Leiden University
Medical Center

Update on myasthenia gravis

Jan Verschuuren

Living with myasthenia gravis

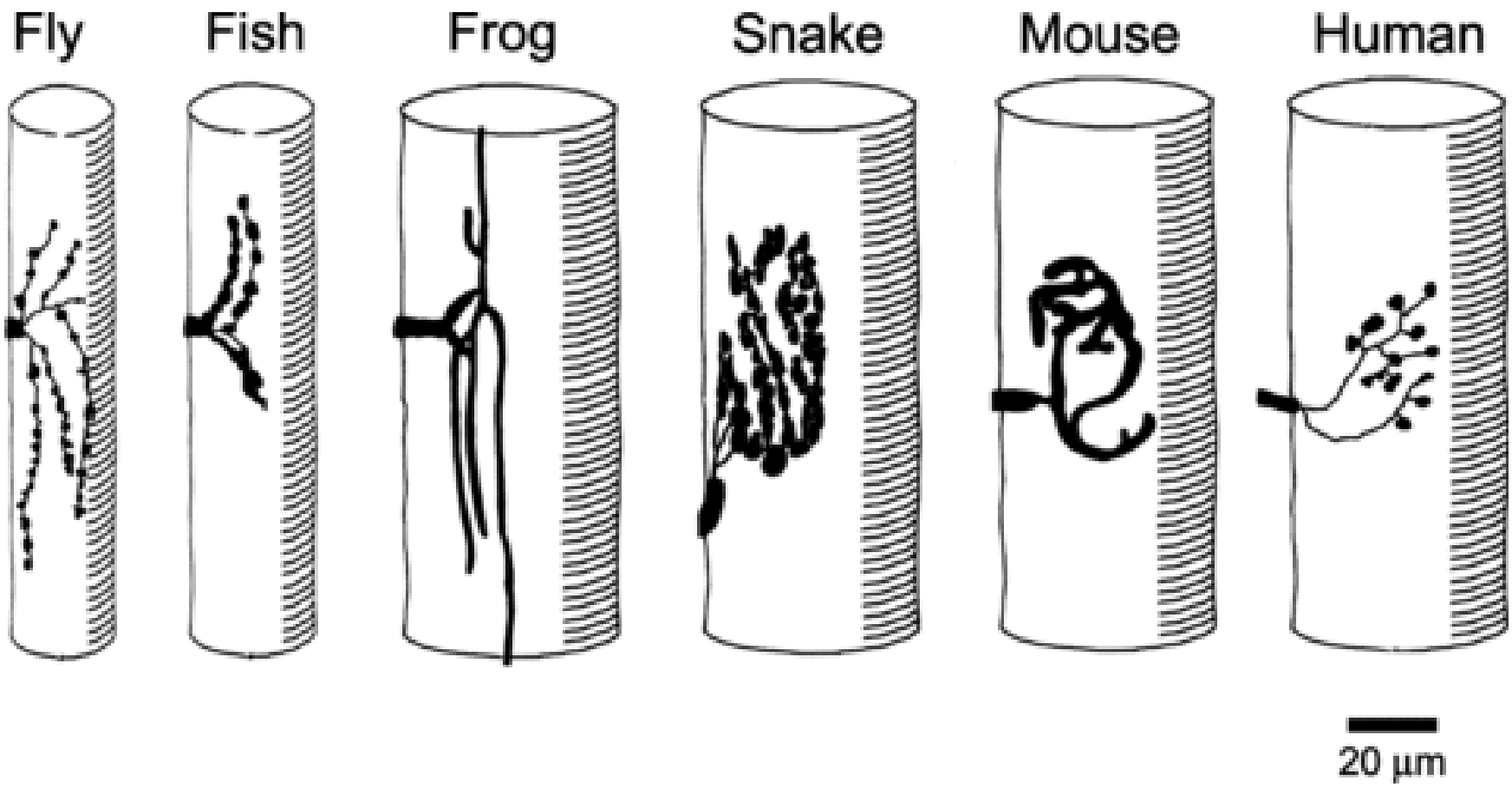
Updates on psychosocial issues and training

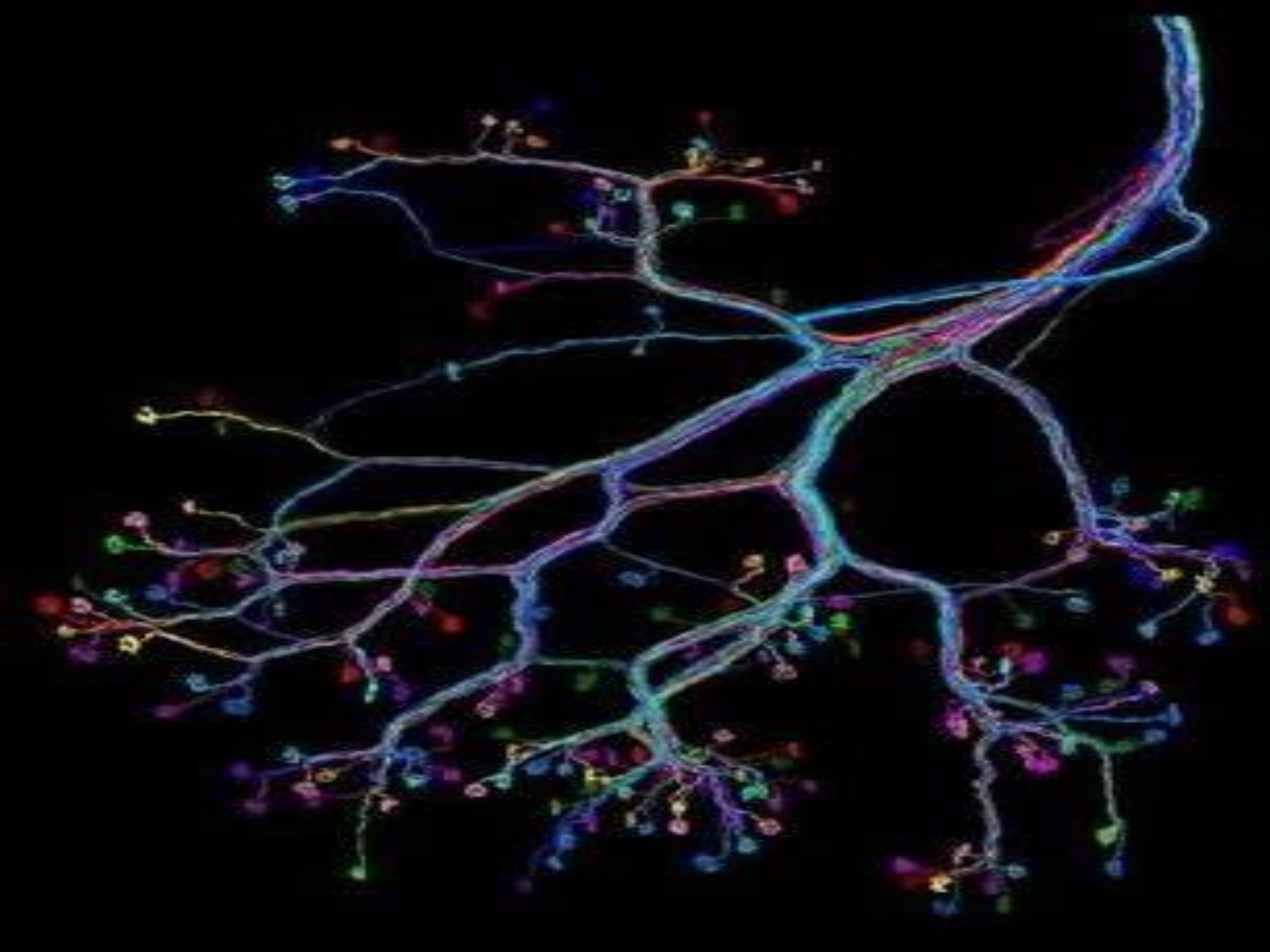
Friday 30 September - Saturday 1 October, 2022
Musholm, Denmark

MUSKELSVINDFONDEN

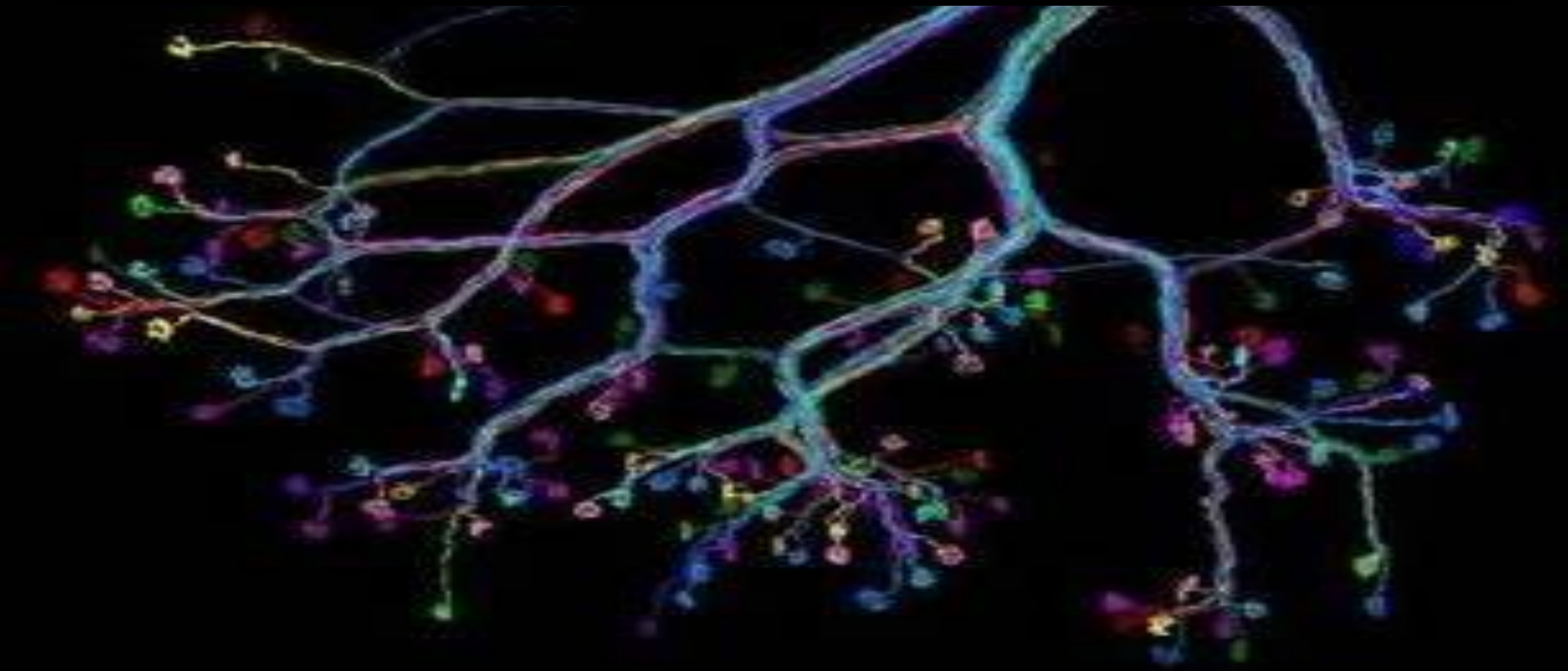
The National Rehabilitation Center for Neuromuscular Diseases

Neuromuscular junctions



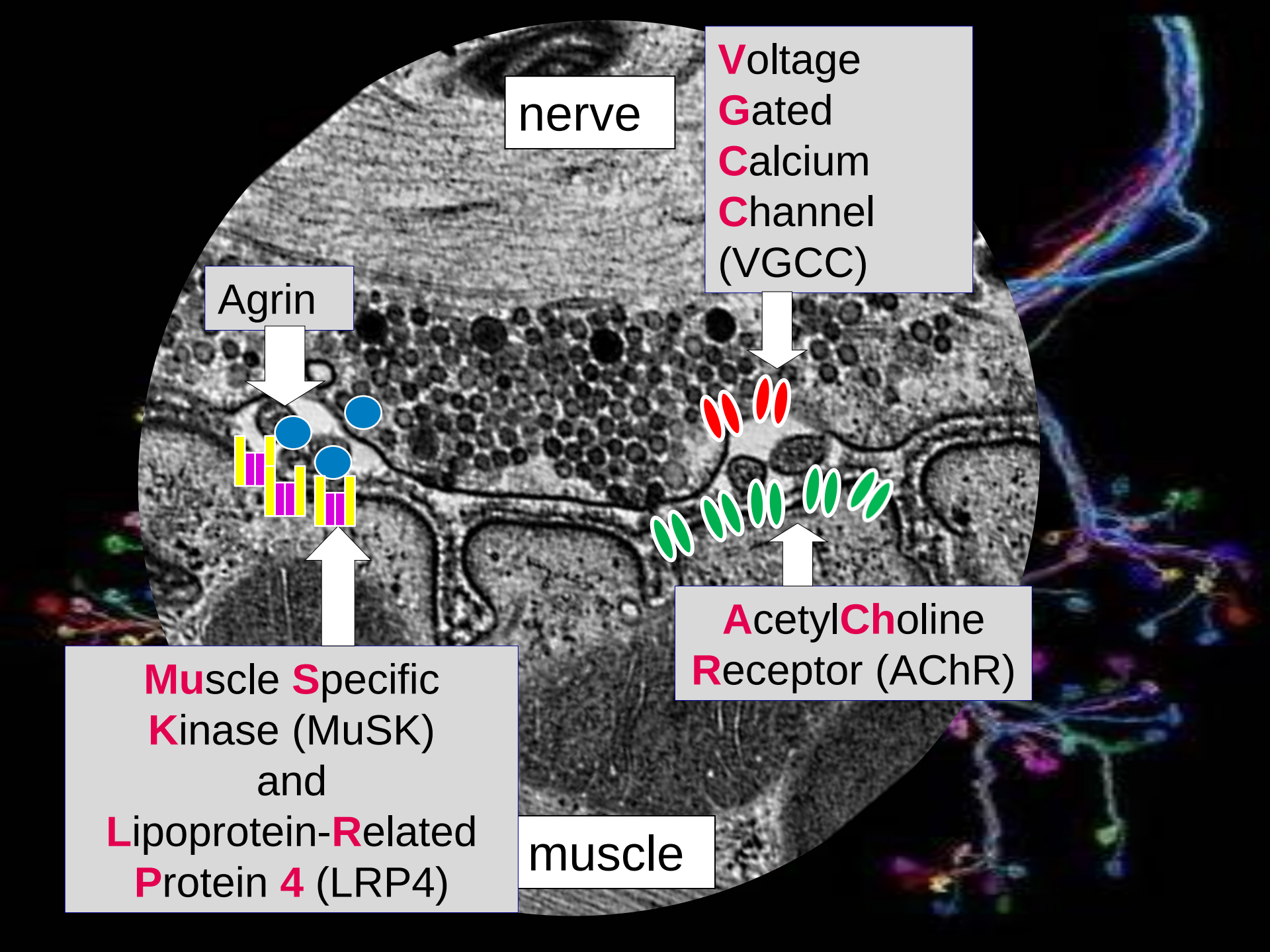


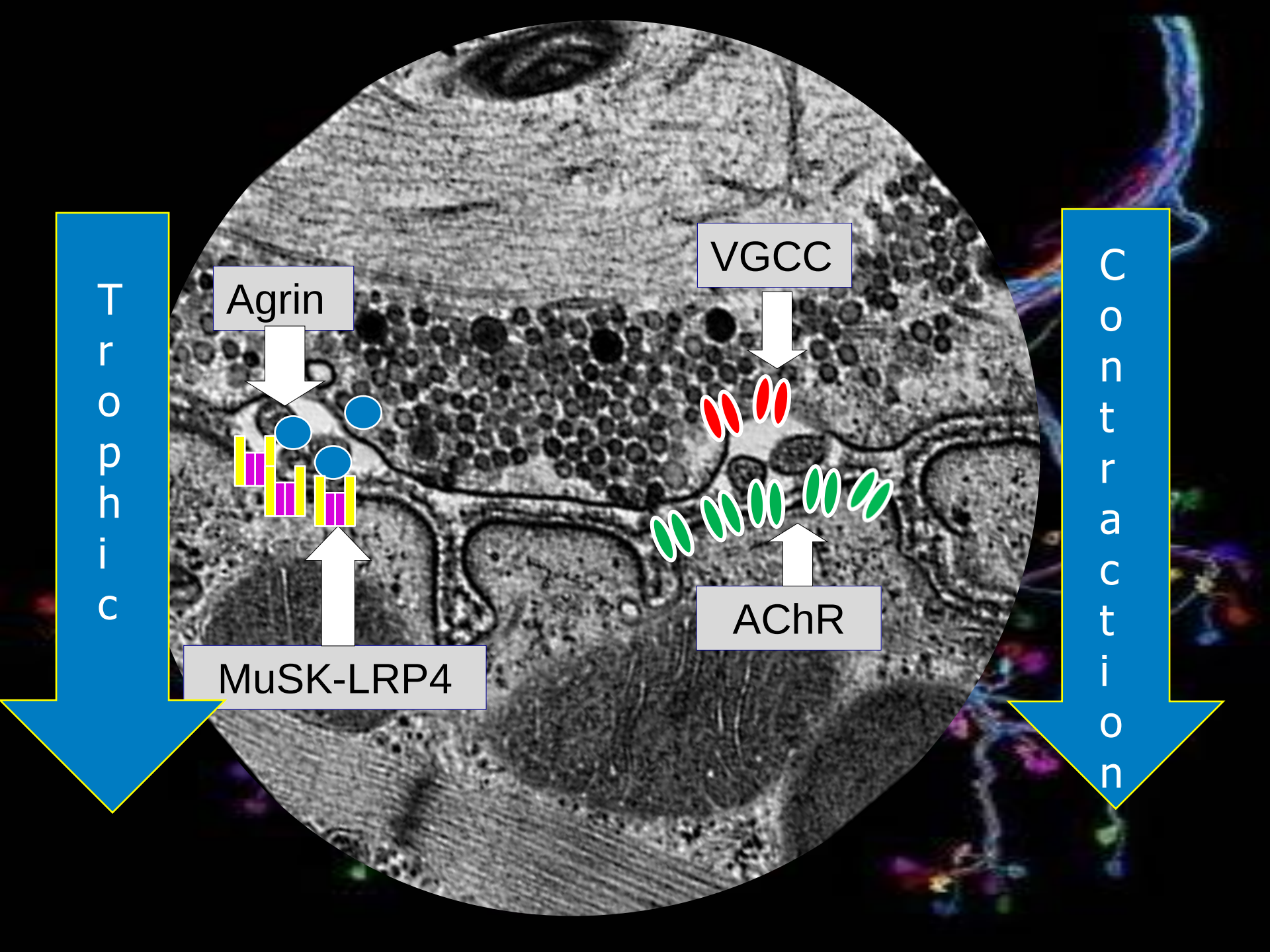
External eye muscle: 5.000 muscle fibers and 200 neurons (1:25)

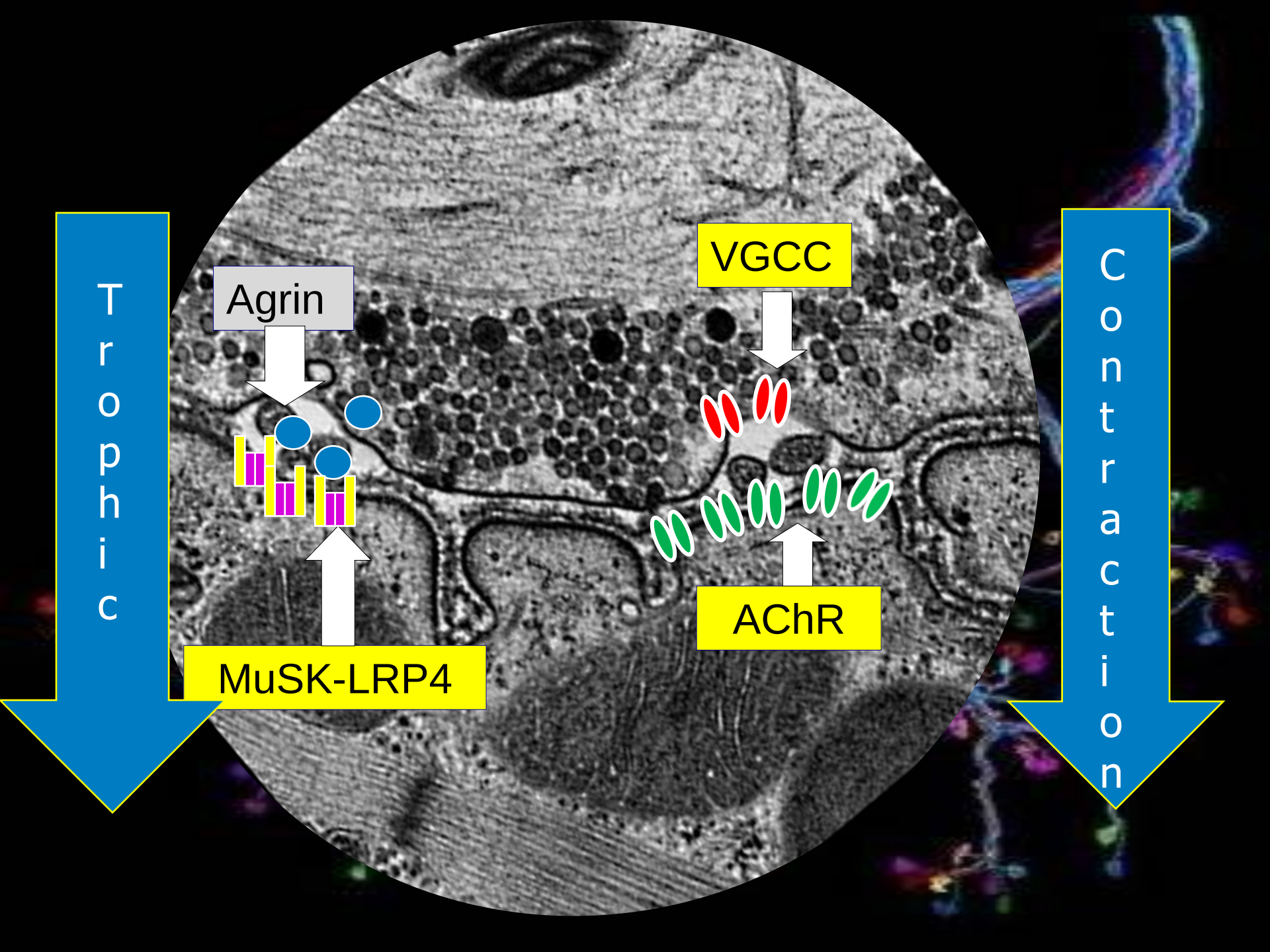


External eye muscle: 5.000 muscle fibers and 200 neurons (1:25)

Biceps: 580.000 muscle fibers and 775 neurons (1:750)

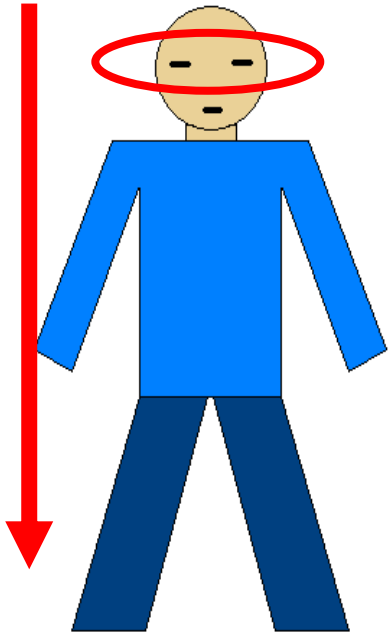

nerve
Voltage Gated Calcium Channel (VGCC)
Agrin
AcetylCholine Receptor (AChR)
Muscle Specific Kinase (MuSK) and Lipoprotein-Related Protein 4 (LRP4)
muscle


Trophic
Agrin
MuSK-LRP4
VGCC
AChR
Contraction


Trophic
Agrin
MuSK-LRP4
VGCC
AChR
Contraction

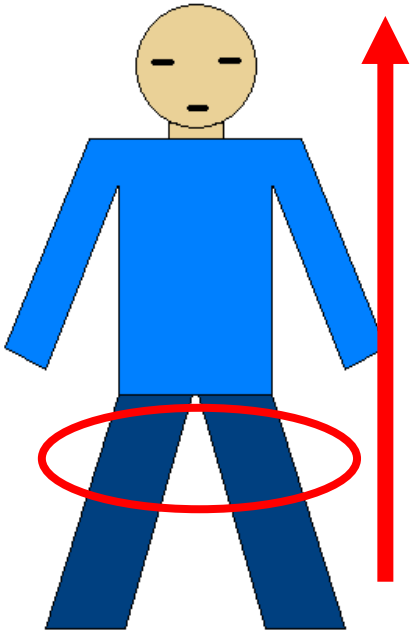
Clinical phenotype

MG (AChR)



