Advances in Therapies for Myasthenia Gravis

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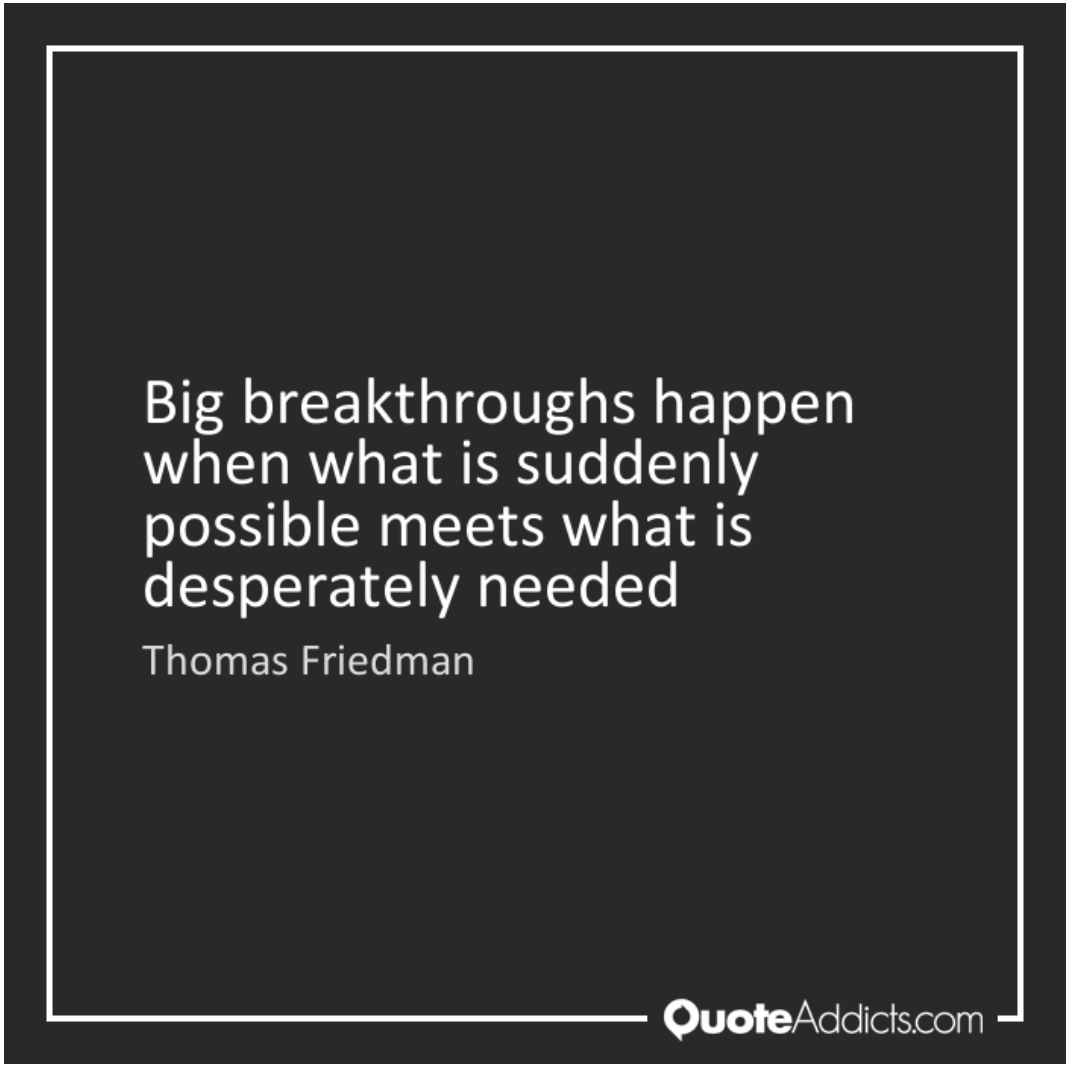
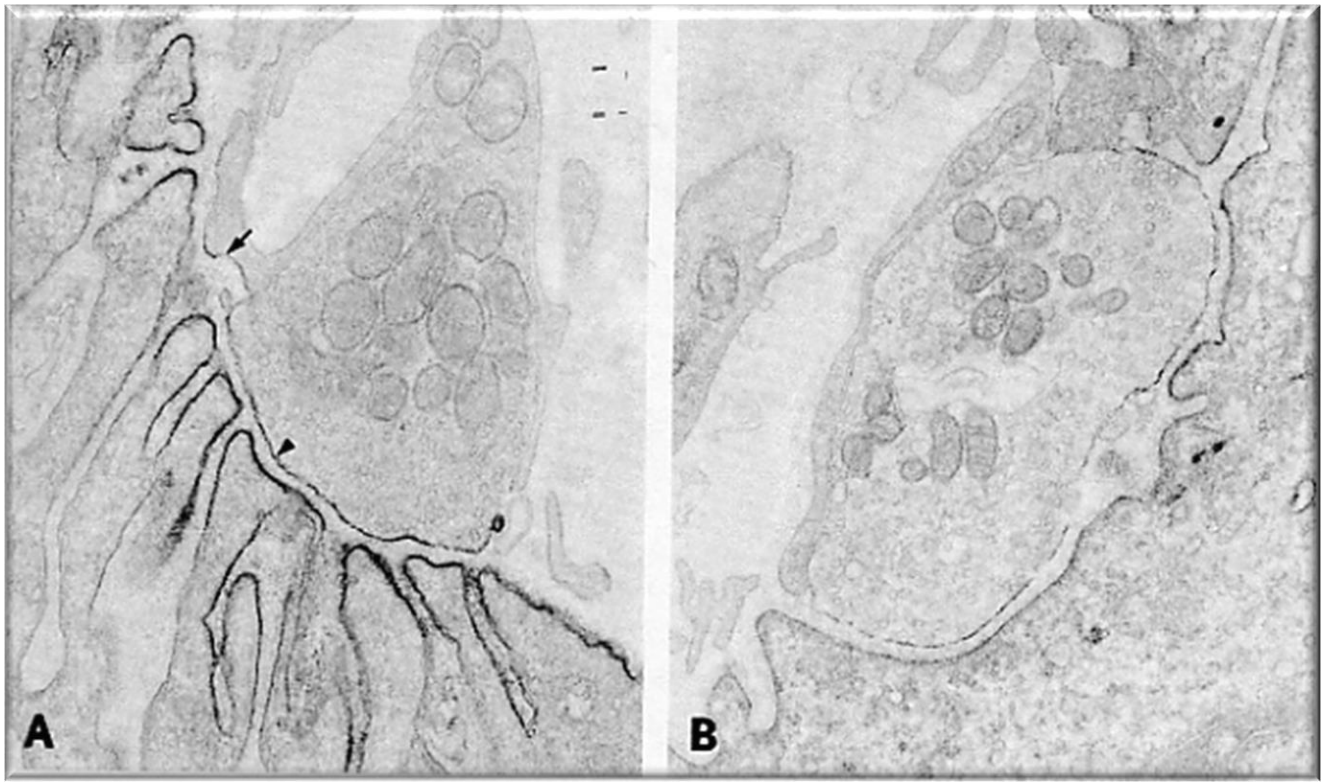

Big breakthroughs happen when what is suddenly possible meets what is desperately needed
Thomas Friedman
QuoteAddicts.com

Myasthenia Gravis

NMJ Alterations in MG



Normal **Myasthenia Gravis**

Engel AG, et.al., Neurology 1977, 27:307-315 (Fig 3)

Immune Therapy

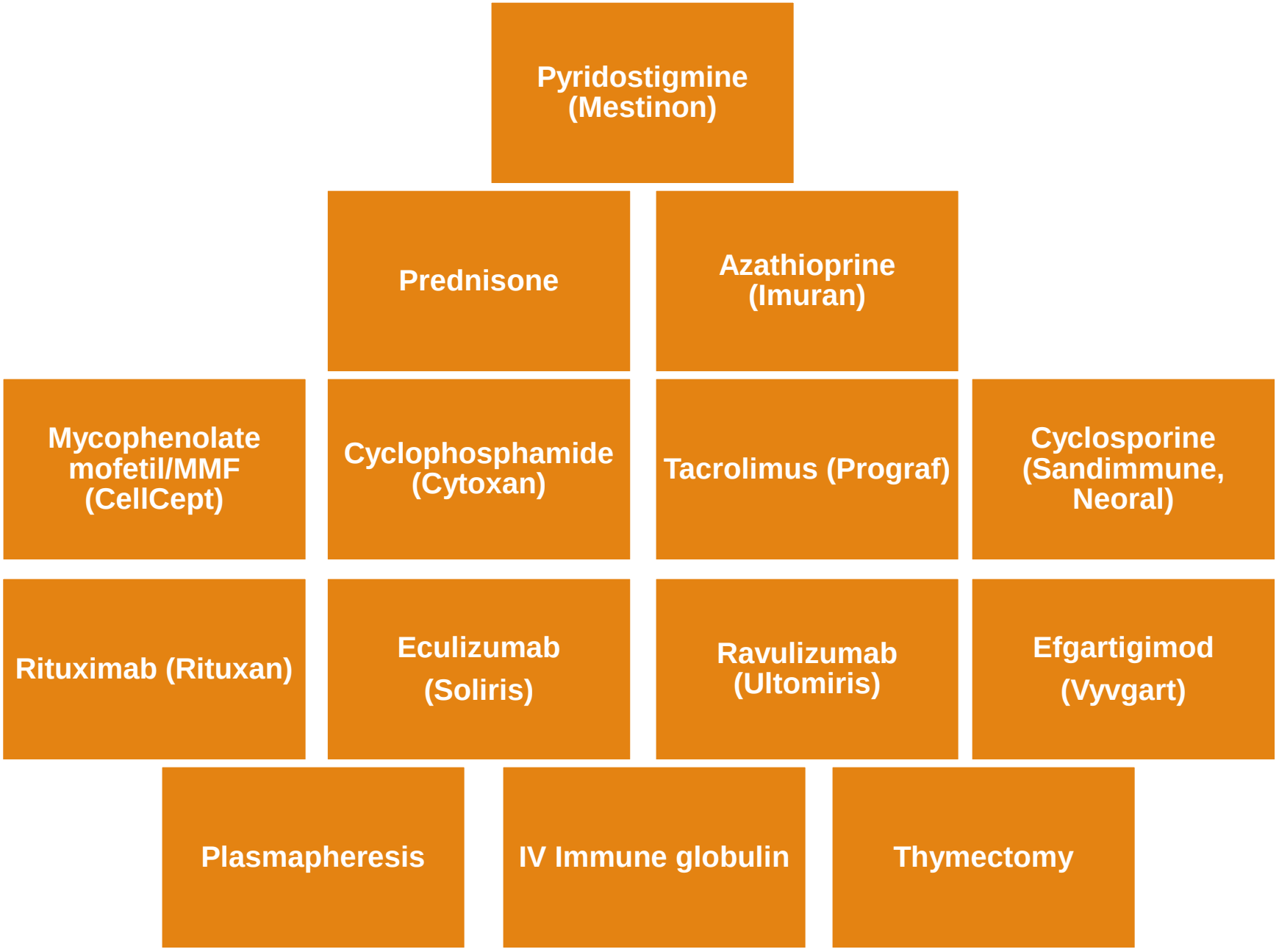
First thymectomy performed in 1911 by Ernst Ferdinand Sauerbruch (1875–1951). Blalock reported improvement in myasthenic patients after thymectomy (1937)

Hemodialysis (1960), Lymphatic drainage(1973)

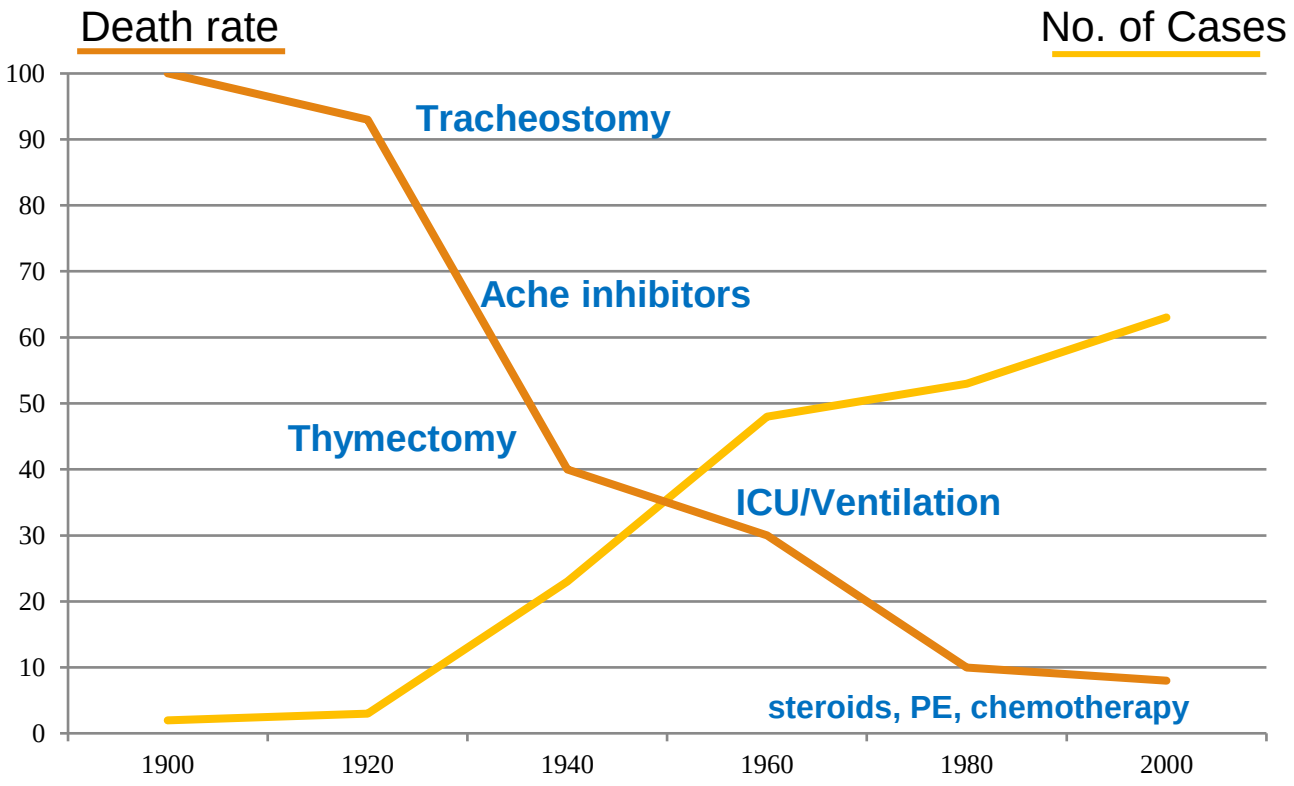
Advent of constant-care units and assisted respiration allowed safe trials of steroids in myasthenia gravis

