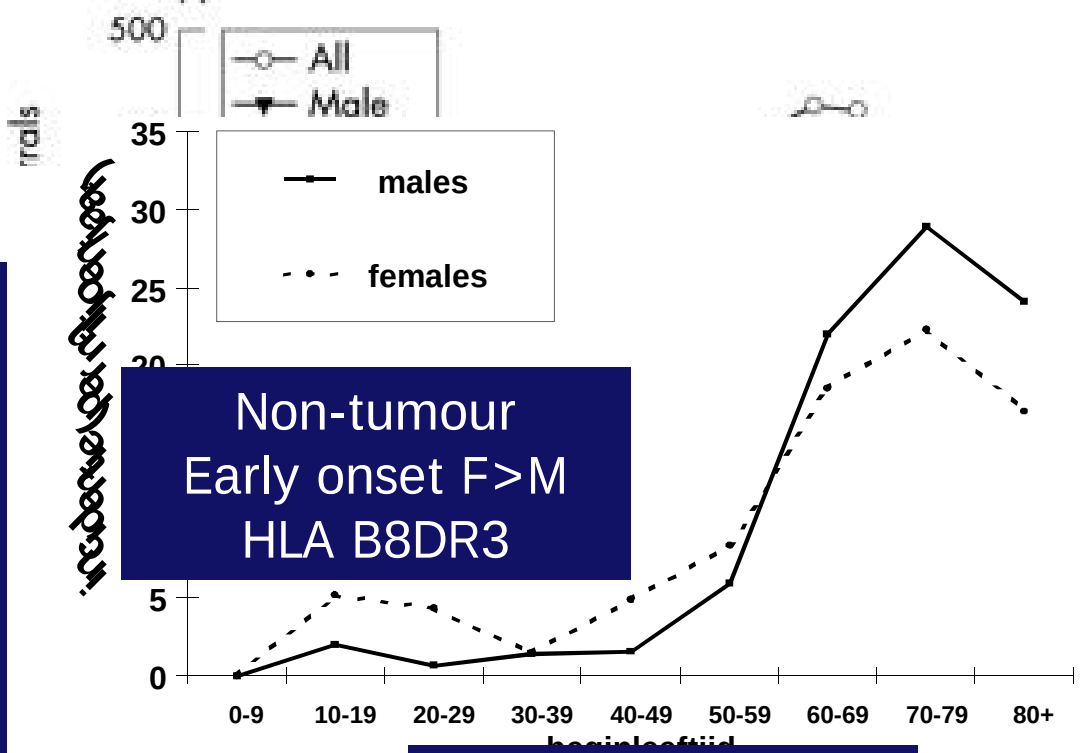
Vincent, J Neurol Neurosurg Psychiatry 2003;74:1105

Incidence of Myasthenia gravis

the Netherlands

Highest incidence in young females and older males

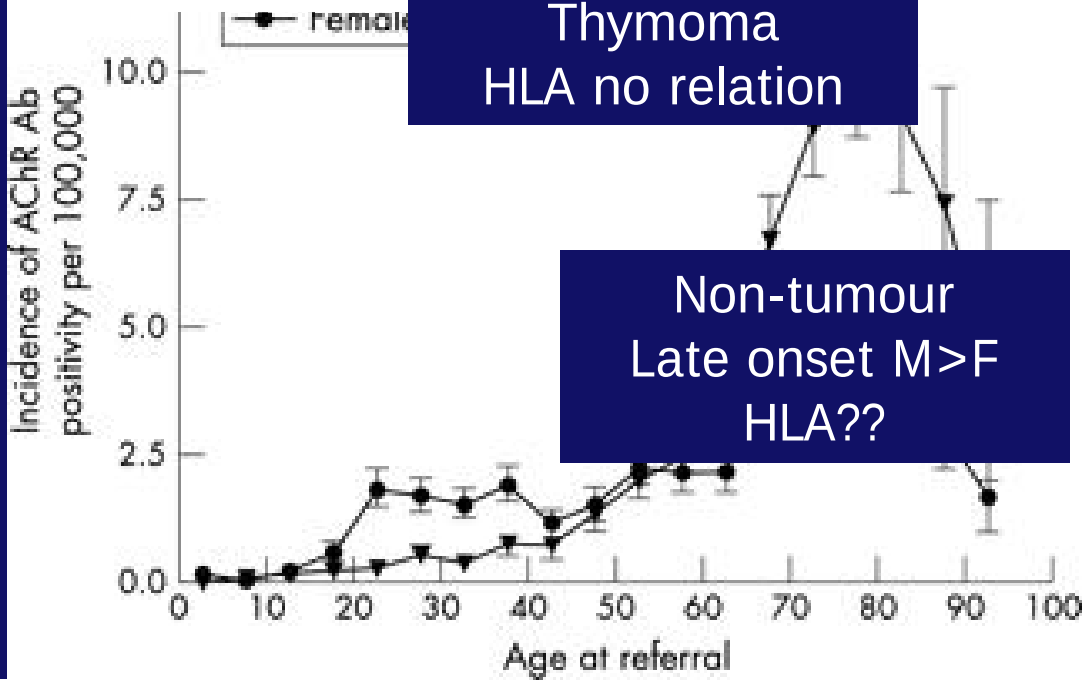
Oxford



Non-tumour
Early onset F>M
HLA B8DR3

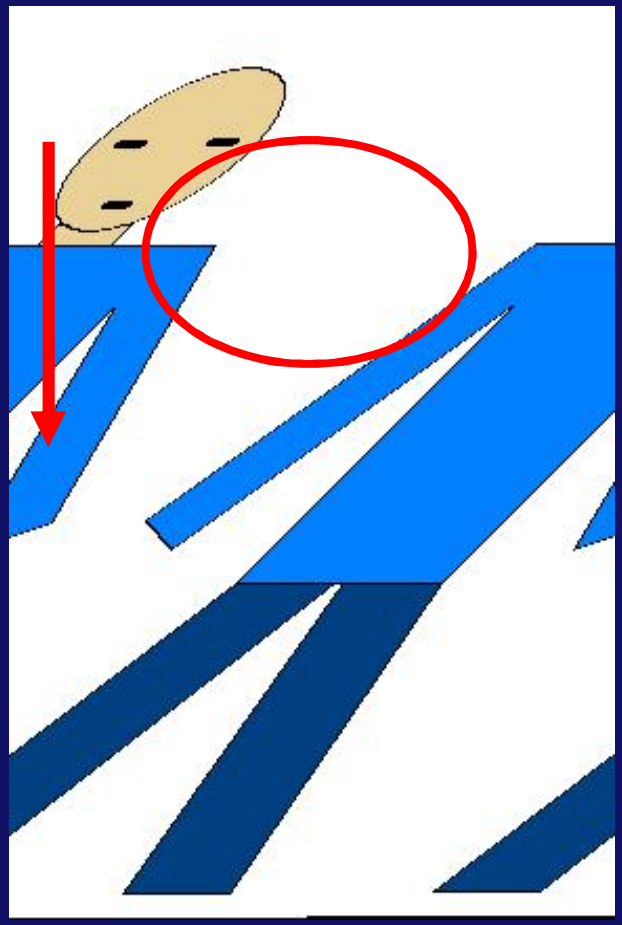
Thymoma
HLA no relation

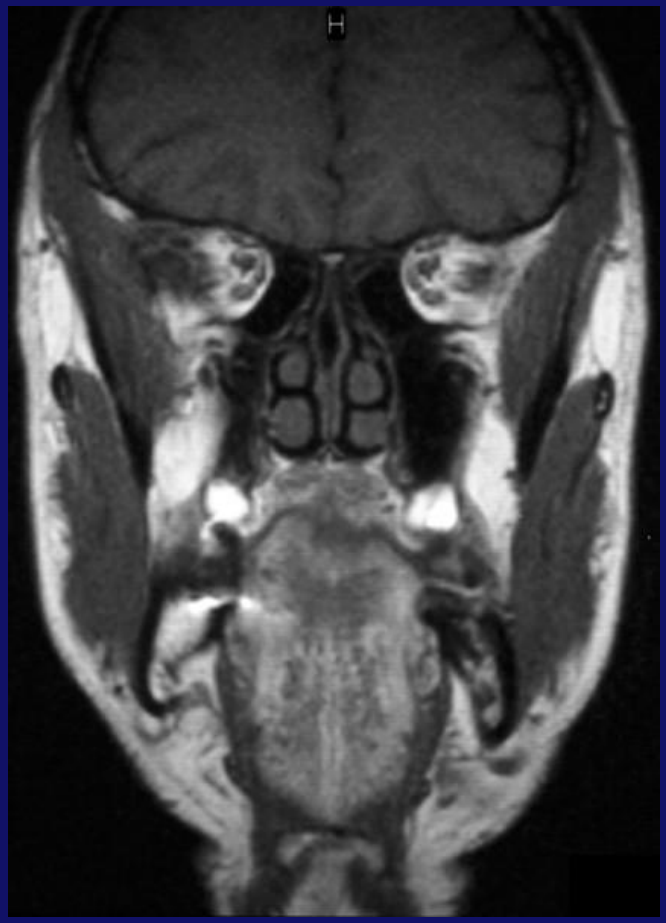
Non-tumour
Late onset M>F
HLA??