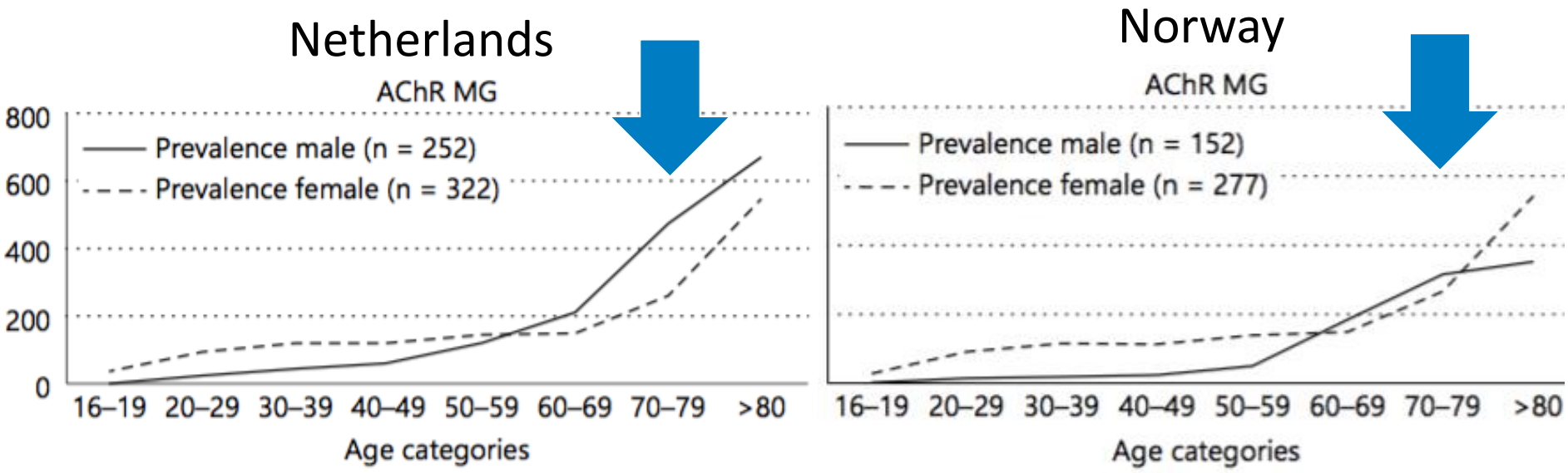
85 %

LEMS (VGCC)



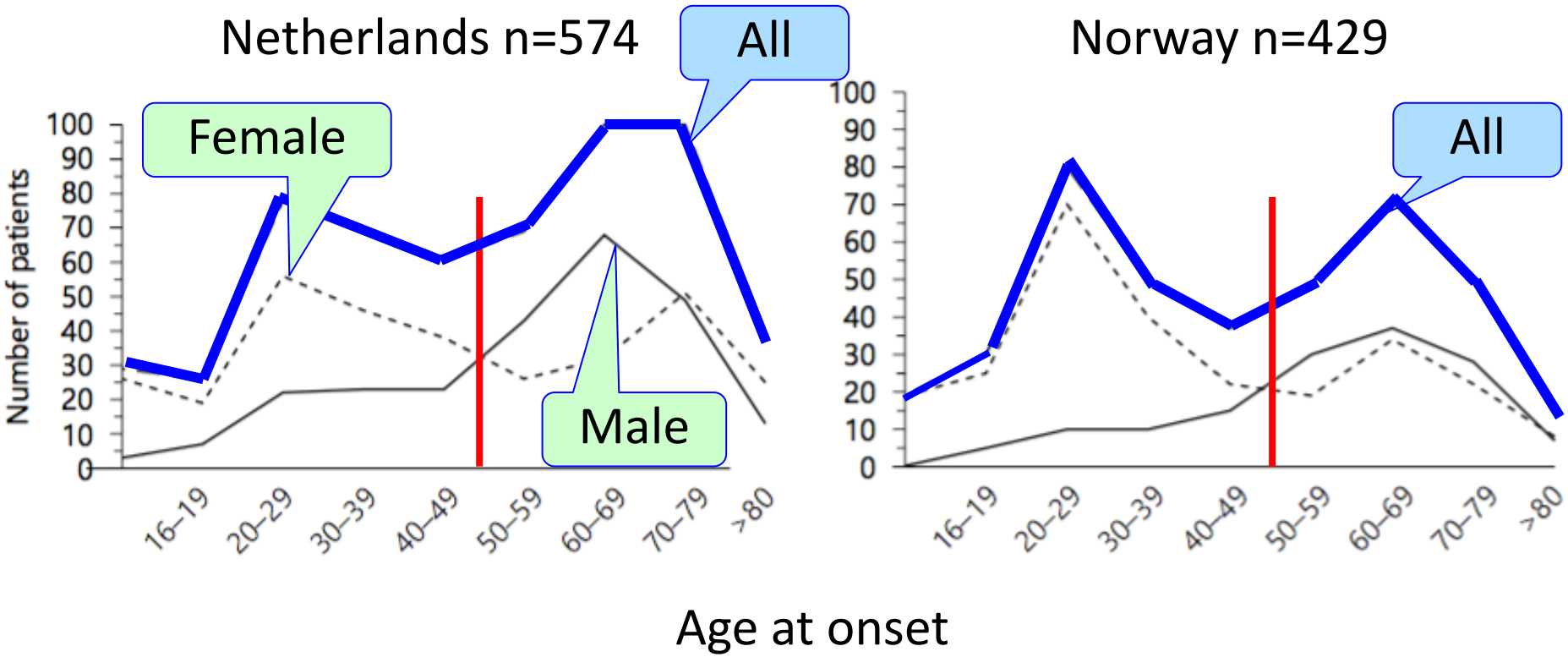
2 %

Prevalence of AChR Myasthenia gravis

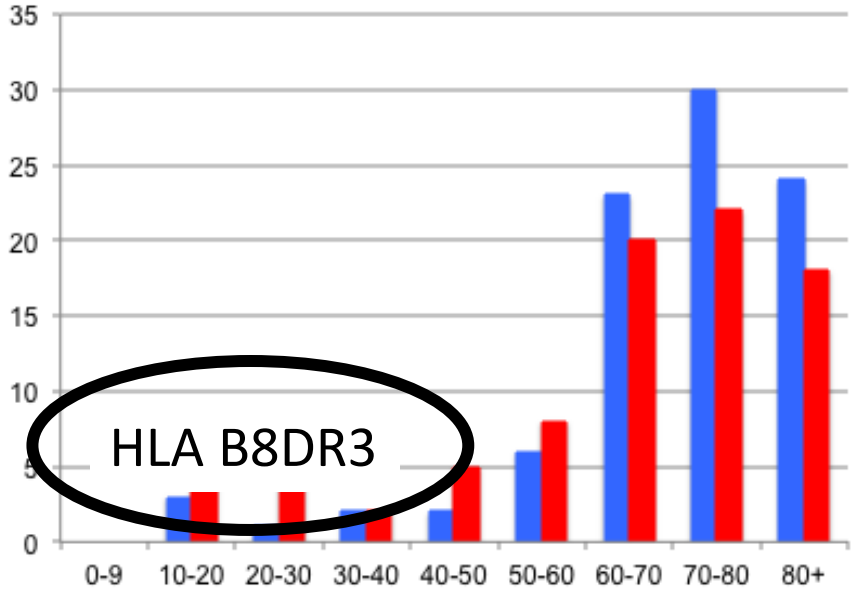


Age-specific prevalence per million inhabitants

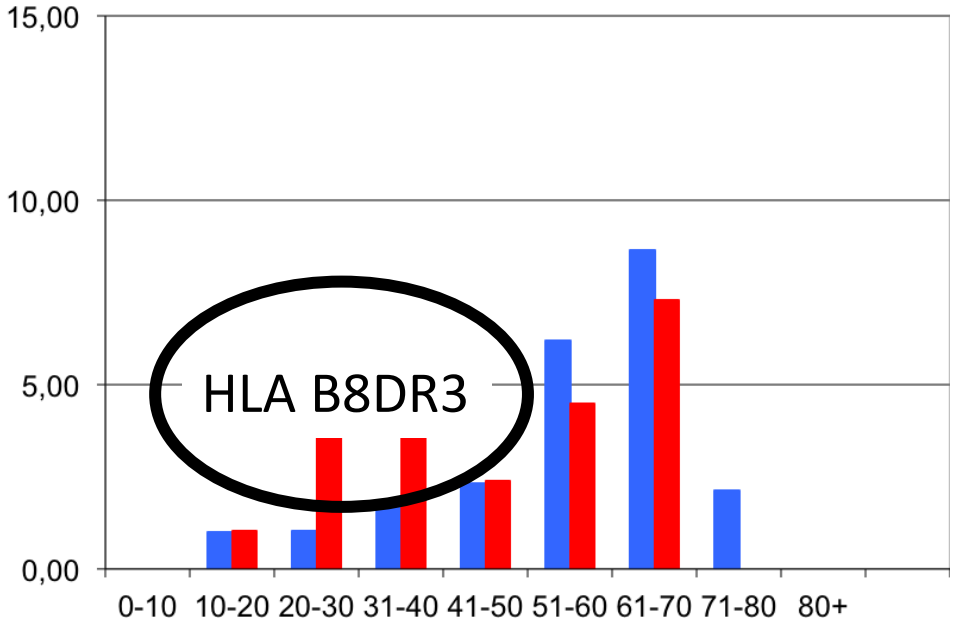
Age at onset in AChR MG



Incidence of non-tumour AChR-MG and LEMS: Young females and Old males



AChR MG



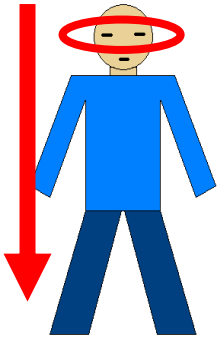
LEMS

male

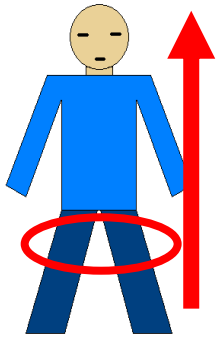
female

Different clinical phenotypes, similar immunogenetics

AChR MG

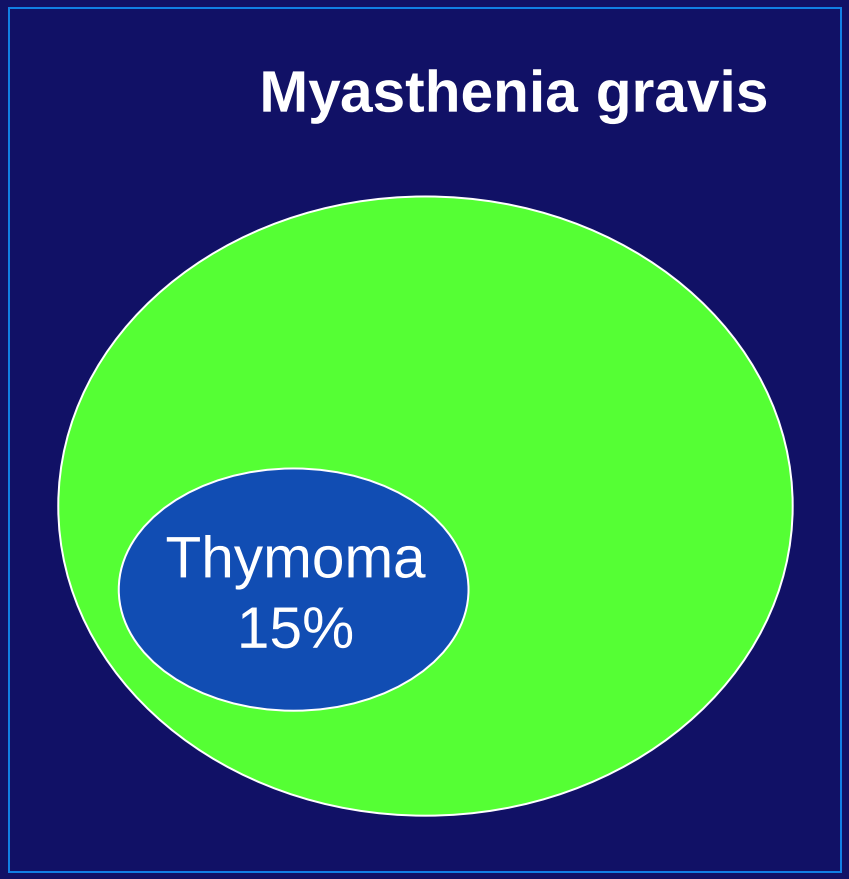


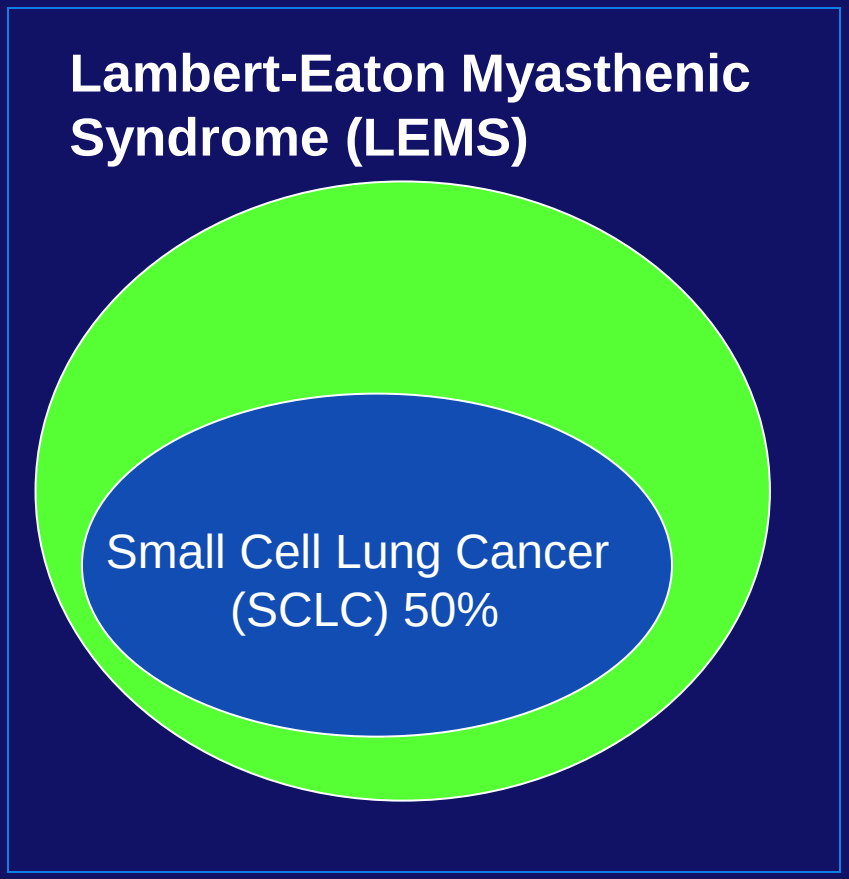
LEMS



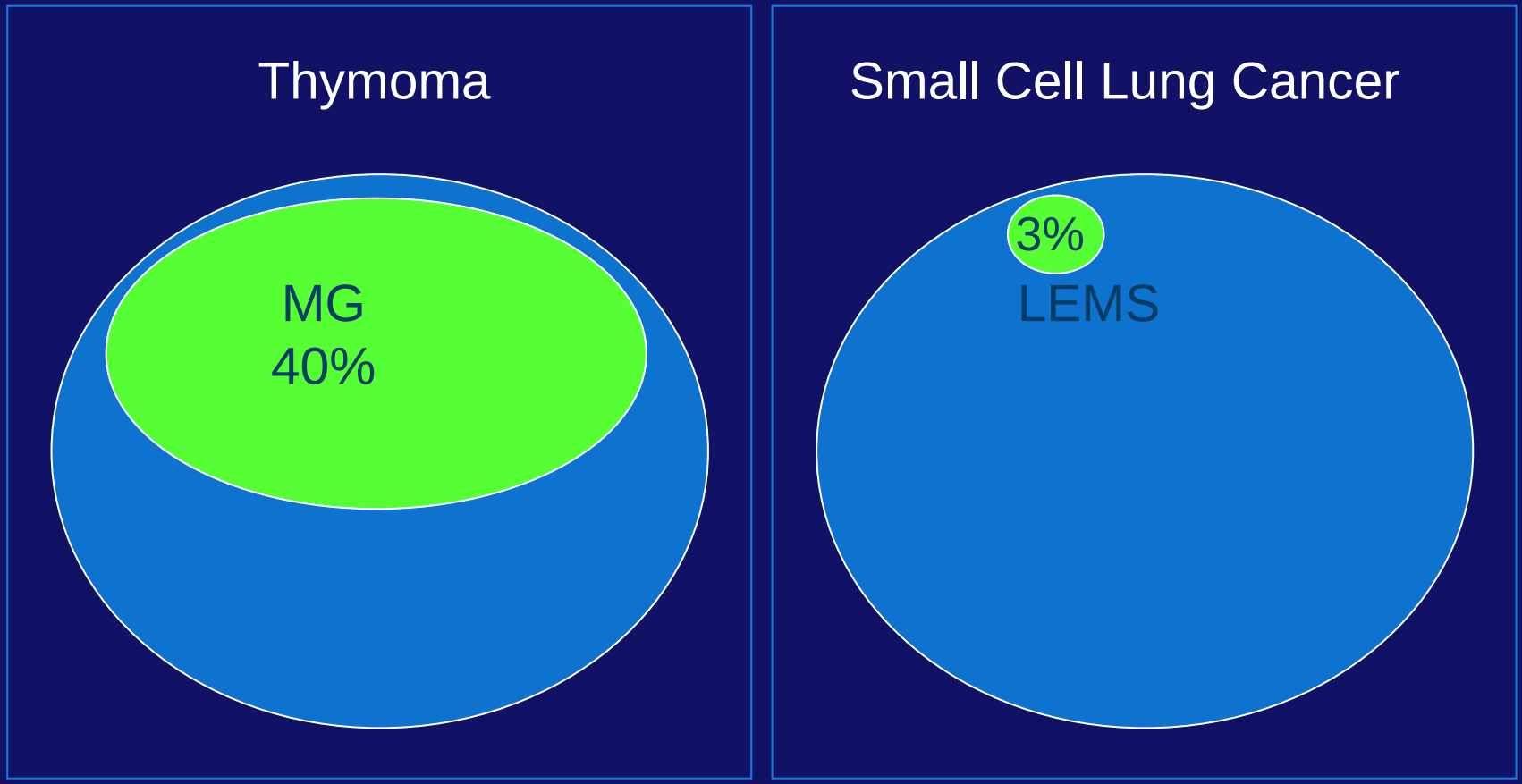
Incidence	Young female, Old male	Young female, Old male
HLA	B8-DR3	B8-DR3
Antibodies	IgG1	IgG1