Benefit of plasma exchange reported in 1979 by John Newsome-Davis

Currently there up to >10 commonly used treatments for Myasthenia Gravis

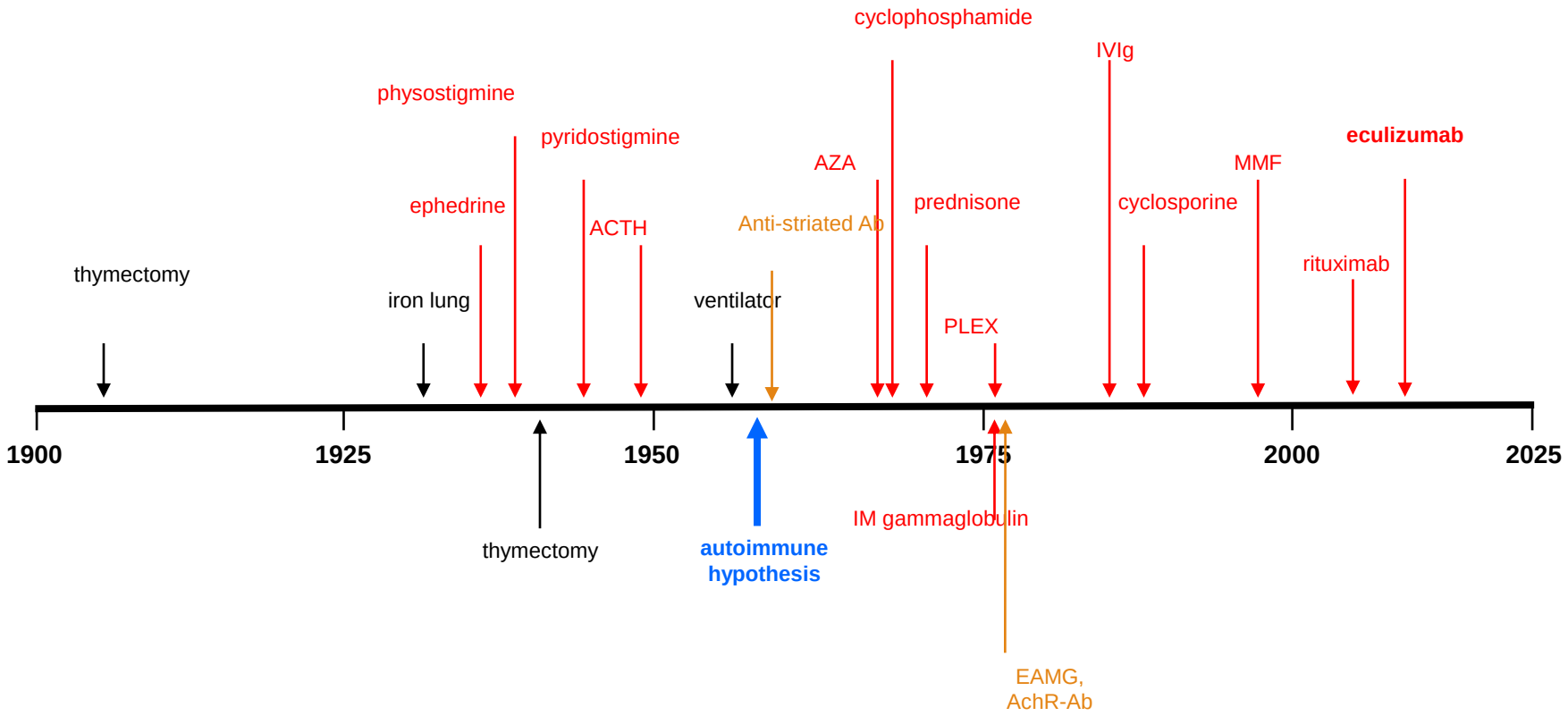

Pyridostigmine (Mestinon)
Prednisone
Azathioprine (Imuran)
Mycophenolate mofetil/MMF (CellCept)
Cyclophosphamide (Cytoxan)
Tacrolimus (Prograf)
Cyclosporine (Sandimmune, Neoral)
Rituximab (Rituxan)
Eculizumab (Soliris)
Ravulizumab (Ultomiris)
Efgartigimod (Vyvgart)
Plasmapheresis
IV Immune globulin
Thymectomy

Natural History of Myasthenia Gravis



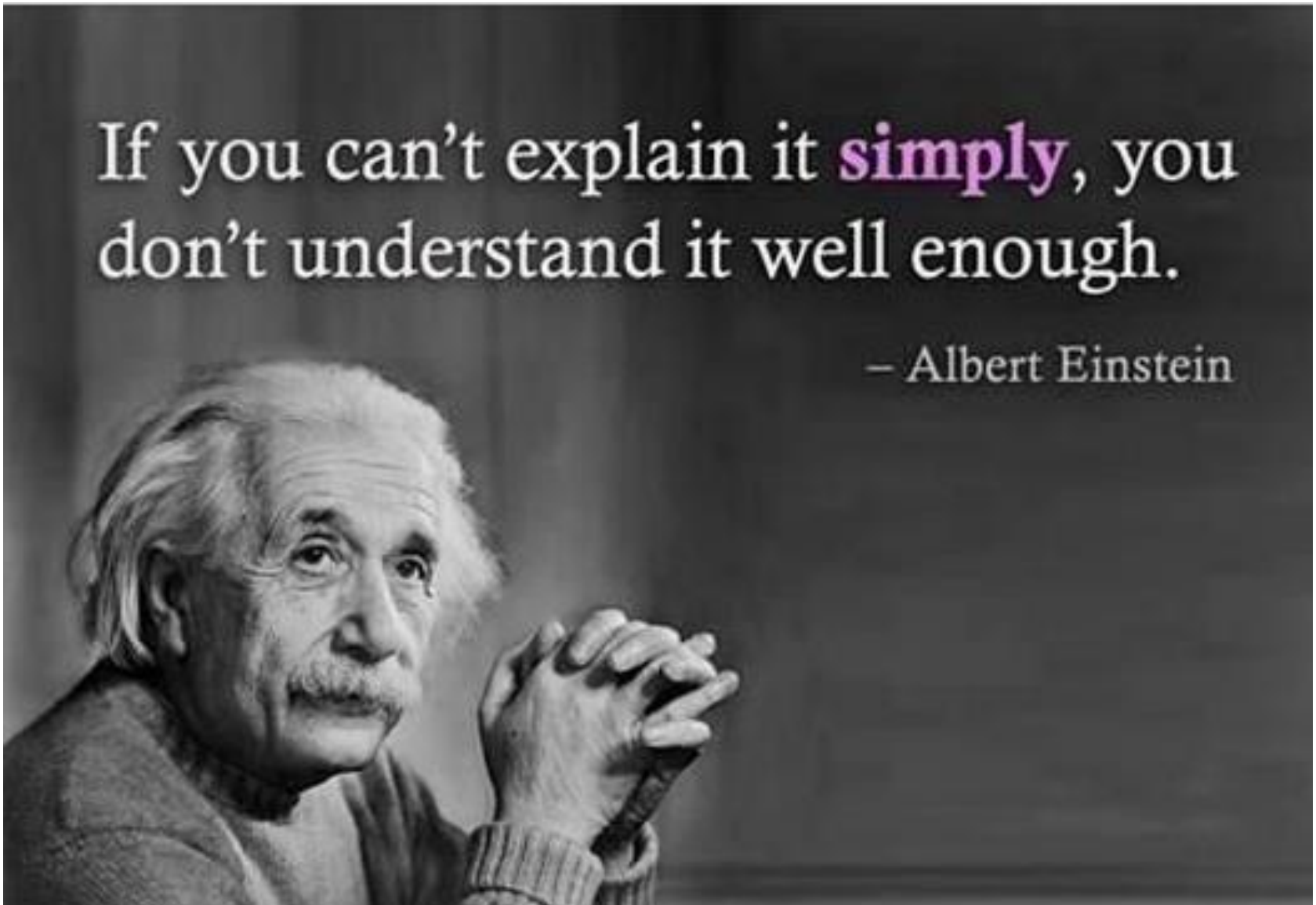
% percentage achieving remission has not significantly changed

The Evolution of MG Therapy



Keesey JC. A history of treatments for myasthenia gravis. 2004. *Semin Neurol*, 24(1):5-16.
courtesy Gordon Smith, MD VCU)

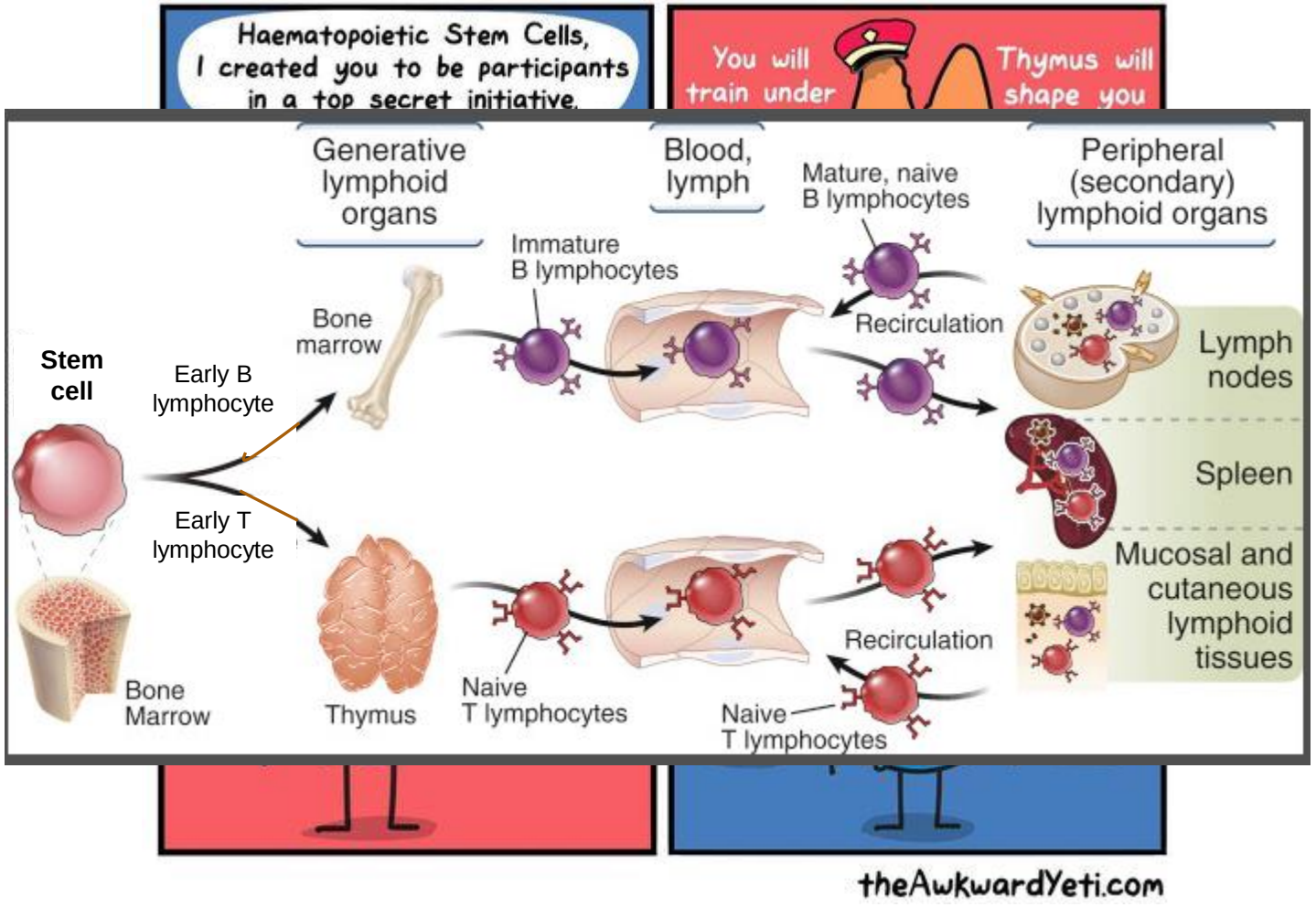
What is the Immune system



Immunity System
The Military Analogy

"The Immune System is the equivalent of an army, air force, marines, navy along with a national guard seeking out and destroying enemy invaders. It is the primary and sometimes secondary defense against both invaders and insurgents."