Myasthenia with MuSK antibodies

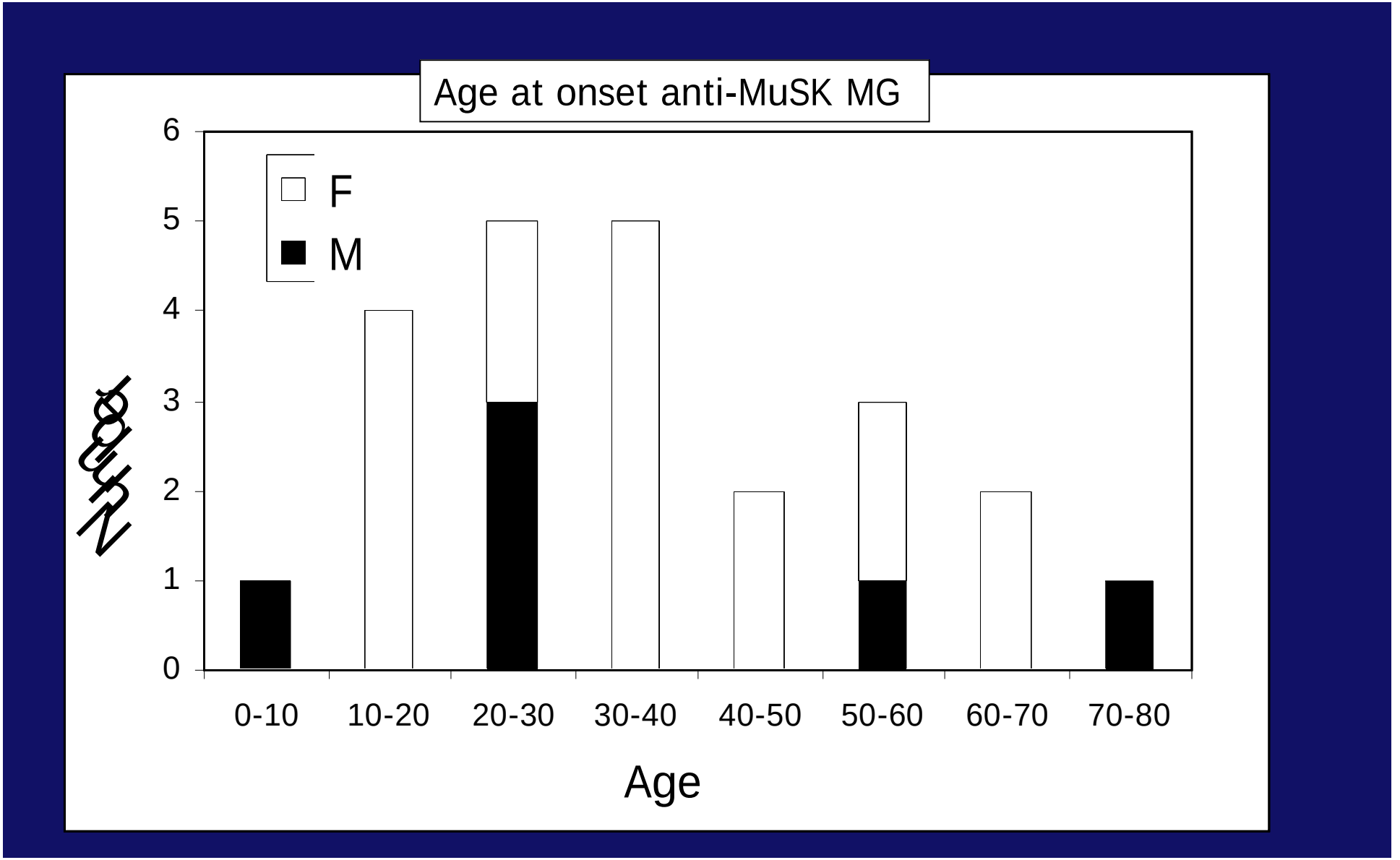
MG with MuSK antibodies



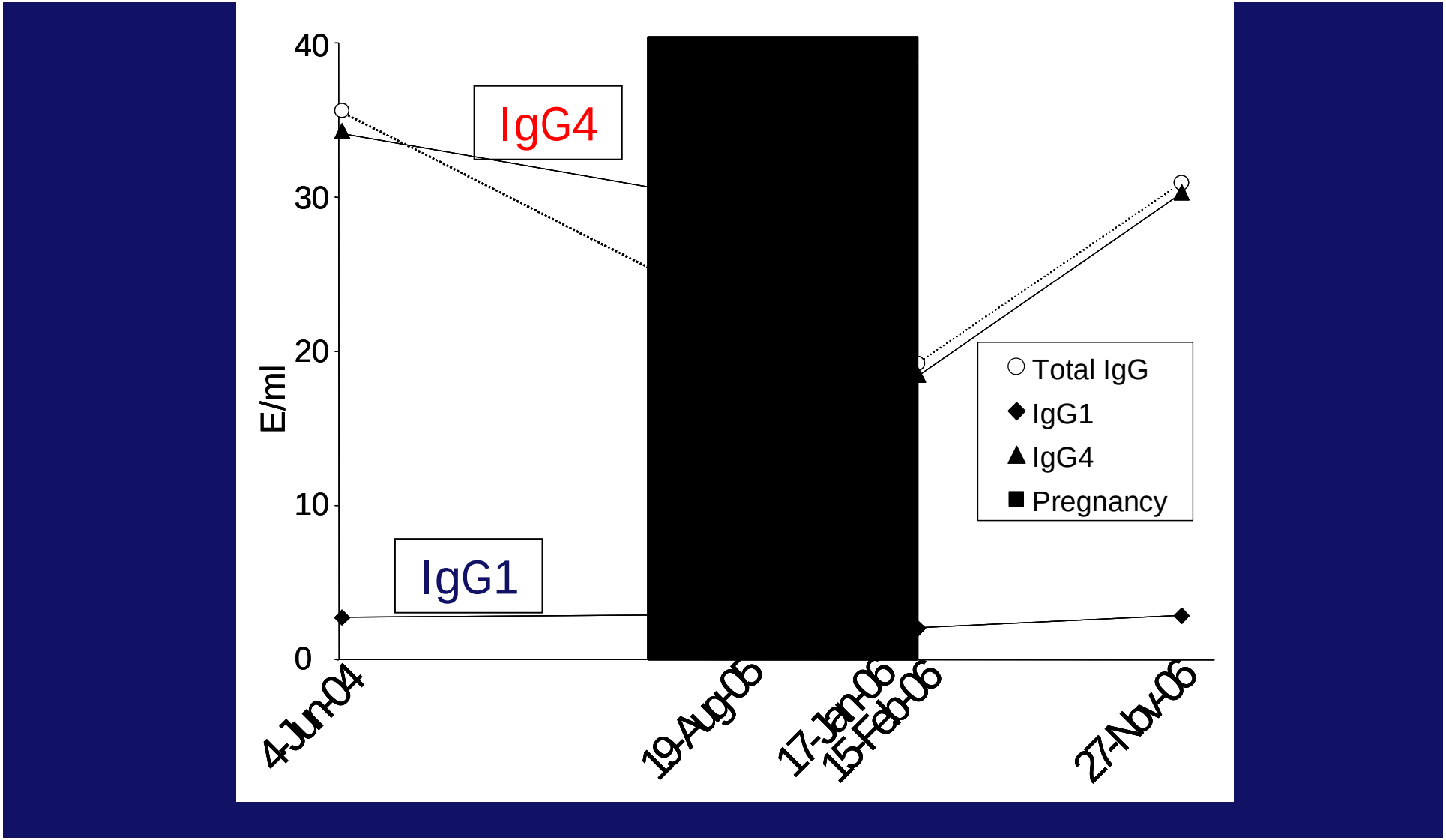


Evoli, Brain 2003;126:2304

MuSK MG: Peak incidence in young females

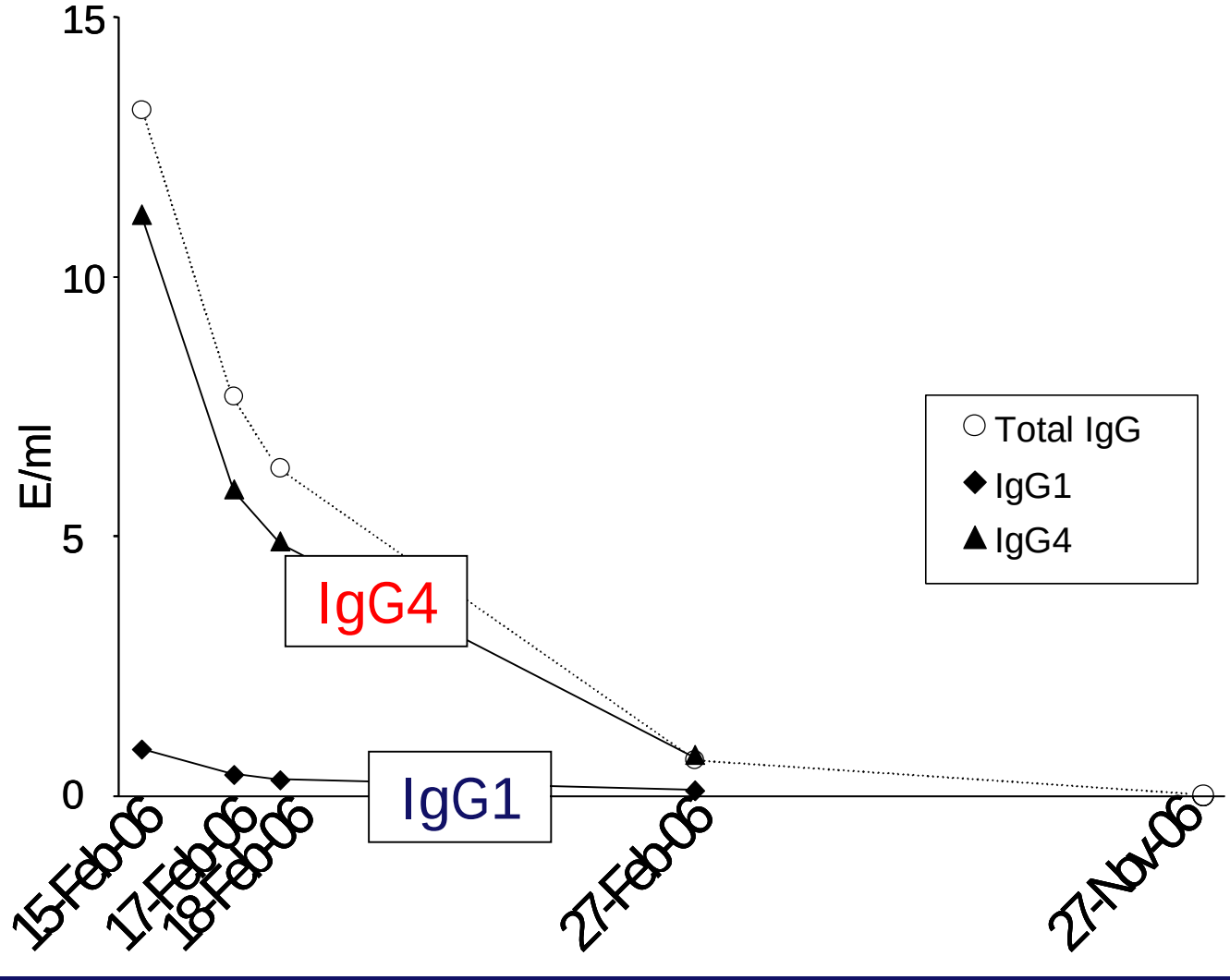


Anti-MuSK MG van moeder naar kind: Maternale serum antistoffen



Niks, Verrips et al, Neurology,2008

Neonaat met anti-MuSK MG: Serum antistoffen bij kind



Niks, Verrips et al, Neurology,2008

Passive transfer of autoantibodies results in neonatal weakness in humans in AChR-MG, MuSK MG or LEMS

- Fetal acetylcholine receptor inactivation syndrome and maternal myasthenia gravis.

  Oskoui M, et al Neurology 2008;71:2010

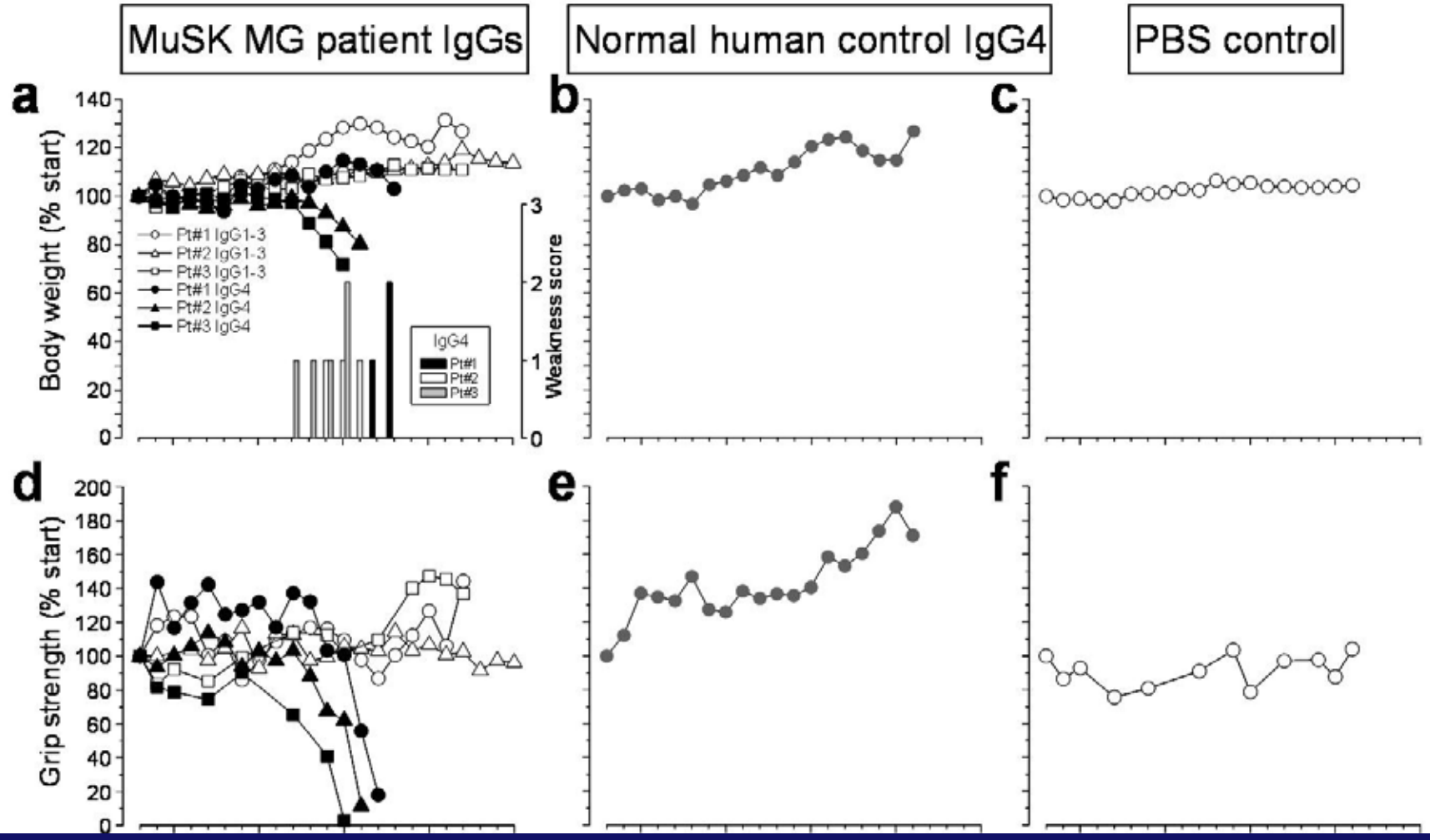
- Transient neonatal Lambert-Eaton syndrome.

  Reuner U, et al. Journal of Neurology 2008;255:1827

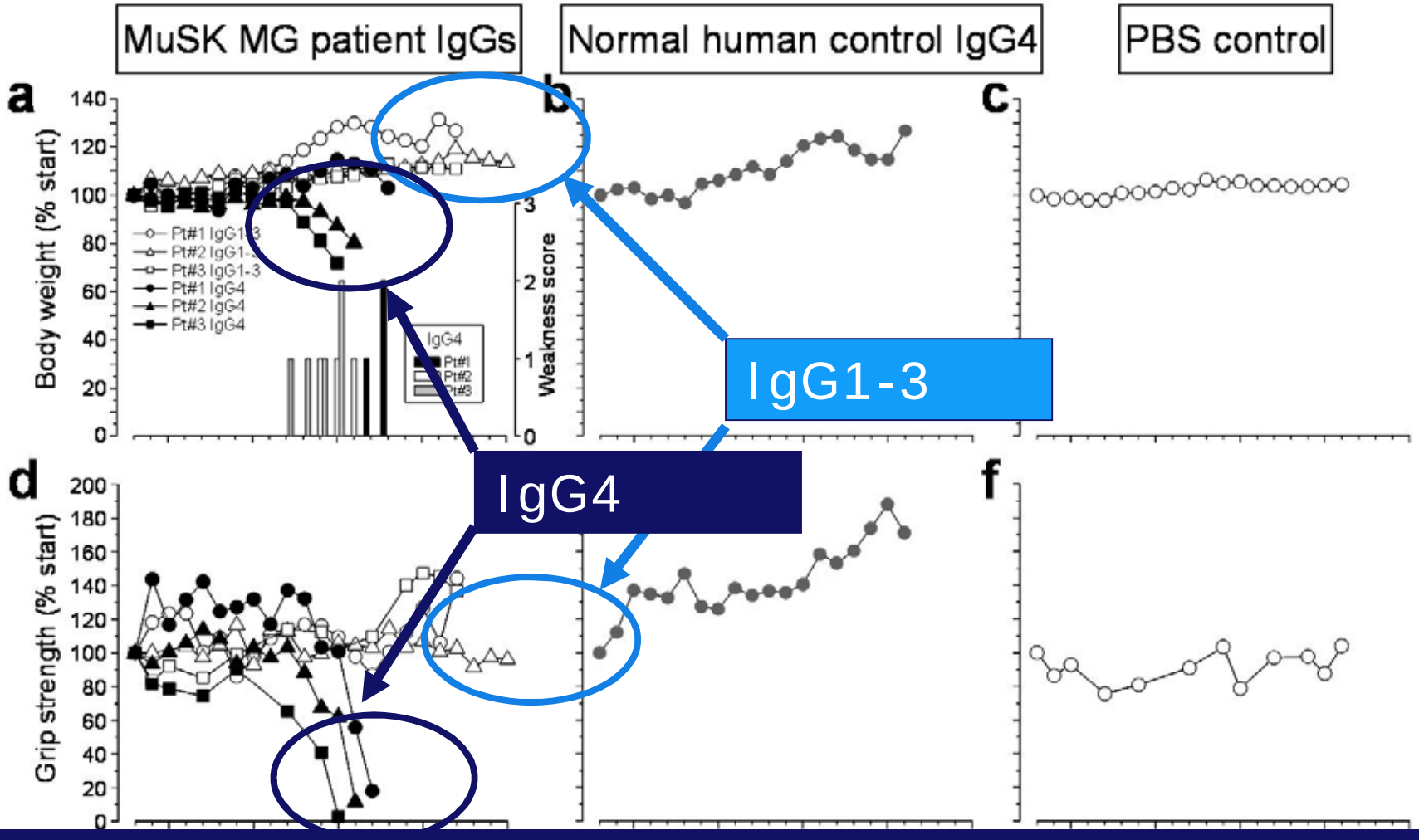
- A transient neonatal myasthenic syndrome with anti-MuSK antibodies.

  Niks EH, et al. Neurology 2008;70:1215

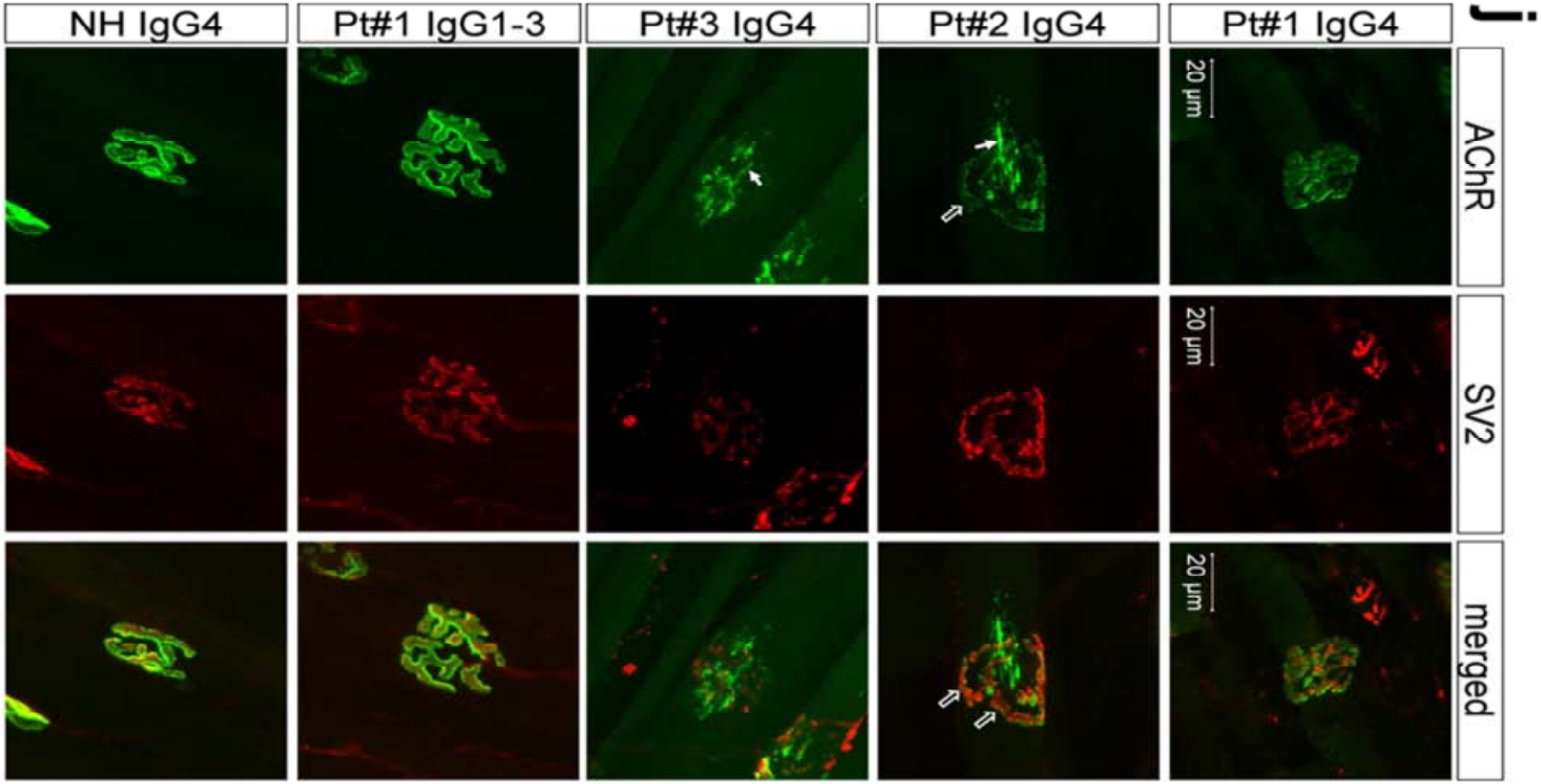
Passive transfer of MuSK IgG to NOD/SCID mice