Autoimmunity and tumour

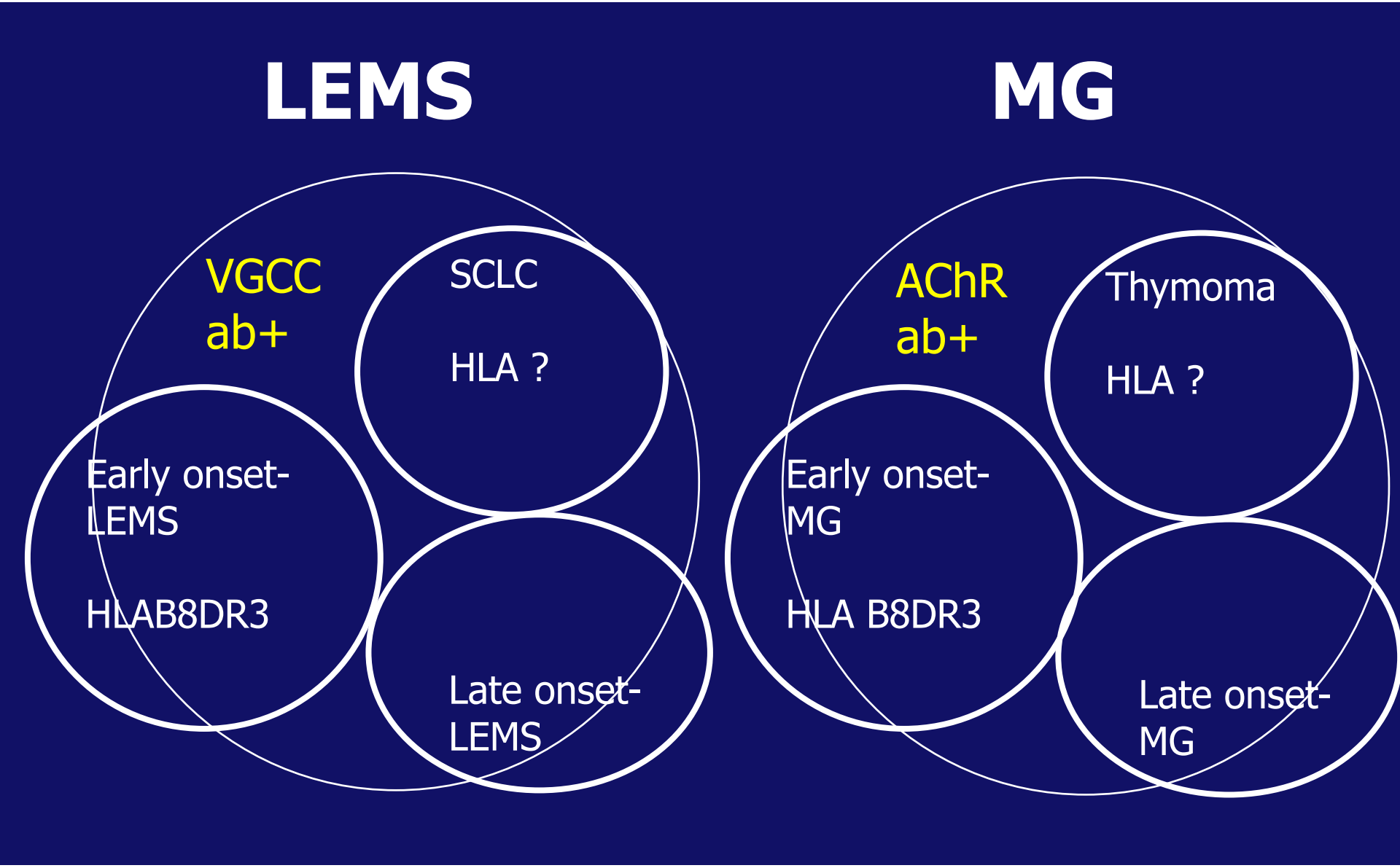




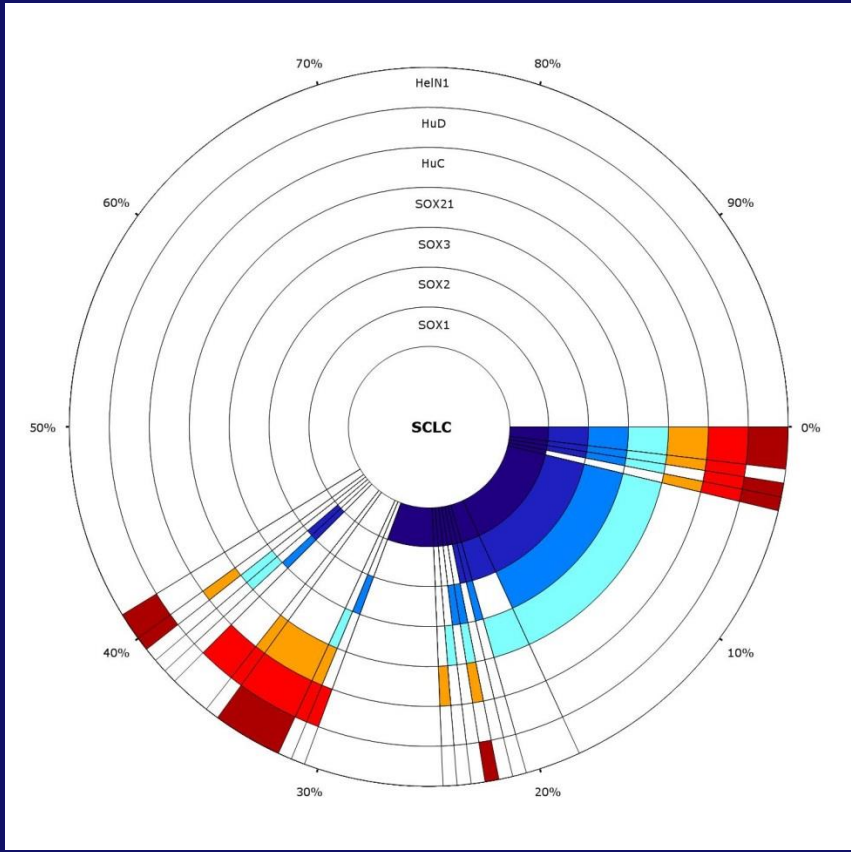
Autoimmunity and tumour



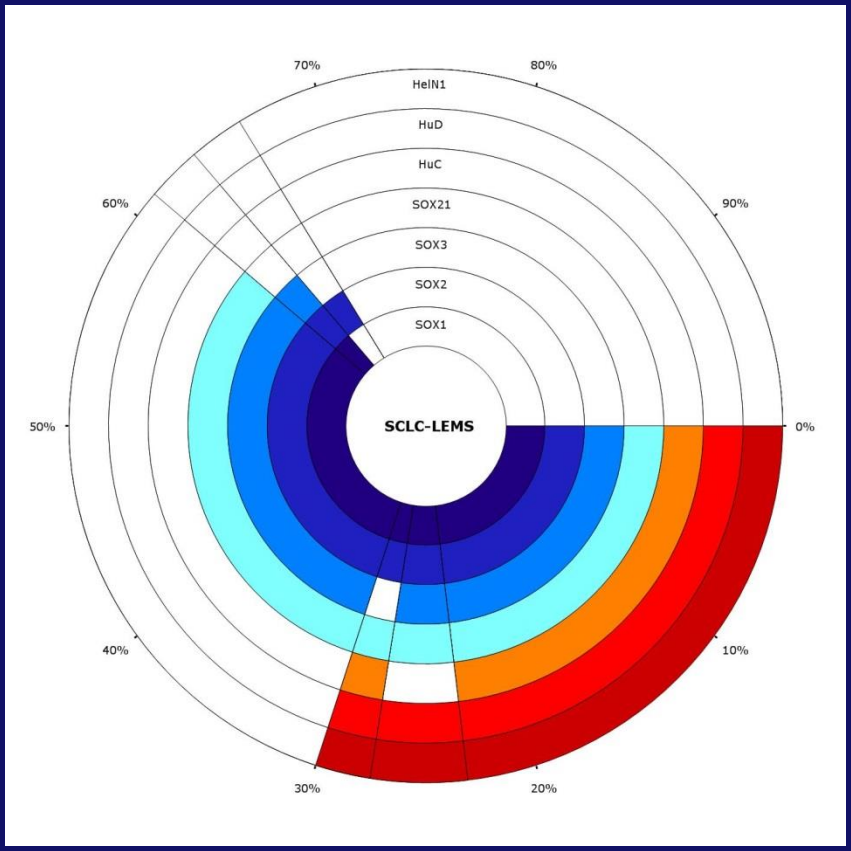
Subgroups in myasthenia



Sox and Hu antibodies: SCLC vs SCLC-LEMS



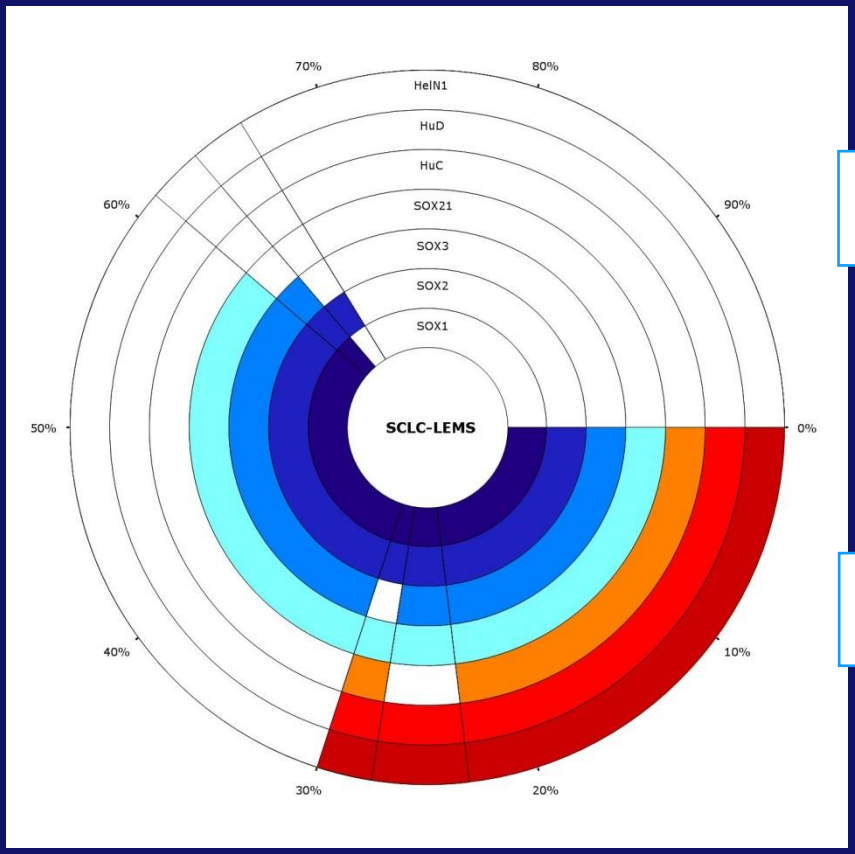
SCLC



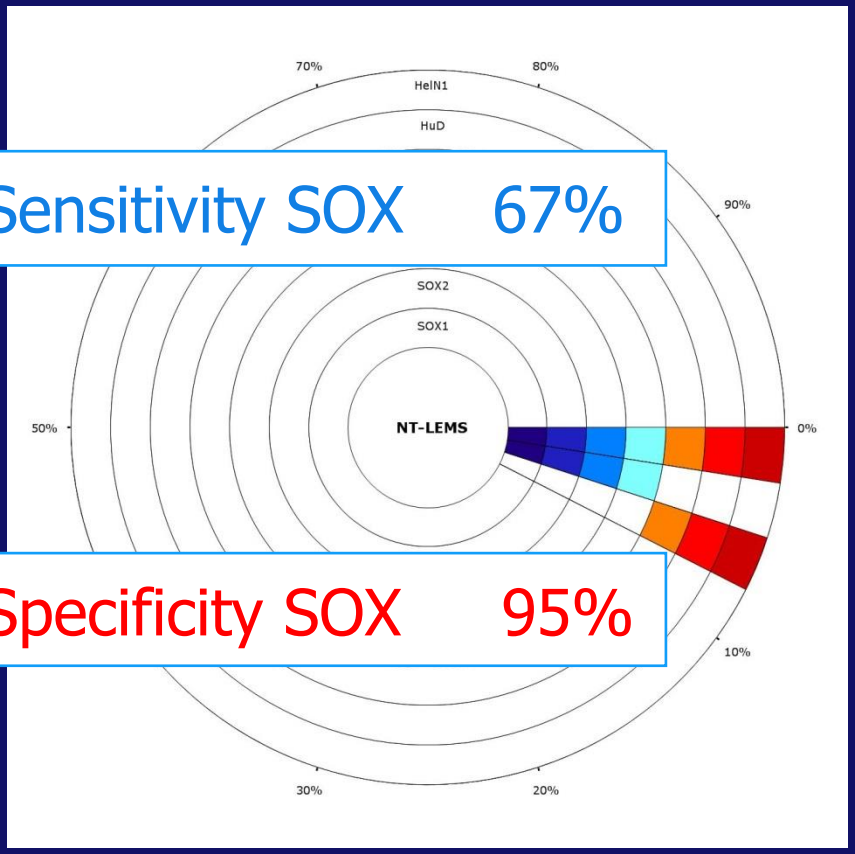
SCLC-LEMS

SOX and Hu Antibodies: SCLC-LEMS vs NT-LEMS

SCLC-LEMS n=43



Non tumour-LEMS n=43



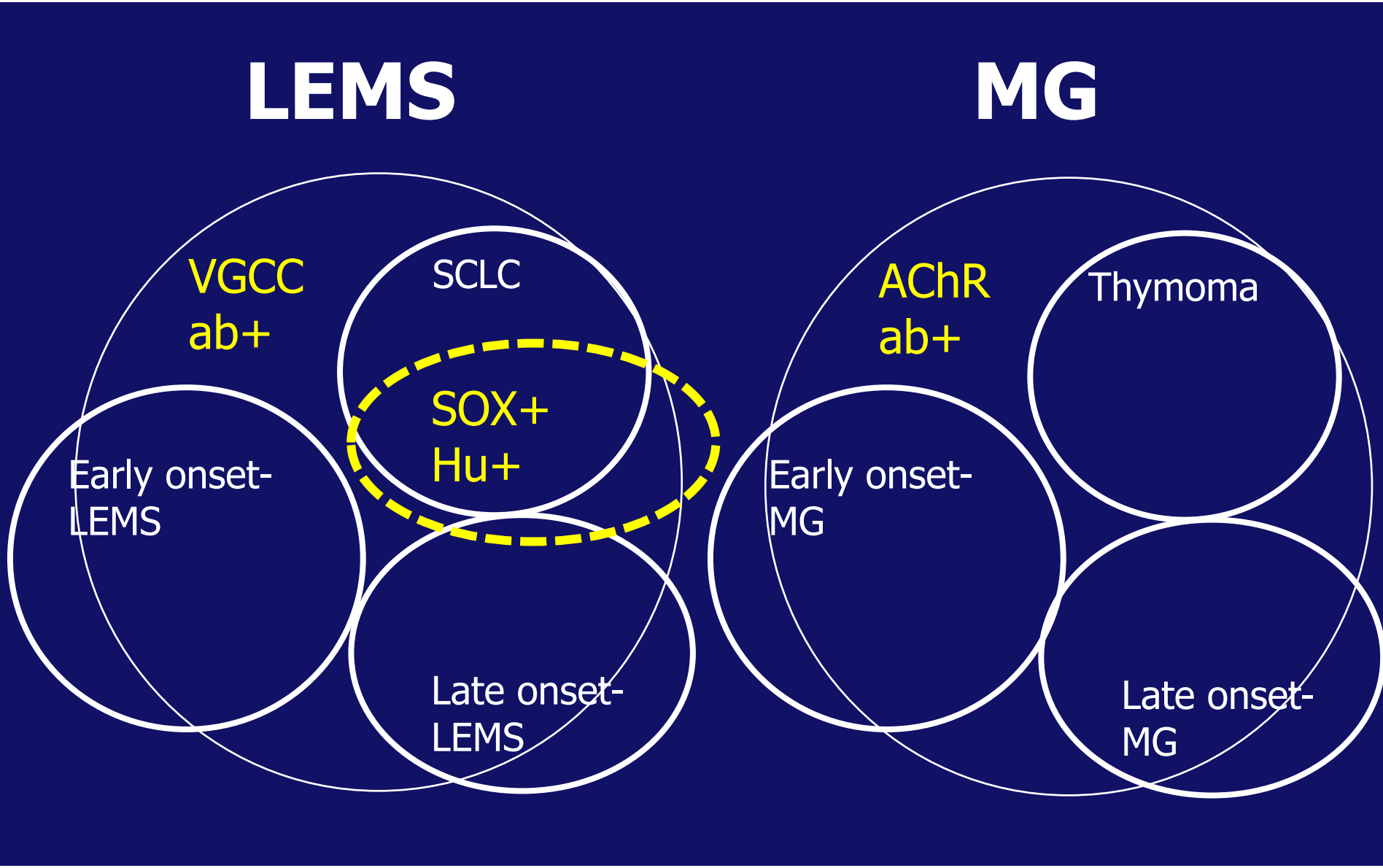
Sensitivity SOX 67%

Specificity SOX 95%

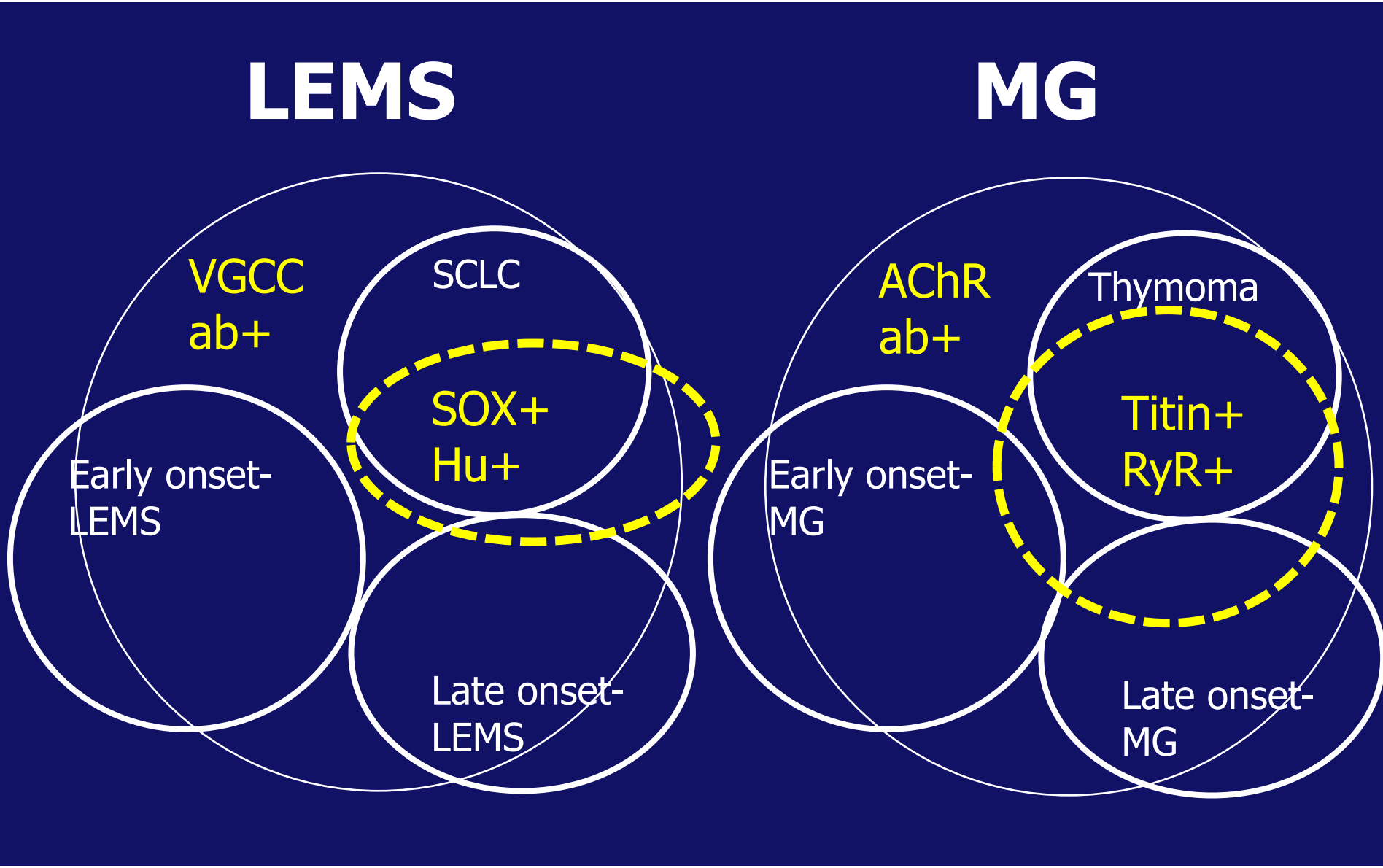
$p < 0.0001$

Titulaer et al, J Clin Oncol 2009

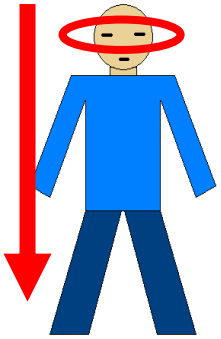
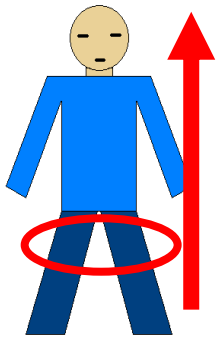
Additional (non-pathogenic) antibodies



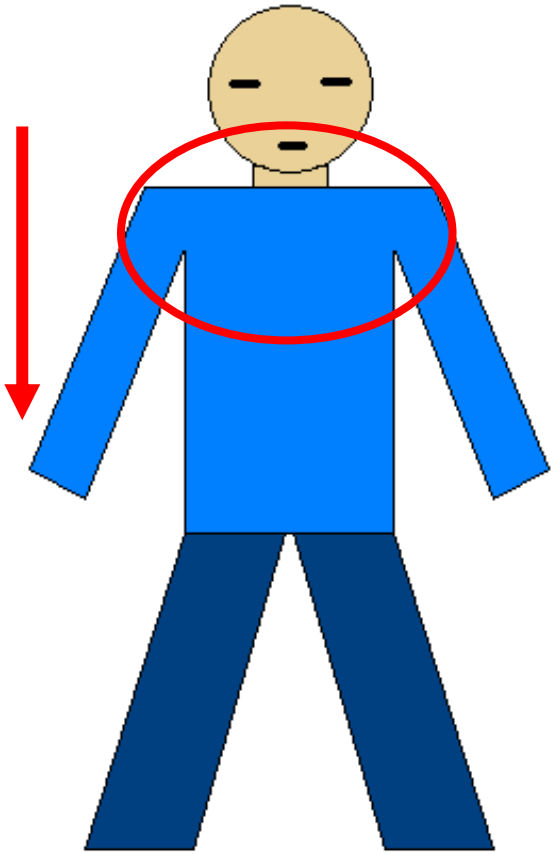
"Antibody profiling" in myasthenia



AChR MG versus LEMS

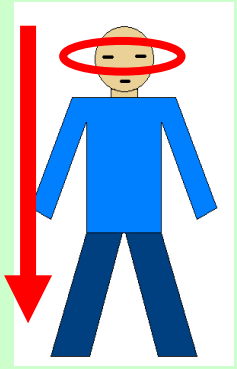
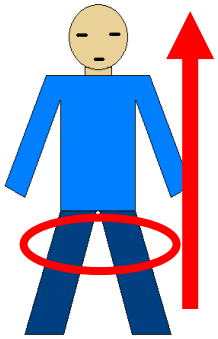
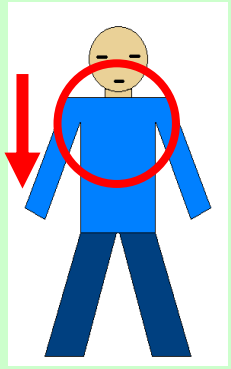
	AChR MG	LEMS
		
Tumour	Thymoma	SCLC
Incidence	Young female, Old male	Young female, Old male
HLA	B8-DR3	B8-DR3
Antibodies	IgG1	IgG1

Myasthenia gravis with MuSK antibodies

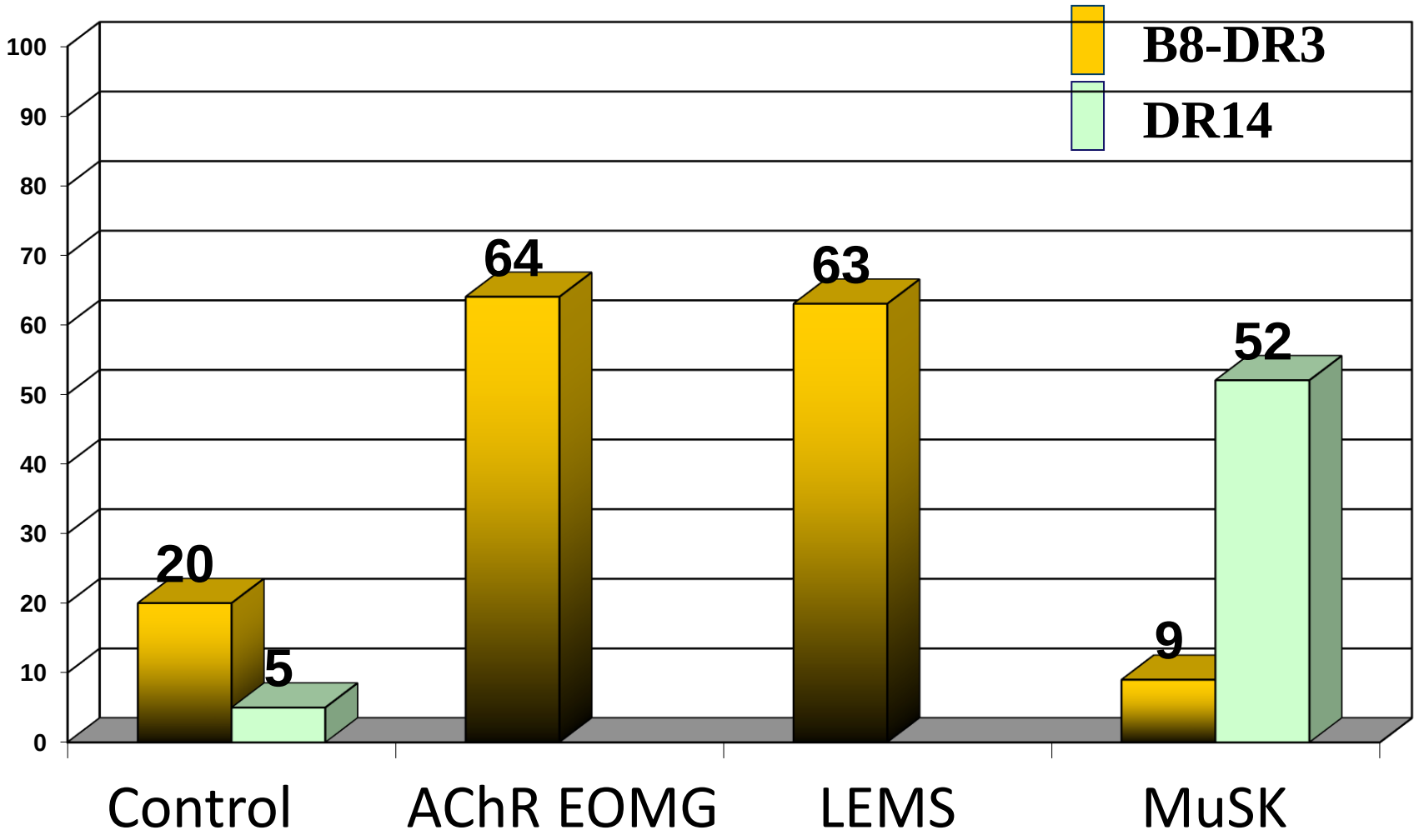


Evoli, Brain 2003

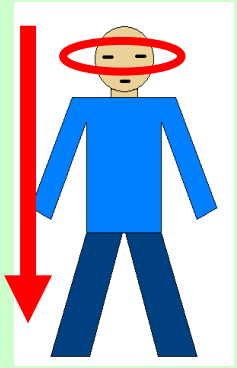
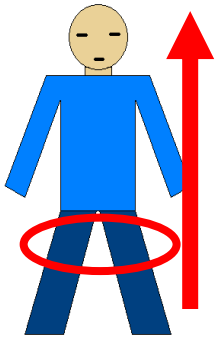
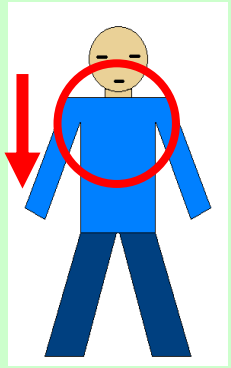
Myasthenia phenotypes

AChR MG	LEMS	MuSK MG
		
Thymoma	SCLC	No tumour
Young female Old male	Young female Old male	Young female
B8-DR3	B8-DR3	DR14-DQ5
IgG1	IgG1	

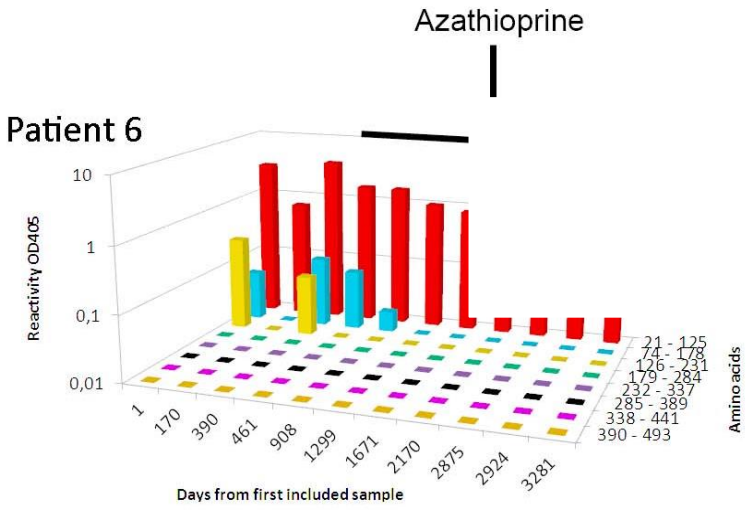
HLA in MuSK myasthenia gravis is different

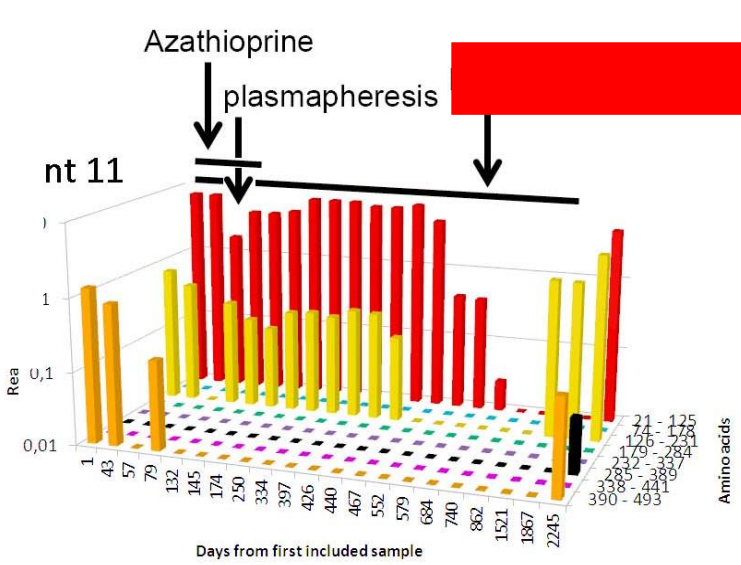


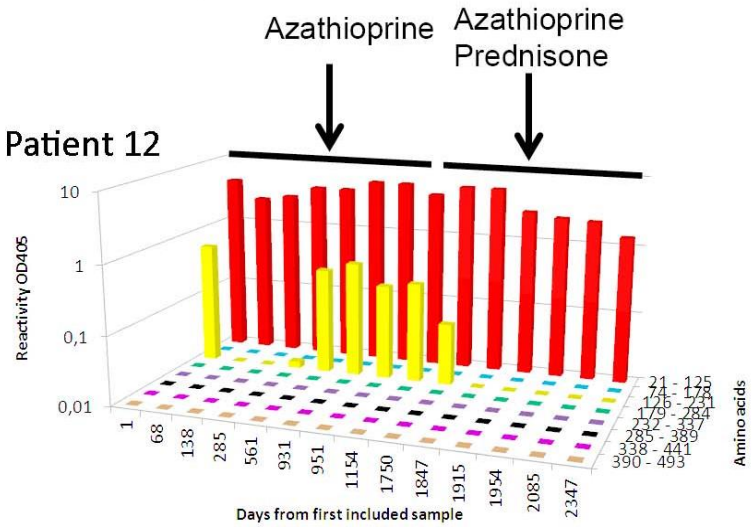
Myasthenia phenotypes

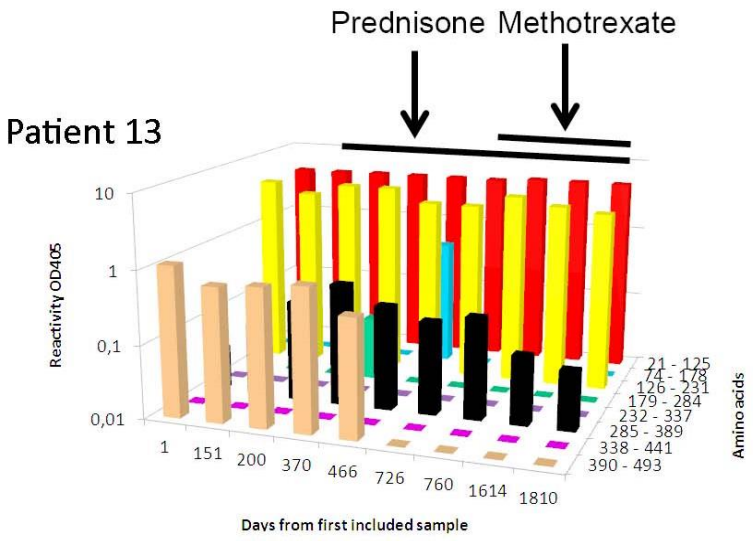
AChR MG	LEMS	MuSK MG
		
Thymoma	SCLC	No tumour
Young female Old male	Young female Old male	Young female
B8-DR3	B8-DR3	DR14-DQ5
IgG1	IgG1	IgG4