Immune *Bootcamp*



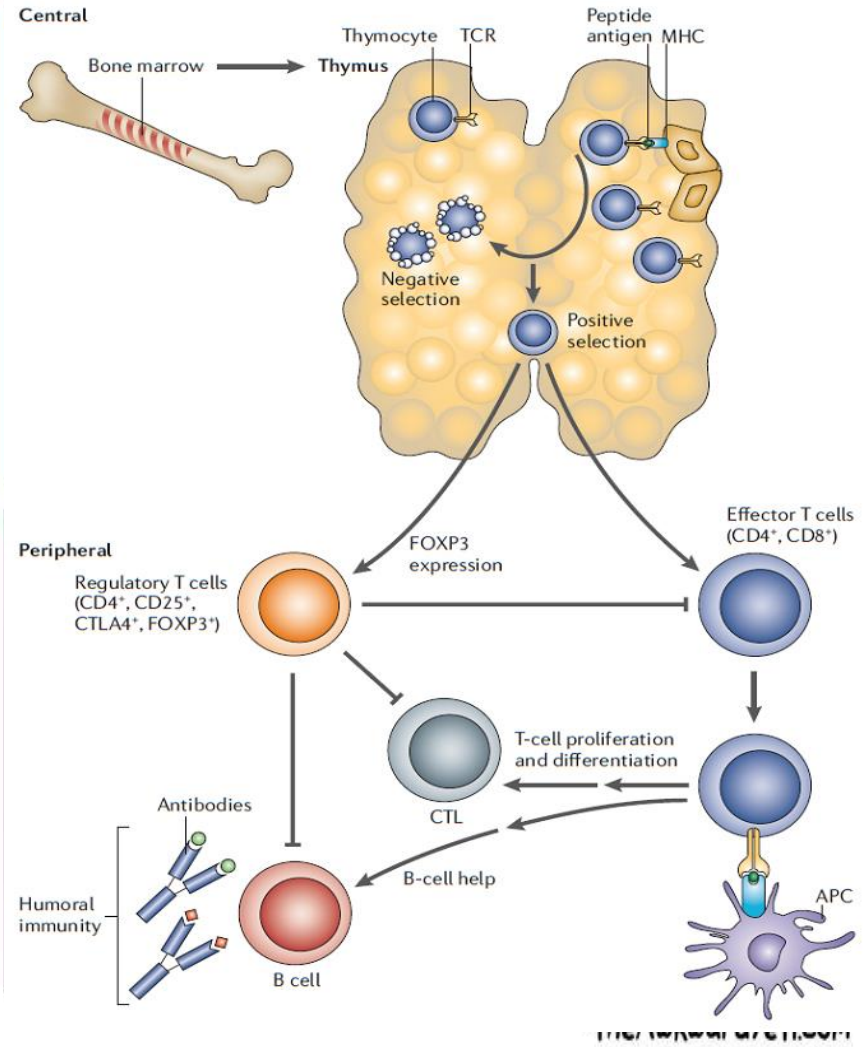
Autoimmune Myasthenia Gravis

The ***basic training*** of those T cells ***(T helper, T cytotoxic, T regulatory)*** in the thymus is inadequate

T cells are released for duty without ability to detect self from non-self and to 'shut down' the attack

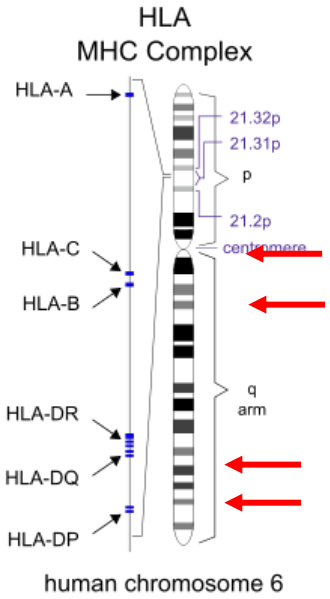
Those T cells determine that **AchR, MUSK, LRP4 proteins** necessary for nerve –muscle communication and muscle function are the **'enemy"**

Genetic and environmental factors may determine why and when autoimmune disease occurs



Antigen	Age of onset (years)	M:F	Weakness pattern	% ocular myasthenia	Thymus changes (predominant)
	≤50	1:4.5	Any	10–15%	Follicular hyperplasia
AChR	40–60 (mainly)	1:1	Any	2–3%	AB, B thymoma
	>50	1.8:1	Any	20%	Atrophy with rare germinal centers
MuSK	Any	1:4	Bulbar (mainly)	Rare	–
Lrp4	Any	1:2	Mild generalized (mainly)	20%	?[a]

Genomic-Wide Association Studies



HLA-C*07:01-Early onset AChR Ab MG MG

HLA-B*08:01-Early onset AChR Ab MG

HLA-DQA1-Late onset AChR Ab MG

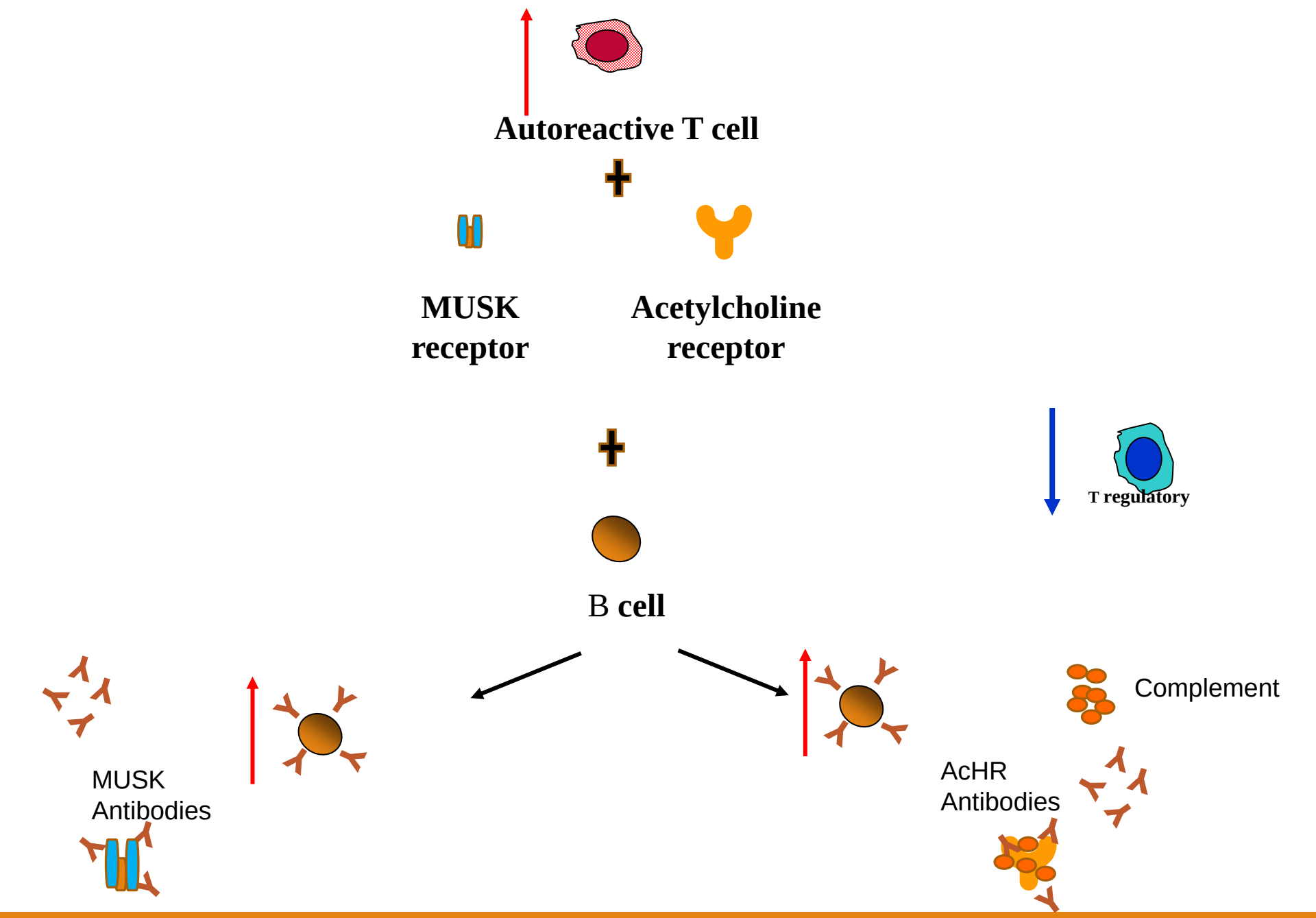
HLA-DQB1 *05:02-MUSK Ab MG MG

Other gene associations related to altered immune tolerance

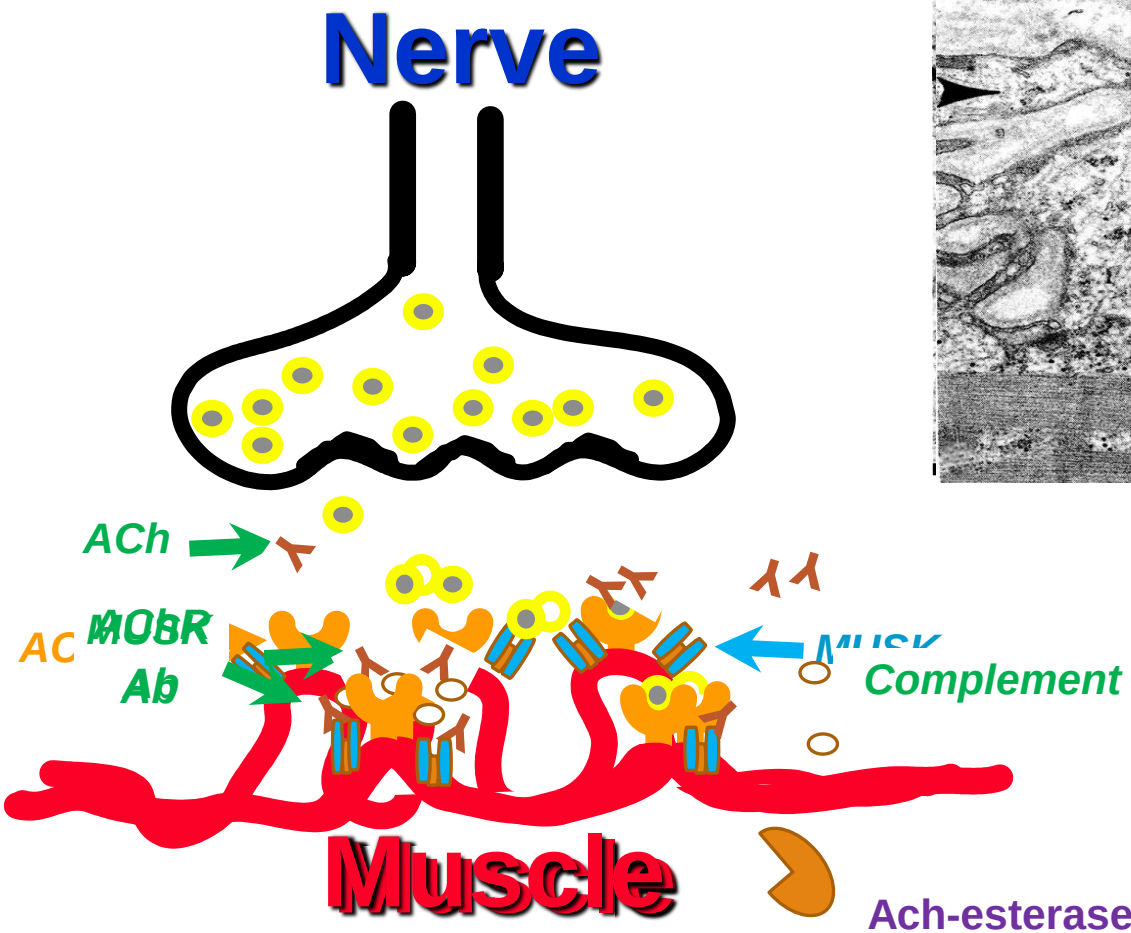
CTLA4 gene-suppresses activated T cells

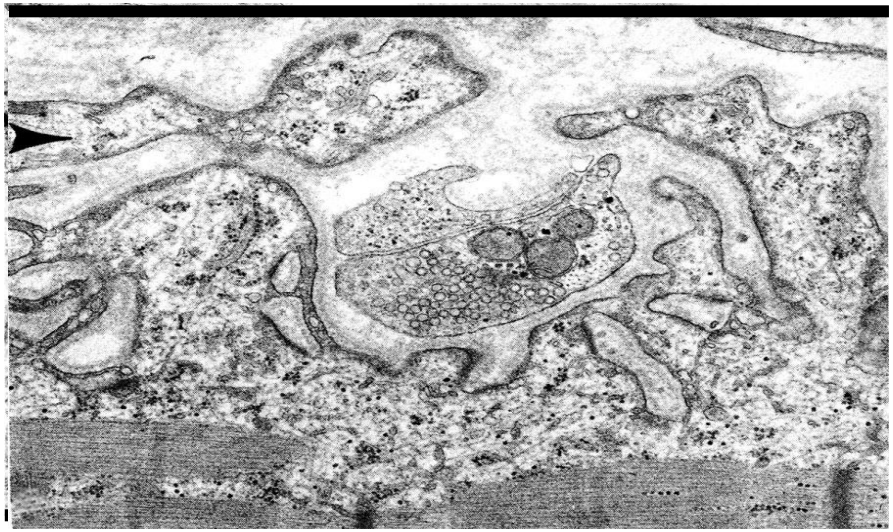
TNFSR11A-regulates T cell tolerization

ZBTB10-regulates IL-10 expression


Autoreactive T cell
MUSK receptor
Acetylcholine receptor
T regulatory
B cell
MUSK Antibodies
Complement
AcHR Antibodies