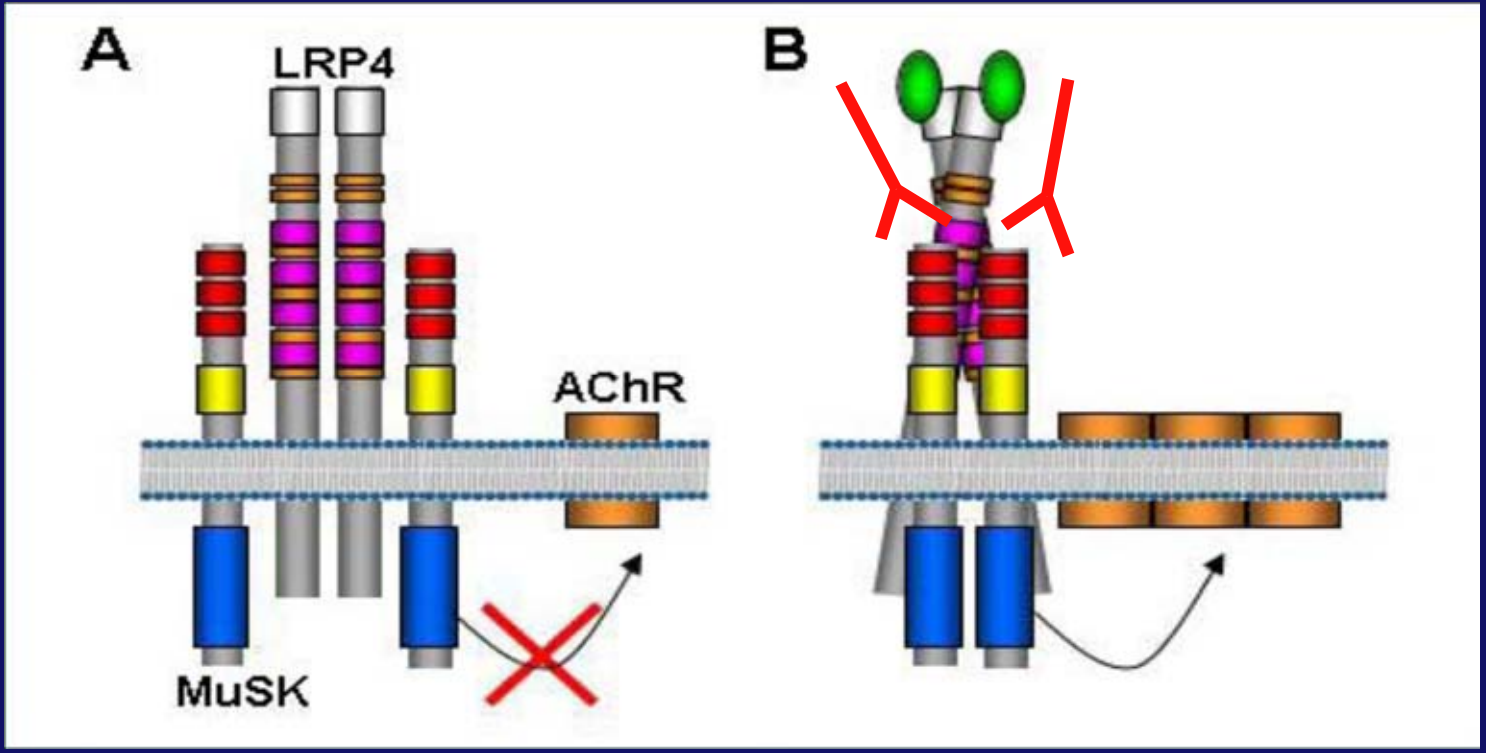
Passive transfer of MuSK IgG to NOD/SCID mice



MuSK IgG4, but not IgG1-3, destroys the neuromuscular synapse



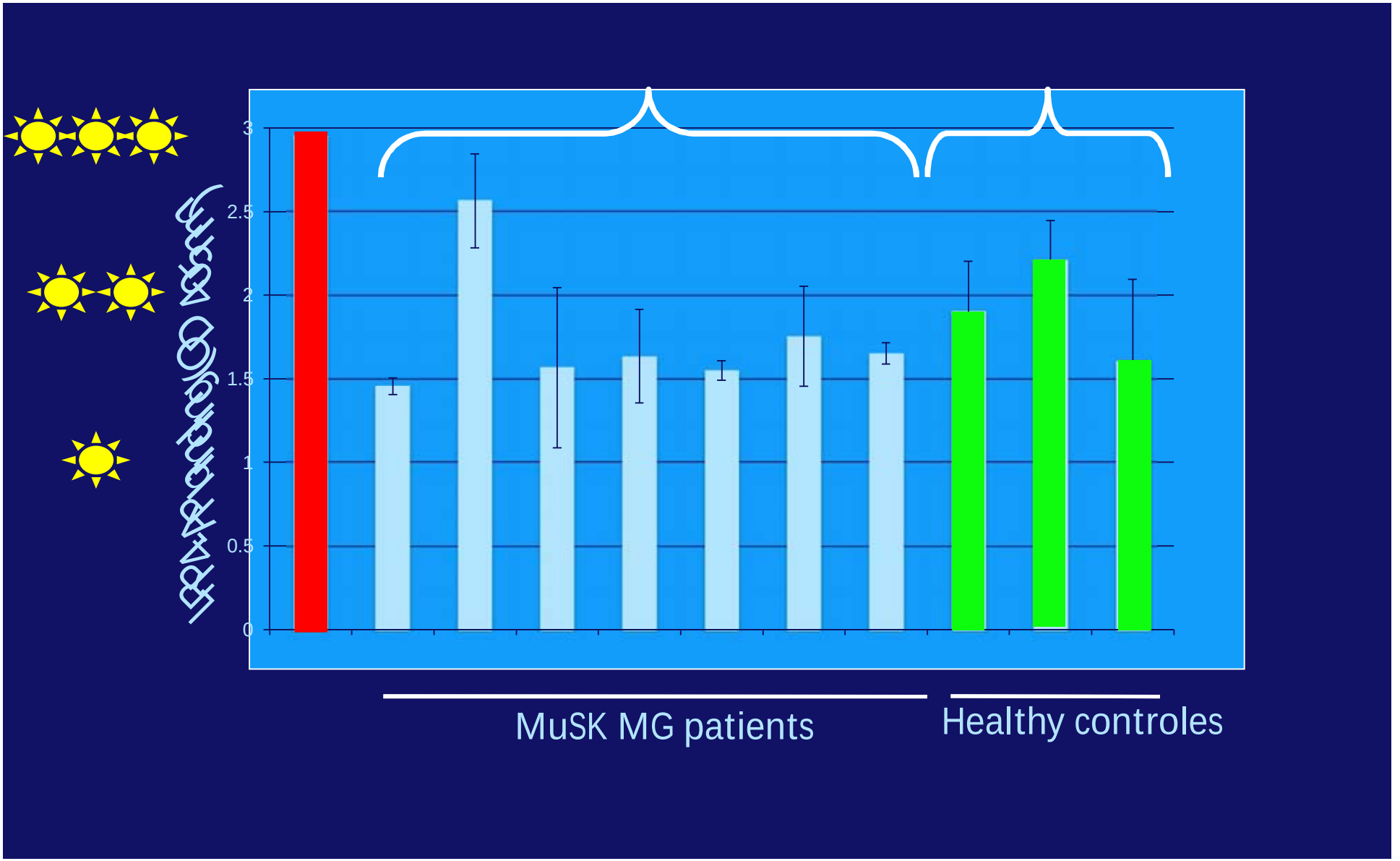
MuSK and Lrp4 collaborate to cluster AChR



Cole *et al.* 2008, Mori *et al.* 2012

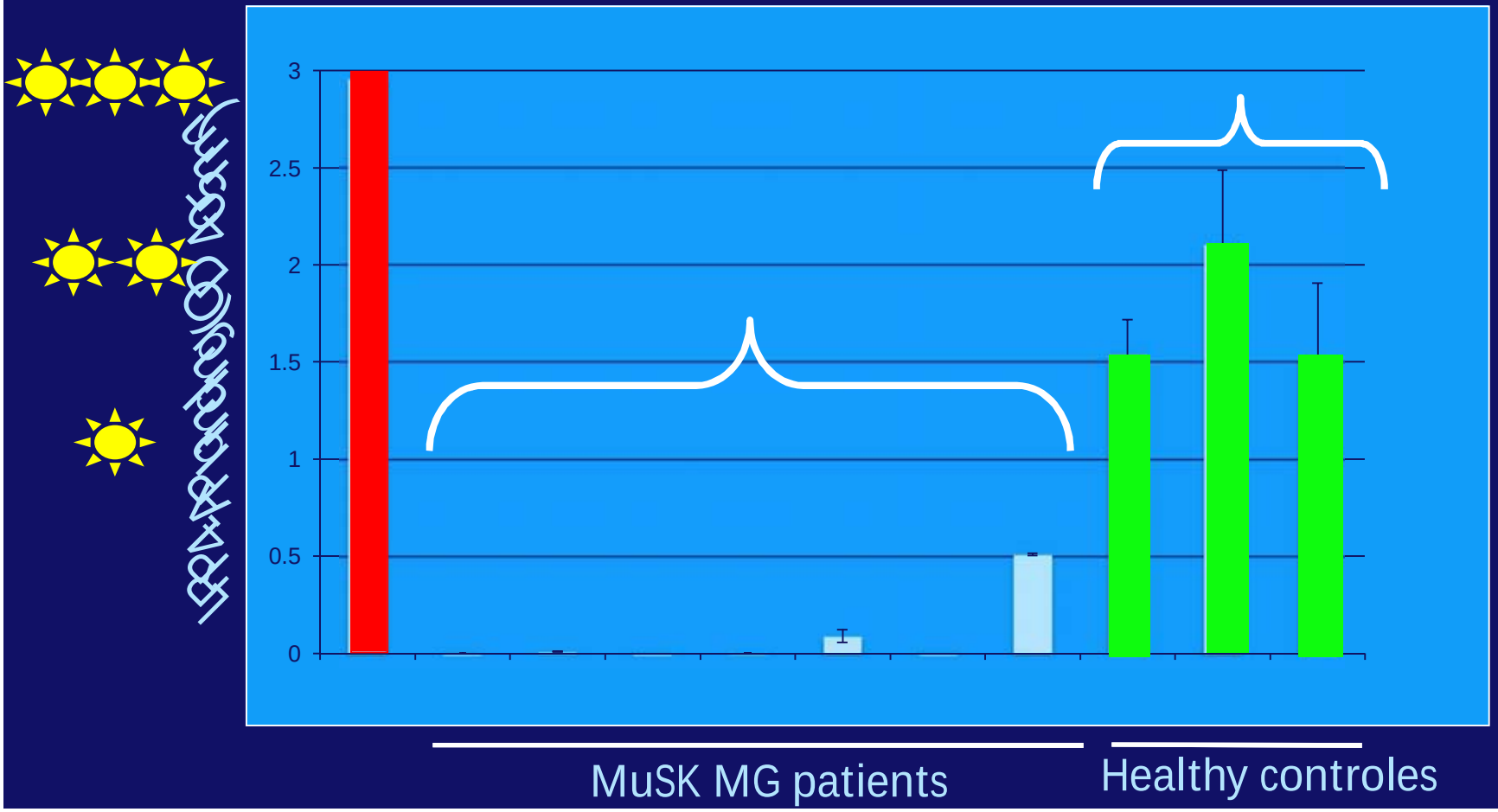
McConville *et al*. 2004;Klooster & Plomp *et al.* 2012

MuSK IgG1-3 does not block MuSK-LRP4 interaction



MuSK IgG4 blocks MuSK-LRP4 interaction

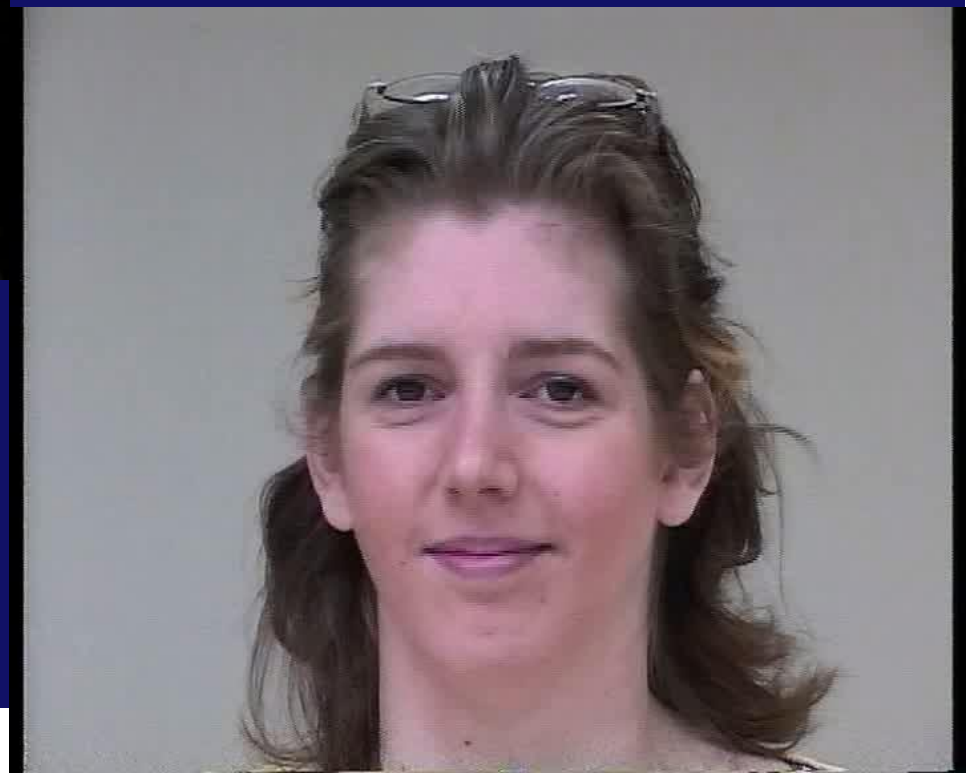
	MuSK MG patients	Controls
Purified IgG4	7	3



MuSK myasthenia gravis

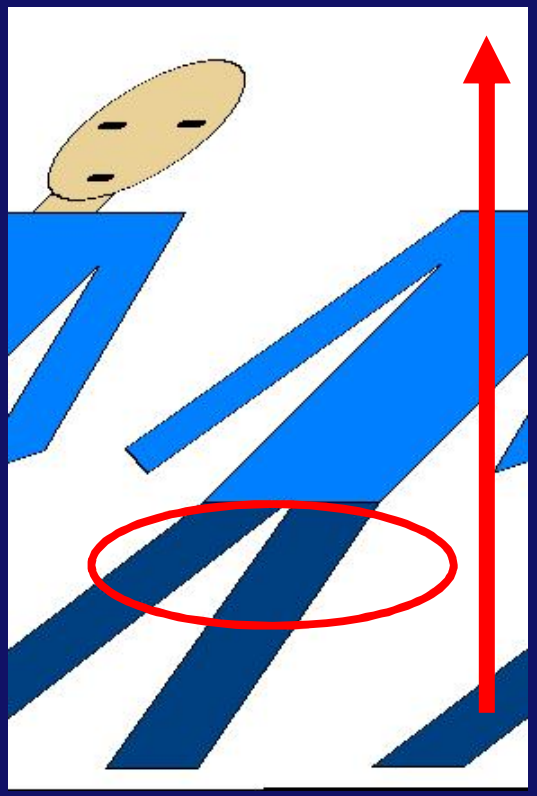
- Unique disease entity
  - Characteristic clinical presentation
  - IgG4 antibody mediated

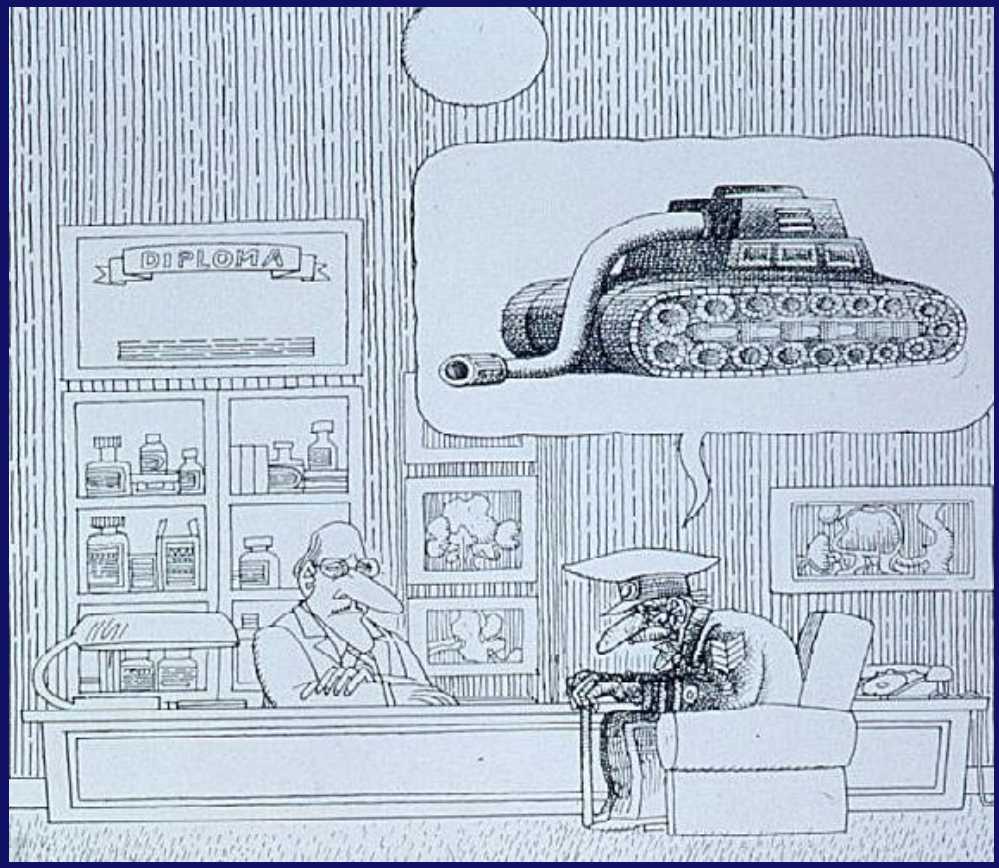
Lambert-Eaton myasthenic syndrome with VGCC antibodies