Dominant epitope in MuSK MG

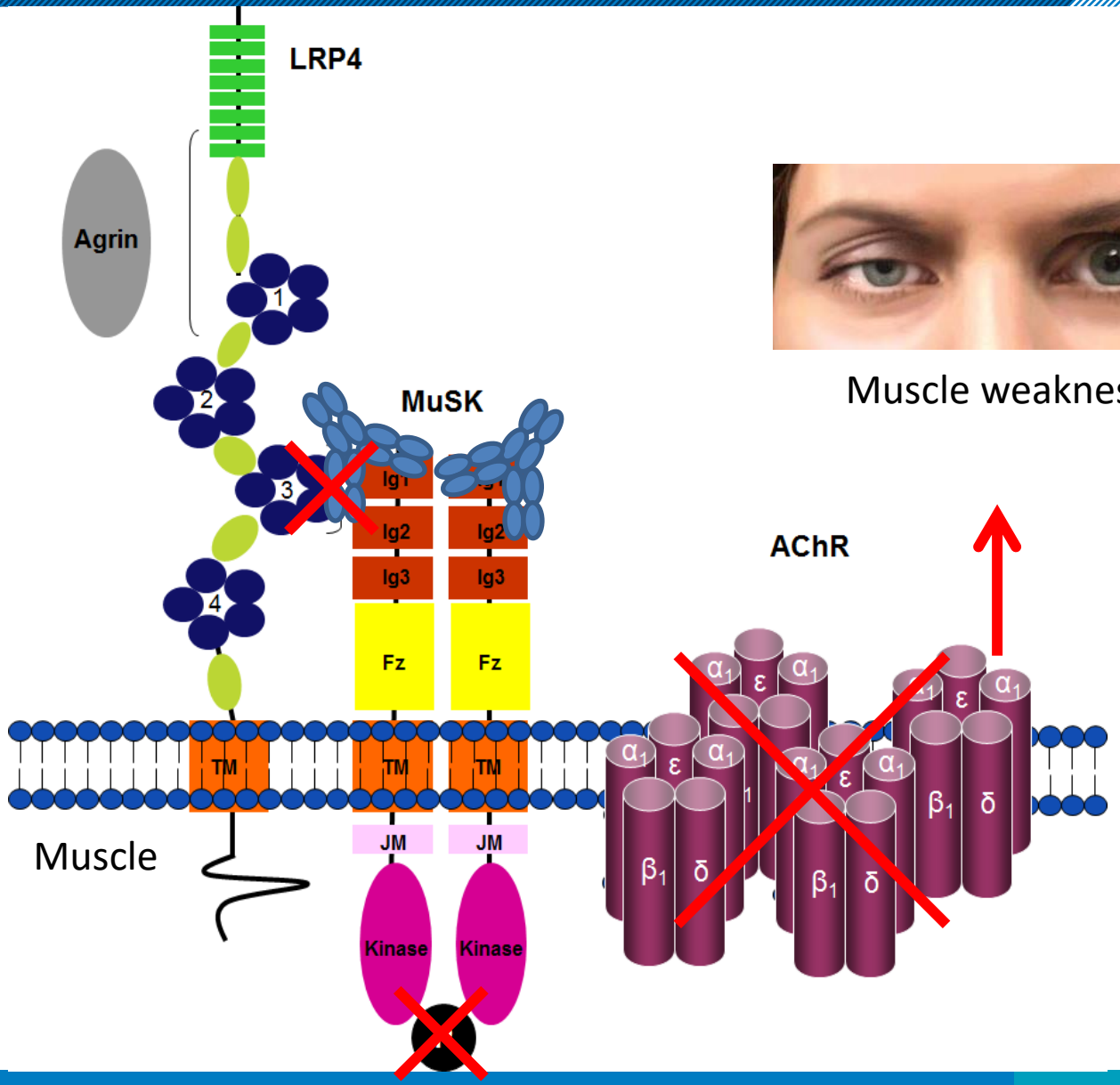








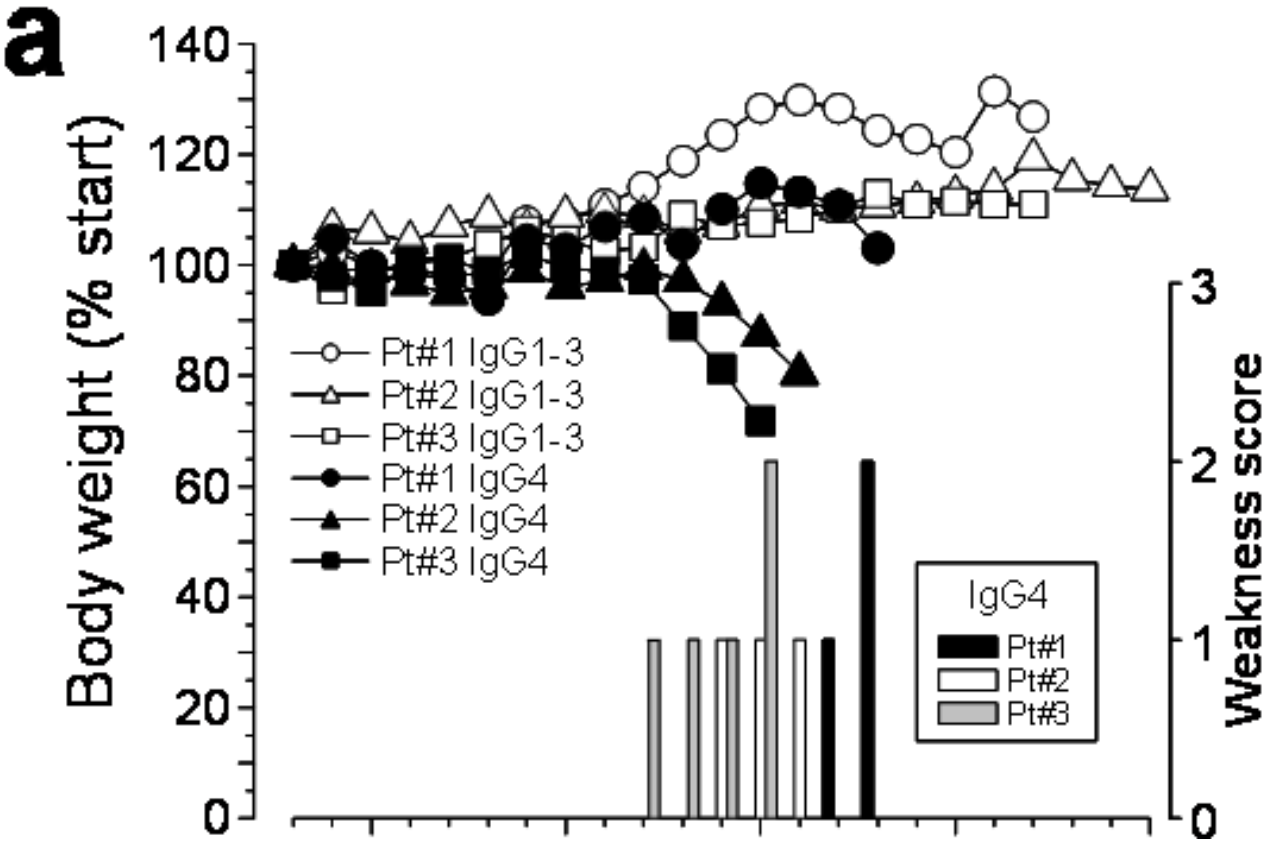
Pathophysiology of MuSK MG



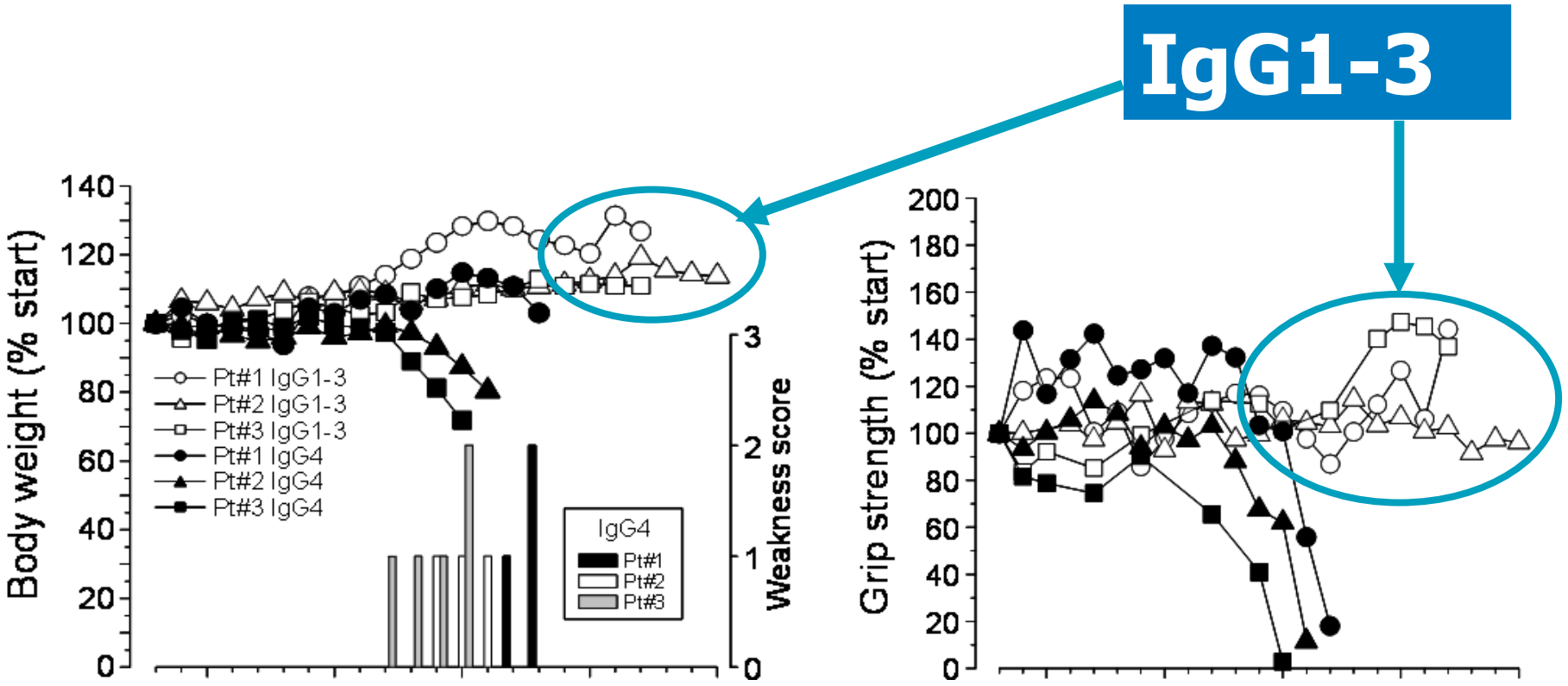
Muscle weakness

Passive transfer of human MuSK IgG4 or IgG1-3

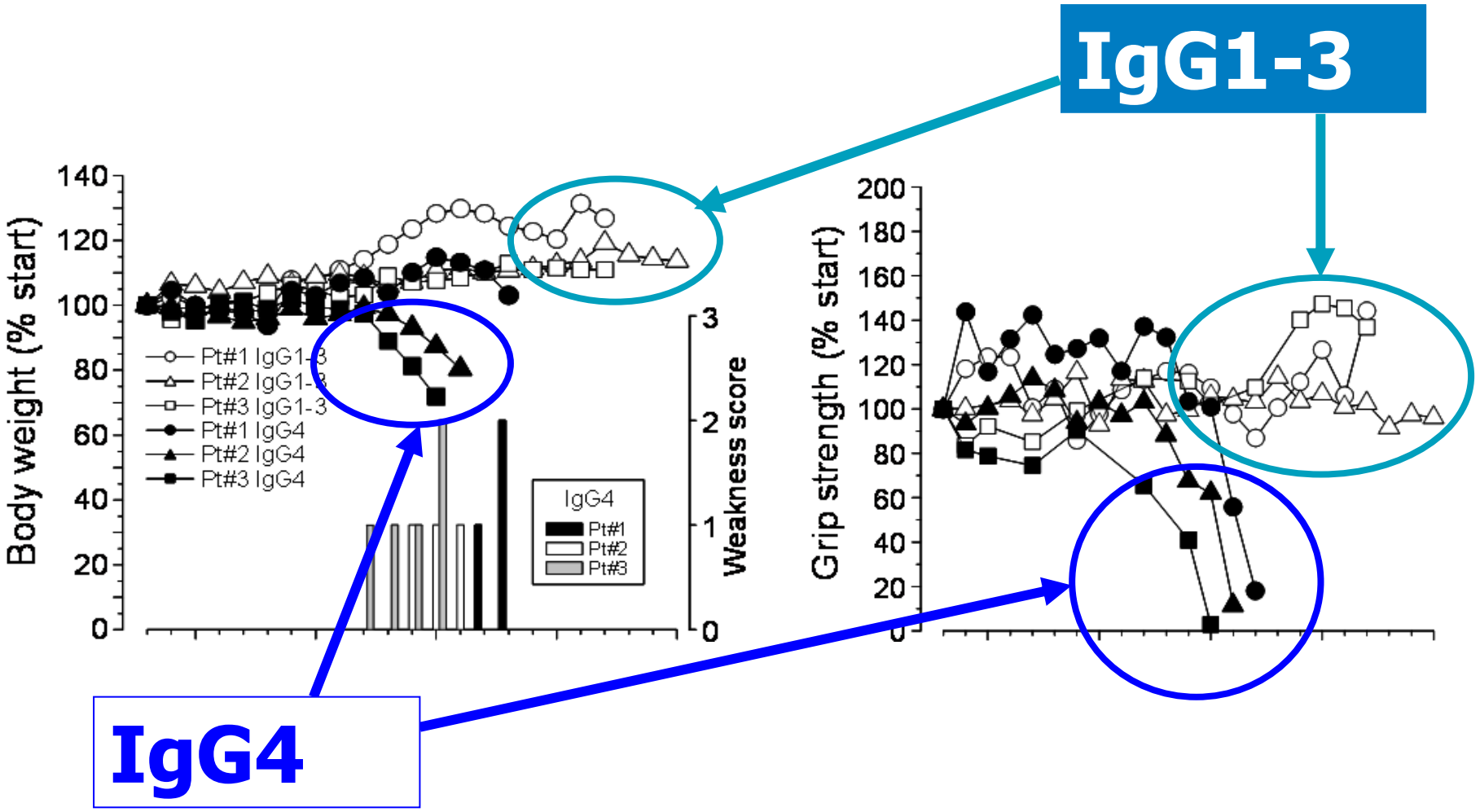
Progressive weightloss in MuSK-IgG4 treated NOD-SCID mice



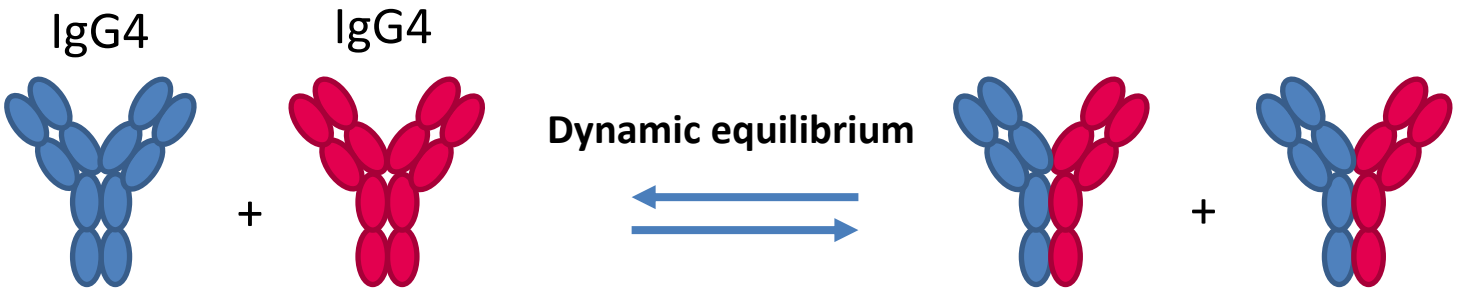
Progressive loss of weight and strength in MuSK-IgG4 treated NOD-SCID mice



Progressive loss of weight and strength in MuSK-IgG4 treated NOD-SCID mice



IgG4 antibodies can undergo Fab-arm exchange



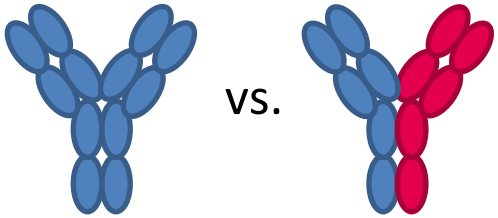
- Monospecific
- Bivalent antigen binding

- Bispecific
- Monovalent antigen binding

Half-molecules dissociate and re-associate with half-molecules of other IgG4

Research question

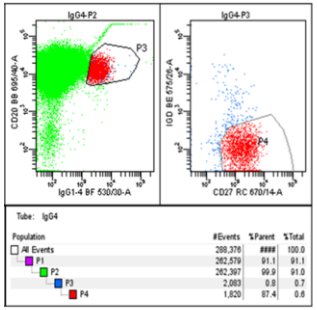
Does functional monovalency of IgG4 MuSK antibodies contribute to the pathophysiology of MuSK MG?



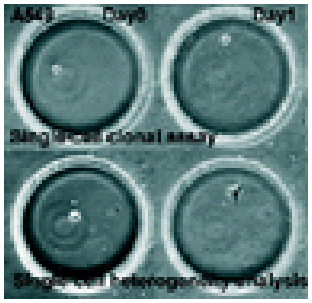
Isolation of monoclonal MuSK antibodies from patients

Patient PBMC

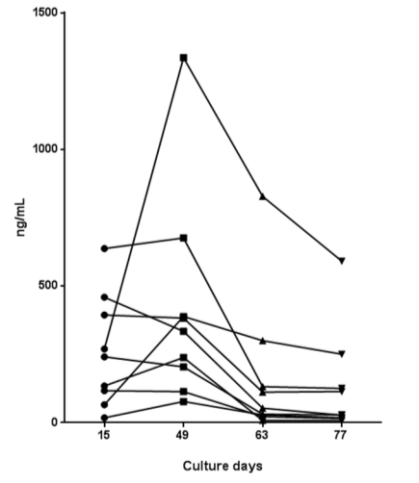
MuSK-specific FACS sort



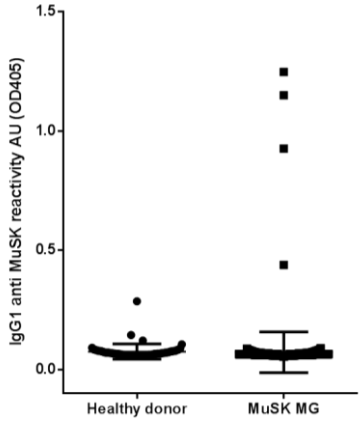
Single cell culture



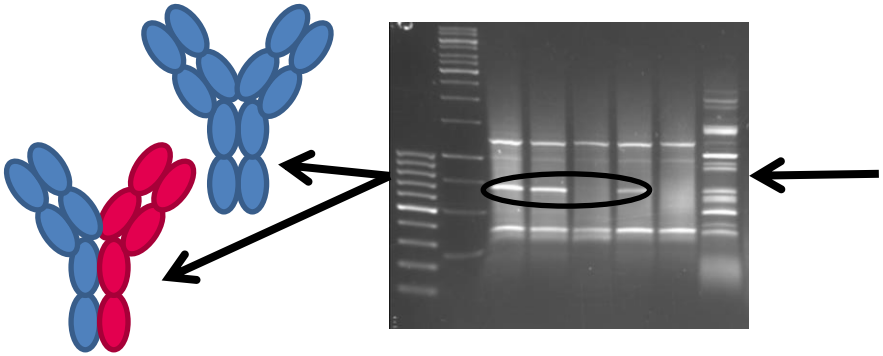
IgG production/ELISA



MuSK clone identification



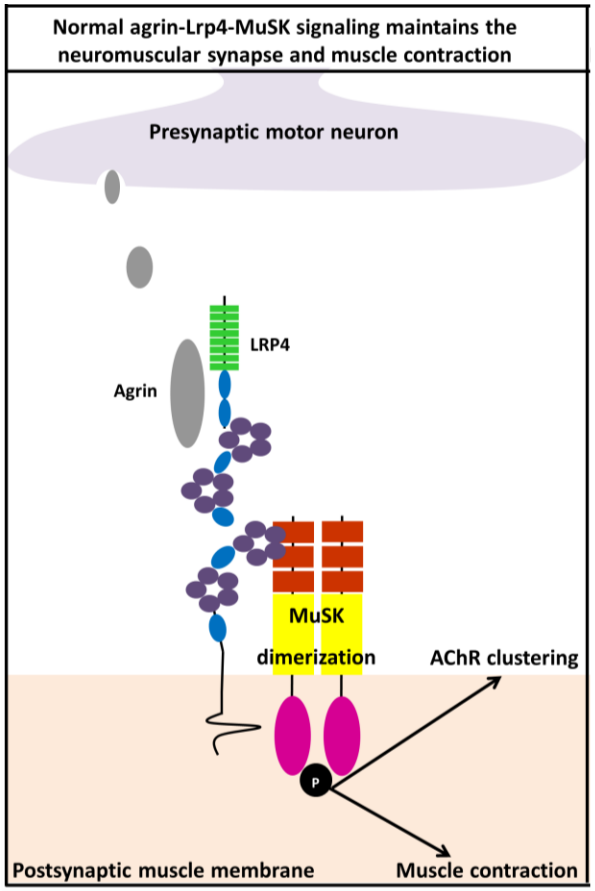
Sequence isolation



The LUMC B cell platform: IHB, Hematology, Reumatology, Neurology, Humane Genetics, LGTC

Huijbers et al, Neurol Neuroimmunol Neuroinflamm, 2019

Fab-arm exchange dependent myasthenia gravis, A new disease mechanism in autoimmune disease



Huijbers et al, Neurol Neuroimmunol Neuroinflamm, 2019

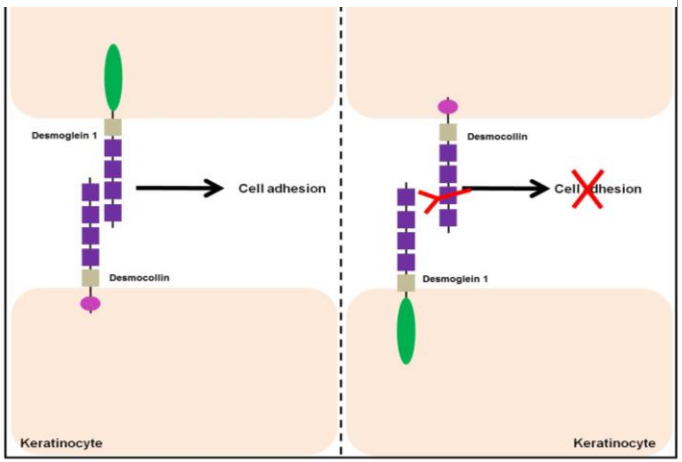
The expanding field of IgG4 autoimmunities

Peripheral Nervous System		HLA	Discover/IgG4 date
MuSK	Myasthenia Gravis	DR14/DQ5	2001-2012
Neurofascin155	CIDP & Guillain Barré syndrome		2011
Contactin-1	CIDP & Guillain Barré syndrome		2013
CASPR1	CIDP		2013
Central Nervous System			
IgLON5	Non-REM and REM parasomnia with sleep breathing dysfunction and a tauopathy	DQ5	2014
LGI1	Limbic Encephalitis		2010-2011
CASPR2	Limbic Encephalitis, neuromyotonia and Morvan syndrome		2010-2015
Non neurological diseases			
Desmoglein1	Pemphigus	DR14/DQ5	1965-1999
Desmoglein3	Pemphigus	DR14/DQ5	1965-1999
PLA2R1	Membranous nephropathy		2014
Collagen IV	Good pasture disease		2014
ADAMTS13	Thrombotic thrombocytopenic purpura		1998-2009
THSDA7A	Membranous nephropathy		2014