Myasthenia Gravis

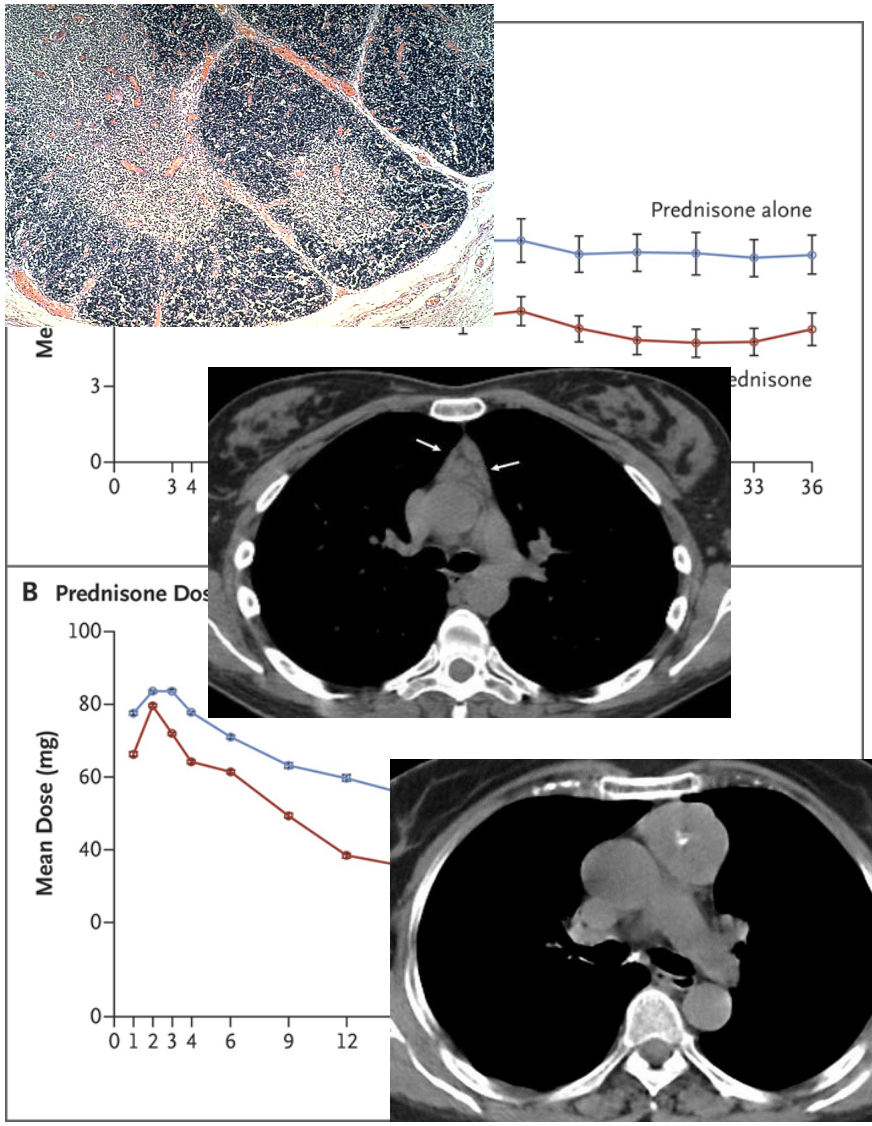




MUSK-Ab+

MGMG

NMJ



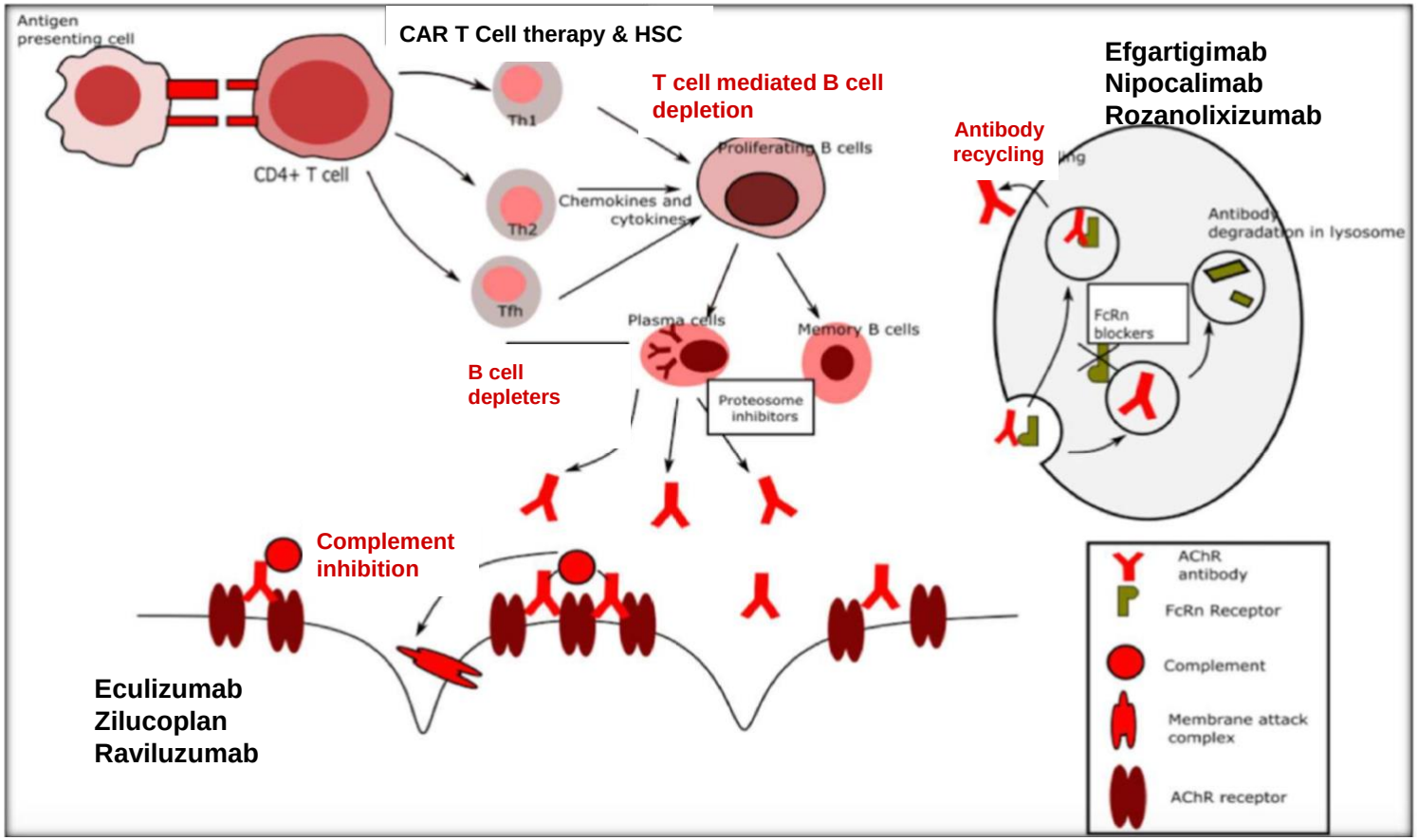
Treatment

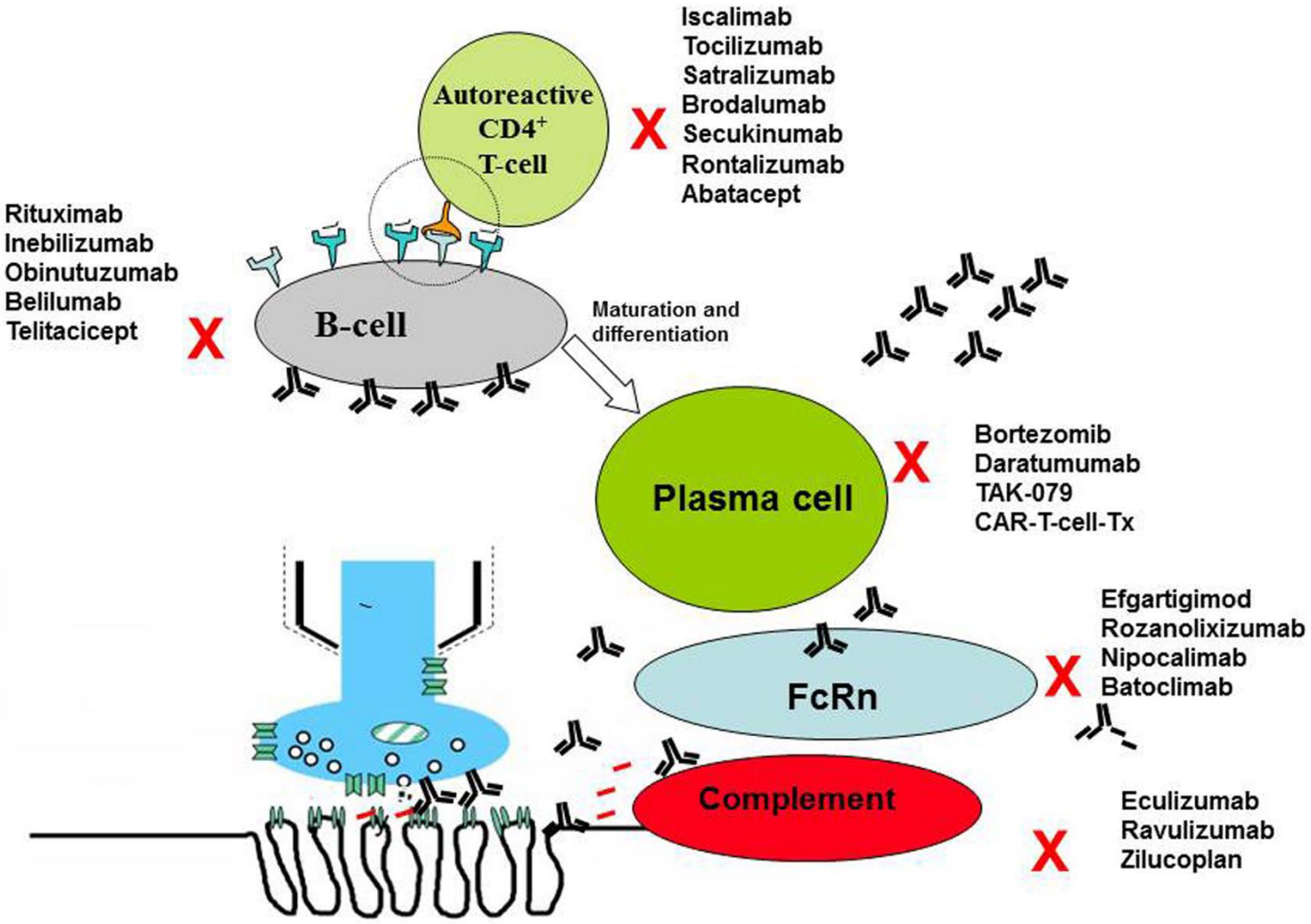
Thymectomy Trial

- Disability was less in Thymectomy + Prednisone group
- Average prednisone, dose at year 3 years was less in thymectomy group
- Less crisis, hospitalizations, rescue therapy
- Side effects similar in both groups

  - Prednisone naïve patients showed no difference with prednisone alone or with thymectomy.
  - No effect in males
  - Less effect in subjects > 40yrs *(p=0.02)*

Myasthenia Gravis: Novel and Emerging therapies




Iscalimab
Tocilizumab
Satralizumab
Brodalumab
Secukinumab
Rontalizumab
Abatacept
Autoreactive
CD4+
T-cell
X
Rituximab
Inebilizumab
Obinutuzumab
Belilumab
Telitacicept
X
B-cell
Maturation and
differentiation
Plasma cell
X
Bortezomib
Daratumumab
TAK-079
CAR-T-cell-Tx
FcRn
X
Efgartigimod
Rozanolixizumab
Nipocalimab
Batoclimab
Complement
X
Eculizumab
Ravulizumab
Zilucoplan