Lambert-Eaton Myasthenic Syndrome

Weakness and autonomic dysfunction

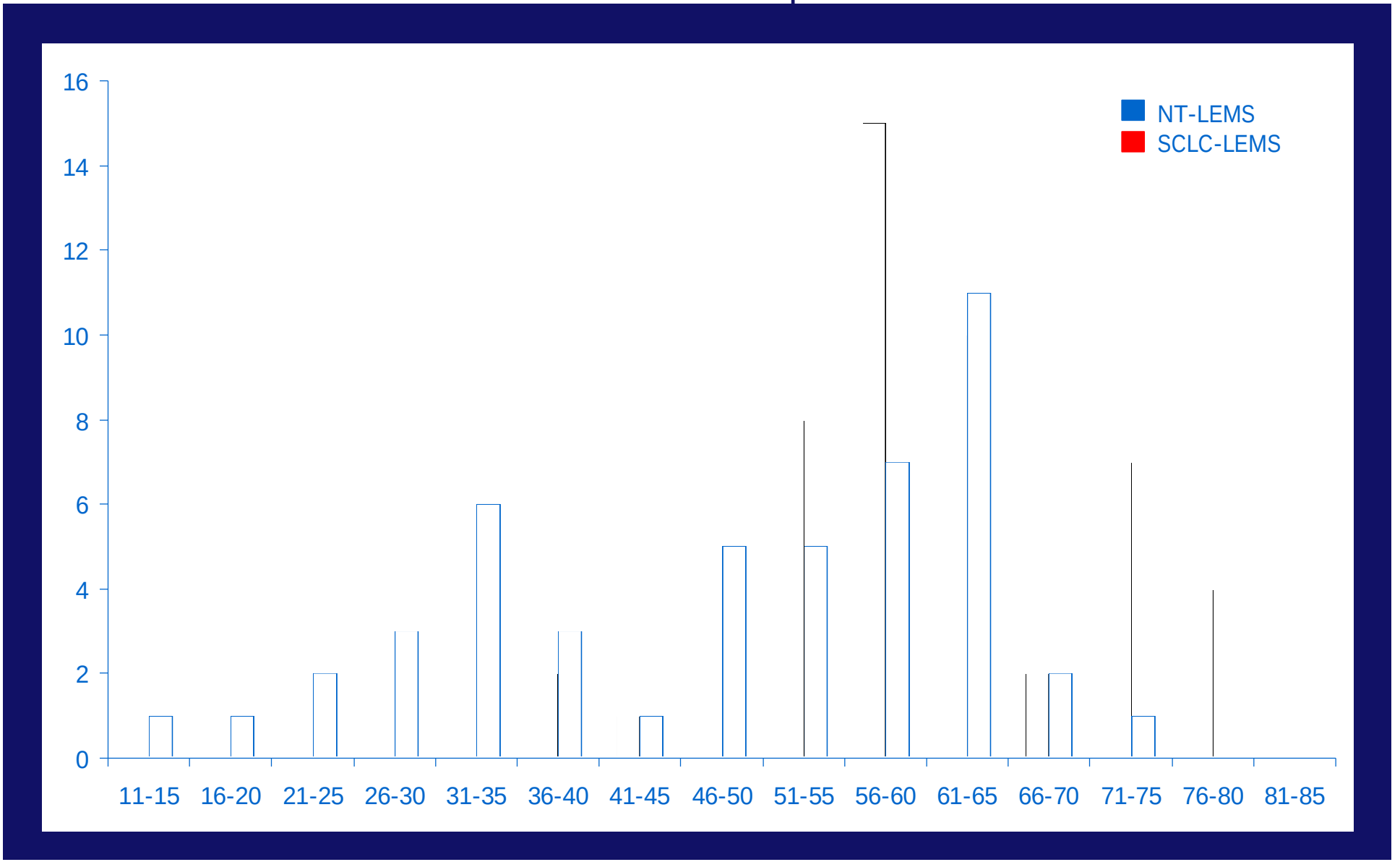




O'Neill, Brain 1988;111:577

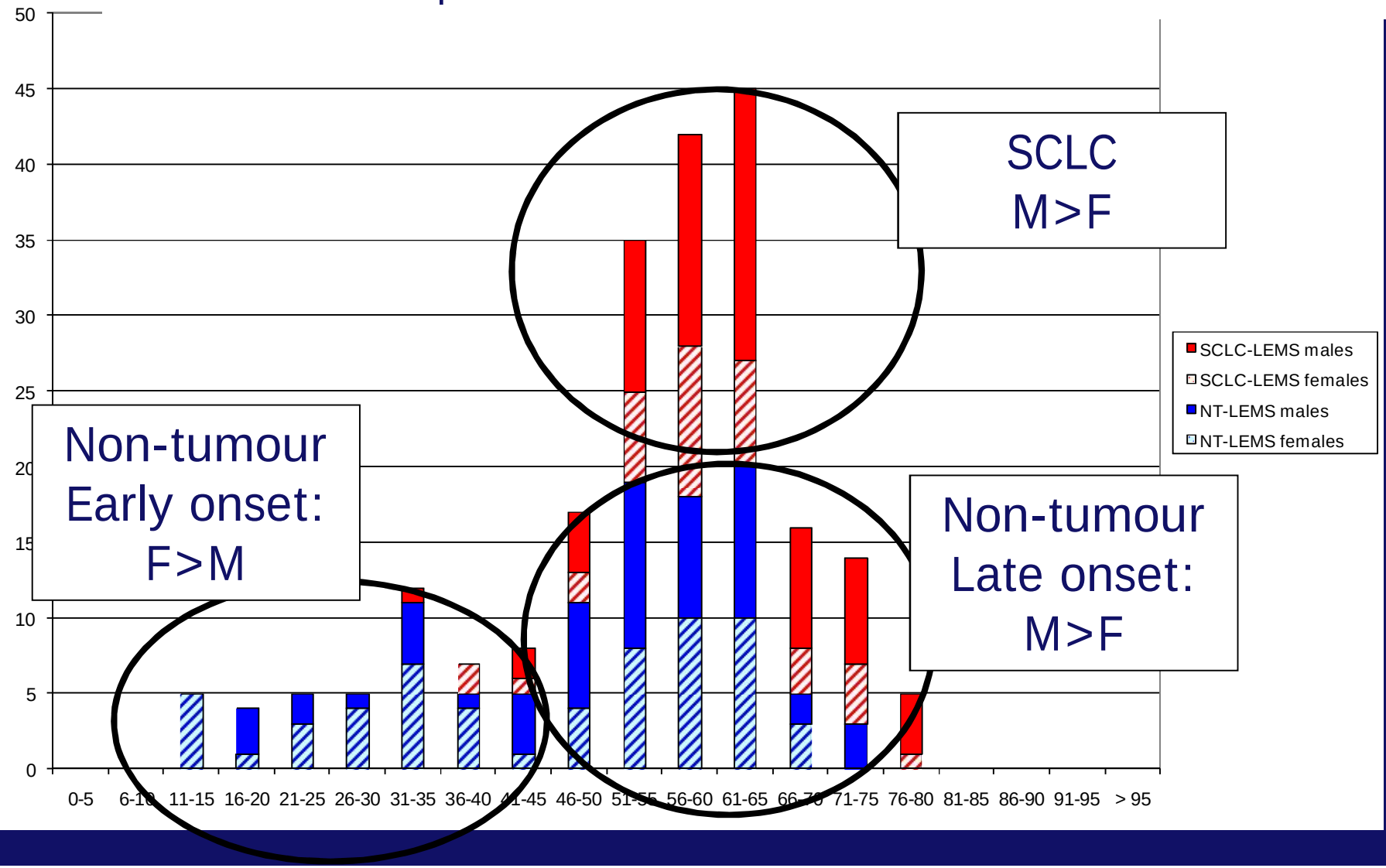
Incidence of non-tumor LEMS and SCLC-LEMS

107 Dutch patients



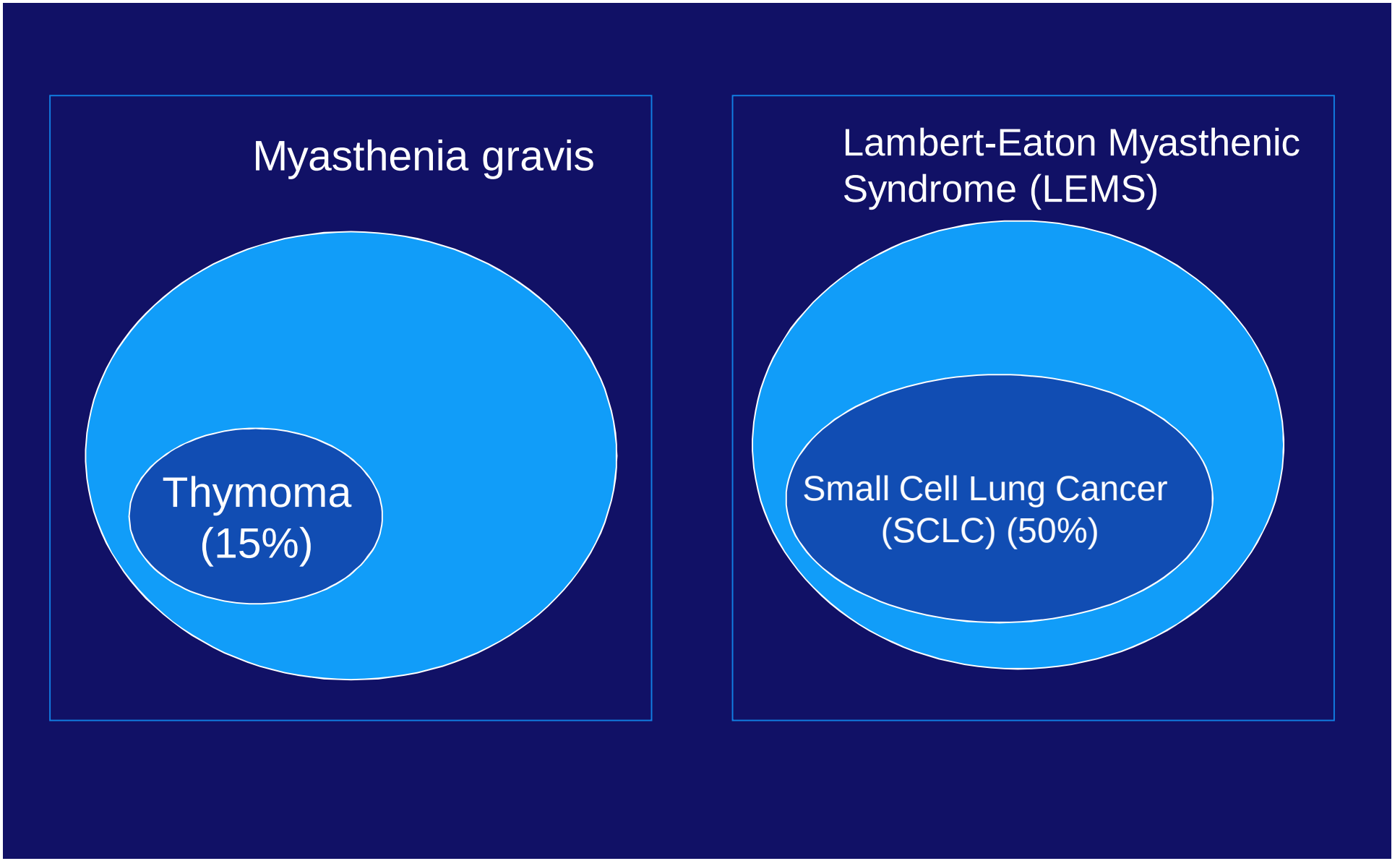
Age distribution of incidence of LEMS is similar to AChR-MG

220 patients from the Netherlands and UK



Titulaer, et al. unpublished

Autoimmunity and tumour



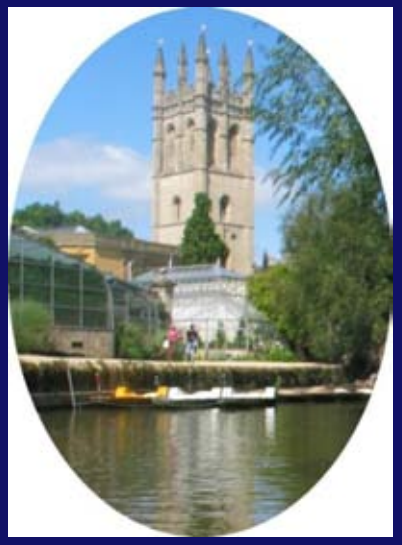
Predicting SCLC in LEMS

Multivariate analysis

ü Derivation

Leiden cohort

n = 107



ü Validation

Oxford and Nottingham

n = 112

European Neurological Society

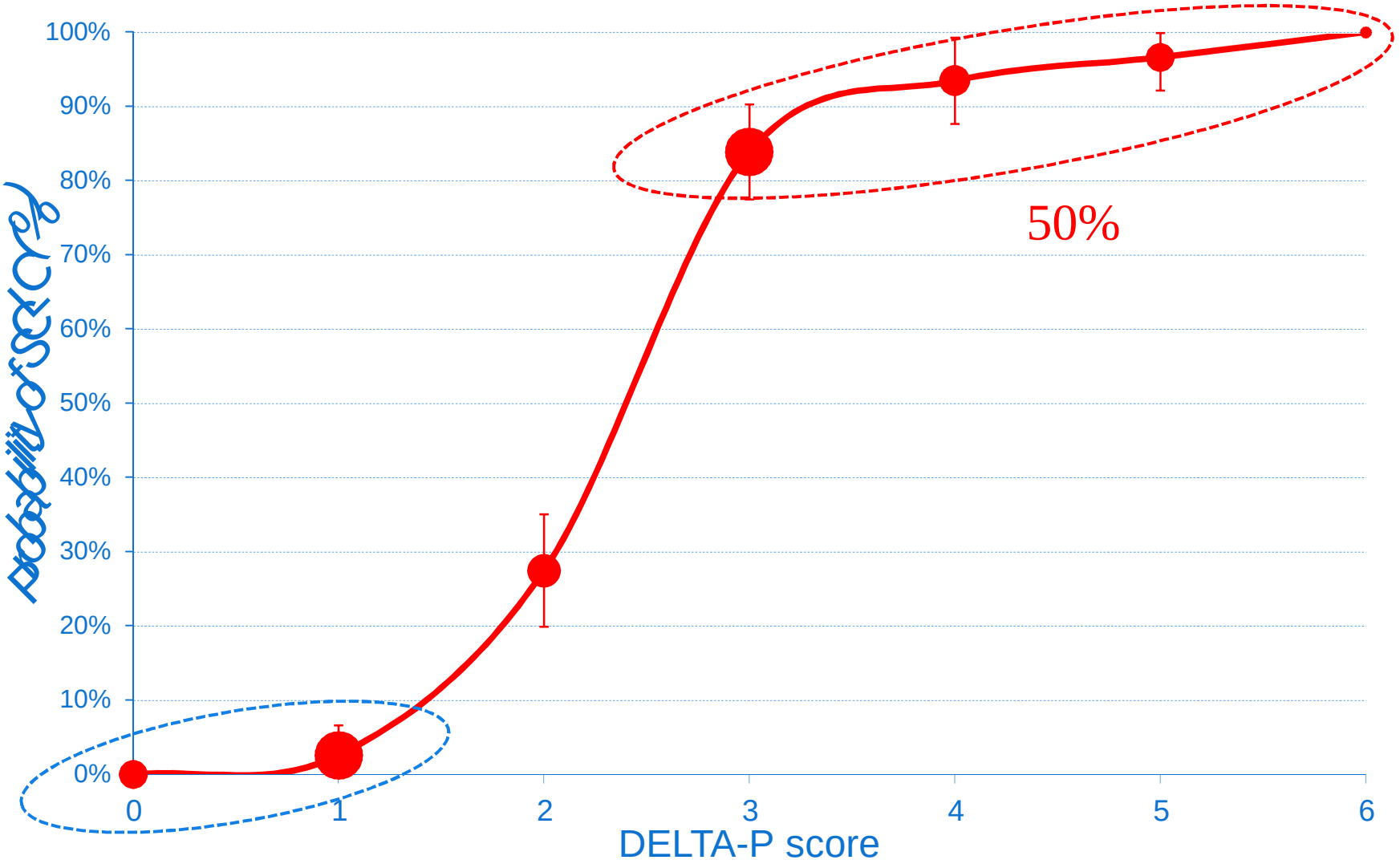
Screening for SCLC in LEMS: DELTA-P score