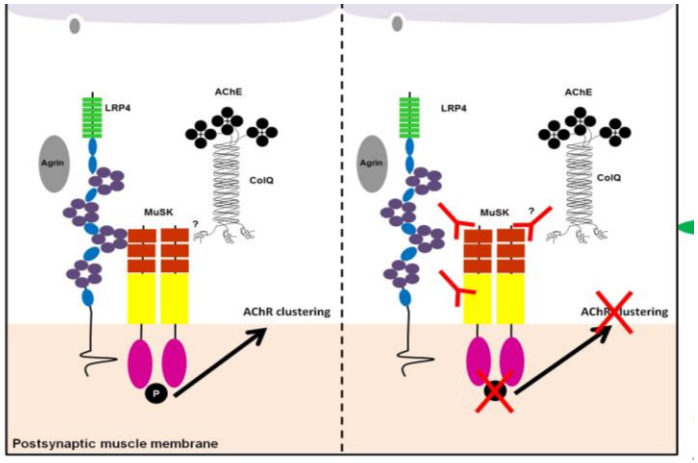
Huijbers et al. Eur J Neurol, 2015

The expanding field of IgG4 autoimmunities

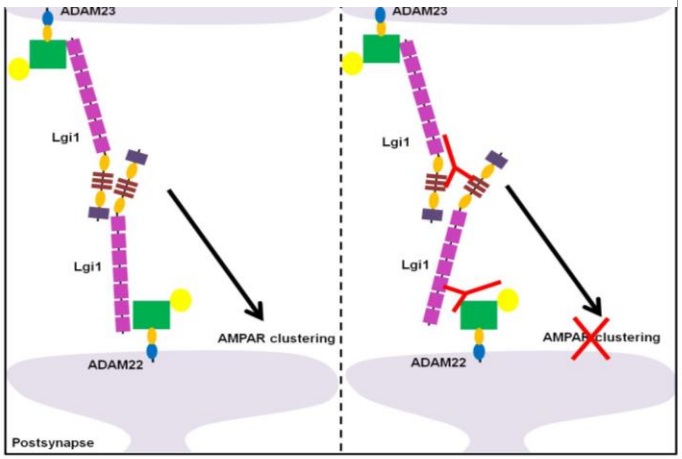
Pemphigus



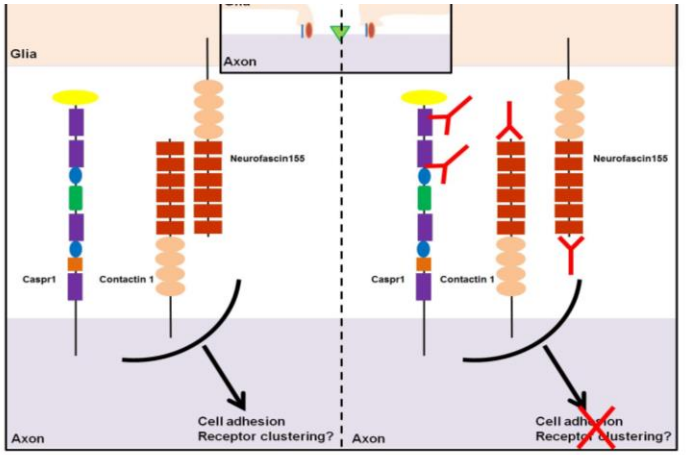
MuSK Myasthenia gravis



Lgi1 Limbic Encephalitis



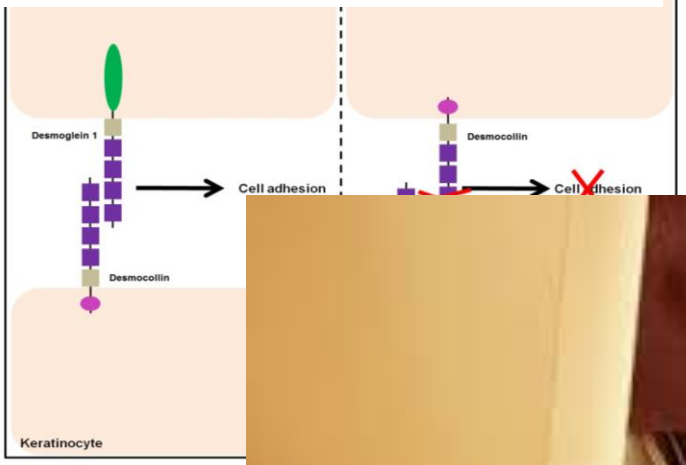
CIDP



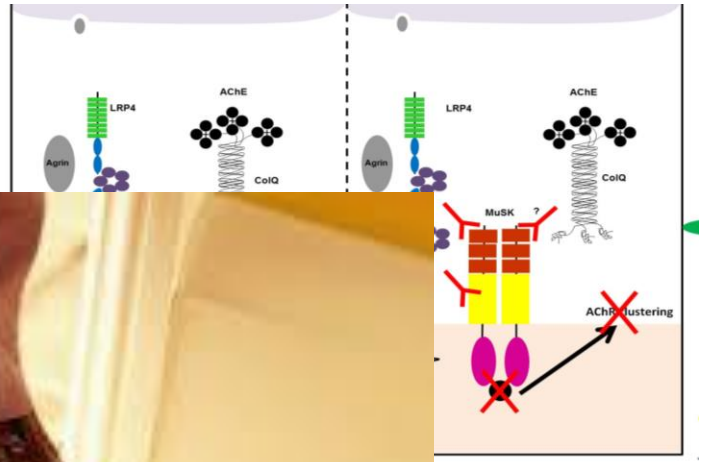
Huijbers et al. Eur J Neurol, 2015

The expanding field of IgG4 autoimmunities

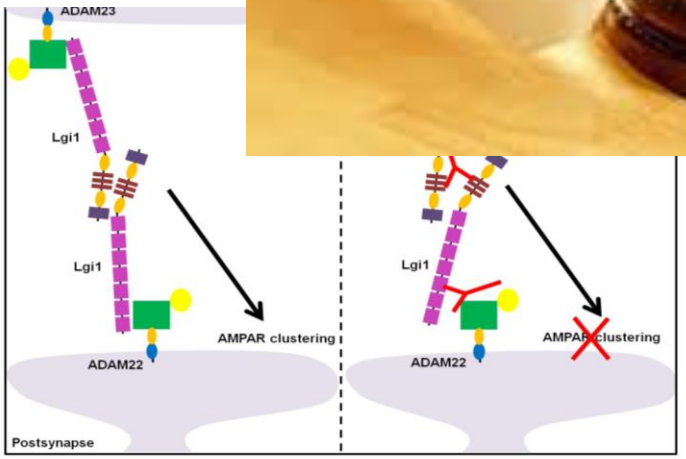
Pemphigus

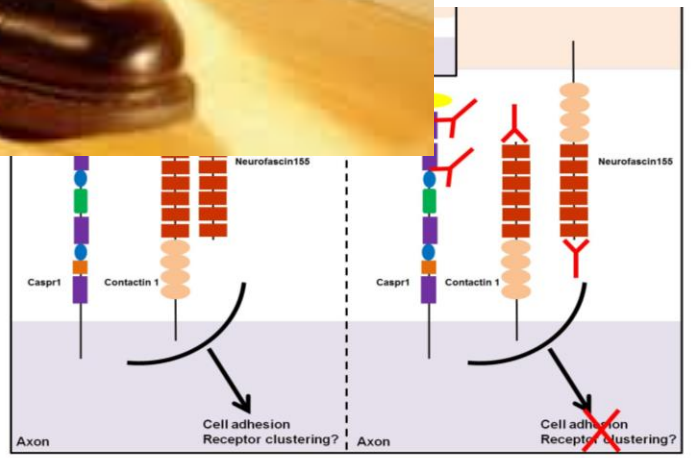


MuSK Myasthenia gravis



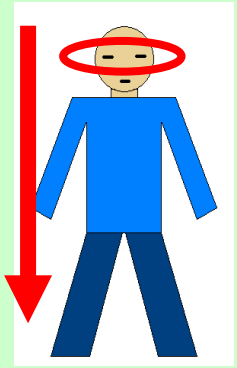
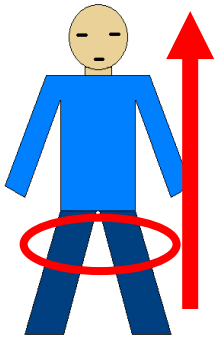
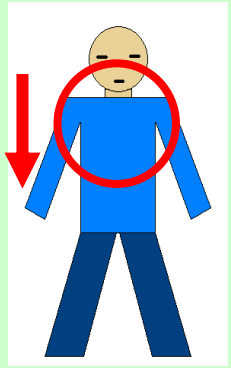
Lgi1 Limbic





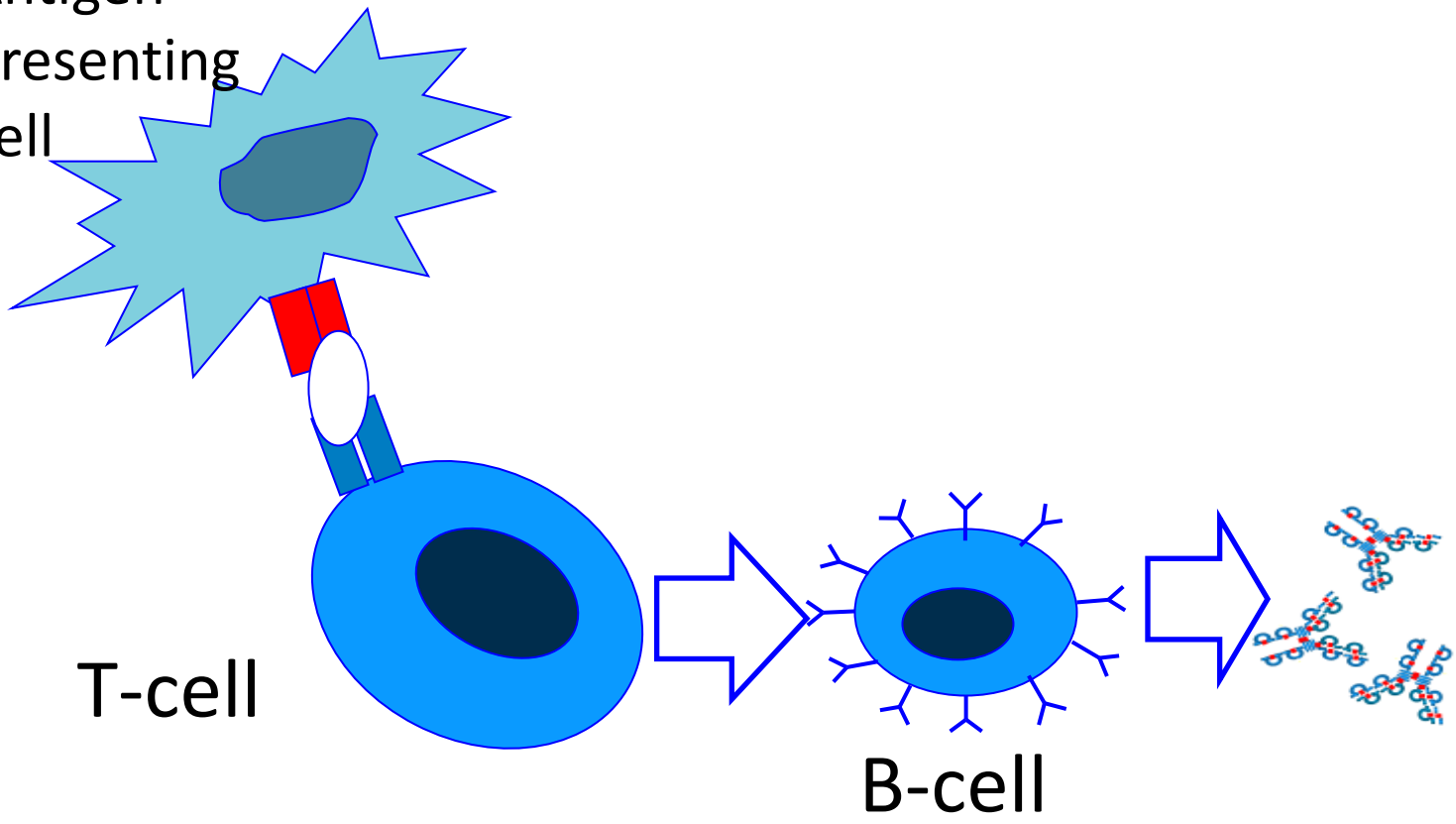
Huijbers et al. Eur J Neurol, 2015

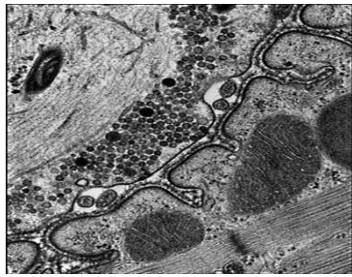
Myasthenia phenotypes

AChR MG	LEMS	MuSK MG
		
Thymoma	SCLC	No tumour
Young female Old male	Young female Old male	Young female
B8-DR3	B8-DR3	DR14-DQ5
IgG1	IgG1	IgG4