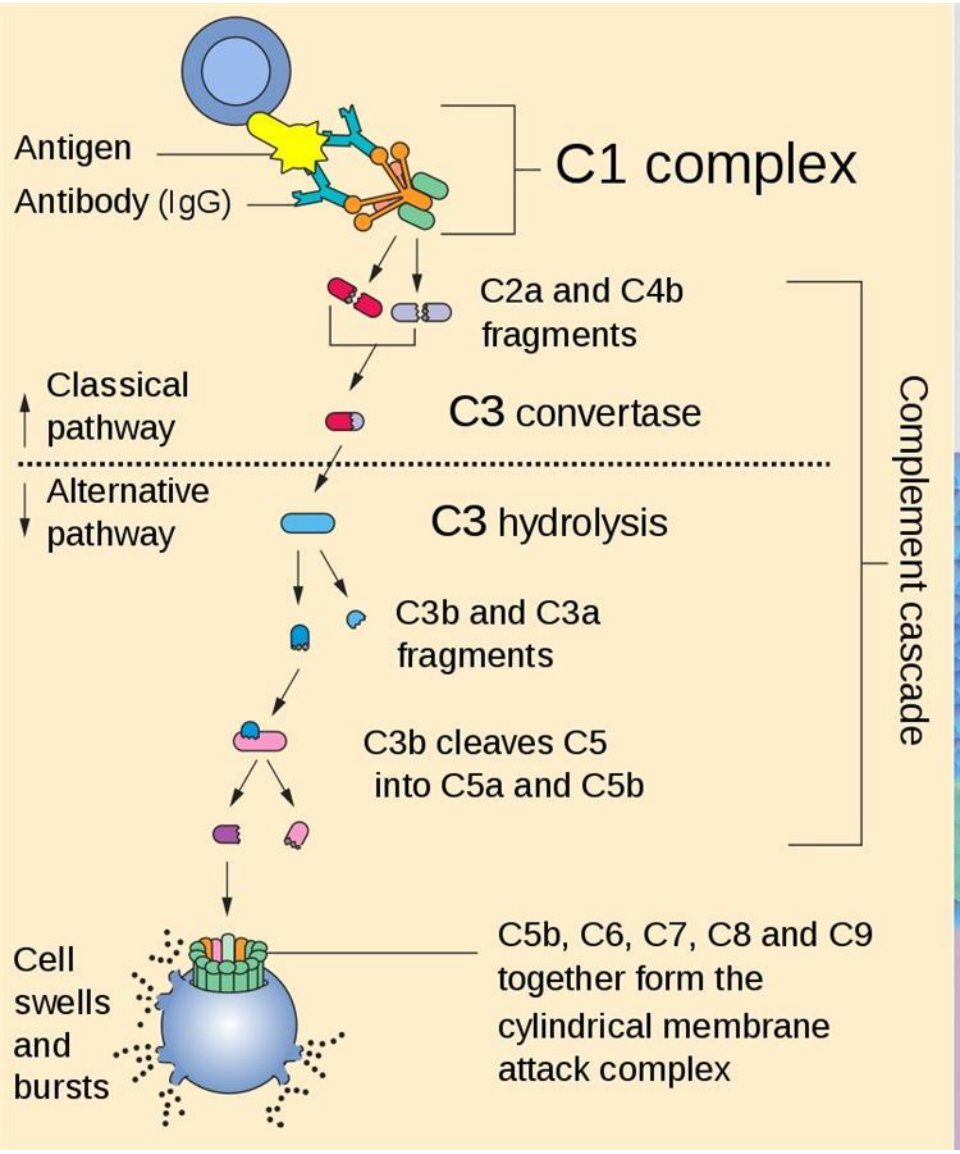
Clinical Trials

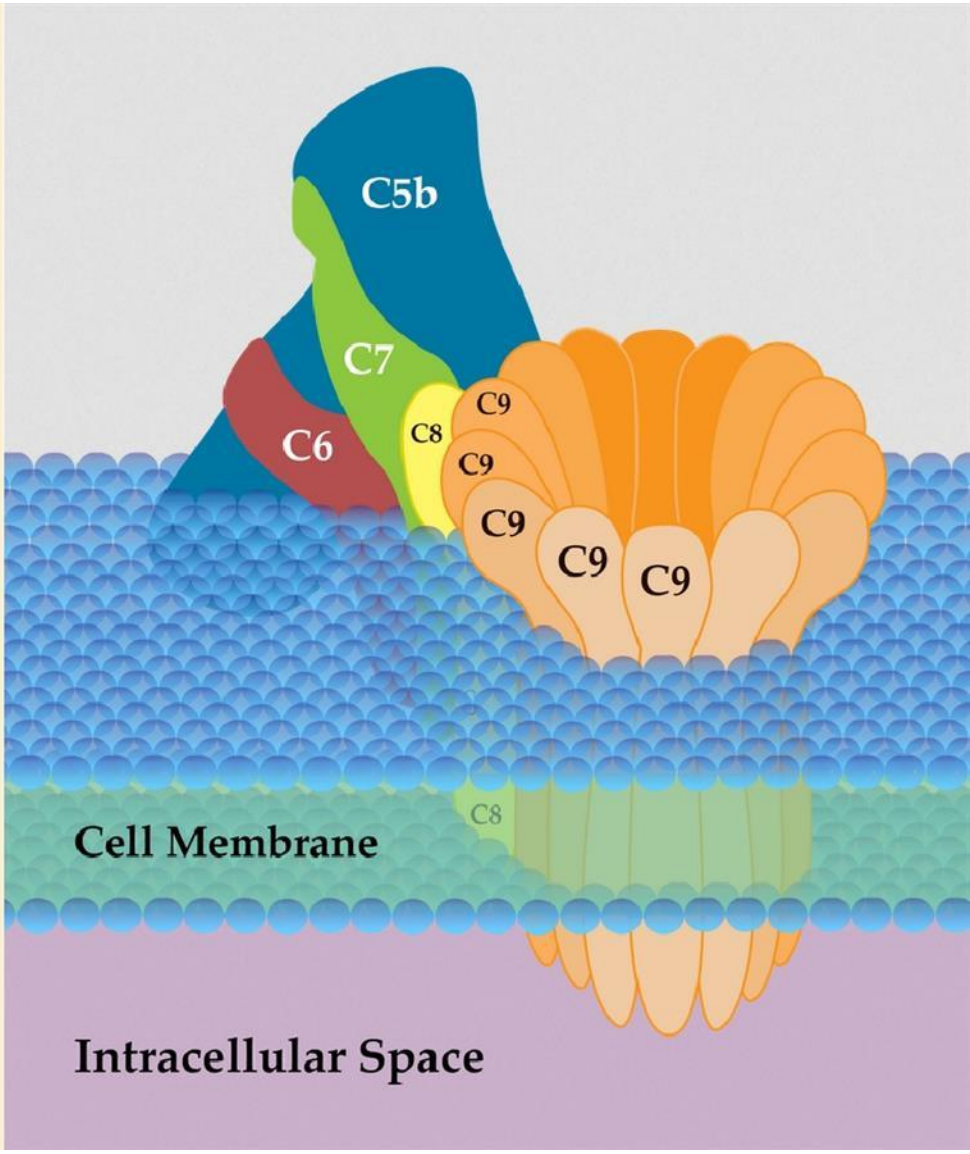
1. Abatacept (Orencia®, CTLA-4 FC Fusion Protein – prevents T cell activation)
2. Rozanolixizumab (FCRN)
3. M281 (Nipocalimab – FCRN)
4. RVT-1401 (FCRN)
5. Efgartidimod (FCRN)*
6. Ravulizumab (Monoclonal C5 inhibitor)
7. Zilucoplan (C5 peptide inhibitor)

Stops recycling of Immunoglobulin (antibody)

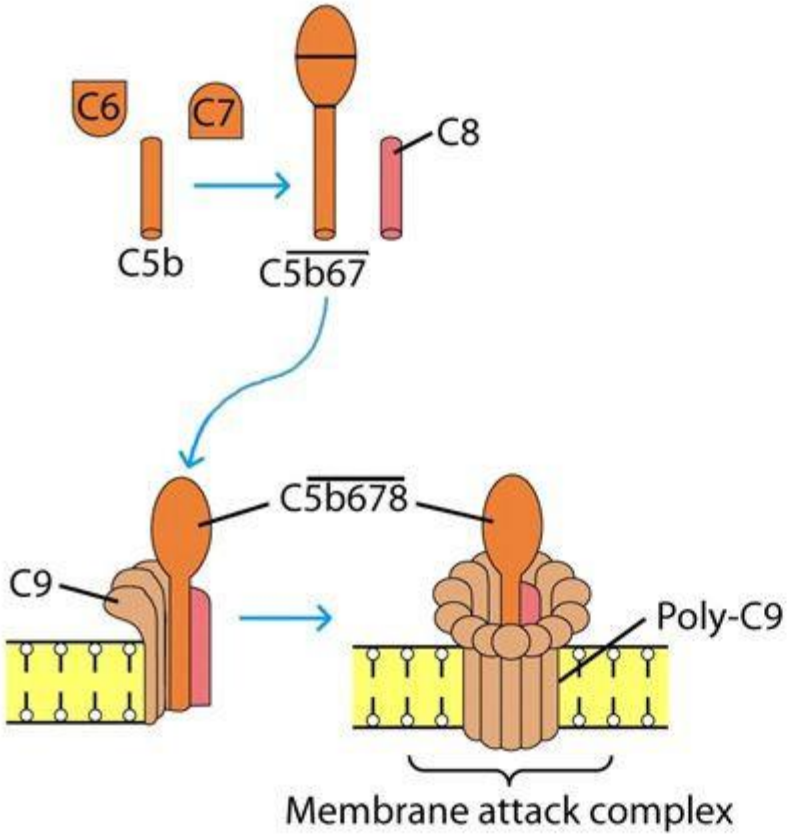
Complement inhibition

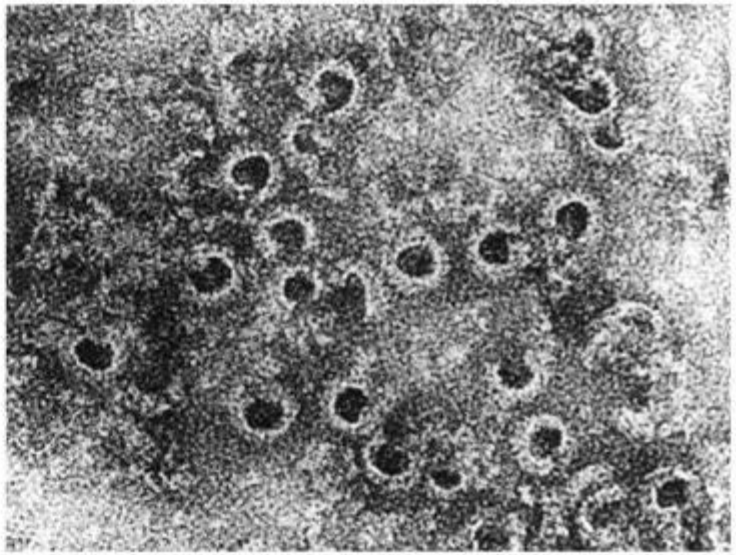
Complement Cascade





C5b triggers formation of the Membrane Attack Complex



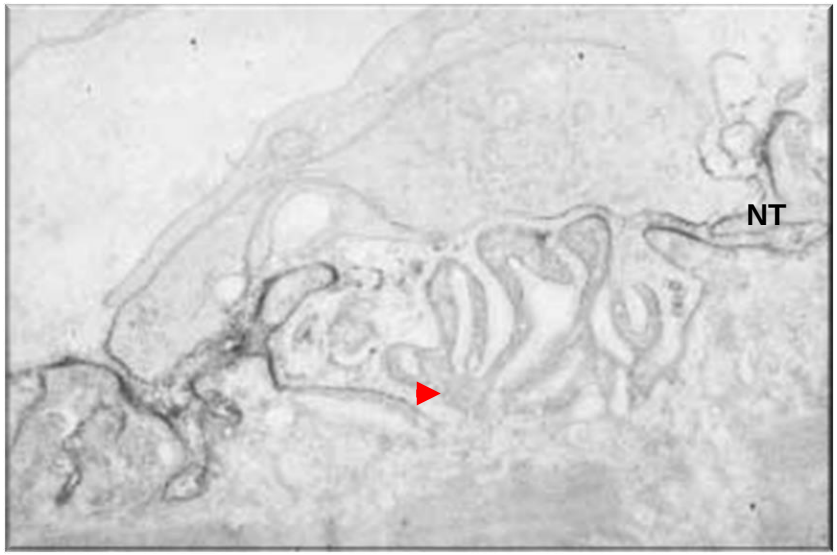


MAC is most effective against

- Gram-negative bacteria
- Nucleated cells
- Enveloped viruses

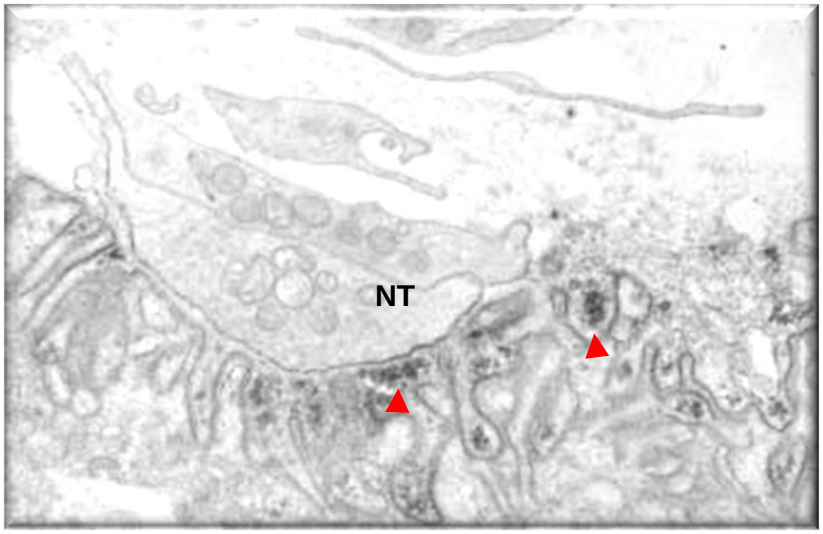
Myasthenia Gravis

Nerve Terminal Ultrastructure



IgG binding to Post Junctional Membrane

Terminal complement component (C9) binding to membrane debris



Engel, A. G., Lambert, E. H., Howard, F. M. Immune complexes (IgG and C3) at the motor end-plate in myasthenia gravis: ultrastructural and light microscopic localization and electrophysiologic correlations. *Mayo Clin. Proc. 52, 267–280 (1977).*

REGAIN Study: Eculizumab in MG (Soliris)

Primary Endpoint

- Change in Activities of Daily Living score at end of study (26 weeks)

Selected Inclusion Criteria

- Patients with disease burden (MGFA II-IV)
- Positive tests for anti-AChR antibodies
- Failed prior therapy over ≥1 year with
  - Taking 2 or more immune suppressive drugs or at least using plasma exchange or IVIG

>90% were taking at least 2 immune suppressive therapies

Up to 50% hospitalized

+20% had crisis and/or were ventilated

All were still symptomatic despite therapy

MG-ADL-Myasthenia Gravis Activities of Daily Living; QMG-Quantitative Myasthenia Gravis; MGC-Myasthenia Gravis Composite; MG-QOL15-Myathenia Gravis Quality of Life 15

MG-Activities of Daily Function

Grade	0	1	2	3
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube
Swallowing	Normal	Rare episode of choking	Frequent choking, necessitating changes in diet	Gastric tube
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant
TOTAL MG-ADL SCORE				

(From Wolfe GI et al. Myasthenia gravis activities of daily living profile. Neurology 1999;52:1487.)

MG –Quality of Life 15

Statements	Not at all	Very much	All the time
I am frustrated by MG			
I have trouble using my eyes			
I have trouble eating because of MG			
I have limited my social activity because of my MG			
My MG limits my ability to enjoy hobbies and fun activities			
I have trouble meeting the needs of my family because of my MG			
I have to make plan around my MG			
My occupational skills and job status have been negatively affected by MG			
I have difficulty speaking due to MG			
I have trouble driving due to MG			
I am depressed about MG			
I have trouble walking due to MG			
I have trouble getting around public places because of my MG			
I feel overwhelmed by my MG			
I have trouble performing my personal grooming needs			

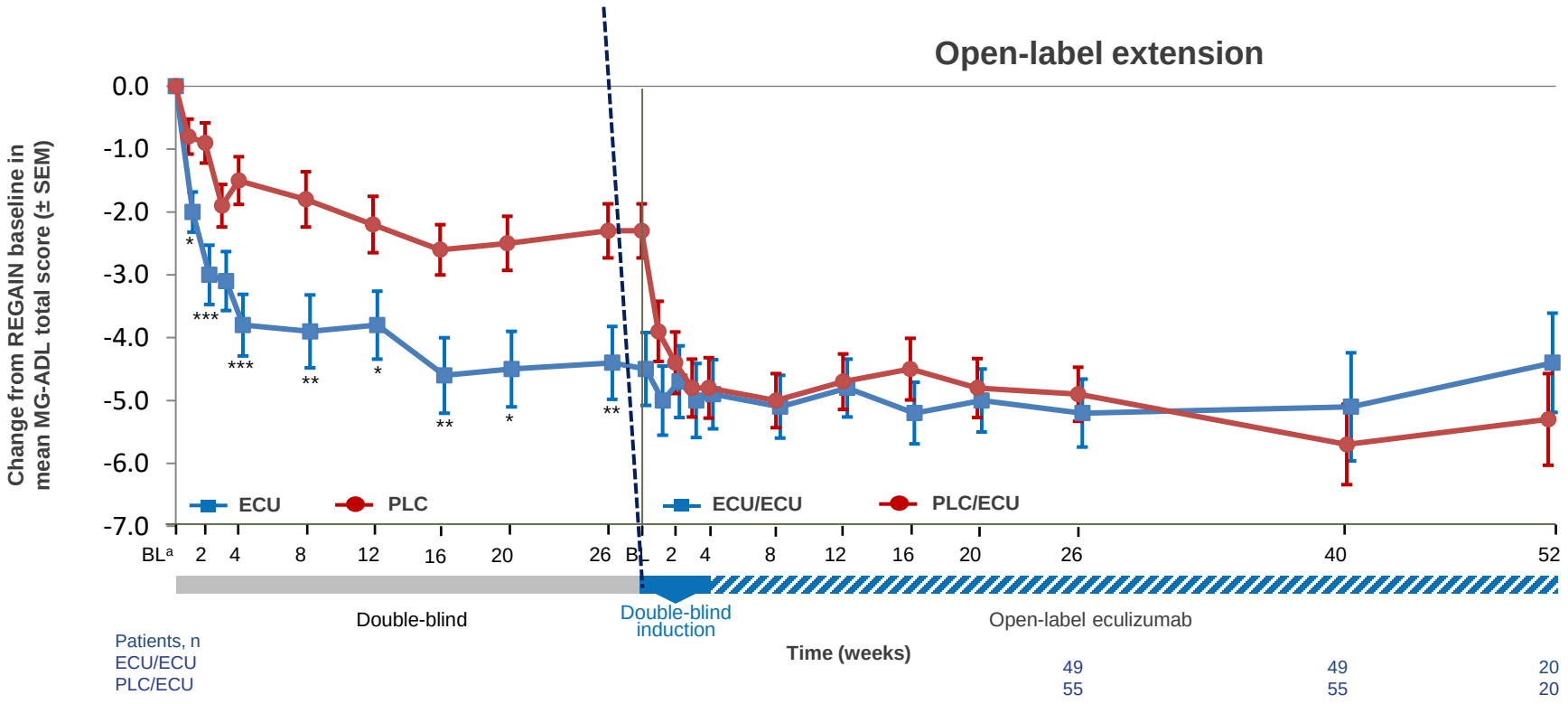
MG - Myasthenia gravis, MGFA - Myasthenia Gravis Foundation of America