Dutch - English LEMS Tumour Association - Prediction

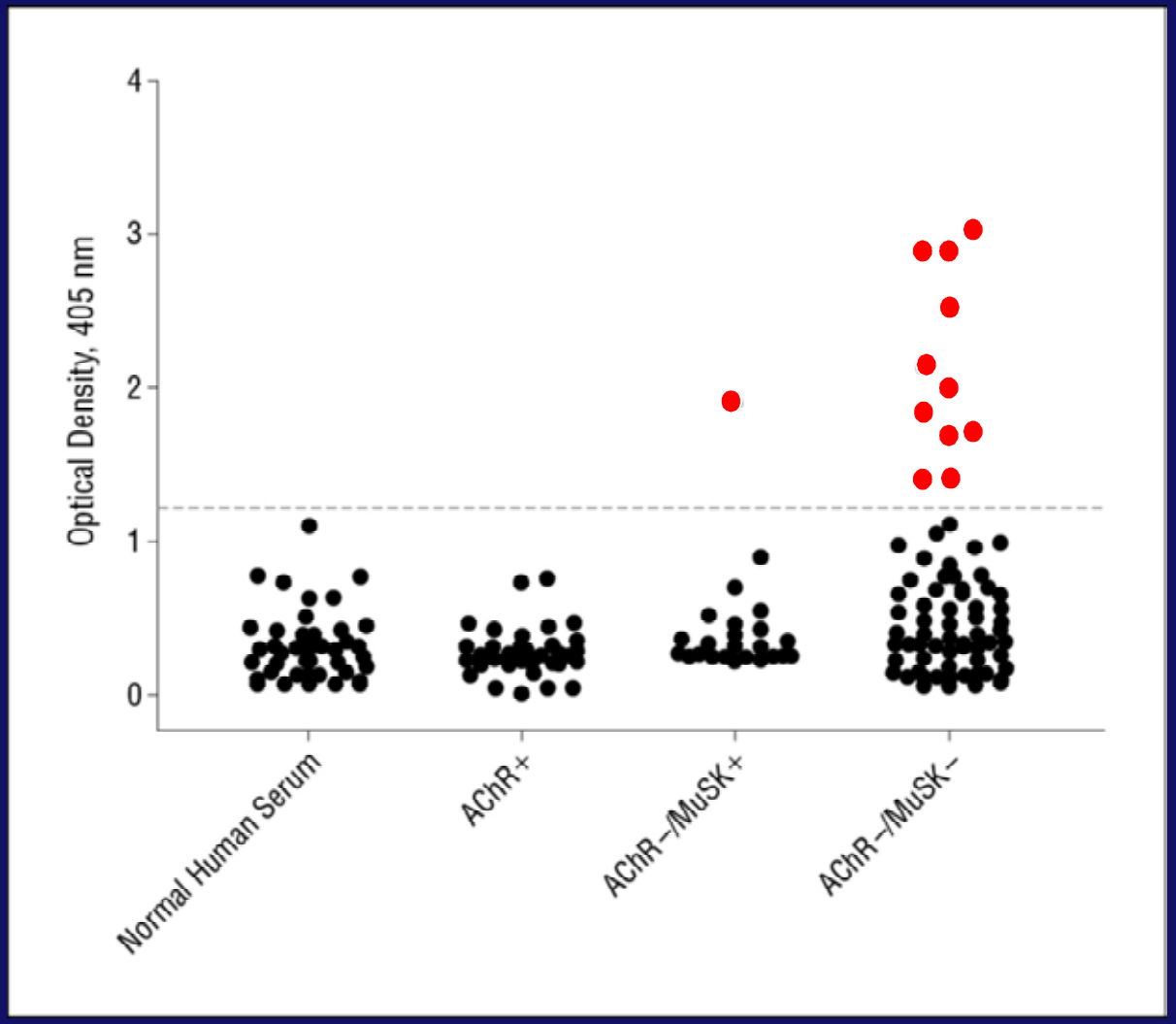
Dysarthria, dysphagia, neck weakness		1
Erectile dysfunction (female also 0)		1
Loss of weight (> 5%)		1
Tobacco use at onset		1
Age at onset (> 50 yr)		1
Karnofsky Performance status	(< 70)	1
		0 - 6

Titulaer, J Clin Oncol 2010

DELTA-P score: prediction

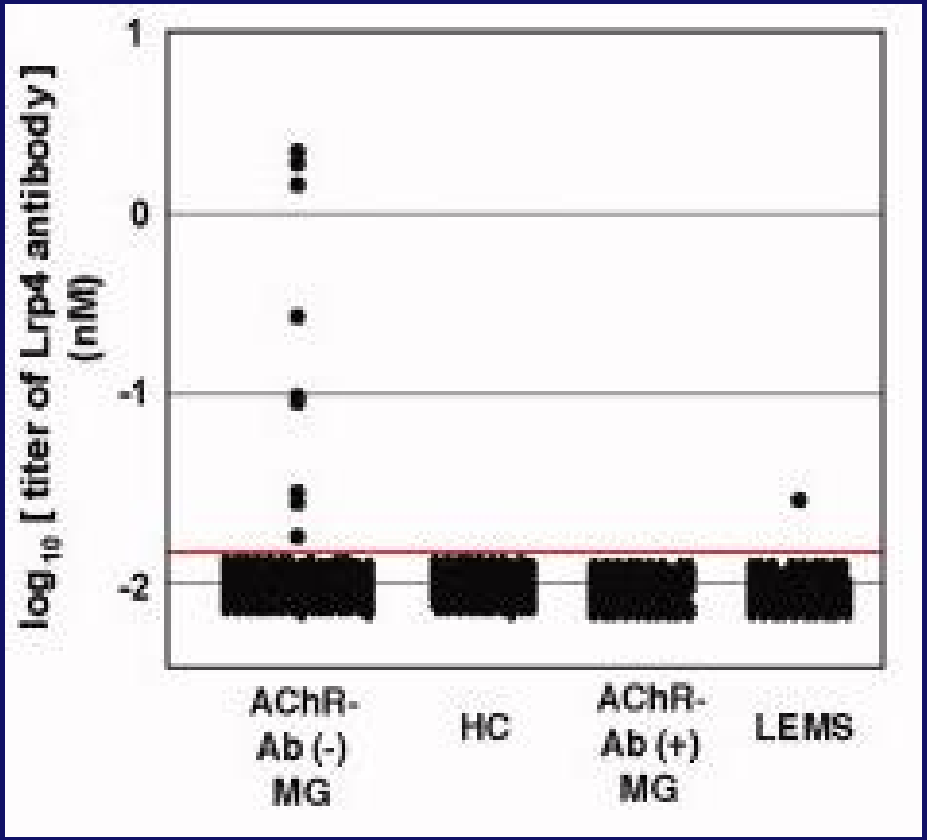


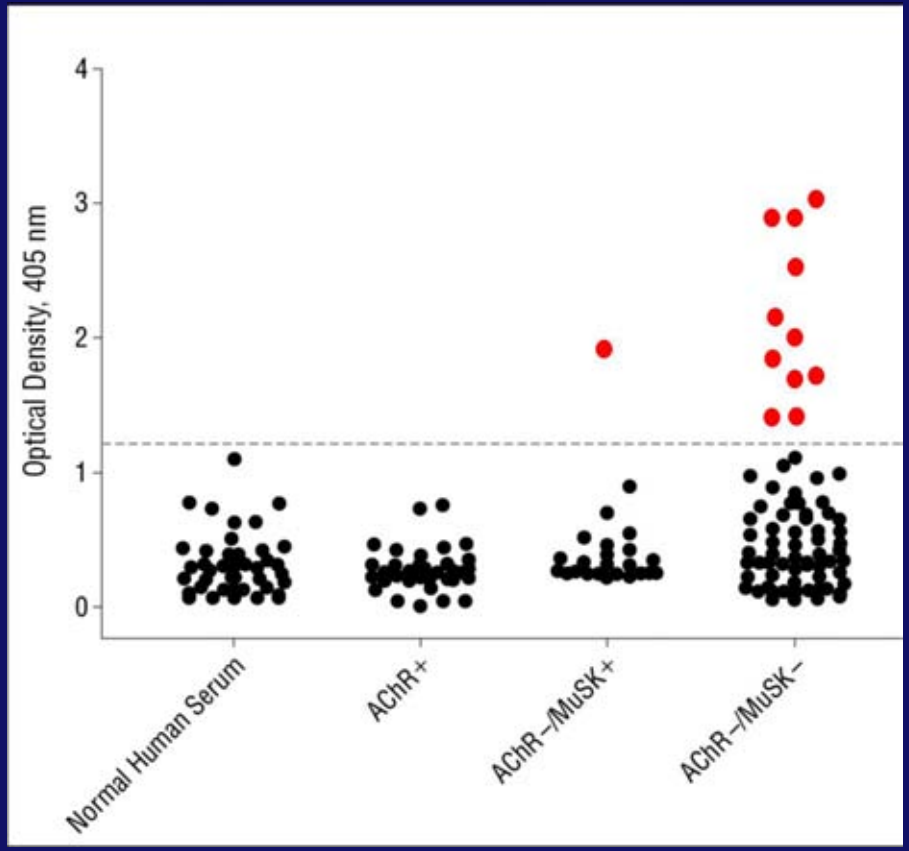
Myasthenia gravis with Lrp4 antibodies



Zang et al. Arch Neurology 2012;69:445

Lrp4 antibodies in myasthenia gravis





Pevzner et al. J Neurol 2011;259:427 ; Zang et al. Arch Neurology 2012;69:445

Lrp4 antibodies in 2% to 9% of “seronegative” MG

	AChR+
Higuchi, 2011	0/100 None
Pevzner, 2011	
Zhang, 2012	0/61 None

Higuchi et al. Ann Neurol 2011;69:418; Pevzner J Neurol 2011;259:427 ; Zang et al. Arch Neurology 2012;69:445

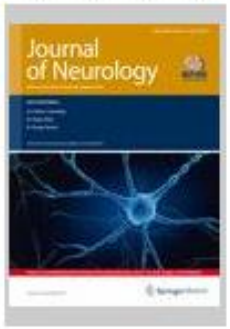
Lrp4 antibodies in 2% to 9% of “seronegative” MG

	AChR+	AChR-		
		MuSK+	MuSK-	VGCC+
Higuchi, 2011	0/100 None	3/28 11%	6/272 2%	1/101 1%
Pevzner, 2011		1/1	7/13	
Zhang, 2012	0/61 None	1/39 3%	11/120 9%	

Higuchi et al. Ann Neurol 2011;69:418; Pevzner J Neurol 2011;259:427 ; Zang et al. Arch Neurology 2012;69:445

Clinical features Lrp4-MG

JOURNAL OF NEUROLOGY
Volume 259, Number 3 (2012), 427-435, DOI: 10.1007/s00415-011-6194-7



ORIGINAL COMMUNICATION

Anti-LRP4 autoantibodies in AChR- and MuSK-antibody-negative myasthenia gravis

Alexandra Pevzner, Benedikt Schoser, Katja Peters, Nicoleta-Carmen Cosma, Andromachi Karakatsani, Berthold Schalke, Arthur Melms and Stephan Kröger

- age at onset 17 to 79 years (mean 47 years)
- 80% female
- ocular symptoms in 50%
- bulbar, neck, limb weakness in 70-80%
- respiratory problems in 29%

MuSK MG-like?

Are there other antibodies?