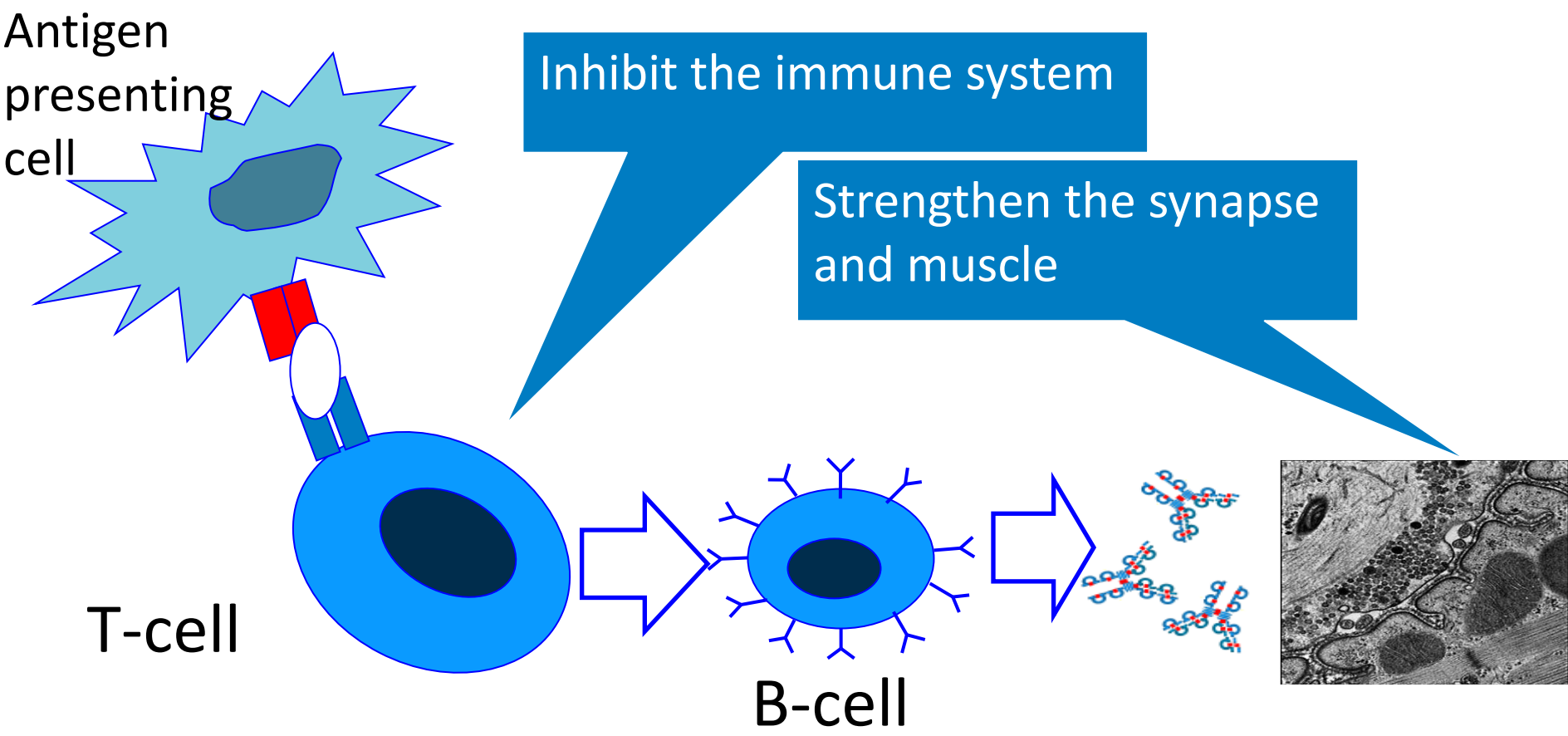
Treatment of myasthenia

Antigen presenting cell

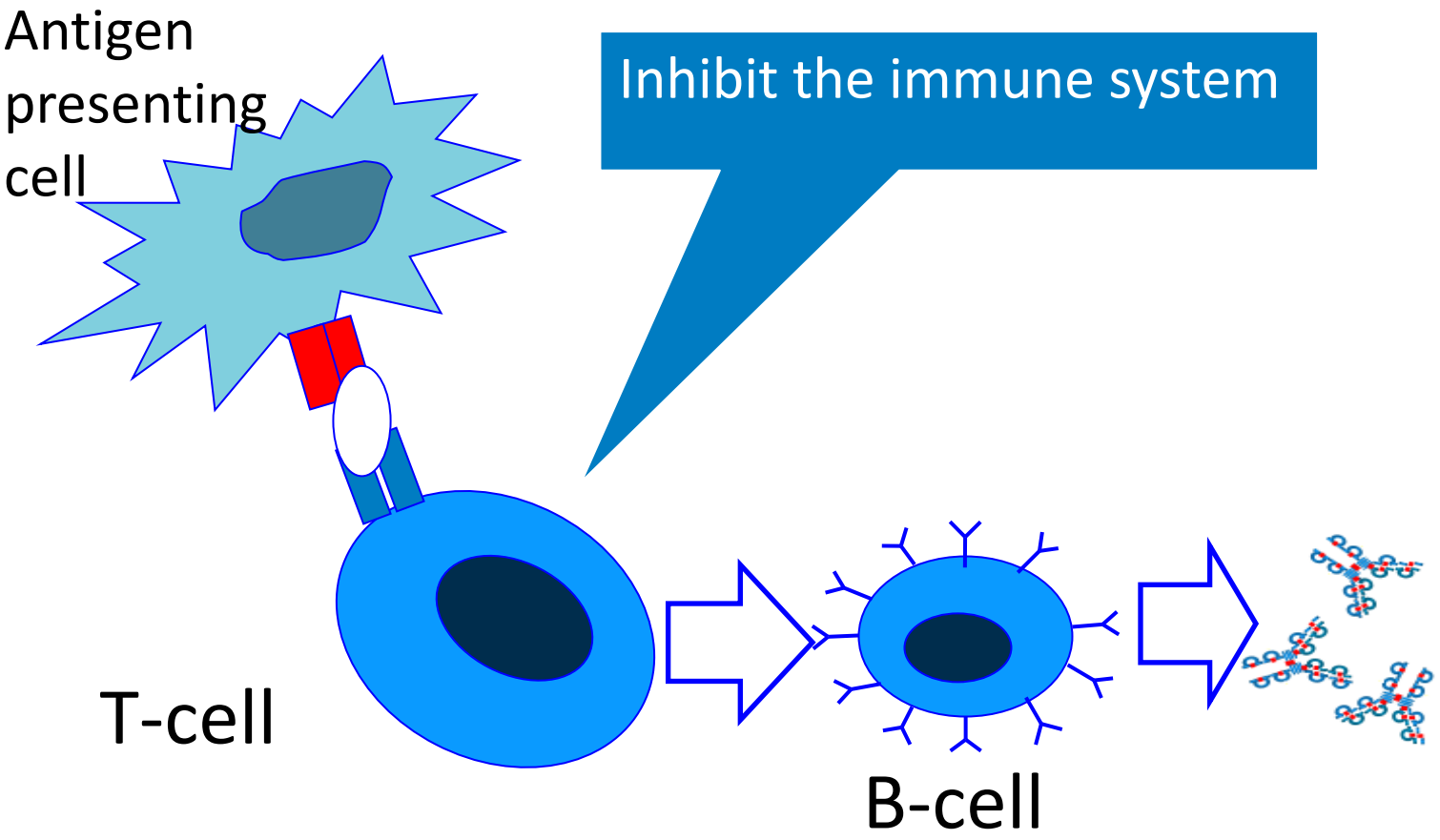


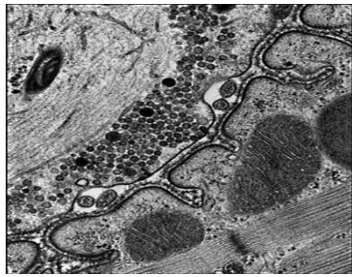


Treatment of myasthenia

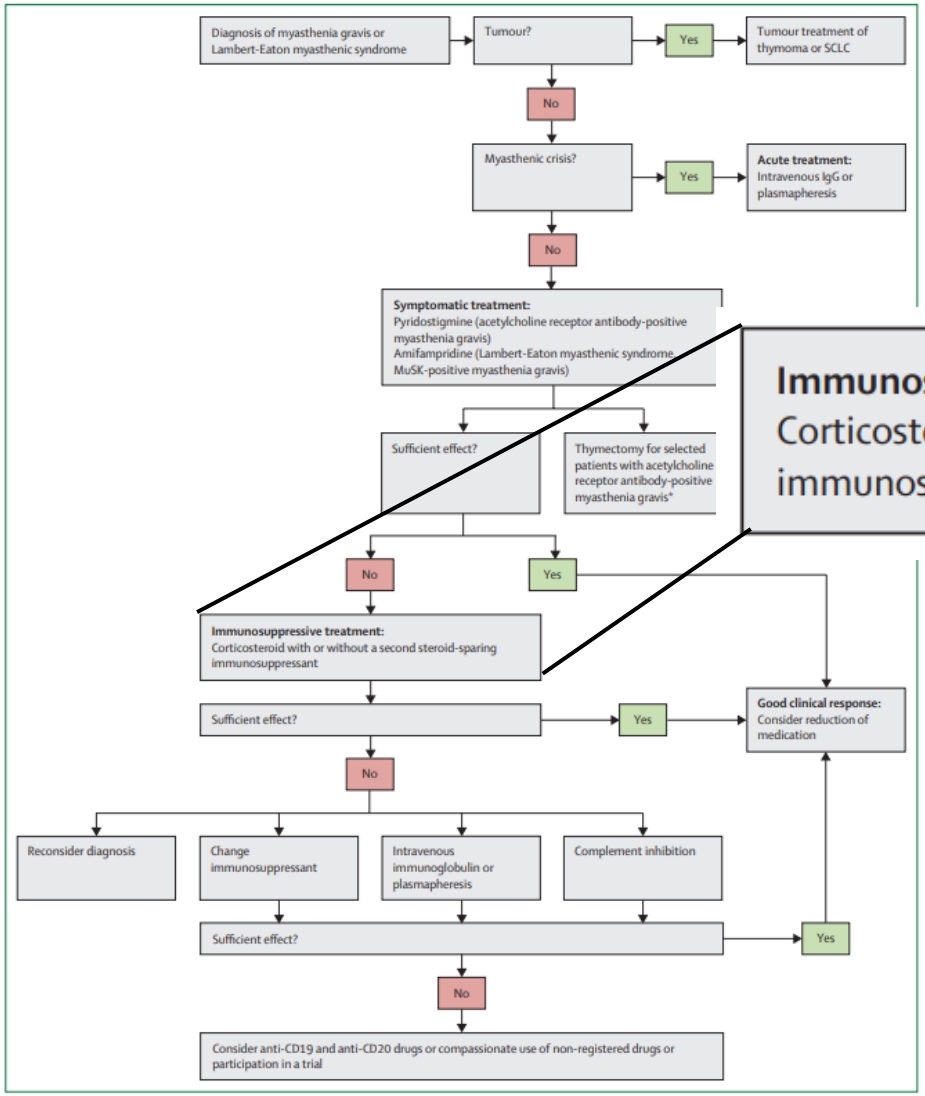


Treatment of myasthenia



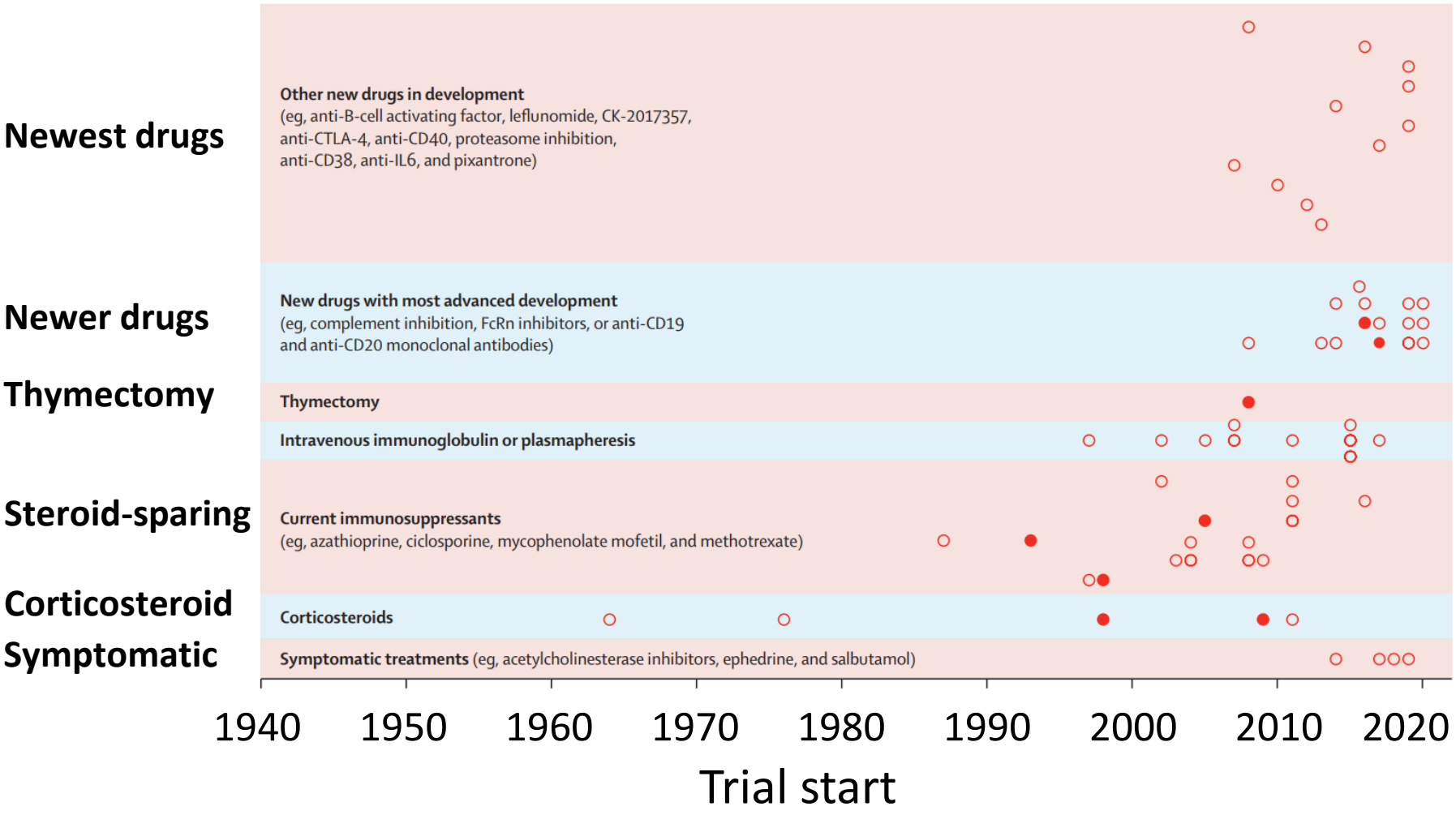


Treatment scheme

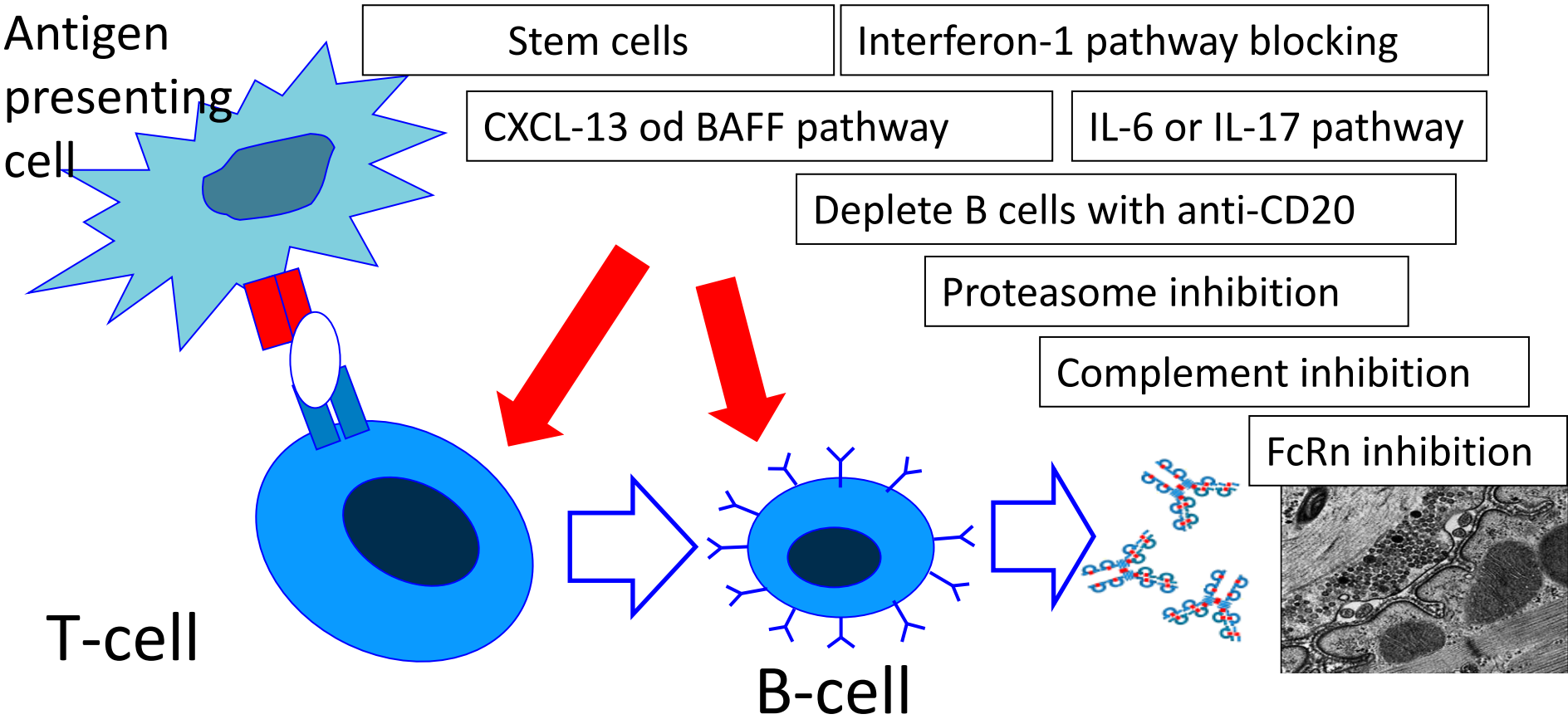


Immunosuppressive treatment:
Corticosteroid with or without a second steroid-sparing immunosuppressant

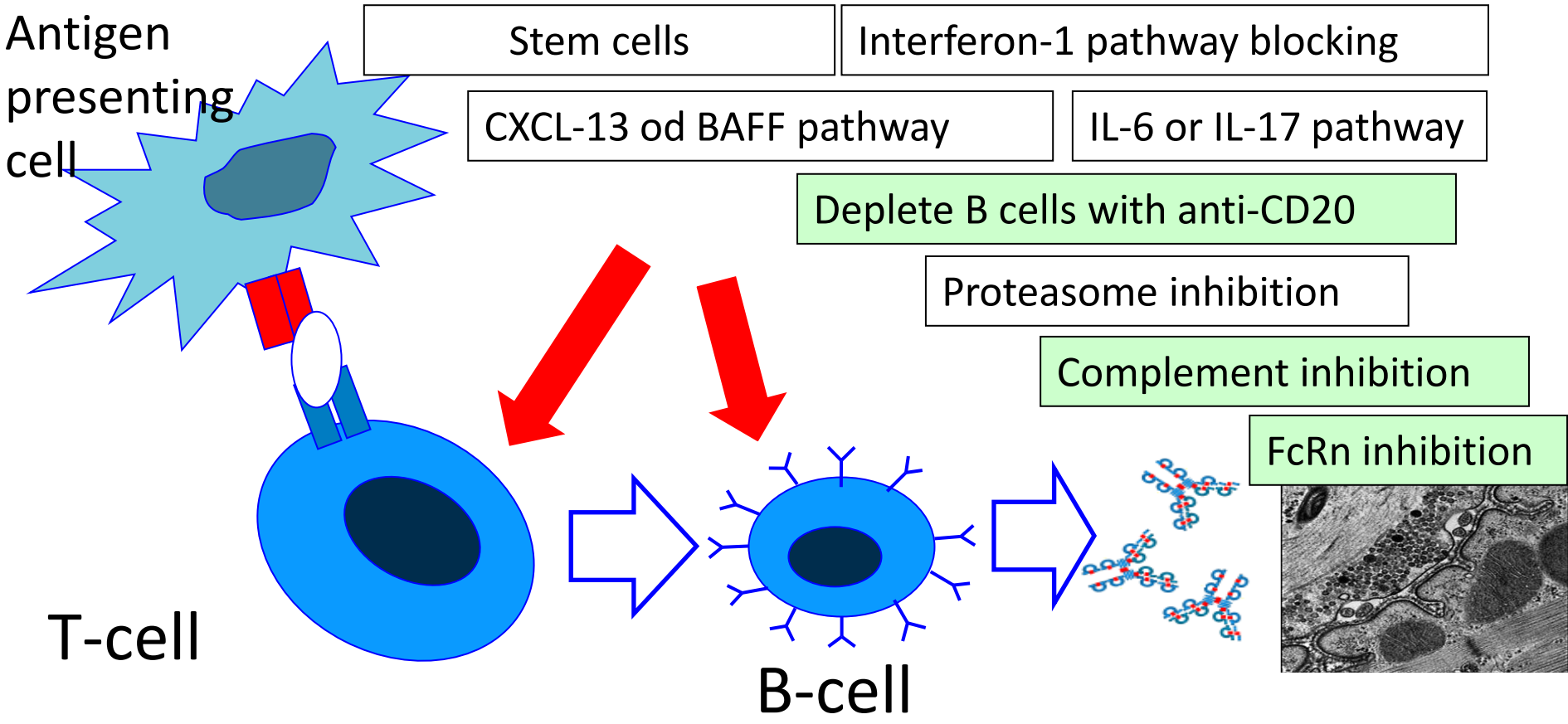
Drug development for autoimmune MG



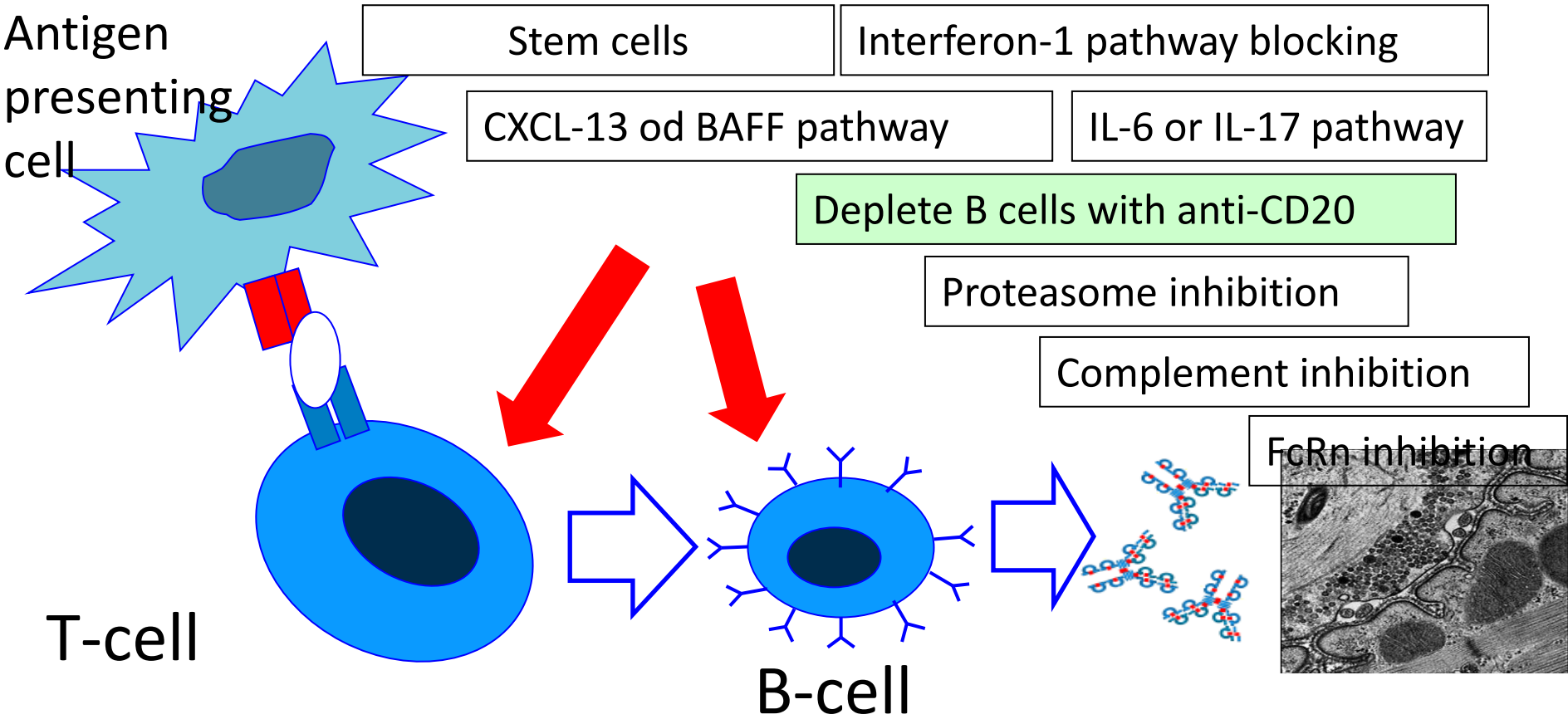
Immunosuppressive treatment of MG



Immunosuppressive treatment of MG



Immunosuppressive treatment of MG



Immunosuppressive treatment of MG

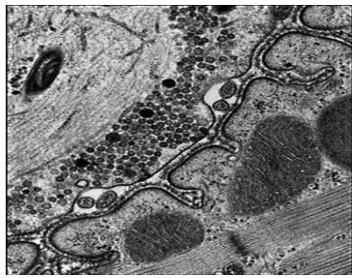
Antigen presenting cell

Rituximab

Kills pre-B cells (CD20+)

T-cell

B-cell



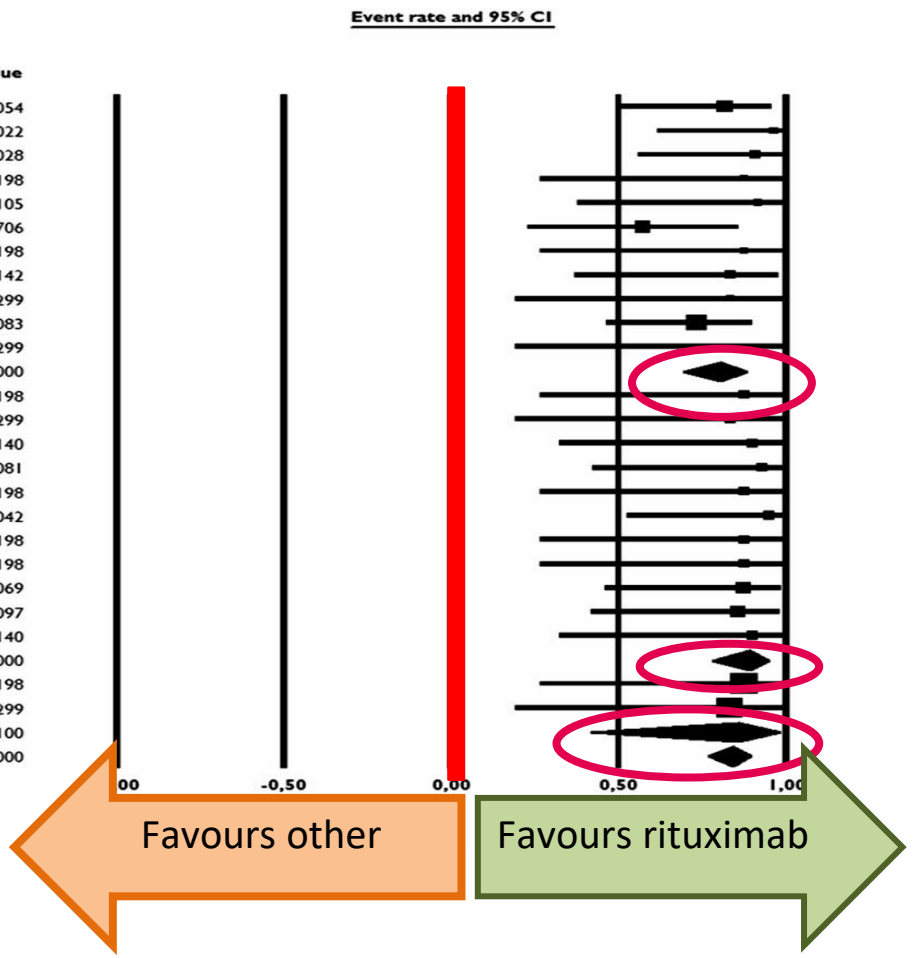
Efficacy and safety of rituximab for MG

Group by Subgroup within study	Study name	Subgroup	Event rate	Lower limit	Upper limit	Z-Value	p-Value
AchR	Blum et al., 2011	AchR	0,818	0,493	0,954	1,924	0,054
AchR	Collongues et al., 2012	AchR	0,964	0,616	0,998	2,289	0,022
AchR	Diaz-Manera et al., 2012	AchR	0,909	0,561	0,987	2,195	0,028
AchR	Illa et al 2008	AchR	0,875	0,266	0,993	1,287	0,198
AchR	Lindberg et al. 2010	AchR	0,917	0,378	0,995	1,623	0,105
AchR	Maddison et al., 2011	AchR	0,571	0,230	0,856	0,377	0,706
AchR	2009	AchR	0,875	0,266	0,993	1,287	0,198
AchR	., 2011	AchR	0,833	0,369	0,977	1,469	0,142
AchR	et al.2009	AchR	0,833	0,194	0,990	1,039	0,299
AchR	013	AchR	0,733	0,467	0,896	1,733	0,083
AchR	Zebardast et al. 2010	AchR	0,833	0,194	0,990	1,039	0,299
AchR			0,804	0,693	0,882	4,618	0,000
Musk	Blum et al., 2011	Musk	0,875	0,266	0,993	1,287	0,198
Musk	Burusnukul et al.2010	Musk	0,833	0,194	0,990	1,039	0,299
Musk	Collongues et al., 2012	Musk	0,900	0,326	0,994	1,474	0,140
Musk	Diaz-Manera et al., 2012	Musk	0,929	0,423	0,996	1,748	0,081
Musk	8	Musk	0,875	0,266	0,993	1,287	0,198
Musk	2013	Musk	0,950	0,525	0,997	2,029	0,042
Musk	2009	Musk	0,875	0,266	0,993	1,287	0,198
Musk	al., 2011	Musk	0,875	0,266	0,993	1,287	0,198
Musk	Nowak et al., 2011	Musk	0,875	0,463	0,983	1,820	0,069
Musk	Sun et al., 2013	Musk	0,857	0,419	0,980	1,659	0,097
Musk	Zebardast et al. 2010	Musk	0,900	0,326	0,994	1,474	0,140
Musk			0,888	0,778	0,947	4,960	0,000
SN	Collongues et al., 2012	SN	0,875	0,266	0,993	1,287	0,198
SN	2009	SN	0,833	0,194	0,990	1,039	0,299
SN			0,856	0,416	0,980	1,647	0,100
Overall			0,839	0,765	0,893	6,856	0,000

AChR

MuSK

SNMG



Efficacy and safety of rituximab for MG

Group by Subgroup within study	Study name	Subgroup	Statistics for each study				
			Event rate	Lower limit	Upper limit	Z-Value	p-Value
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AchR	Diaz-Manera et al., 2012	AchR	0,909	0,561	0,987	2,195	0,028
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AchR	Maddison et al., 2011	AchR	0,571	0,230	0,856	0,377	0,706
AchR						1,287	0,198
AchR						1,469	0,142
AchR						1,039	0,299
AchR						1,733	0,083
AchR	Zebardast et al. 2010	AchR	0,833	0,194	0,990	1,039	0,299
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Musk	Diaz-Manera et al., 2012	Musk	0,929	0,423	0,996	1,748	0,081
Musk						1,287	0,198
Musk						2,029	0,042
Musk						1,287	0,198
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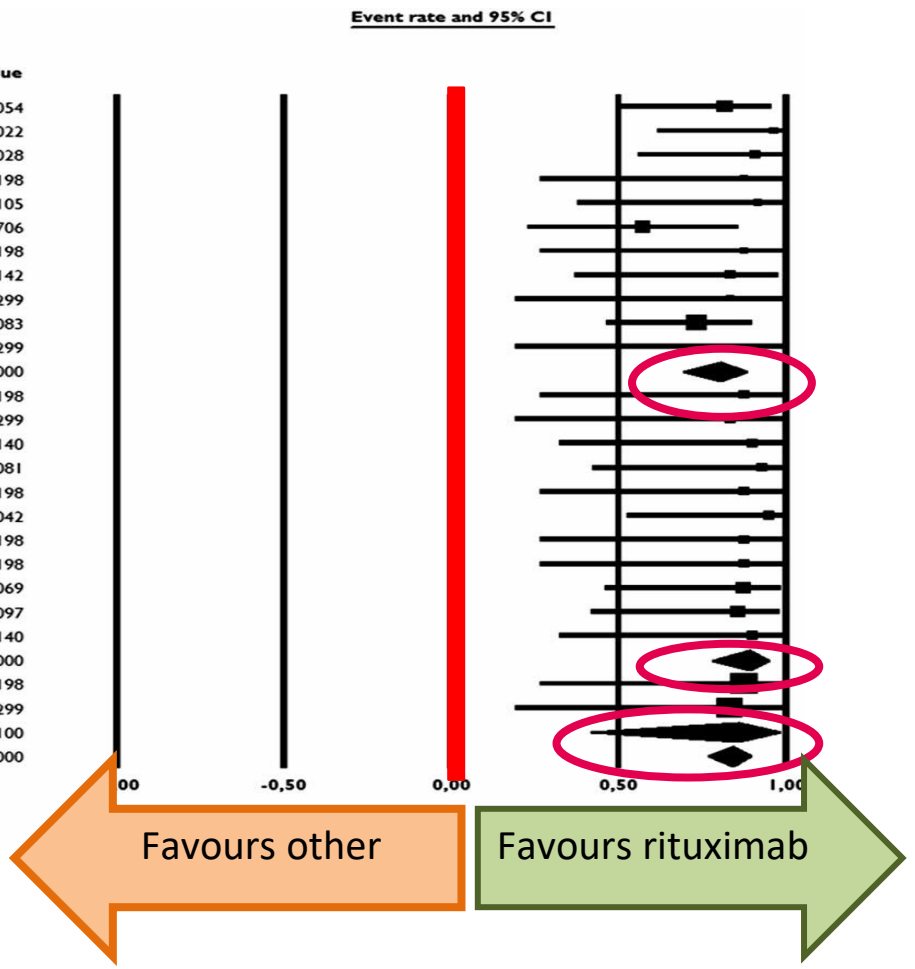
SN	Collongues et al., 2012	SN	0,875	0,266	0,993	1,287	0,198
SN		SN	0,833	0,194	0,990	1,039	0,299
SN			0,856	0,416	0,980	1,647	0,100
Overall			0,839	0,765	0,893	6,856	0,000