Quantitative MG Score (QMG)

Test Item Grade	0	1	2	3
Double vision on lateral gaze **right** or **left** (circle one)	61 sec	11–60 sec	1–10 sec	Spontaneous
Ptosis (upward gaze)	61 sec	11–60 sec	1–10 sec	Spontaneous
Facial muscles	Normal lid	Complete, weak, some resistance	Complete, without resistance	Incomplete
Swallowing 4 oz water (½ cup)	Normal	Minimal coughing or throat clearing	Severe coughing/choking or nasal regurgitation	Cannot swallow (test not attempted)
Speech following counting aloud from 1 to 50 (onset of dysarthria)	None at #50	Dysarthria at #30–49	Dysarthria at #10–29	Dysarthria at #9
Right arm outstretched (90° sitting)	240 sec	90–239 sec	10–89 sec	0–9 sec
Left arm outstretched (90° sitting)	240 sec	90–239 sec	10–89 sec	0–9 sec
Vital capacity (% predicted)	≥80%	65–79%	50–64%	<50%
Right-hand grip (KgW) Male Female	 ≥45 ≥30	 15–44 10–29	 5–14 5–9	 0–4 0–4
Left-hand grip (KgW) Male Female	 ≥35 ≥25	 15–34 10–24	 5–14 5–9	 0–4 0–4
Head, lifted (45° supine)	120 sec	30–119 sec	1–29 sec	0 sec
Right leg outstretched (45° supine)	100 sec	31–99 sec	1–30 sec	0 sec
Left leg outstretched (45° supine)	100 sec	31–99 sec	1–30 sec	0 sec
TOTAL QMG SCORE				

REGAIN and Extension Study-Eculizumab (Soliris)

Percent change from baseline in MG-ADL total score



*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$; eculizumab compared to placebo.
SEM, standard error of the mean; BL, baseline

Data cut-off, 30 September 2016

Howard JF et.al., Presented to AANEM Scientific Session, 2017

REGAIN and Extension Study- Eculizumab (Soliris)

Patients experiencing ‘minimal manifestations of disease”

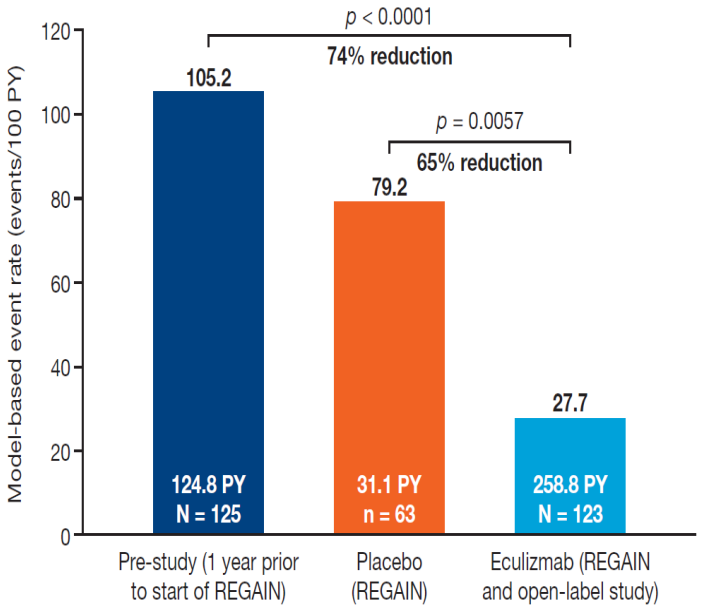
- Placebo 14% at 26 weeks but increased to 52% when placed on drug at 130 weeks
- Treatment group 25% at 26 weeks but increased to 60% when placed on drug at 130 weeks

Exacerbations and Hospitalizations dropped from 70-100 rate calculation to 13-17 at 130 weeks

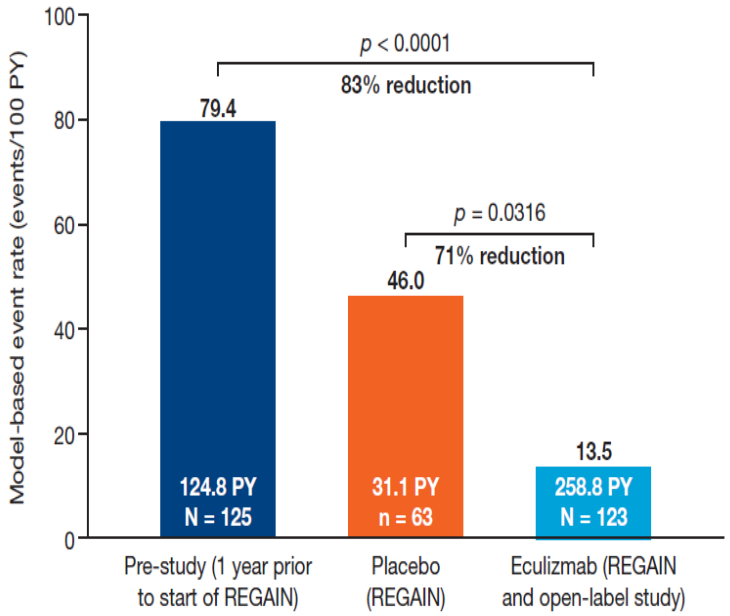
REGAIN and Extension Study- Eculizumab (Soliris)

Exacerbations and Hospitalization Rates

Exacerbation rates[a]



MG-related hospitalization rates[a]

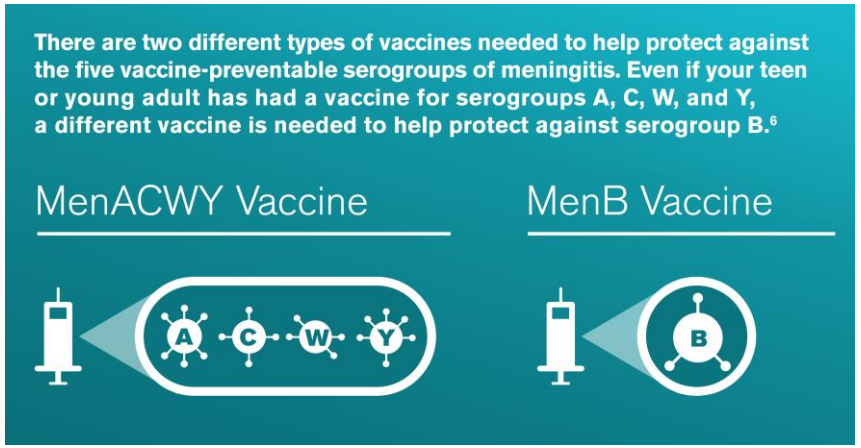


Jacob S, Guptill JT, Meisel A, Fujita KP, Patra, K, Howard JF Jr: Eculizumab reduces myasthenia gravis exacerbation rates. Presented at the 2018 Annual Meeting of the AANEM, Washington DC, 2018

REGAIN and Extension Study- Eculizumab (Soliris)

Safety from Extension Study

- 10-15% experience general aches
- Two patients died during clinical program:
  - One died 89 days after discontinuation from the 301 study, due to complications of myasthenic crisis
  - One died of hepatic failure 25 days after last study dose in study 302
- No meningococcal infections reported thus far
- Treatment requires vaccination to prevent bacterial meningococcal



Ravulizumab (Ultomiris®)

Phase II 1:1 DB:PC 26 week study in175 AchR+ Ag MG Patients

MG ADL and QMG improved above placebo (−3.1 vs. −1.4; P<0.001) and QMG (−2.8 vs. −0.8; P<0.001)

QMG improved > 5 points in a greater proportion of treated patients vs. placebo (30.0% vs. 11.3%; P=0.005).

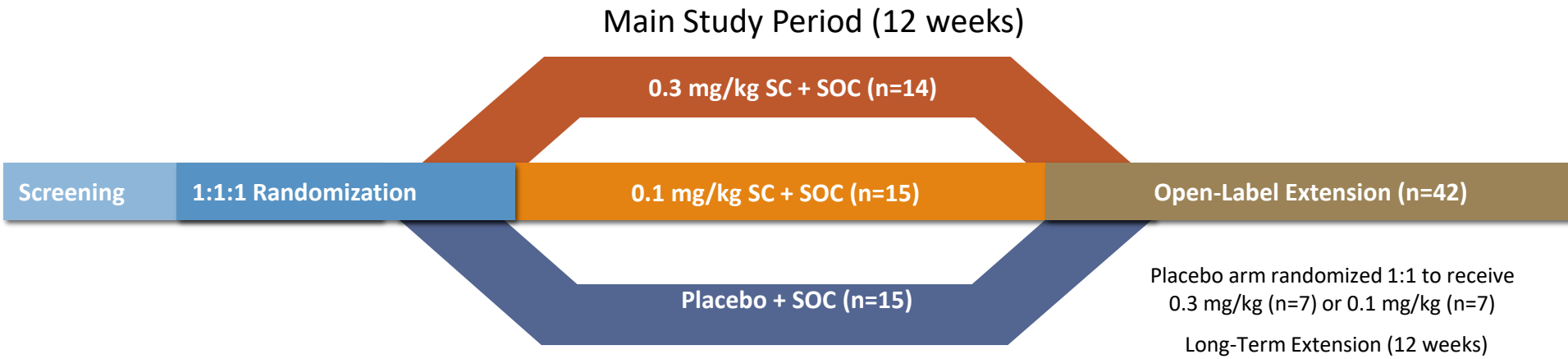
No notable differences in adverse events were observed.

FDA approved April 2022

Day 1 : 2400–3000 mg
Day 15 : 3000–3600 mg
Q8wks : 3000–3600 mg

Vu, 2021 NEJM Evidence

Zilucoplan- Another complement Inhibitor in AchR positive MG Patients



Endpoints:

Primary: Change in Doctor measured disability (QMG score after 12 weeks

Enrollment:

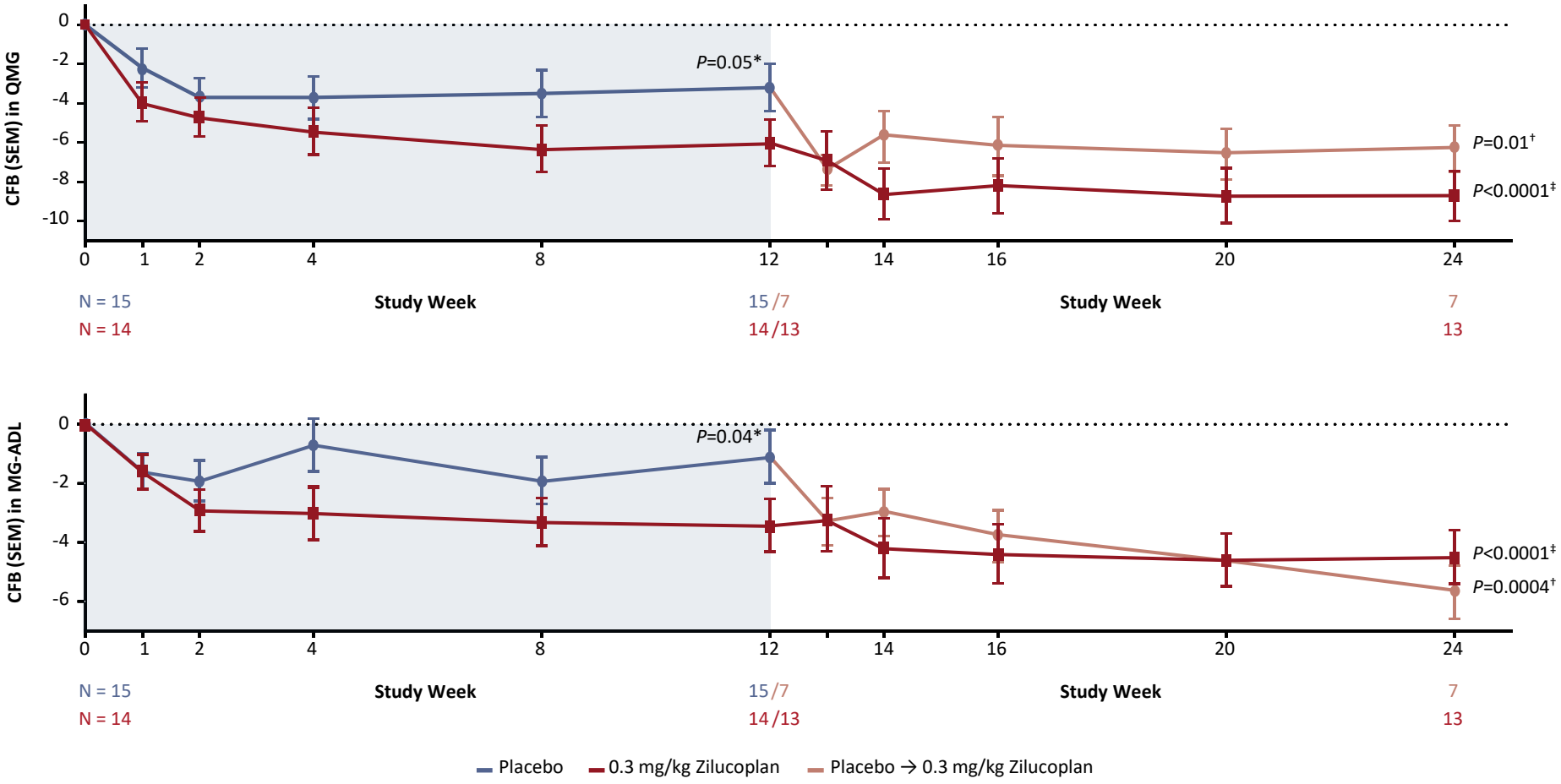
44 patients (vs. target of 36), 25 sites