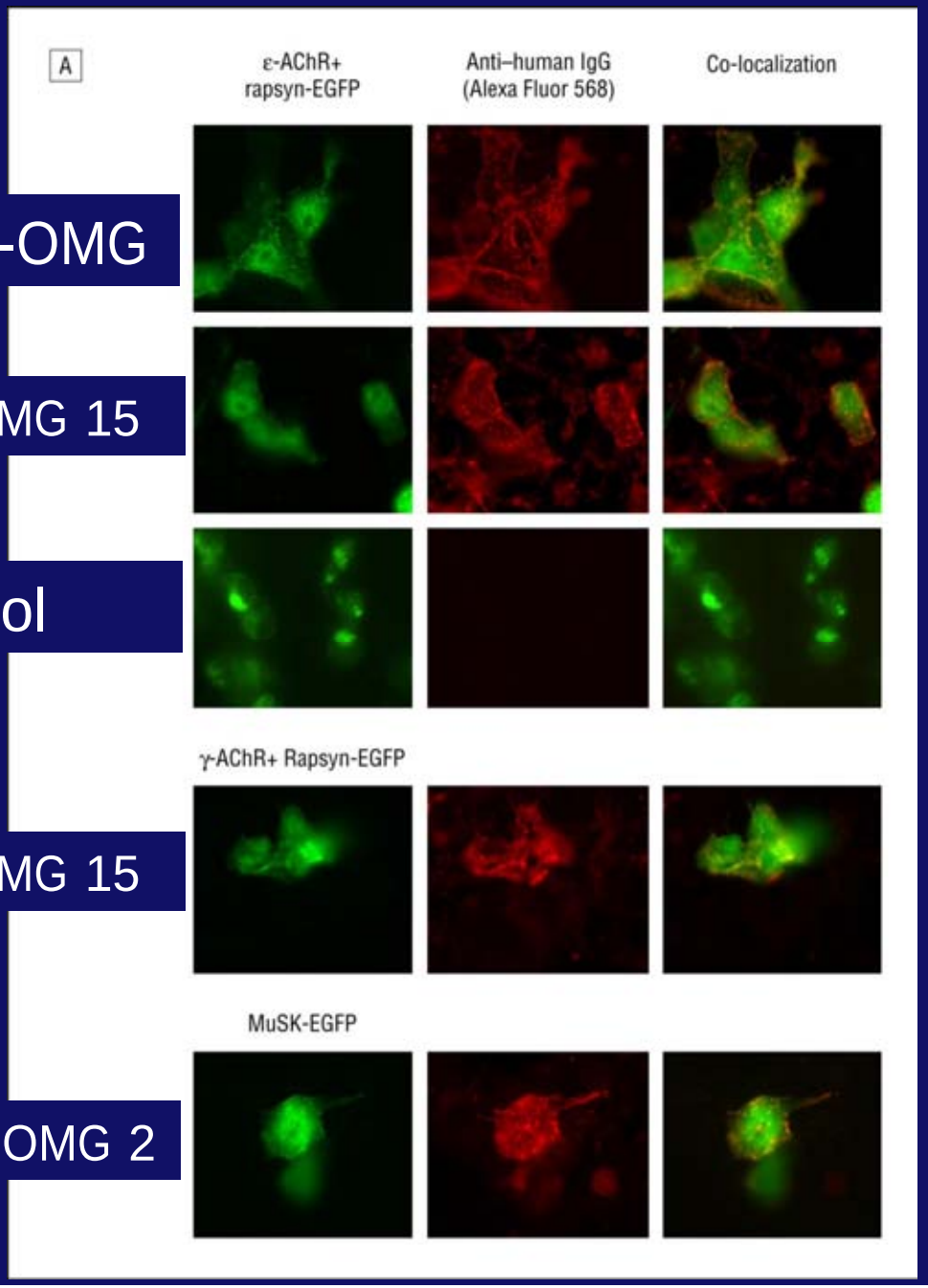
AChR-OMG

Seronegative-OMG 15

Control

Seronegative-OMG 15

Seronegative-OMG 2



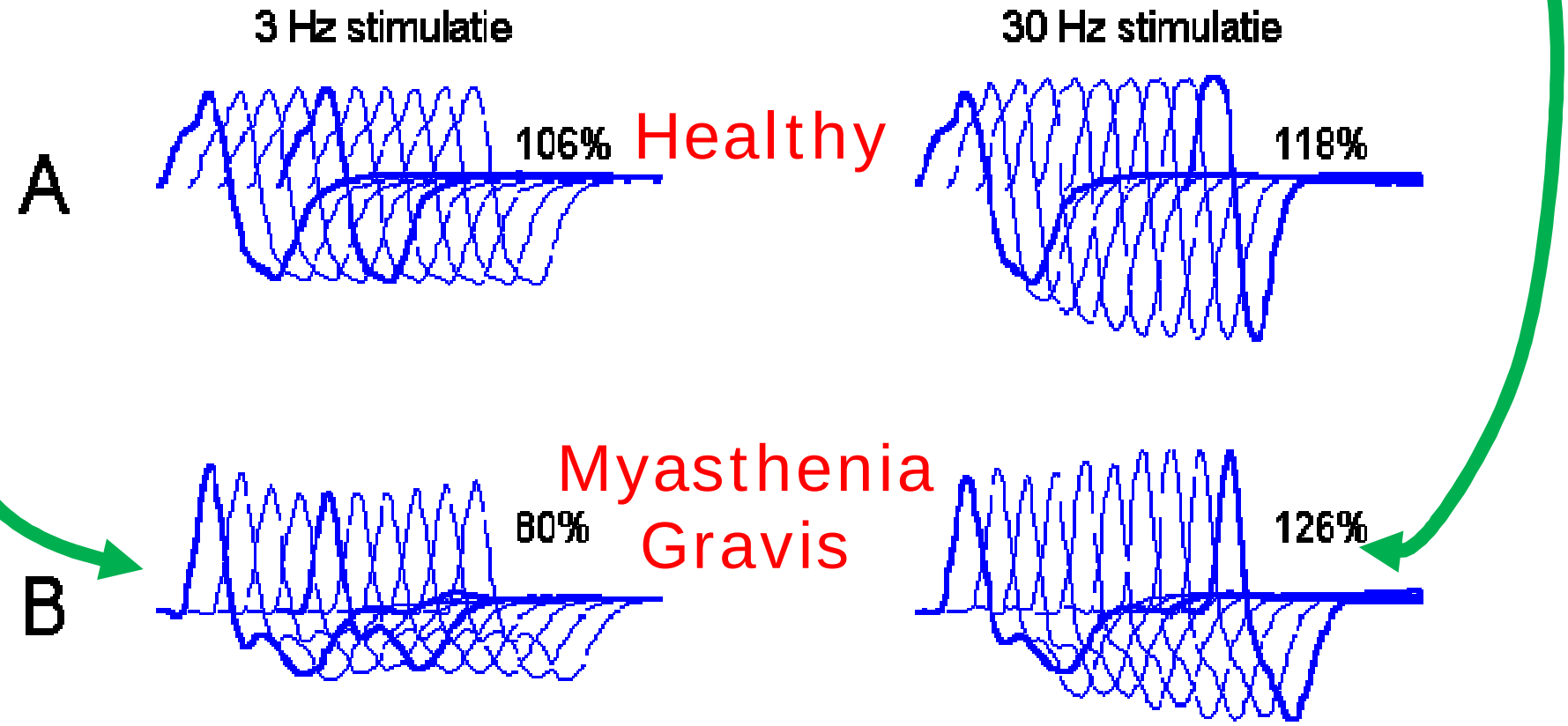
50% of sero-negative ocular MG patients has IgG1 clustered AChR or MUSK antibodies

Jacob, Arch Neurol 2012; 69:994; Leite, Vincent et al, Brain, 2008

Electromyogram: Repetitive stimulation

Myasthenia gravis with AChR or MuSK antibodies:

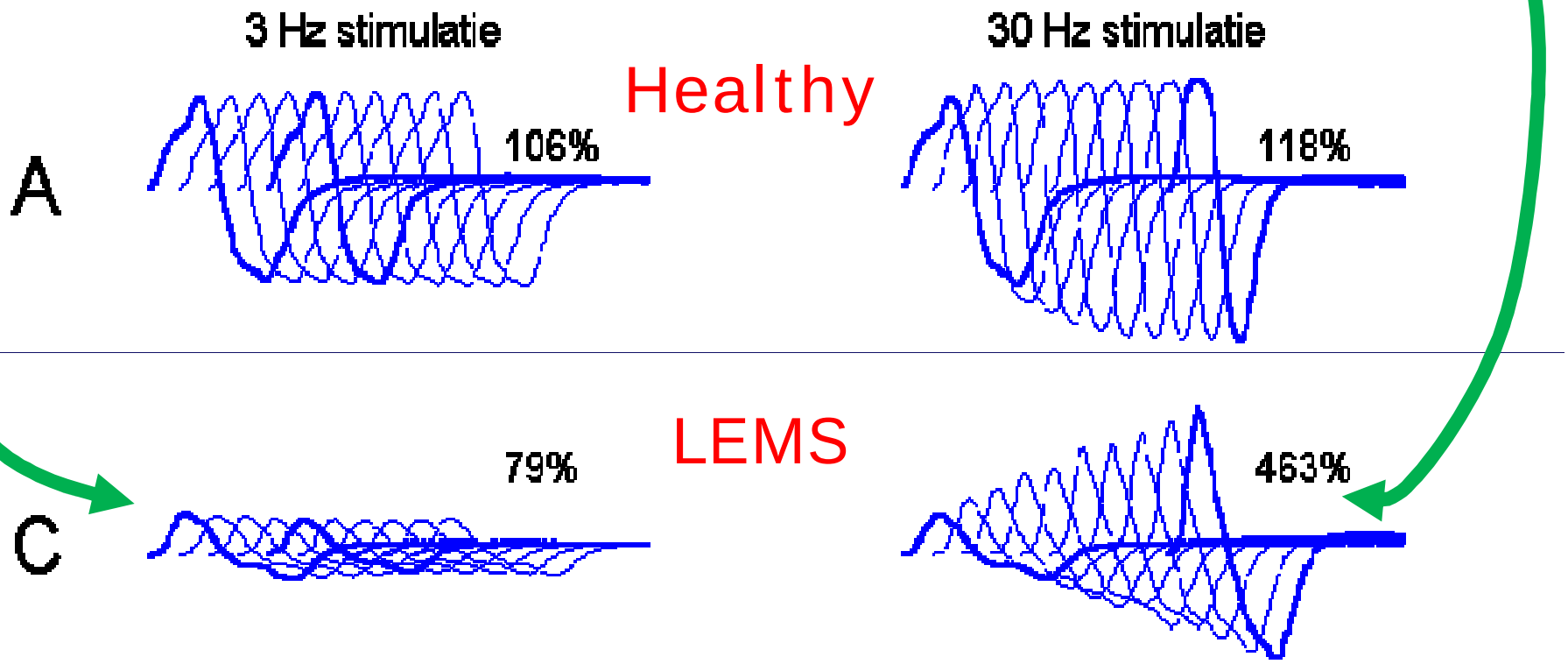
Abnormal decrement at low frequency (more than 10%)
No abnormal increment at high frequency (less than 30%)



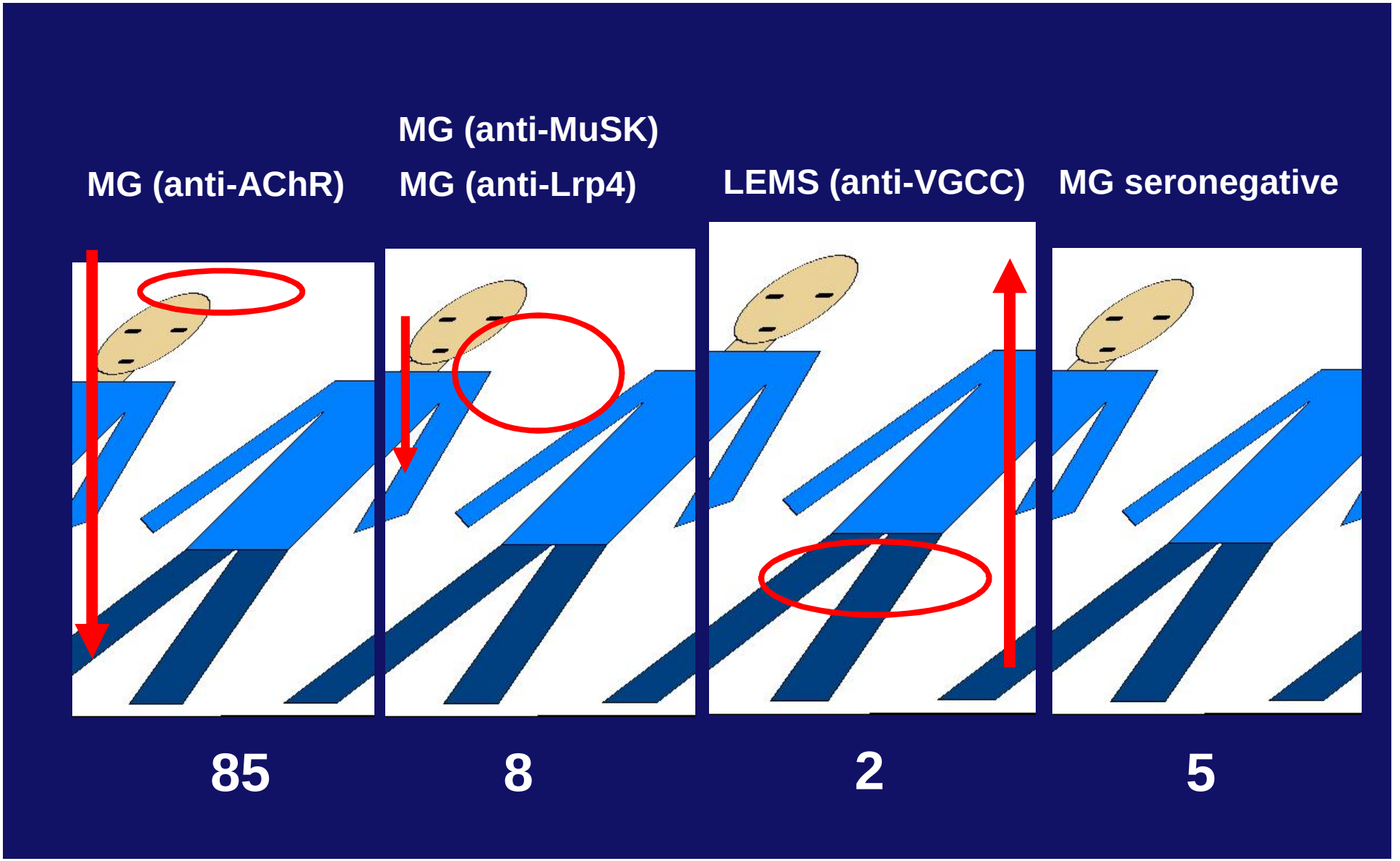
Electromyogram: Repetitive stimulation

LEMS with calcium channel antibodies:

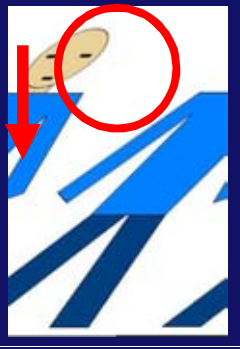
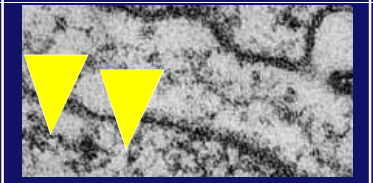
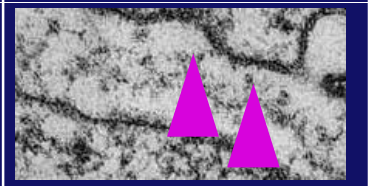
Too small start-amplitude of CMAP
Abnormal decrement at low frequency (more than 10%)
Abnormal increment at high frequency (more than 100%)



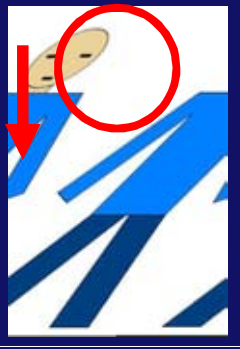
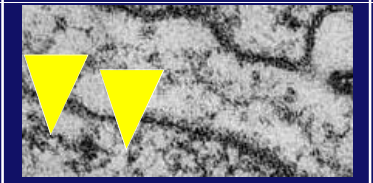
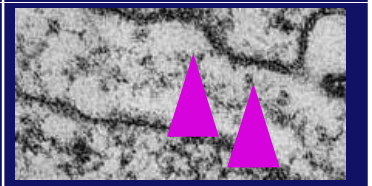
Clinics:100 patients with myasthenia



Four myasthenic syndromes

	AChR MG	LEMS	MuSK MG	Lrp4 MG
Clinic				 ?
Antigen				
Incidence	Young female, Old male	Young female, Old male	Young female	More female, all ages?
HLA	B8-DR3	B8-DR3	DR14-DQ5	?

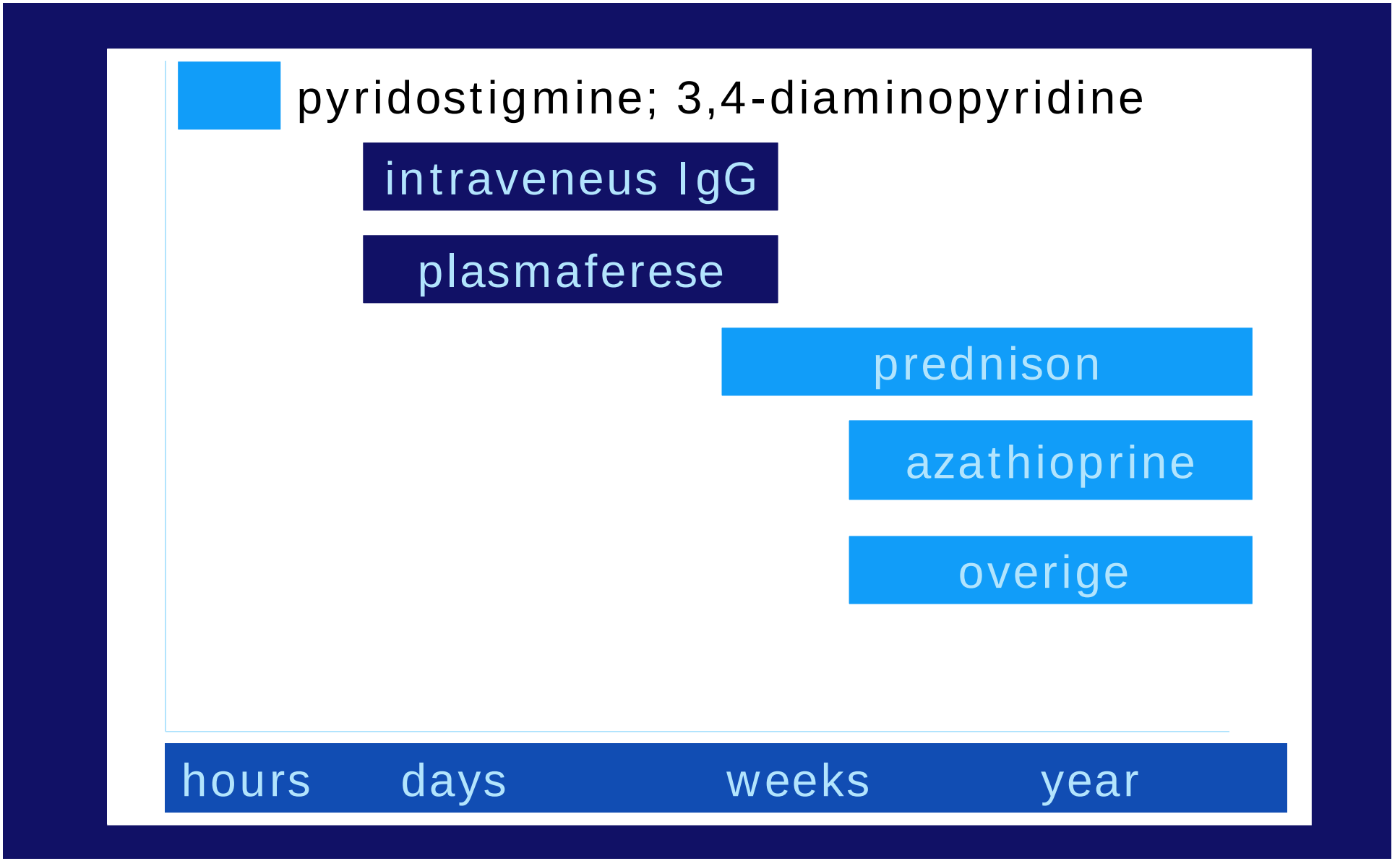
Four myasthenic syndromes

	AChR MG	LEMS	MuSK MG	Lrp4 MG
Clinic				 ?
Antigen				
Incidence	Young female, Old male	Young female, Old male	Young female	More female, all ages?
HLA	B8-DR3	B8-DR3	DR14-DQ5	?
Antibodies	IgG1	IgG1	**IgG4**	IgG1