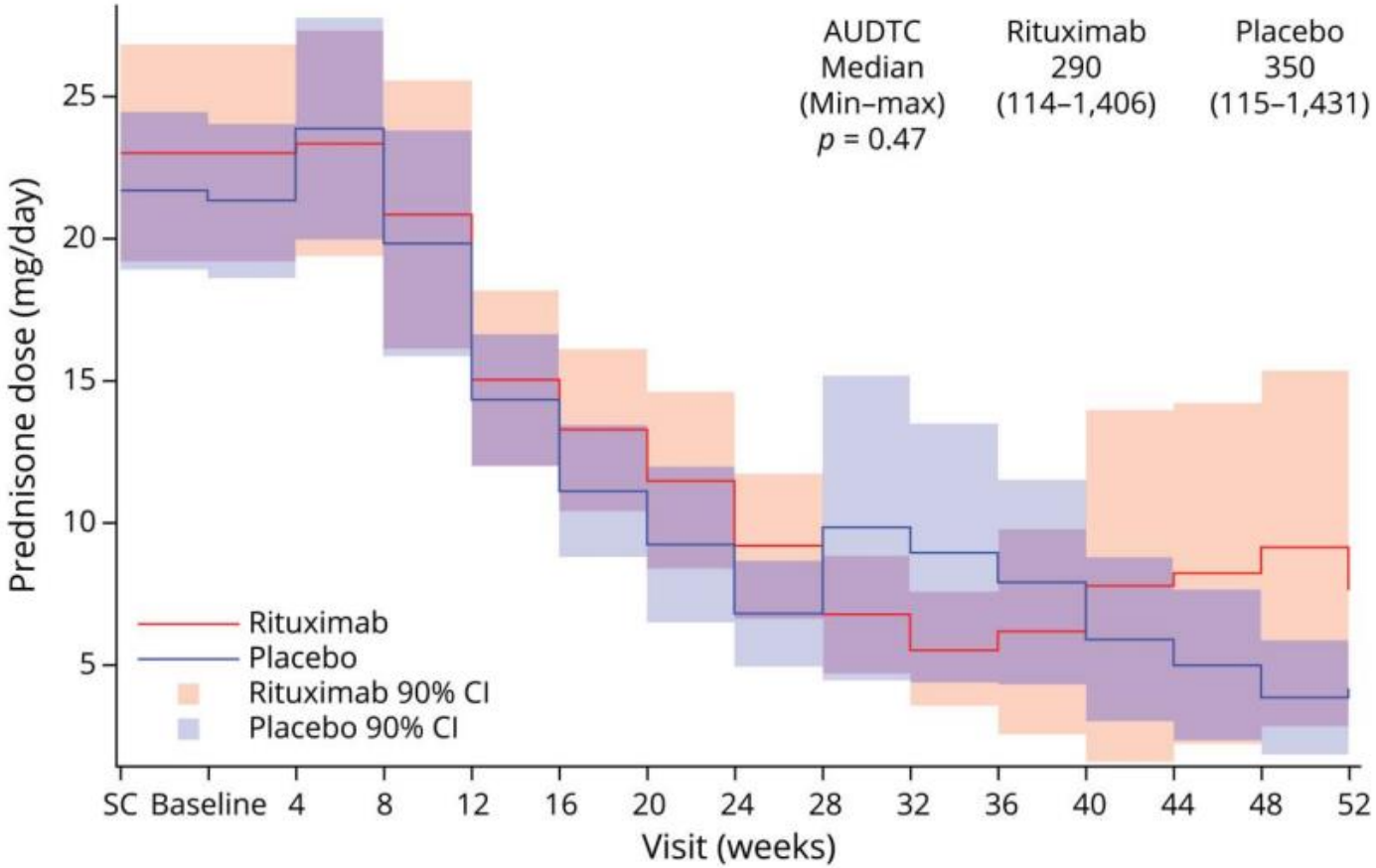
AChR → **IgG1**

MuSK → **IgG4**

SNMG



BEAT-MG: rituximab is safe, but no steroid reduction (>30%) at 1 year

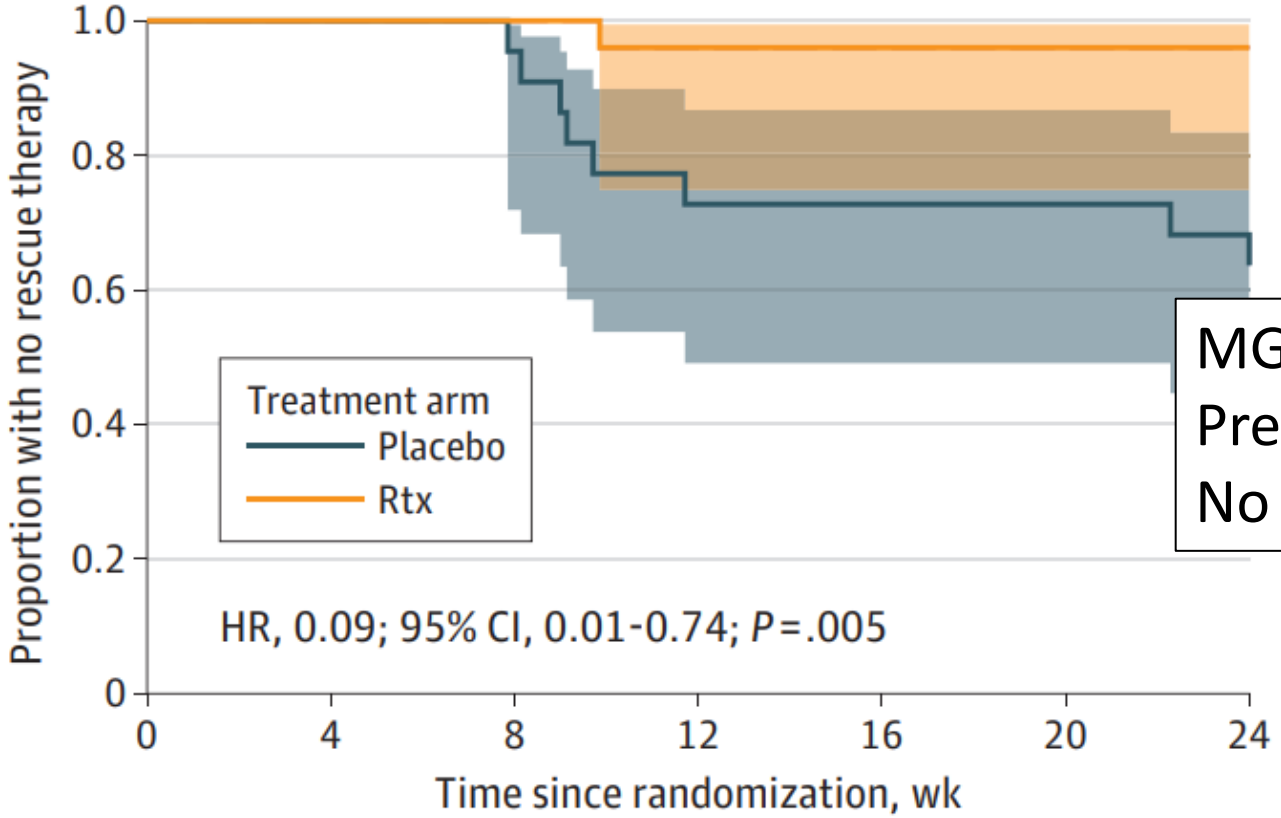


Study with patients with mild to moderate AChR-positive generalized MG

Phase 2 Trial of Rituximab in Acetylcholine Receptor Antibody-Positive Generalized Myasthenia Gravis: The BeatMG Study. Nowak RJ, et al Neurology. 2021 Dec

RINOMAX Randomized Clinical Trial in recent onset MG

B Kaplan-Meier estimate of the proportion with no rescue therapy



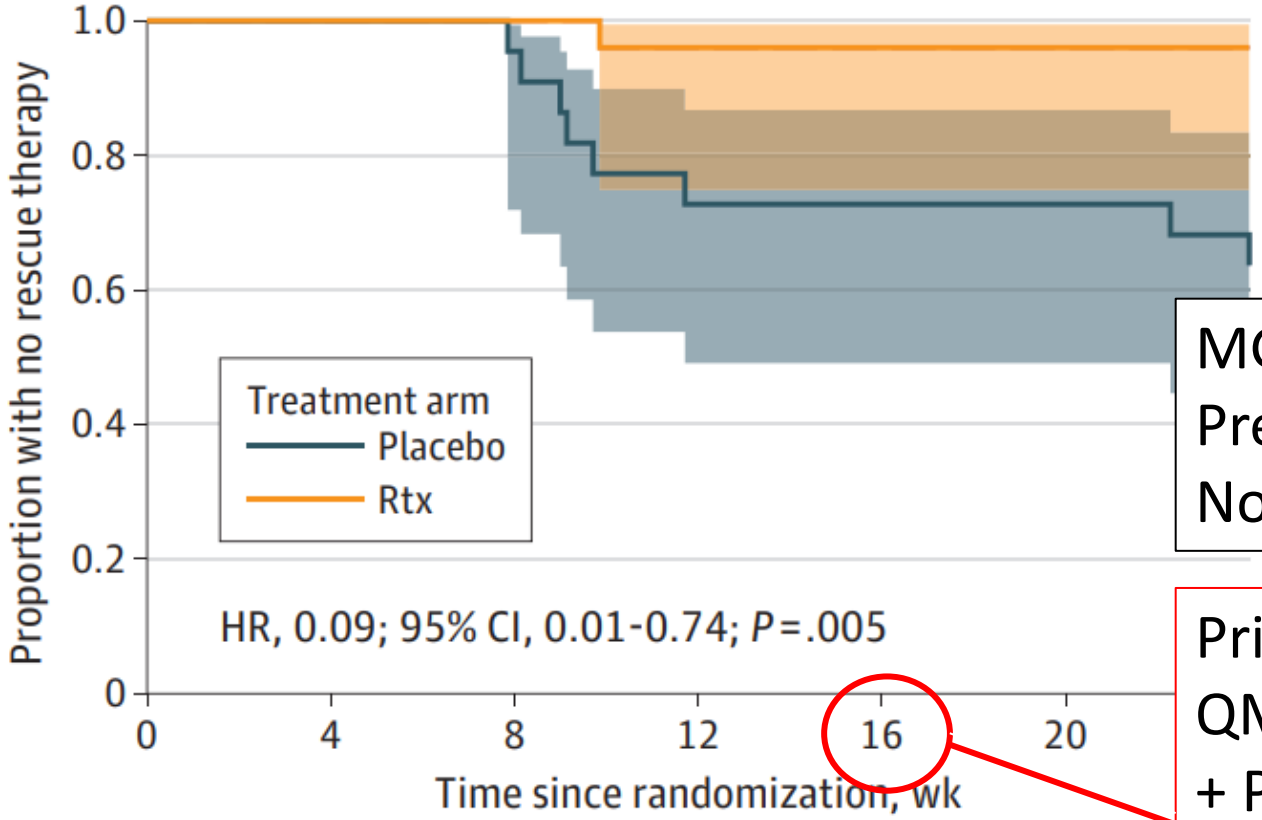
No. at risk							
Placebo	22	22	21	16	16	16	15
Rtx	25	25	25	24	24	24	24

MG < 1 year
Pred < 40 mg/day
No immunosuppr.

Piehl et al., JAMA Neurol 2022

RINOMAX Randomized Clinical Trial in recent onset MG

B Kaplan-Meier estimate of the proportion with no rescue therapy



No. at risk

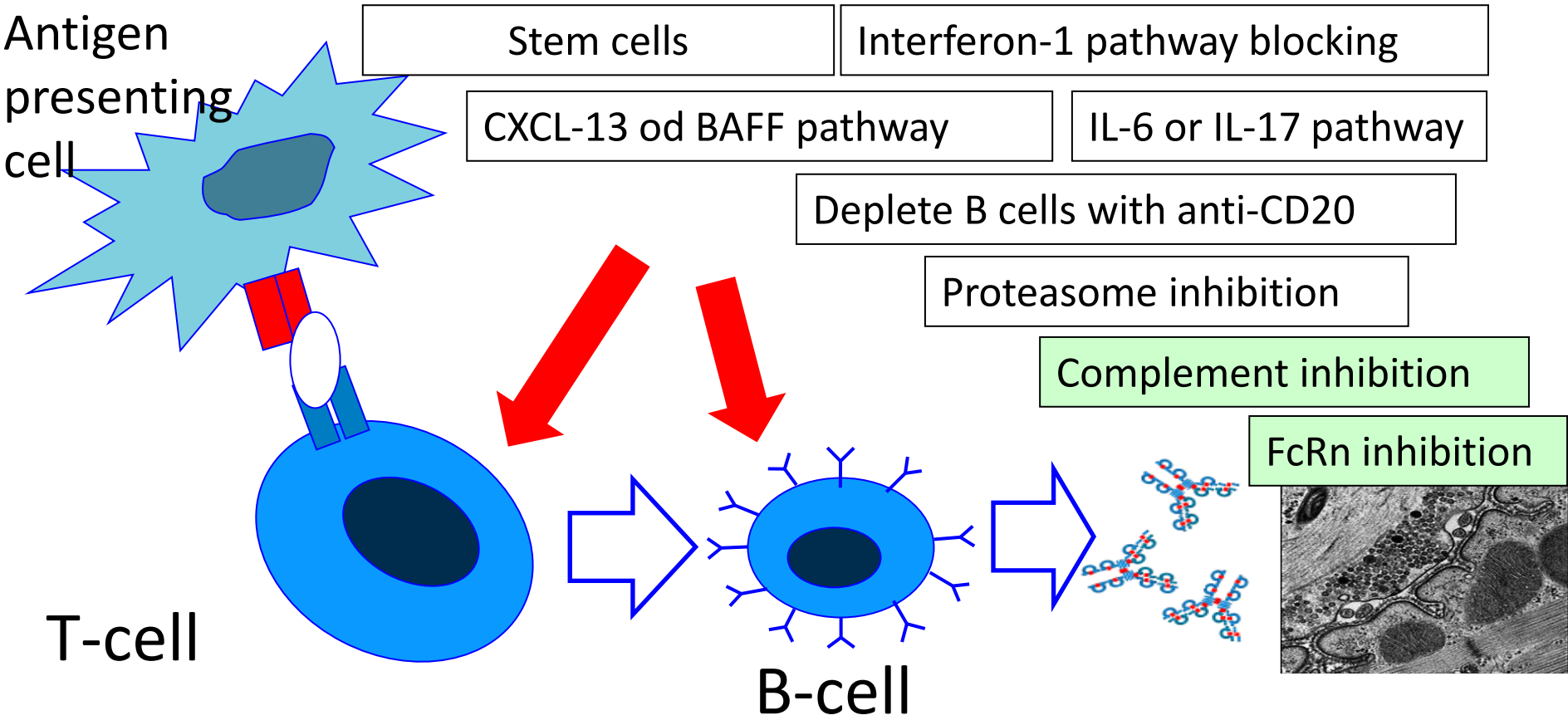
Placebo	22	22	21	16	16	16	
Rtx	25	25	25	24	24	24	24

MG < 1 year
Pred < 40 mg/day
No immunosuppr.

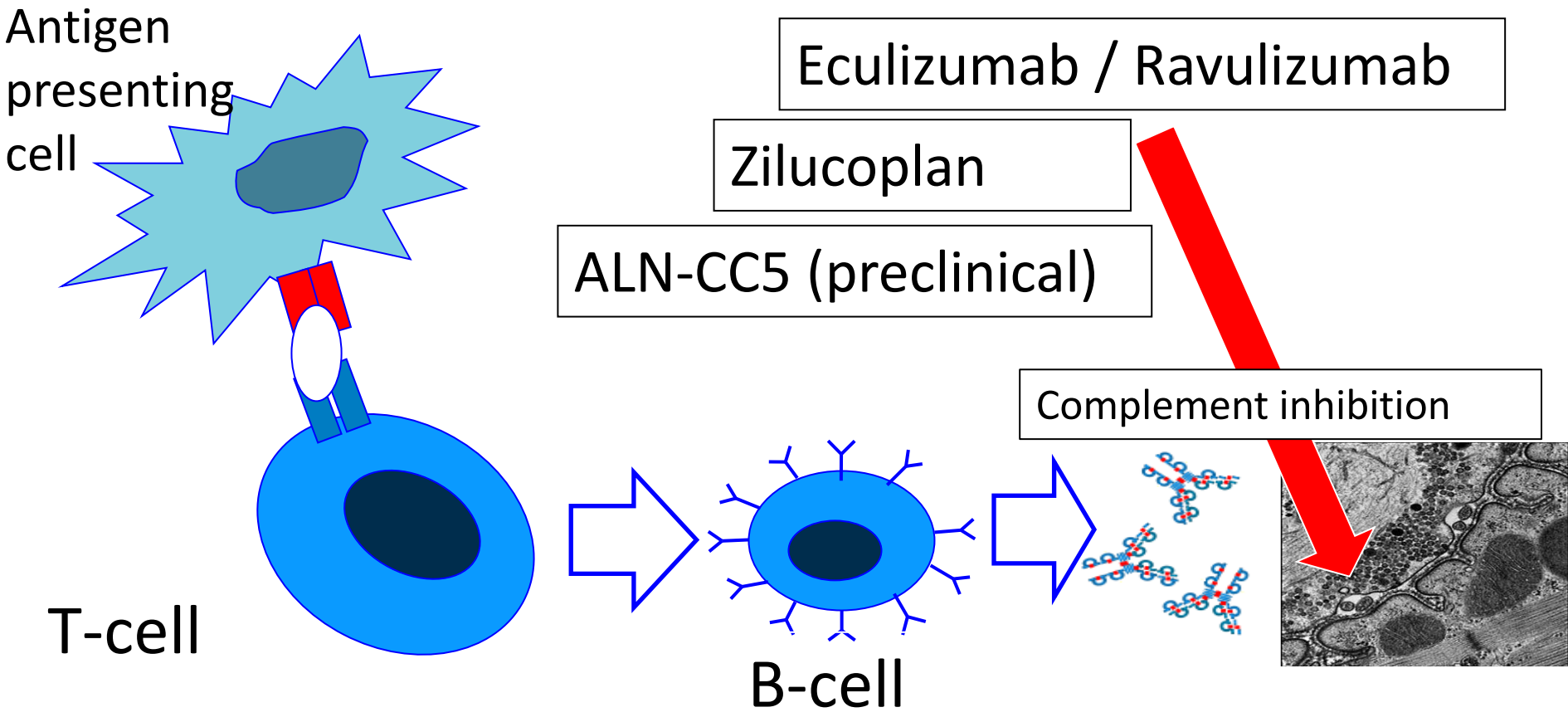
Prim. Outcome:
QMG<4
+ Pred < 10 mg/day
+ No rescue (9-16 wk)

Piehl et al., JAMA Neurol 2022

Immunosuppressive treatment of MG



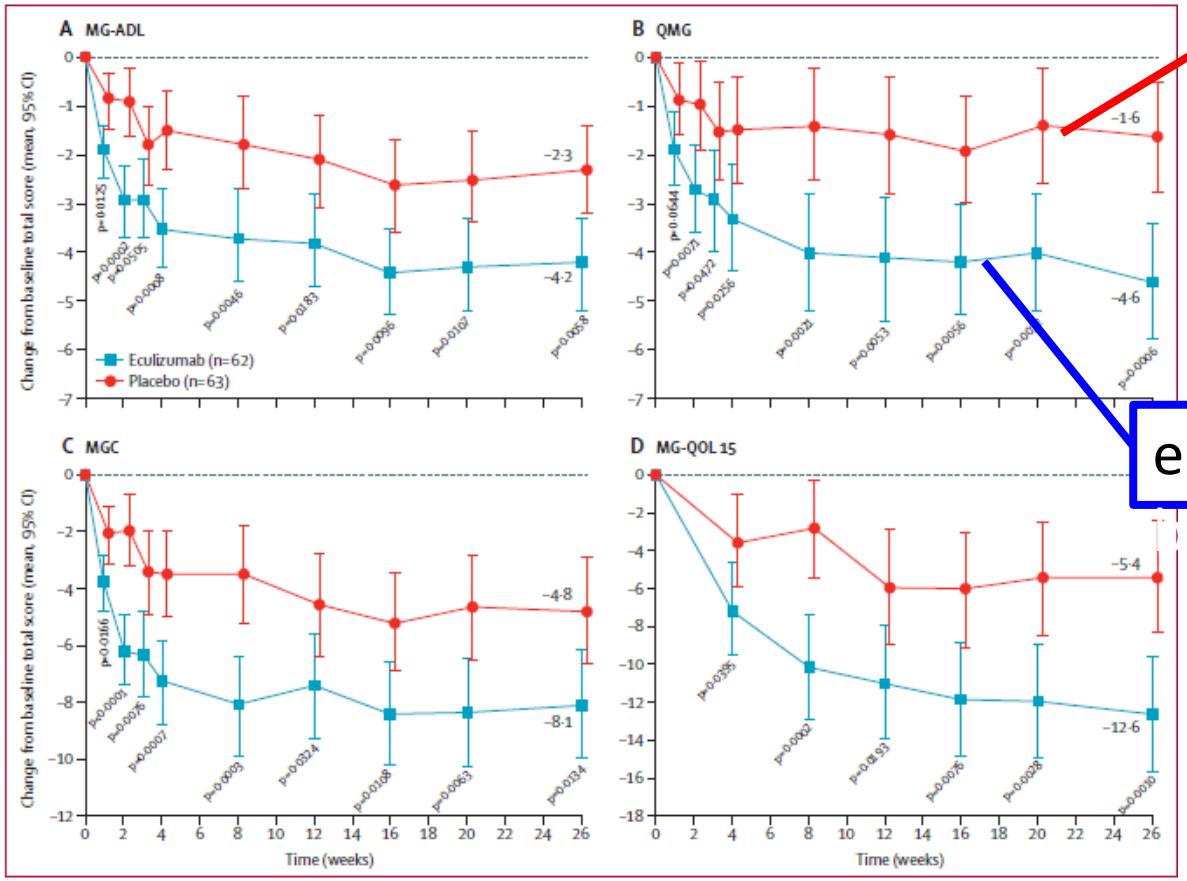
Complement inhibition in AChR MG



Eculizumab in 125 patients with refractory generalized MG

MG-ADL
non-sign.

MGC
non-sign.



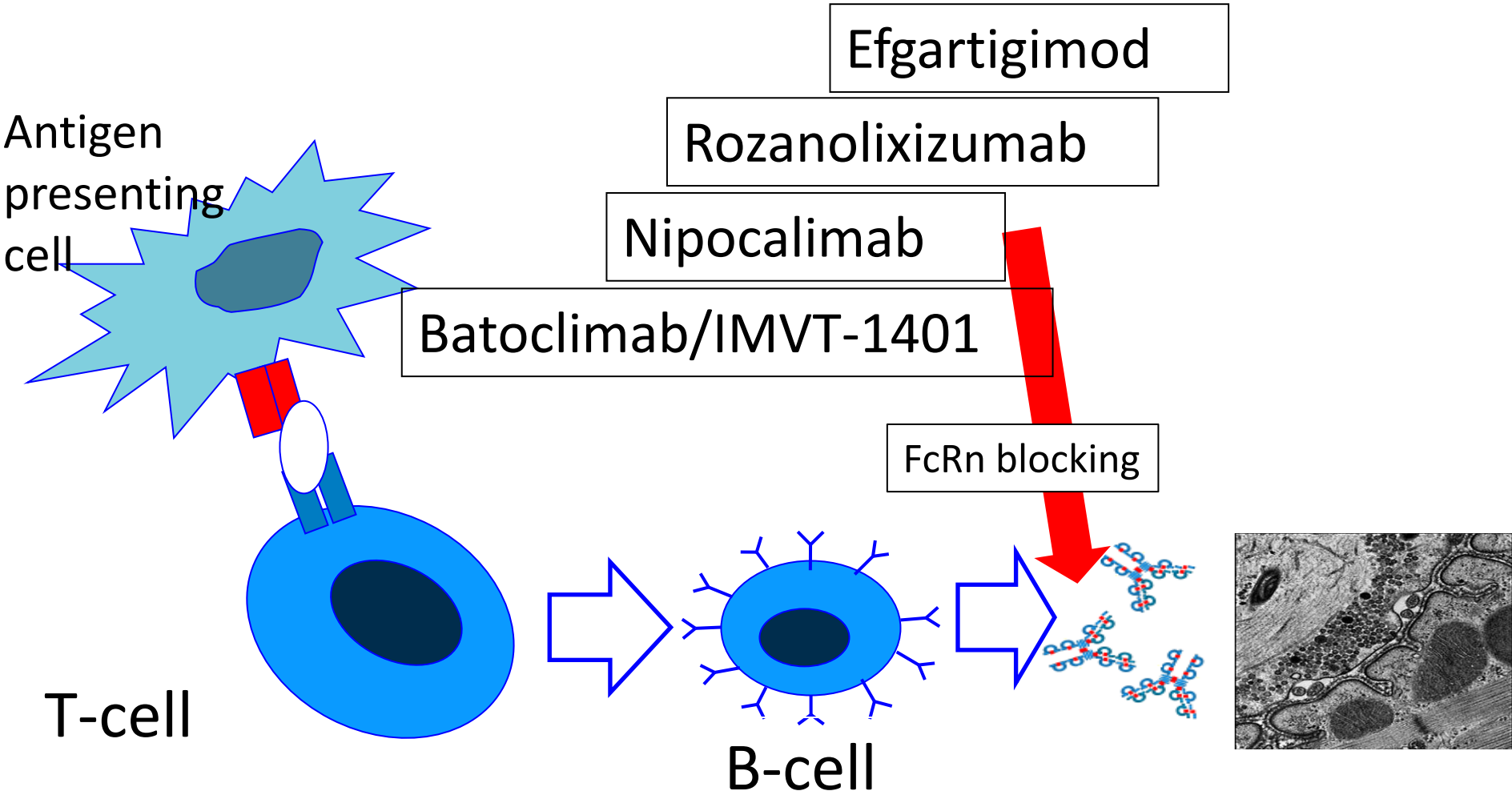
placebo

QMG
p=0.013

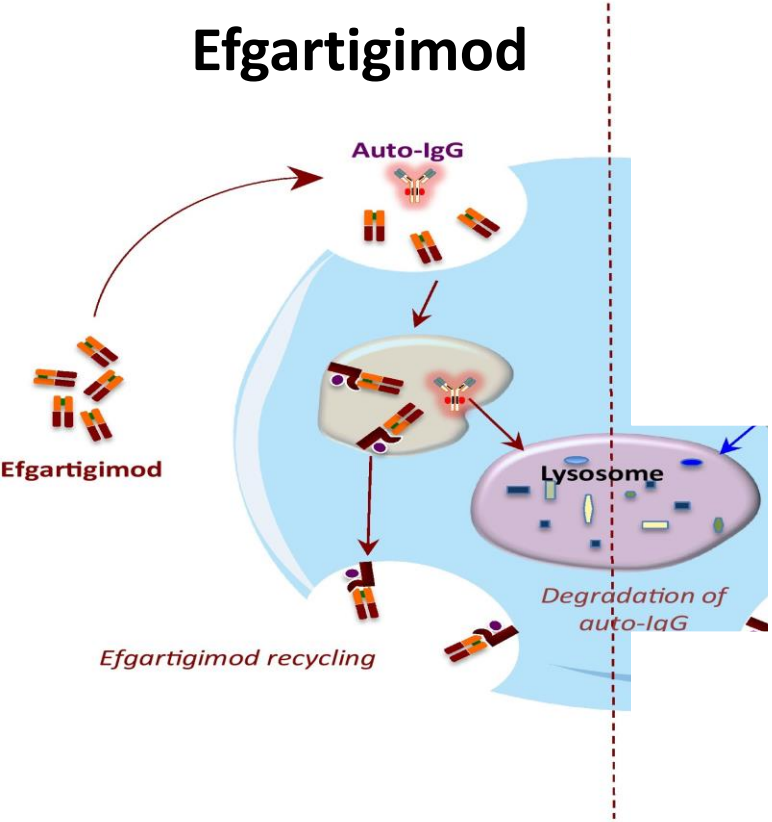
eculizumab

MG-QOL
p=0.028

Neonatal Fc-receptor (FcRn) blocking in MG

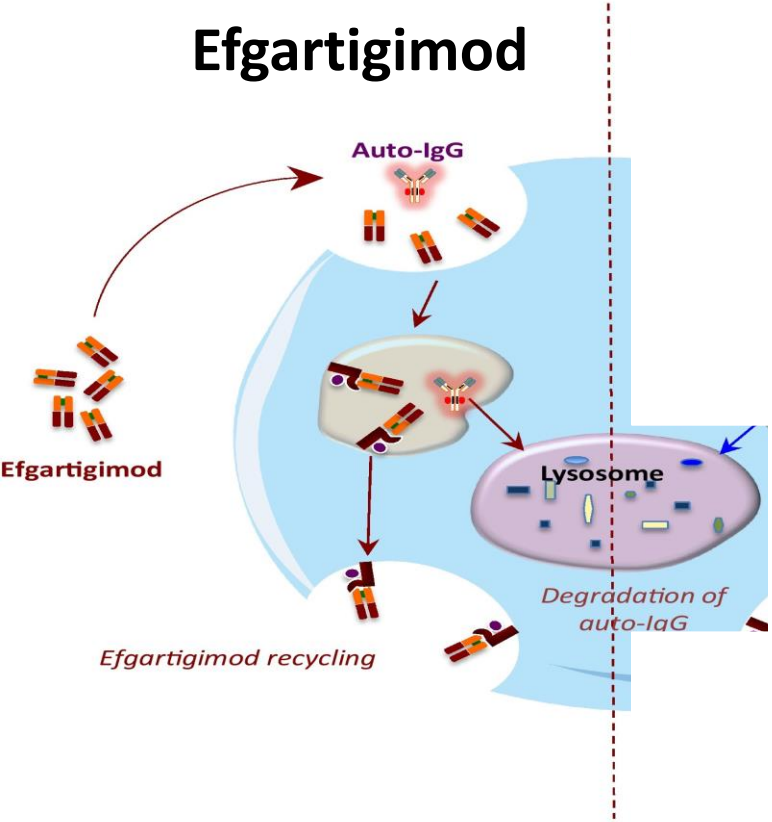


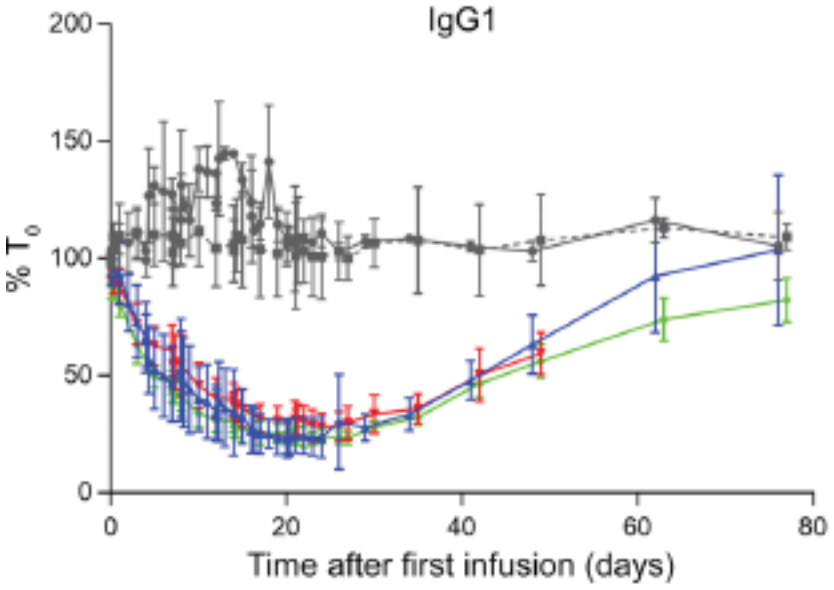
Neonatal Fc-receptor (FcRn) blocking in MG