>80% on 2+ immunosuppressive treatments

50-70% on IVIG

Howard JF Jr etal JAMA Neurology 2020 May 1;77(5):582-592

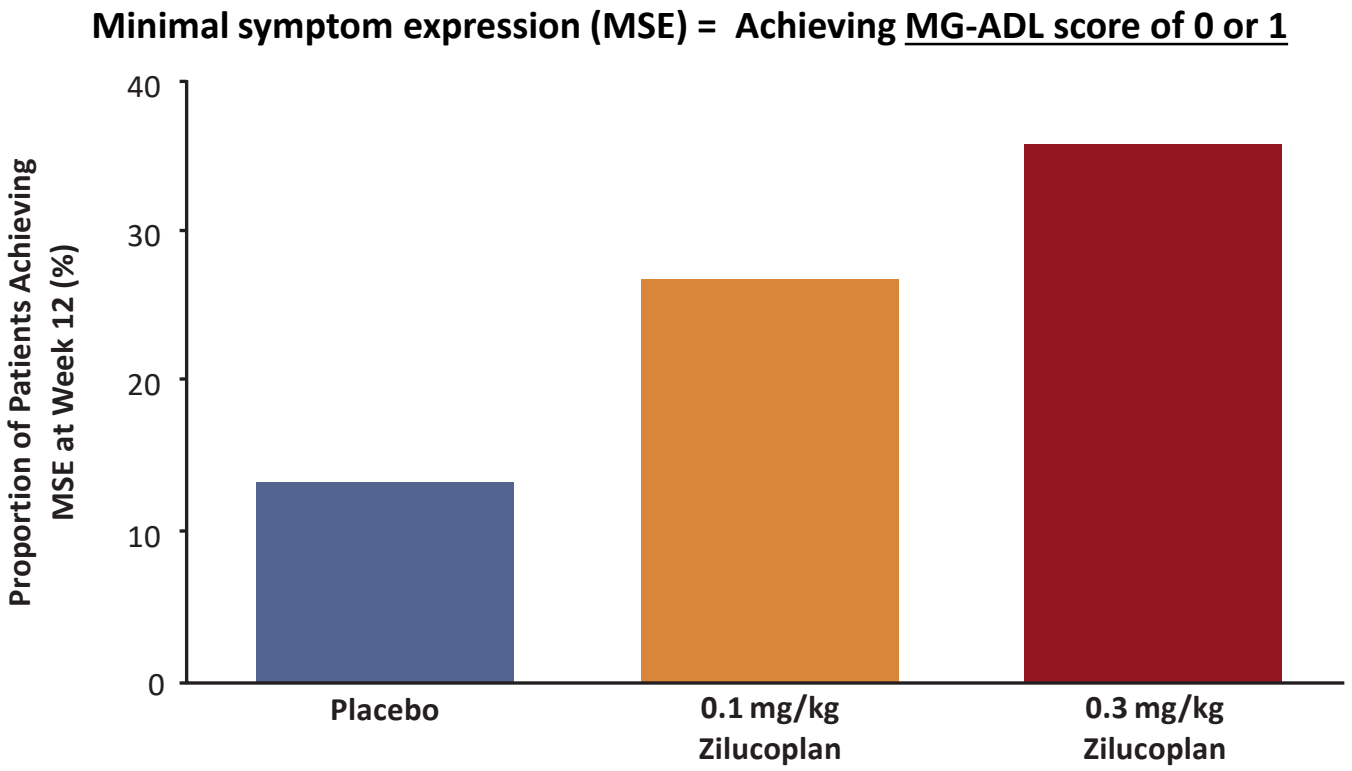
Zilucoplan Phase 2
QMG and MG-ADL



*1-sided analysis of covariance for LS mean change from baseline for 0.3 mg/kg arm vs. placebo; placebo patients re-baselined to zero upon completion of 12-week main study.
†2-sided t test for LS mean change from week 12 to week 24 for placebo patients crossing over to 0.3 mg/kg (n=7).
‡2-sided t test for LS mean change from week 0 to week 24 for 0.3 mg/kg arm.
CFB, change from baseline; LS, least squares; MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis; SEM, standard error of the mean.

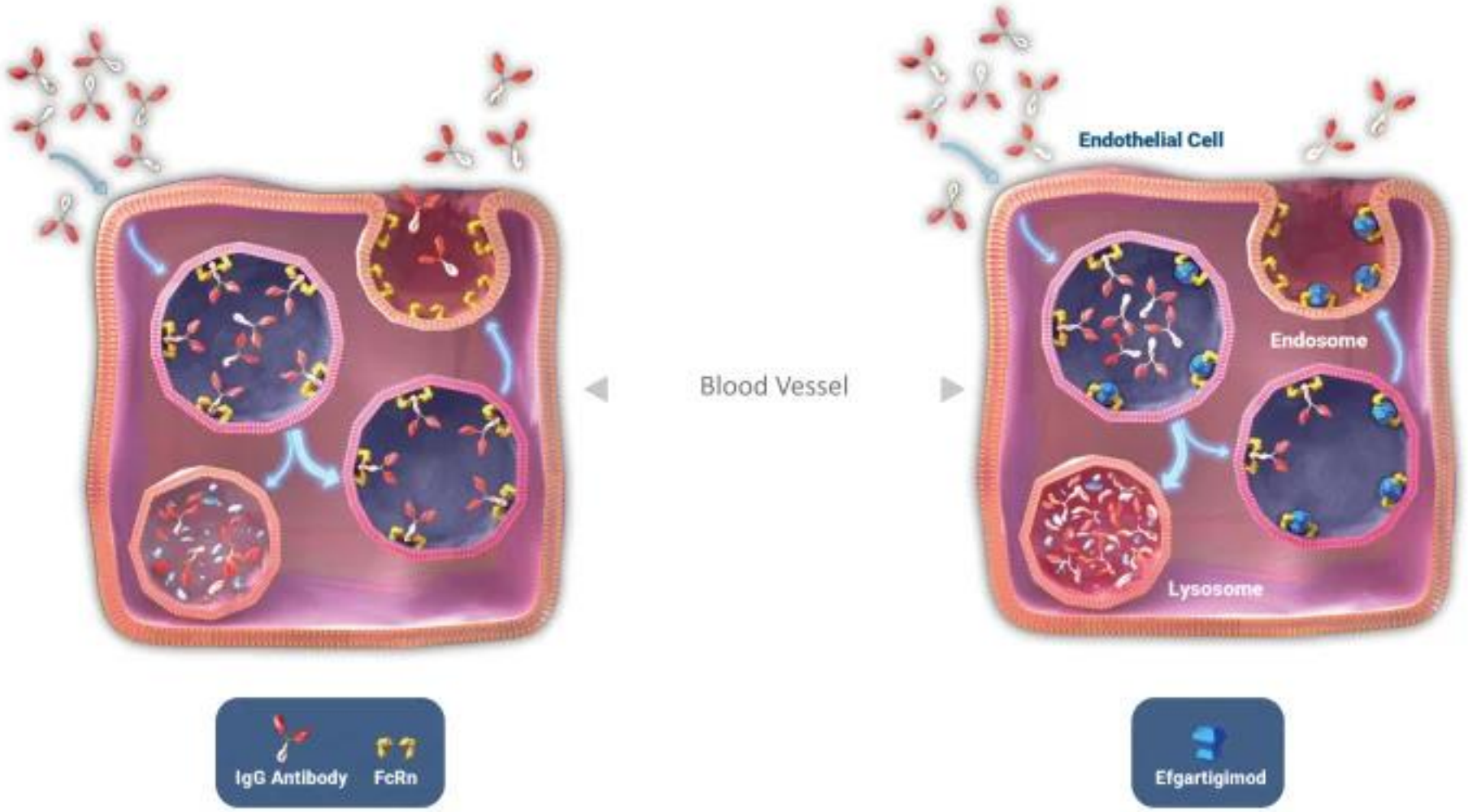
Zilucoplan Phase 2

Minimal Symptom Expression Achieved by Week 12



JF Howard, 2020

MG antibody (IgG) Target FcrN (Neonatal Fc receptor)



Efgartigimod

ADAPT Study Design

DESIGN

167 AchRAB+ gMG patients

MG-ADL score ≥5*

On a minimum of one stable gMG treatment**

2 weeks screening

Patients randomized 1:1 to receive 10 mg/kg IV efgartigimod or placebo

26 weeks

Primary endpoint: MG-ADL responders in AChR-Ab+ patients in cycle 1 (8 weeks)

Open – label Extension

- **151 patients who completed entered the open label cycles**
- **Up to 3 years treatment**

DOSING

Treatment Cycles of 4 weekly IV infusions
(1 hour infusion)

All patients receive initial treatment cycle

Individualized treatment cycles
(*up to 3 cycles in 26 weeks*)

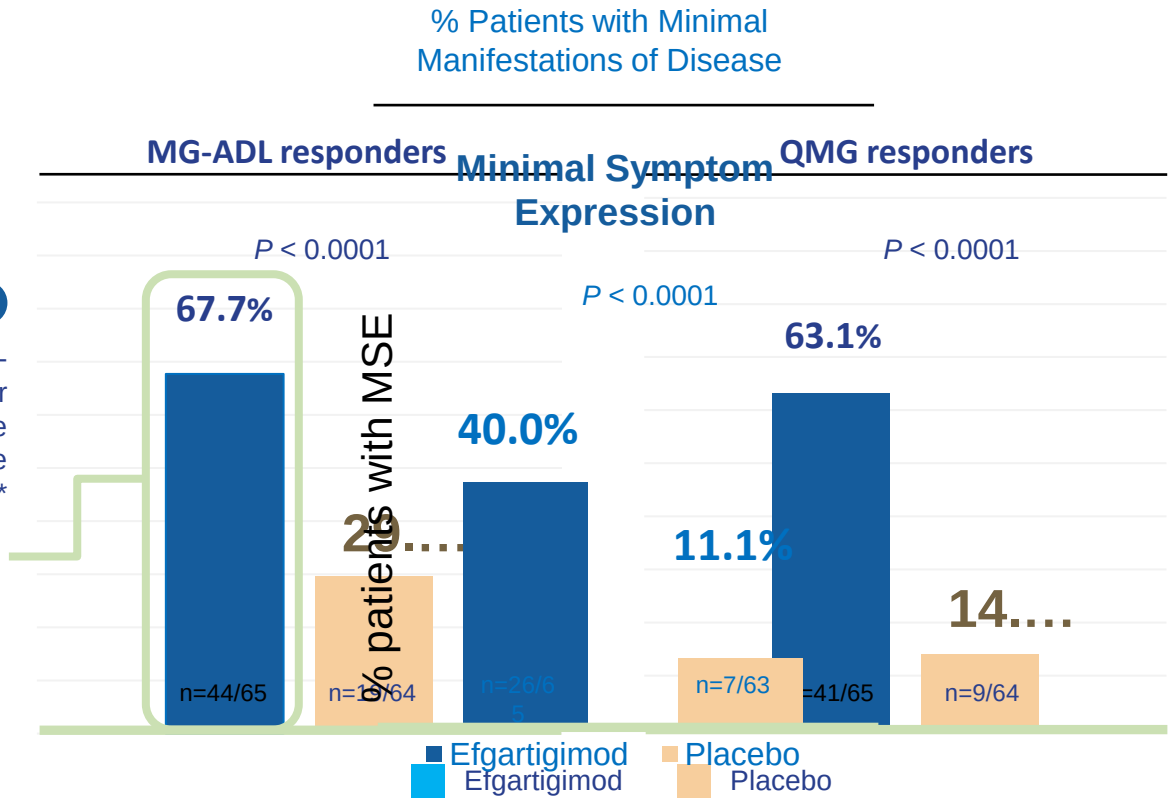
Time between cycles determined by duration of clinically meaningful improvement (CMI)

Retreatment criteria:

- ≥8 weeks since initiation of previous cycle
- Total MG-ADL ≥5 points*
- For MG-ADL responders, no CMI in MG-ADL (i.e., <2-point reduction compared to start of cycle)

Included 20-25% who did not have AchR positive antibodies

Significantly more efgartigimod treated patients had clinically meaningful improvement in function and strength



Primary

MG-ADL responder: ≥2-point improvement for at least four consecutive weeks during the first cycle*

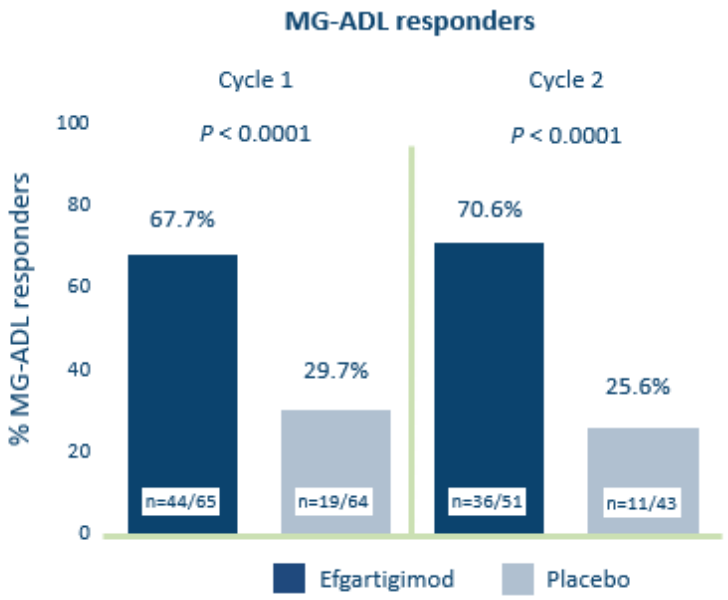
Secondary

QMG responder: ≥3-point improvement for at least four consecutive weeks during the first cycle*