Therapy

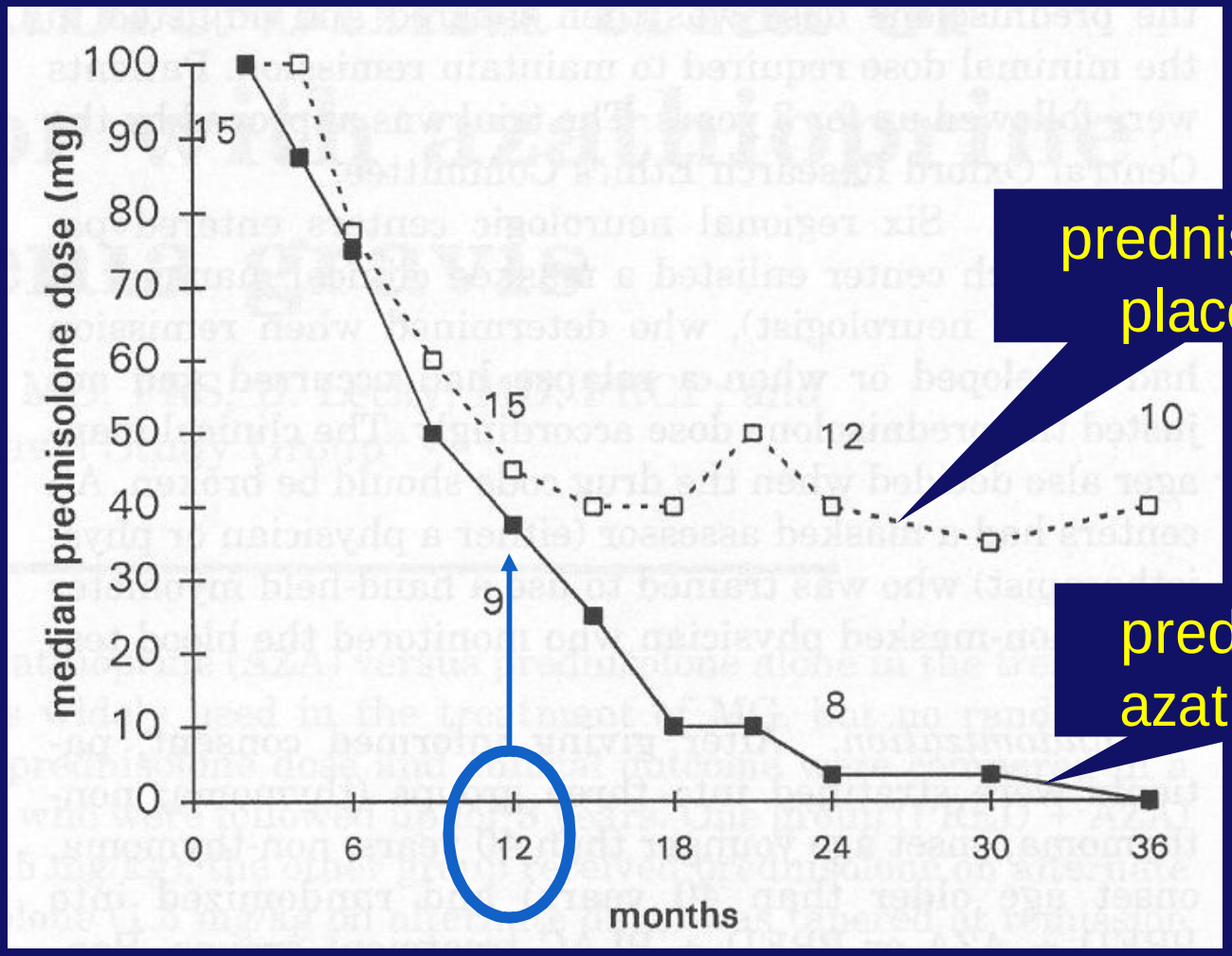
pyridostigmine; 3,4-diaminopyridine

Therapy

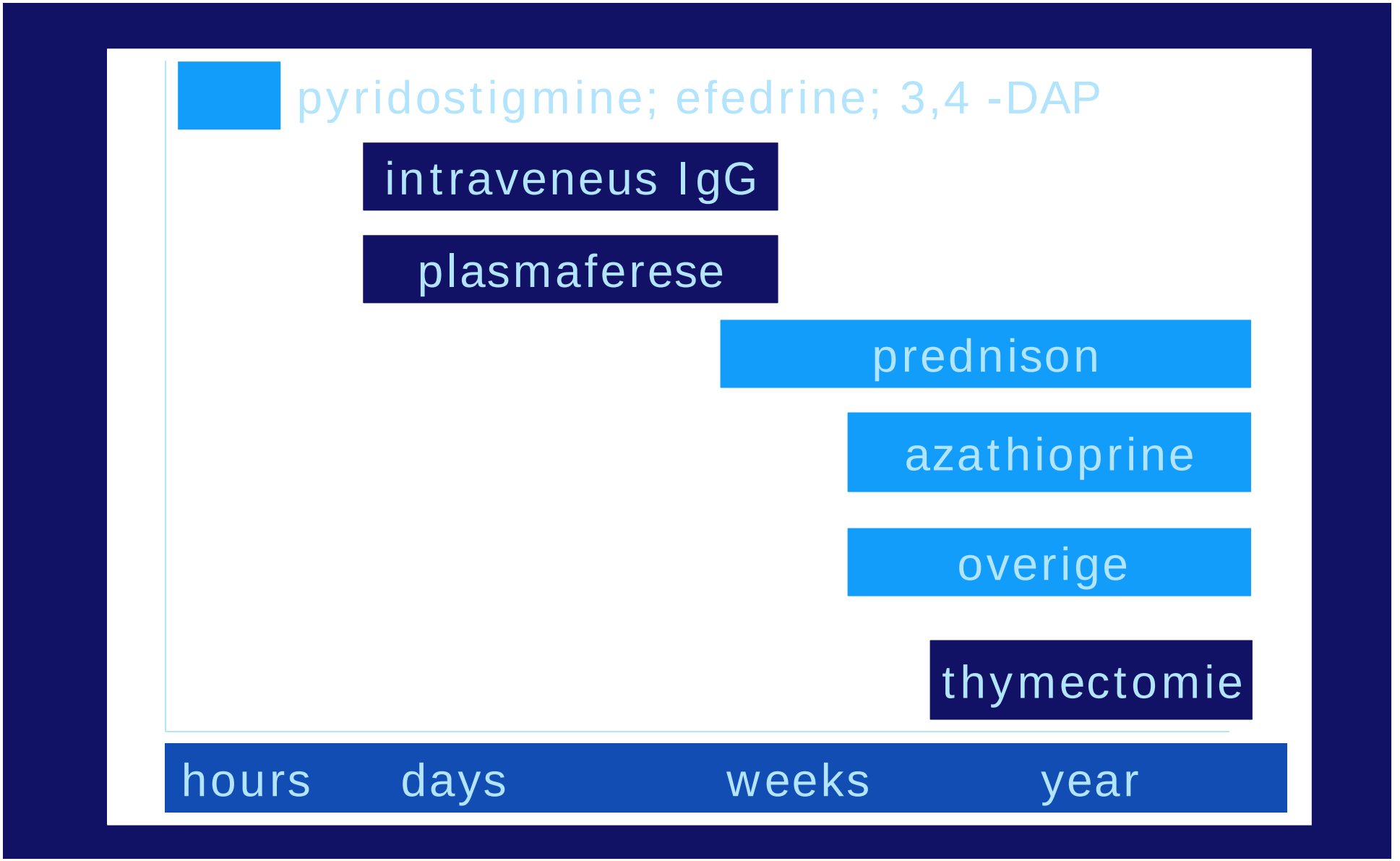

pyridostigmine; 3,4-diaminopyridine
intraveneus IgG
plasmaferese
prednison
azathioprine
overige
hours
days
weeks
year

Prednison en Azathioprine

(Palace, Newsom-Davis; Neurology, 1998)



Therapie


pyridostigmine; efedrine; 3,4 -DAP
intraveneus IgG
plasmaferese
prednison
azathioprine
overige
thymectomie
hours
days
weeks
year

Thymectomy in AChR Myasthenia Gravis

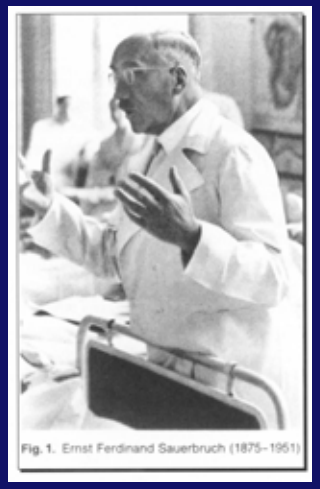


Fig. 1. Ernst Ferdinand Sauerbruch (1875–1951)

1911 Sauerbruch


Sauerbruch's patient before the operation


Same patient post-operatively

2006-2015

Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy

N=150

Adults 18 to 65 years

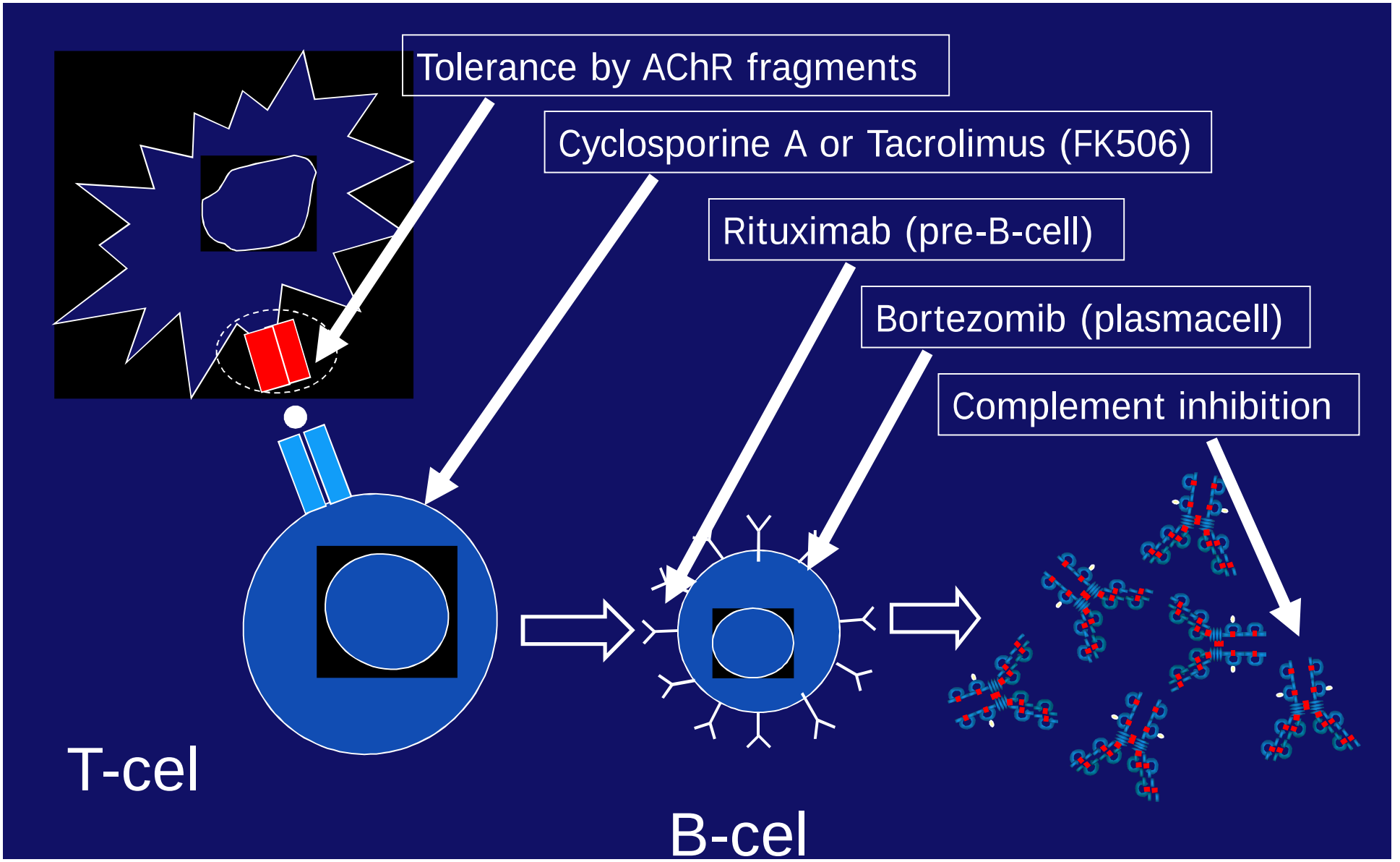
Prednisone versus Prednisone + Thymectomy

Pirmary Outcome:

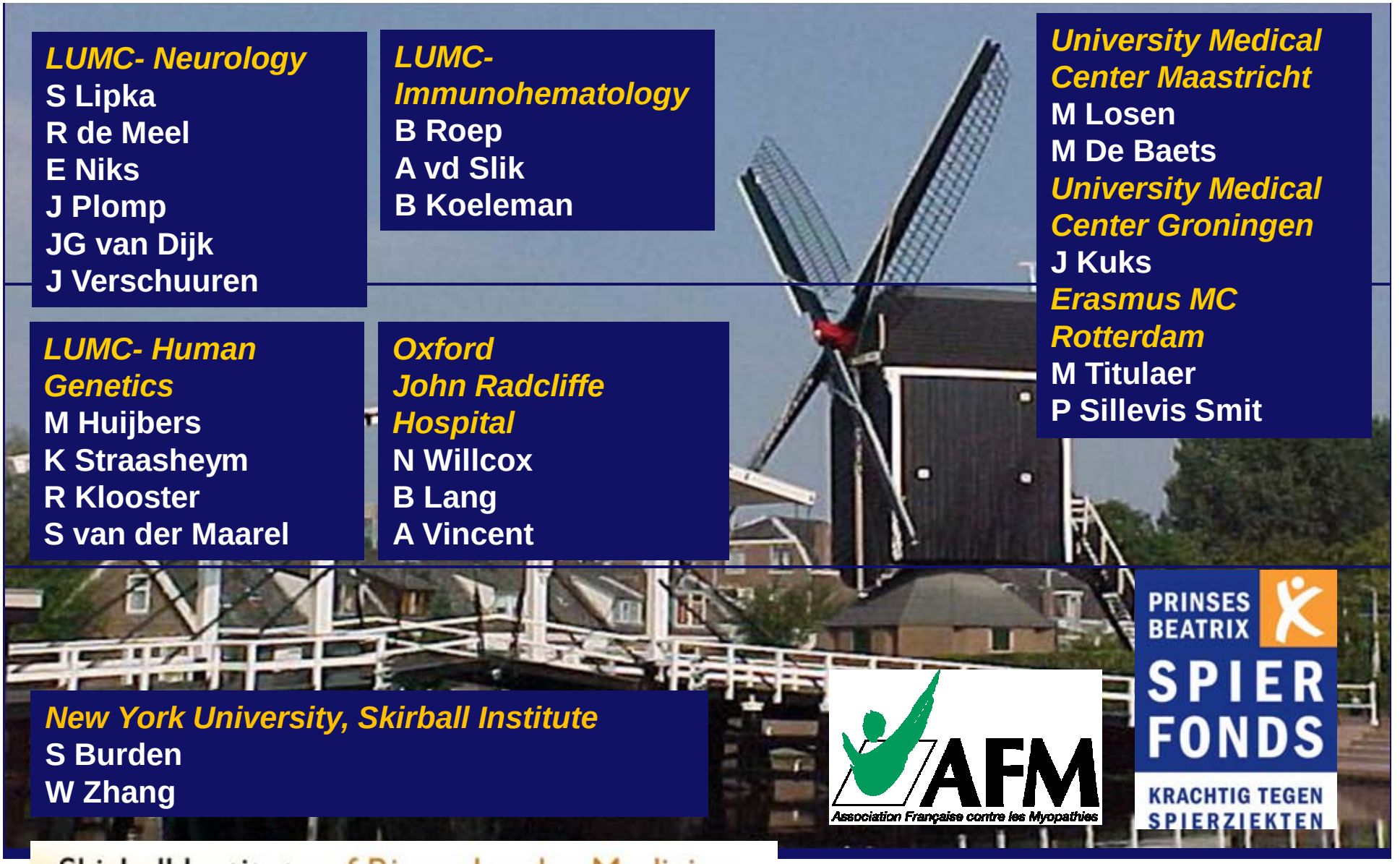
-Area under Quantitative Myasthenia Gravis Weakness Score over 3 years