Trends in Pharmacological Sciences

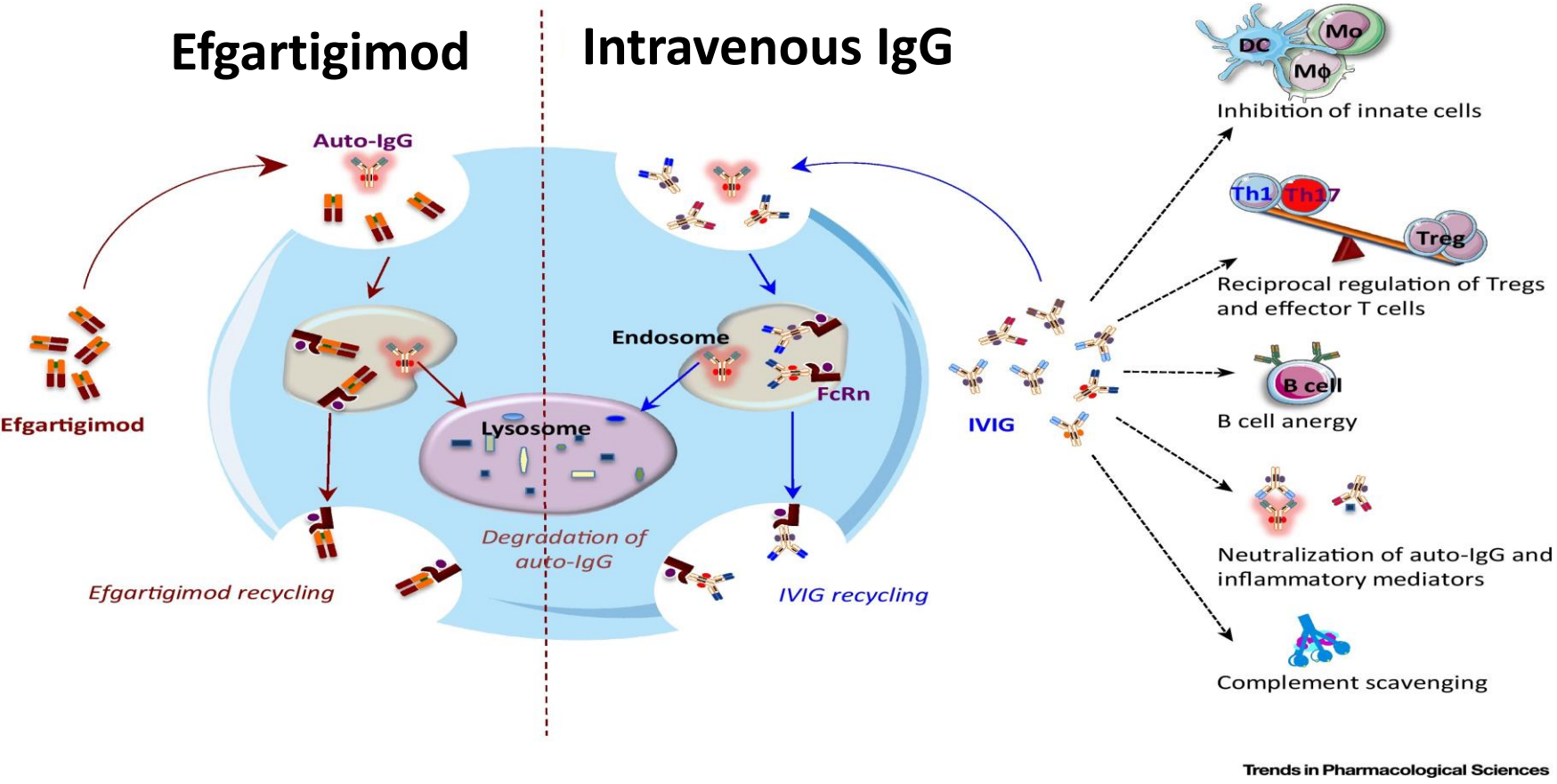
Neonatal Fc-receptor (FcRn) blocking in MG





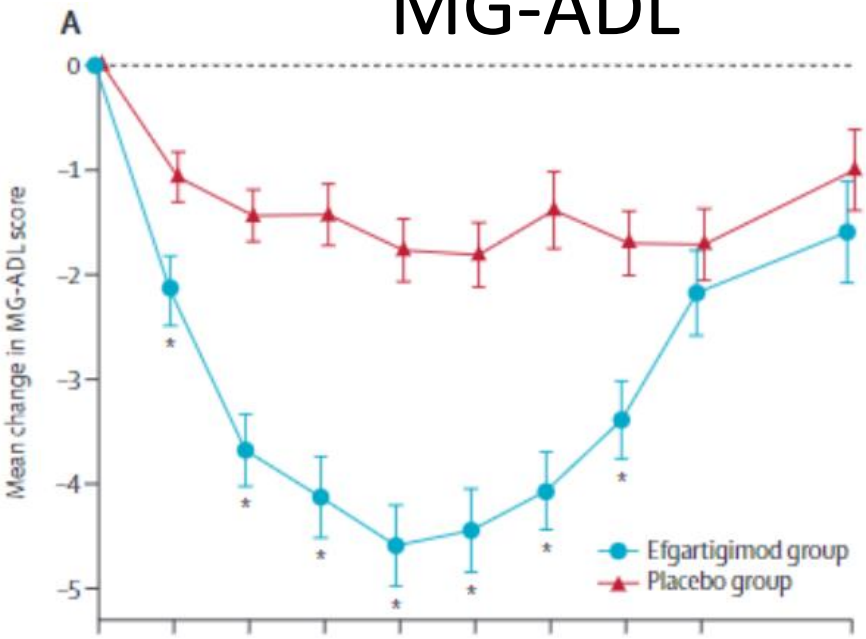
Trends in Pharmacological Sciences

Neonatal Fc-receptor (FcRn) blocking in MG



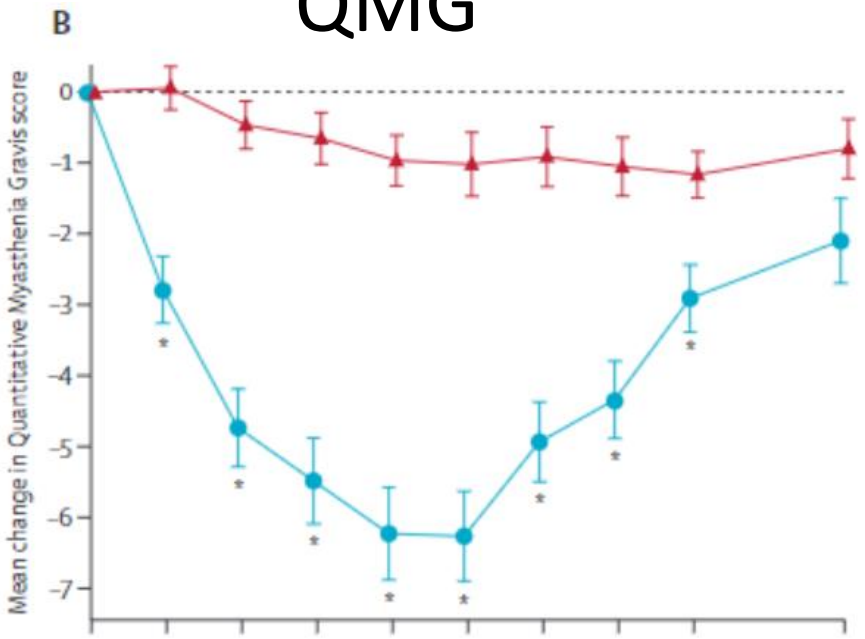
FcRn-blocking: Efgartigimod trial

MG-ADL



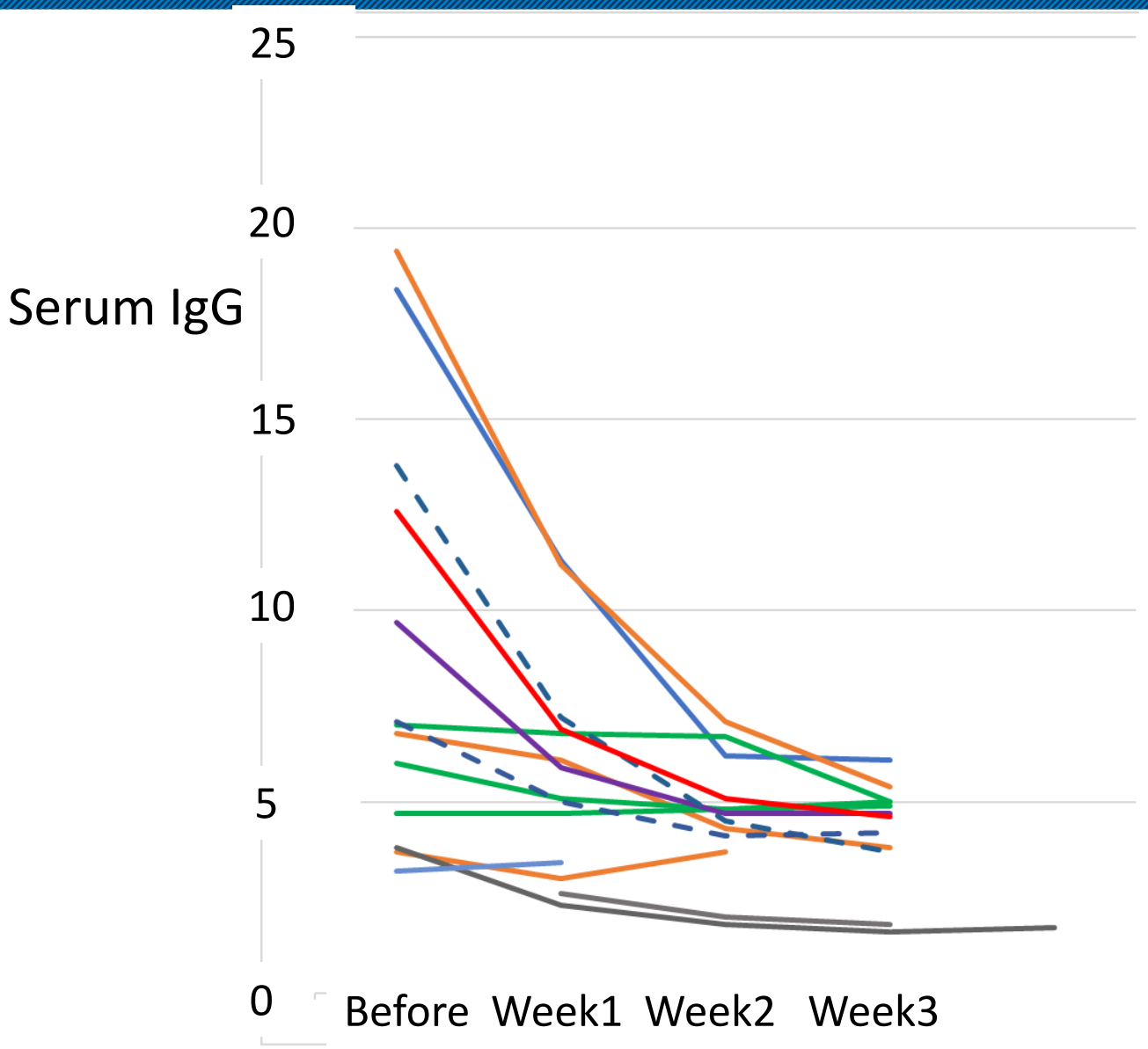
Weeks

QMG

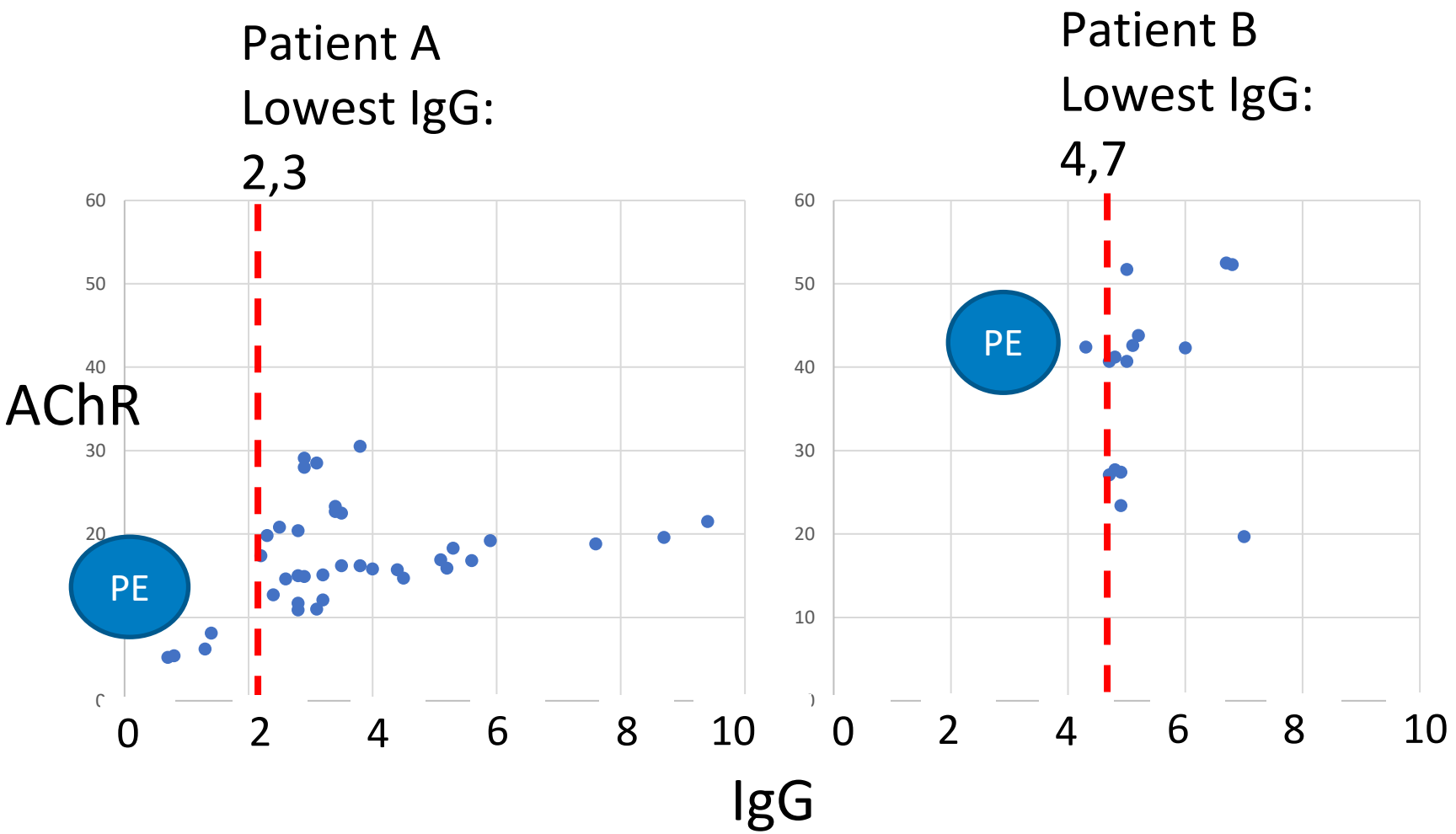


Weeks

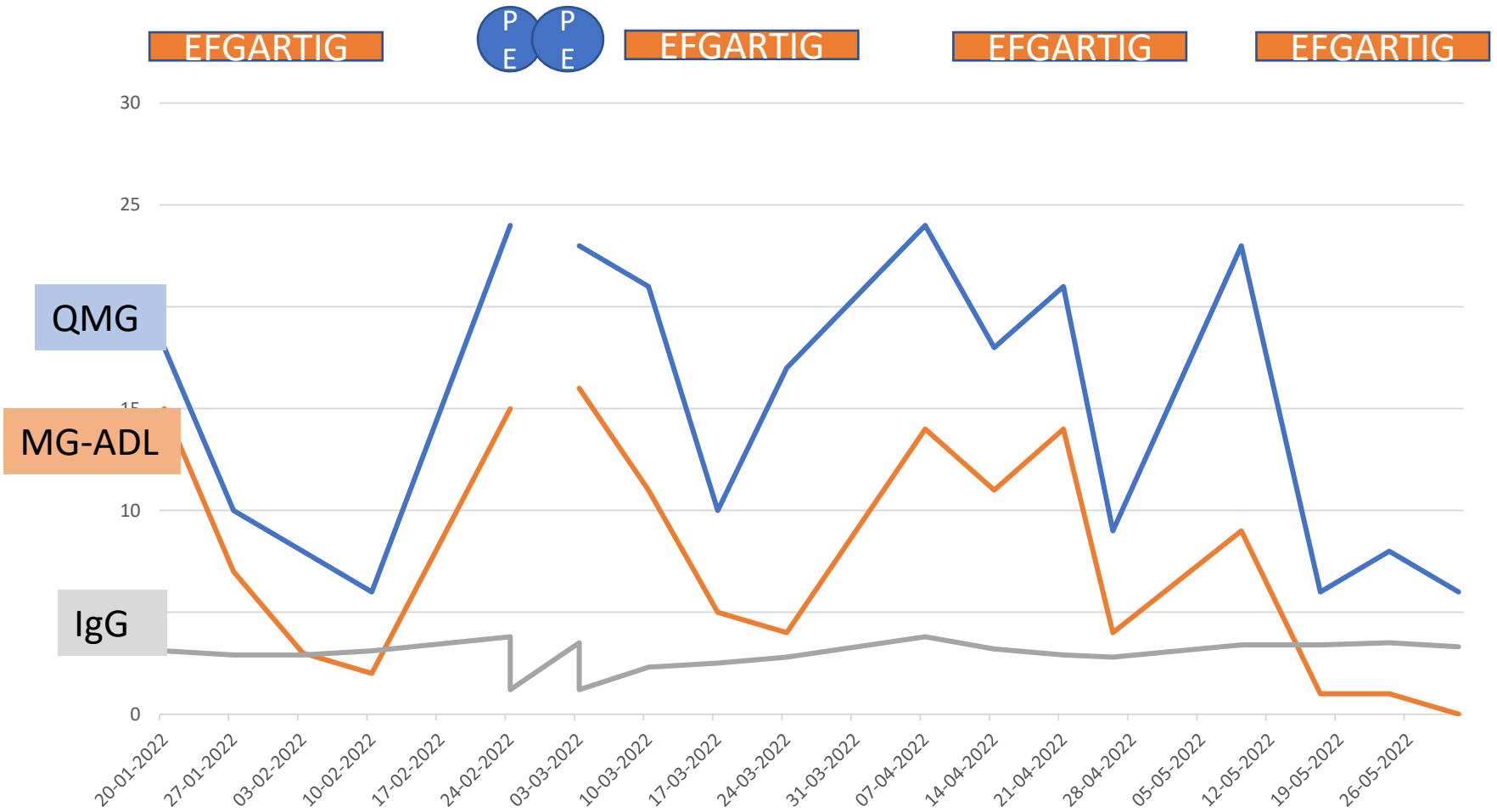
Serum IgG during efgartigimod treatment in compassionate use programme



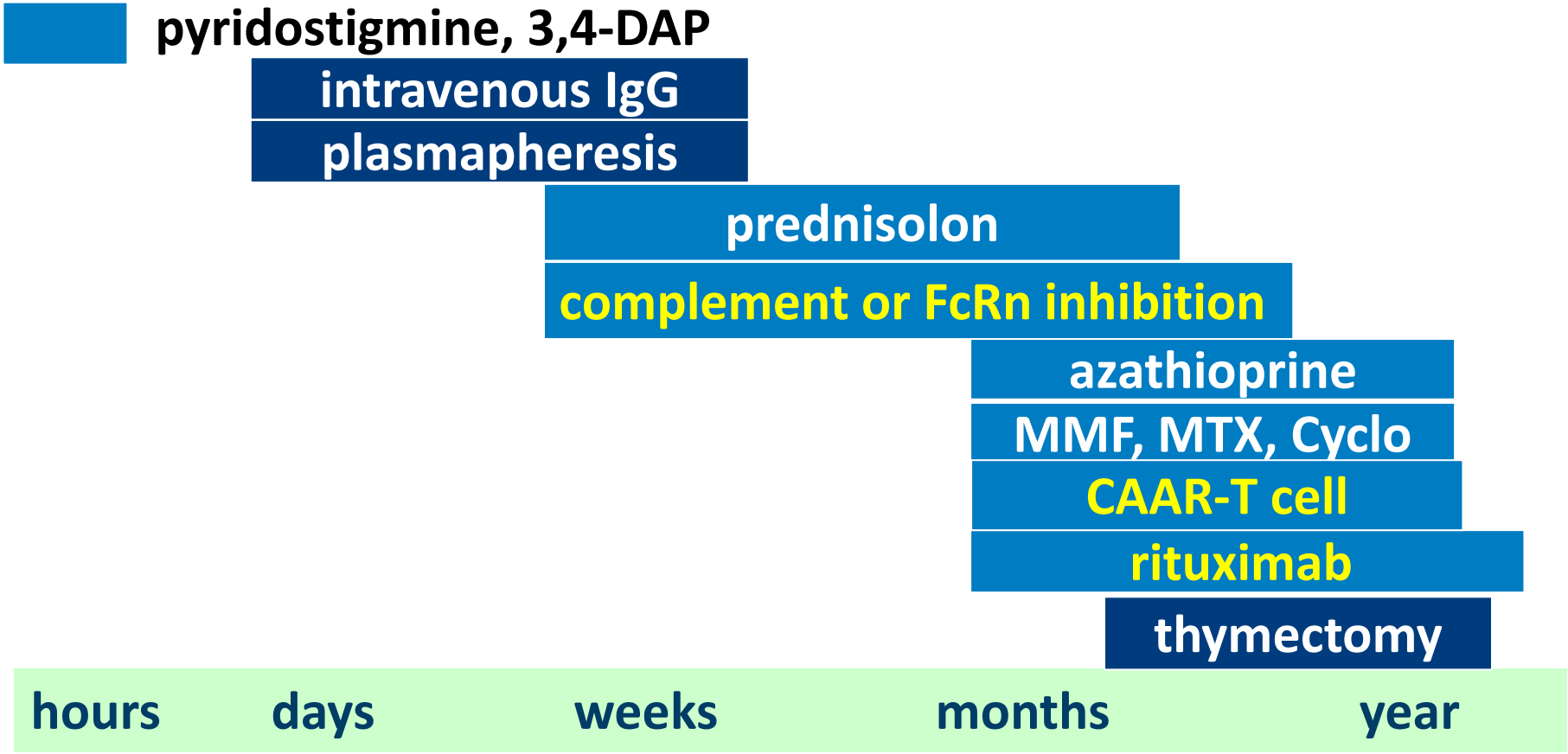
Individual IgG levels during FcRn treatment



Male patient with severe AChR MG



Therapy: short-term versus longterm effect



Leiden University
Medical Center

Conclusions

- Myasthenia consists of clinical subgroups with different treatment requirements
- Increasing treatment options become available for different phases of the diseases

Leids Universitair Medisch Centrum

Acknowledgements

Human genetics

Neuroimmunology group

Maartje Huijbers

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Roy Augustinus

Robyn Verpalen

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Erik Niks

Ellen Strijbos

Kevin Keene

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Linda Remijn-Nelissen

Center of proteomic and metabolomics

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