-Total prednisone over 3 years

Targeting T-cells and (pre)-B-cells



Thank you



LUMC- Neurology
S Lipka
R de Meel
E Niks
J Plomp
JG van Dijk
J Verschuuren

LUMC- Immunohematology
B Roep
A vd Slik
B Koeleman

University Medical Center Maastricht
M Losen
M De Baets

University Medical Center Groningen
J Kuks

Erasmus MC Rotterdam
M Titulaer
P Sillevis Smit

LUMC- Human Genetics
M Huijbers
K Straasheym
R Klooster
S van der Maarel

Oxford John Radcliffe Hospital
N Willcox
B Lang
A Vincent

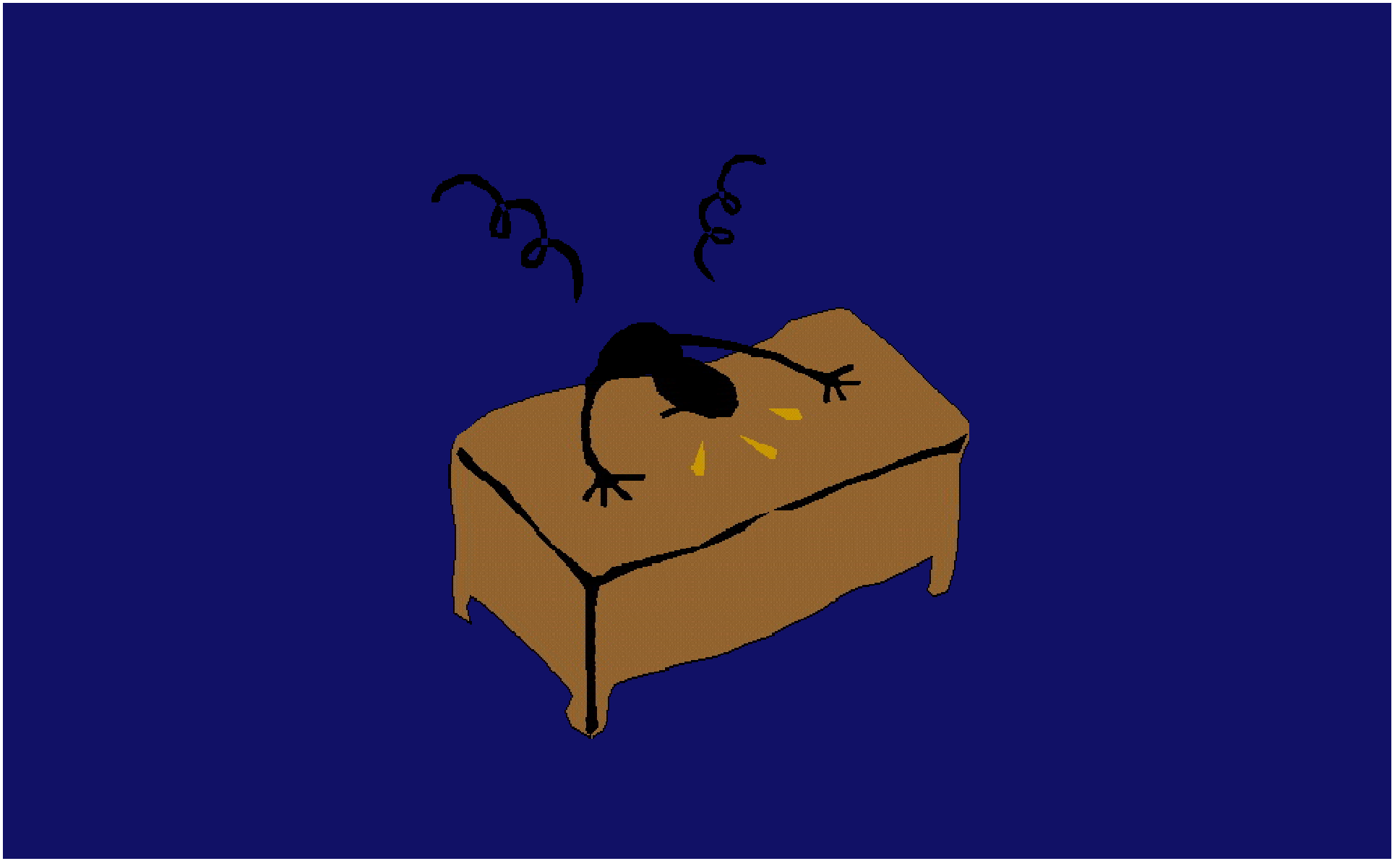
New York University, Skirball Institute
S Burden
W Zhang

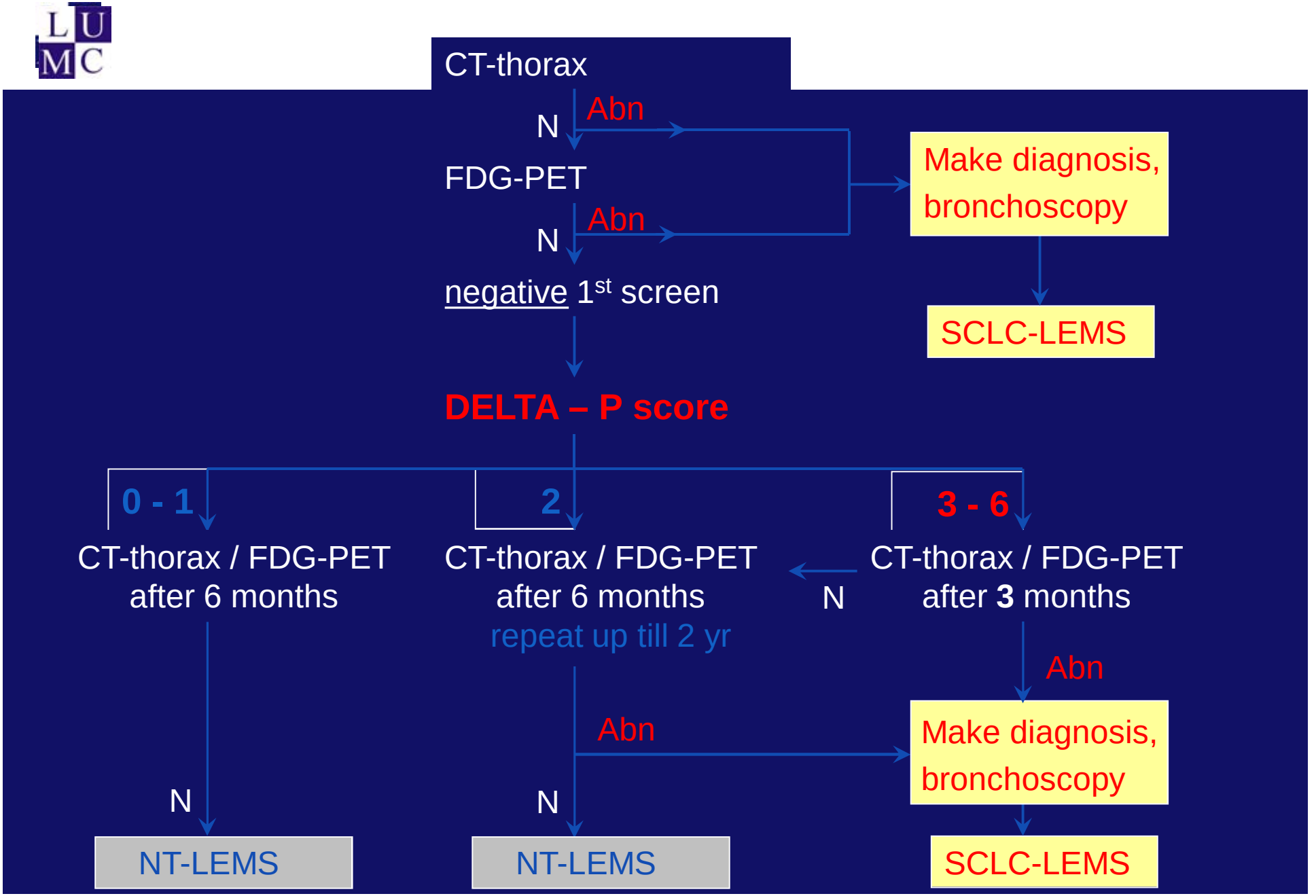
AFM
Association Française contre les Myopathies

PRINSES BEATRIX SPIER FONDS
KRACHTIG TEGEN SPIERZIEKTEN

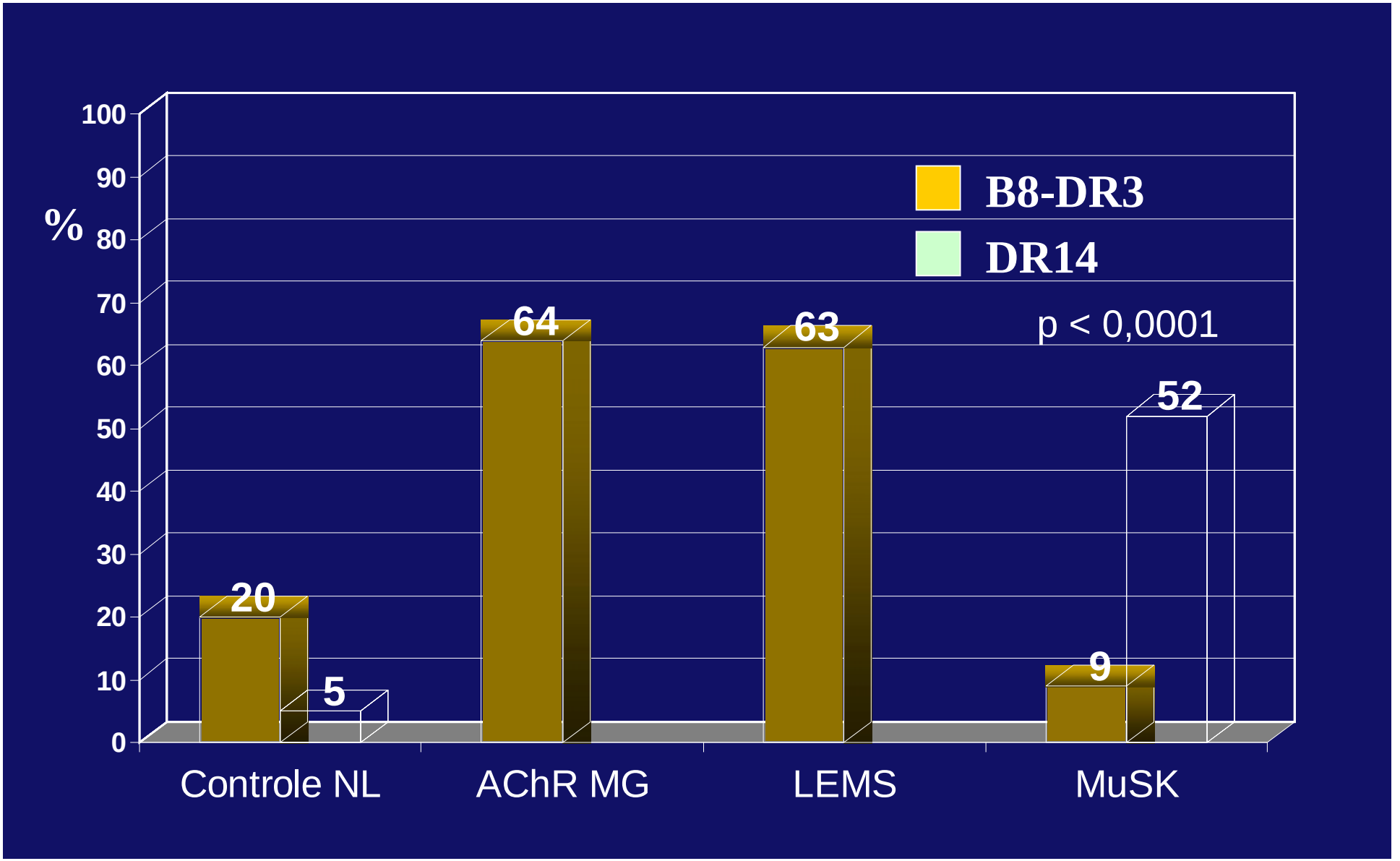
Skirball Institute of Biomolecular Medicine

The End




CT-thorax
N
Abn
FDG-PET
N
Abn
negative 1st screen
Make diagnosis, bronchoscopy
SCLC-LEMS
DELTA – P score
0 - 1
2
3 - 6
CT-thorax / FDG-PET after 6 months
CT-thorax / FDG-PET after 6 months
repeat up till 2 yr
N
CT-thorax / FDG-PET after 3 months
Abn
Abn
Make diagnosis, bronchoscopy
N
N
NT-LEMS
NT-LEMS
SCLC-LEMS

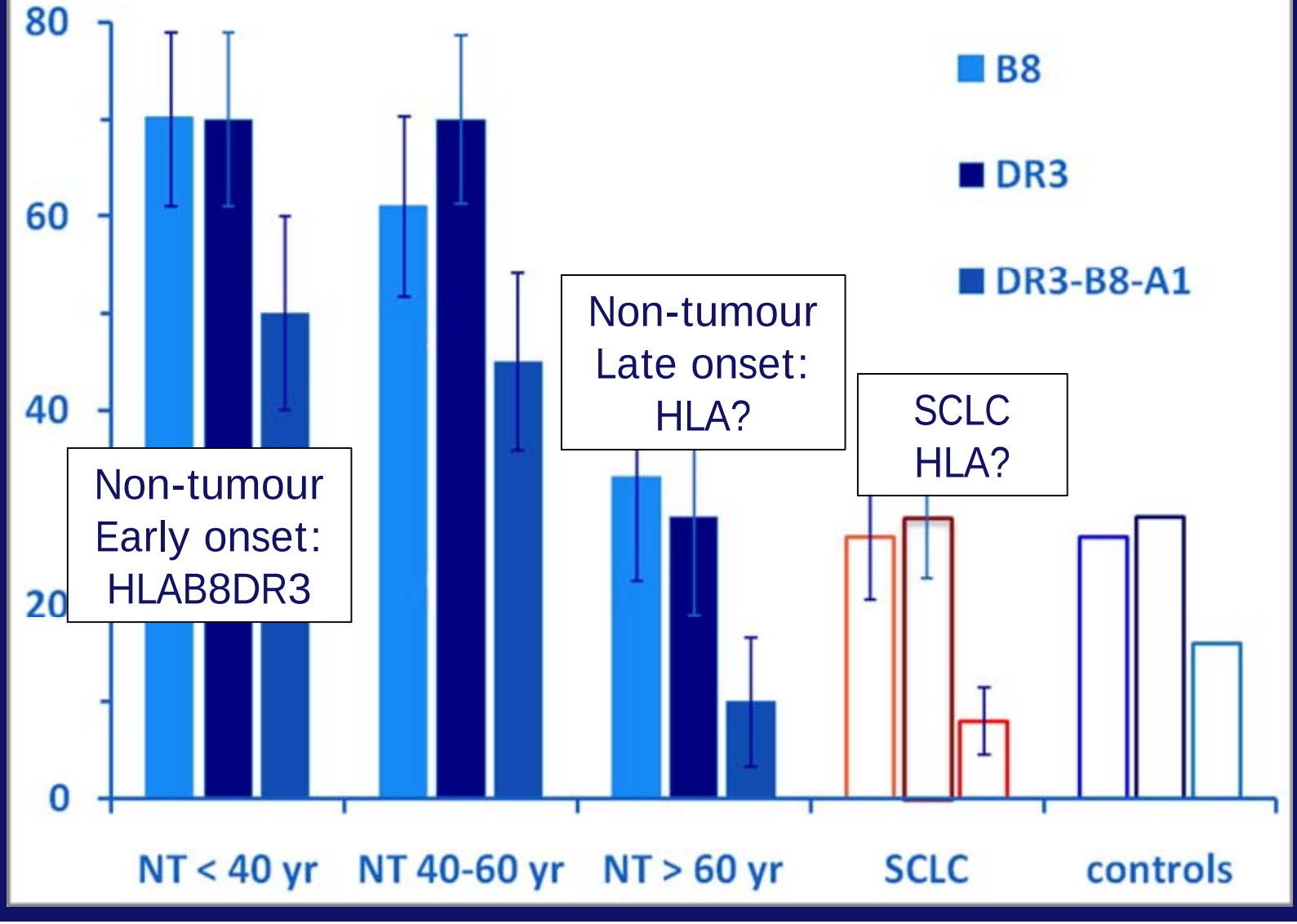
Myasthenie en HLA



Niks, Neurology 2006;66:1772

HLA association of LEMS is similar to AChR-MG

77 NT-LEMS and 48 SCLC-LEMS



Titulaer, unpublished