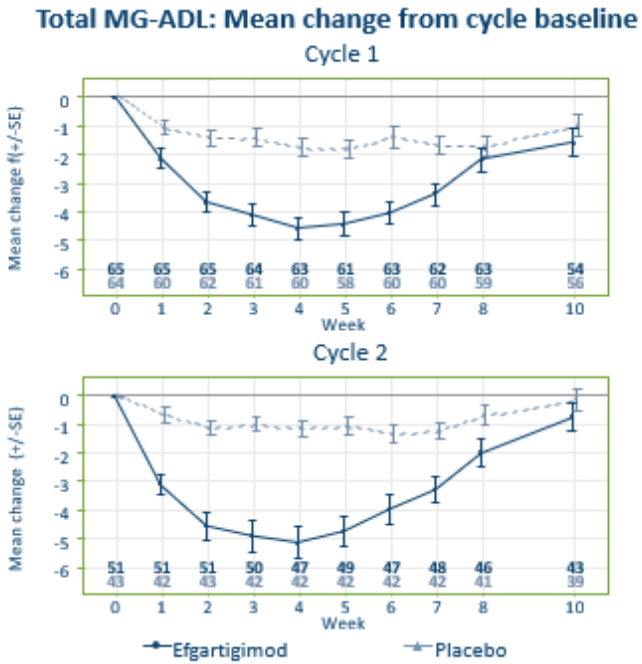
* The first reduction had to occur no later than 1 week after the last infusion
MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis Score

Howard JF Jr etal: MGFA Scientific Session, October 3, 2020

Efgartigimod (MG-ADL Late Responders) Durability of Response



36.8% (7/19) efgartigimod patients who were not MG-ADL responders in cycle 1 and were retreated achieved MG-ADL responder for the first time in cycle 2



Across cycles 1 and 2 **78.5% (51/65)** efgartigimod patients were MG-ADL responders

The number of patients in cycle 2 is smaller as some patients only required one treatment cycle during the study
The numbers below trend lines indicate the number of patient measurements for each data set

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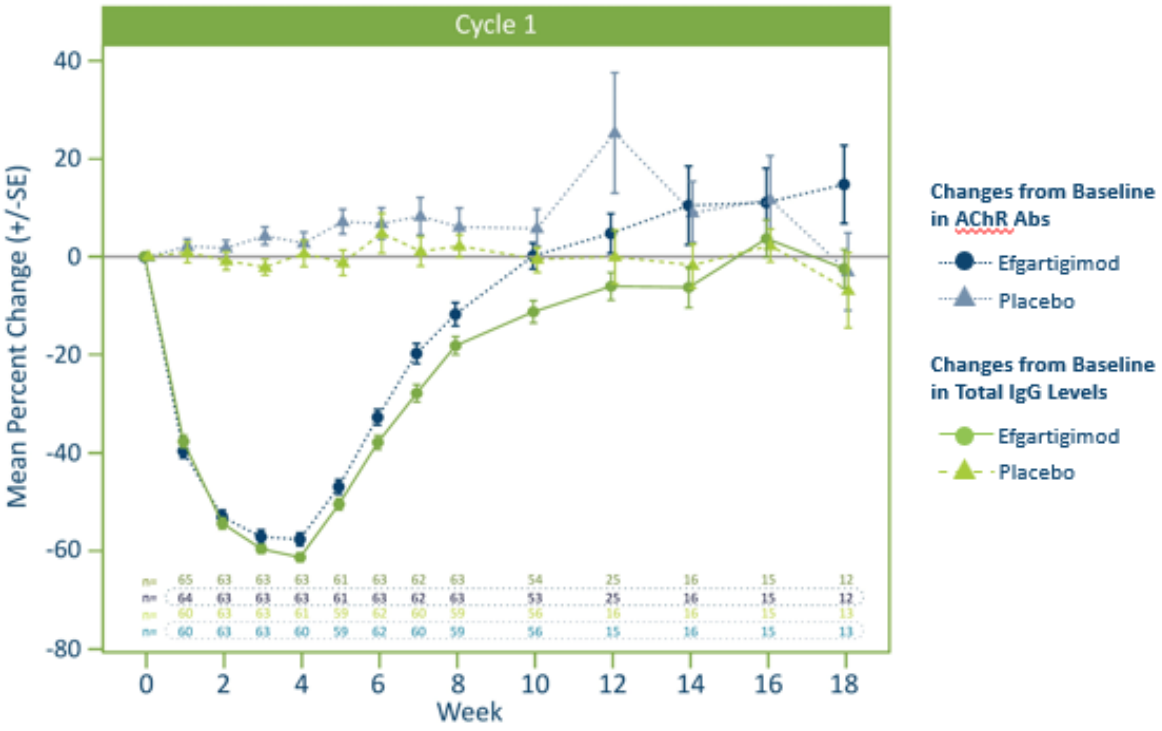
Efgartigimod (MG-ADL Responders)
AChR Ab & IgG Levels

- Maximum mean reduction at week 4: Total IgG 61.3%, AChR-Ab 57.6%
- Similar reduction across subtypes (IgG1, 2, 3, 4)
- Overall population experienced similar reductions (AChR-Ab+ and AChR-Ab negative)
- Albumin levels did not change



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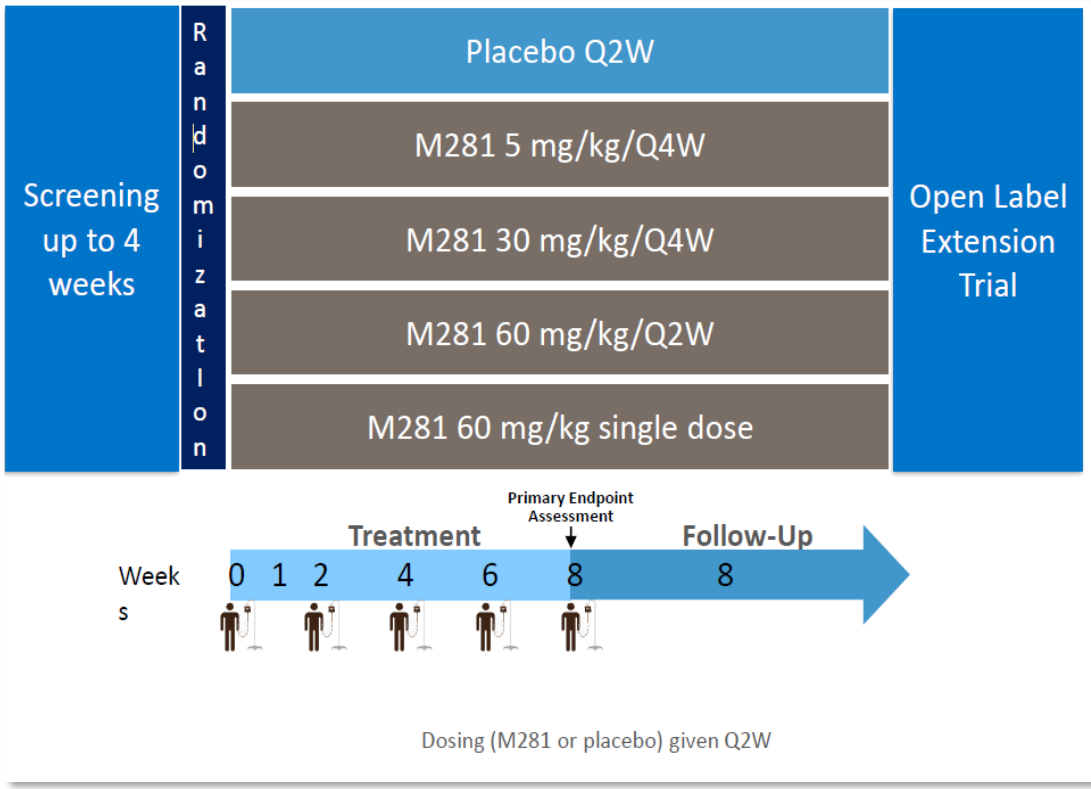
MG Phase 2 Nipocalimab (FcRN target)



68 Subjects Enrolled
Key Eligibility Criteria:

Age >18 years of age

Documented history of gMG (Class II, III, or IVa); both AChR and anti-MuSK enrolled

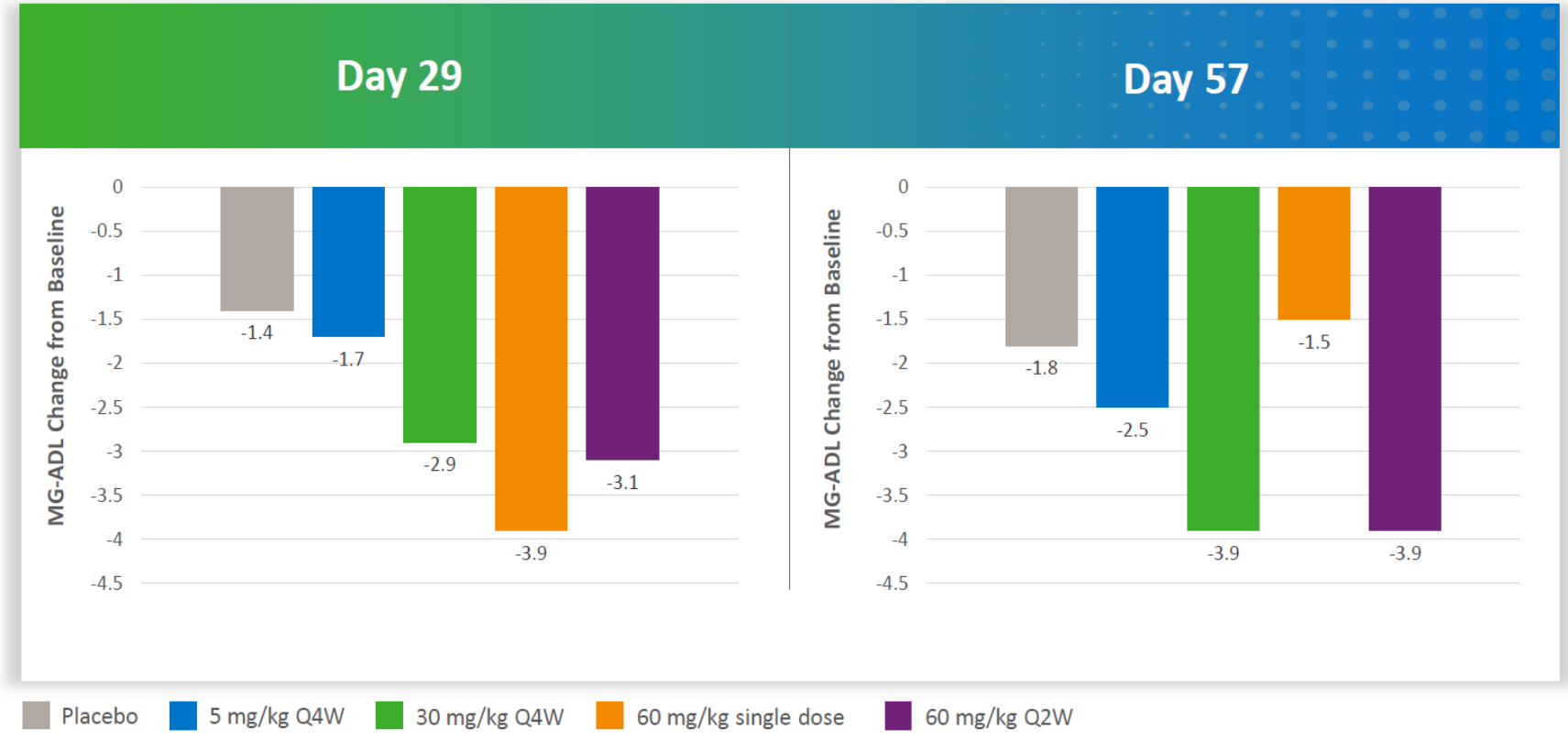
QMG score of >=12 & MG-ADL score of >=4

On stable MG therapy with no changes during treatment period

No plasmapheresis or IVIG within 6 weeks of randomization

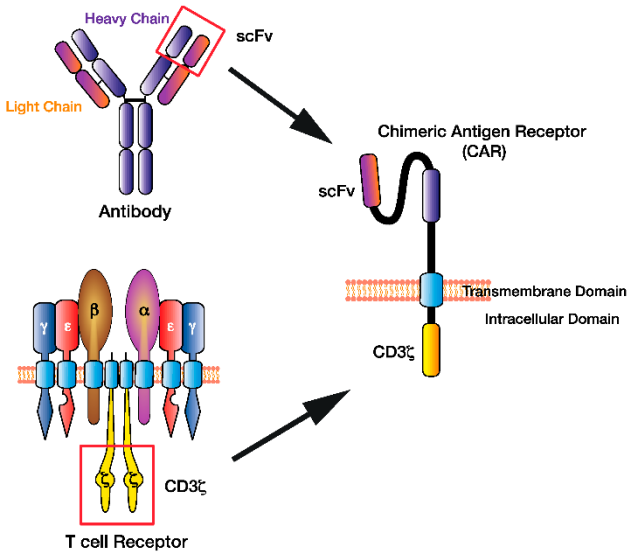
https://s24.q4cdn.com/902352448/files/doc_presentations/2020/06/004-IA-slides-analystcall-final.pdf

Phase 2 Study of Nipocalimab for Treatment of Generalized Myasthenia Gravis



https://s24.q4cdn.com/902352448/files/doc_presentations/2020/06/004-IA-slides-analystcall-final.pdf

FcRn-inhibitor phase II study, in which batoclimab (RVT-1401) was evaluated in MG, have not been published so far. (https://clinicaltrials.gov/ct2. NCT03863080)



On the horizon….

Phase II trials on CD8 positive CAR-T-cell therapy directed against plasma cells) are underway in MG (Oh et al 2020; *Descartes clinicaltrials.gov)*

Subcutaneous immunoglobulins shown to be effective in mild to moderate exacerbations of myasthenia gravis. (Beecher et al, 2017)

Emerging Therapies and Advances in MG

Recent advances included targeted immune therapy that has potentially changed clinical course symptomatic or refractory patients

Future advances will include identifying novel therapies for use in crises

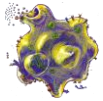
Cost and 3rd party coverage is an ongoing challenge in terms of patient access

Role of flexible dosing for tailored patient specific therapy.

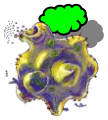
Duration of effect and impact of combination therapy

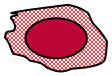
Questions

The Ag
(bacteria, virus, cancer)

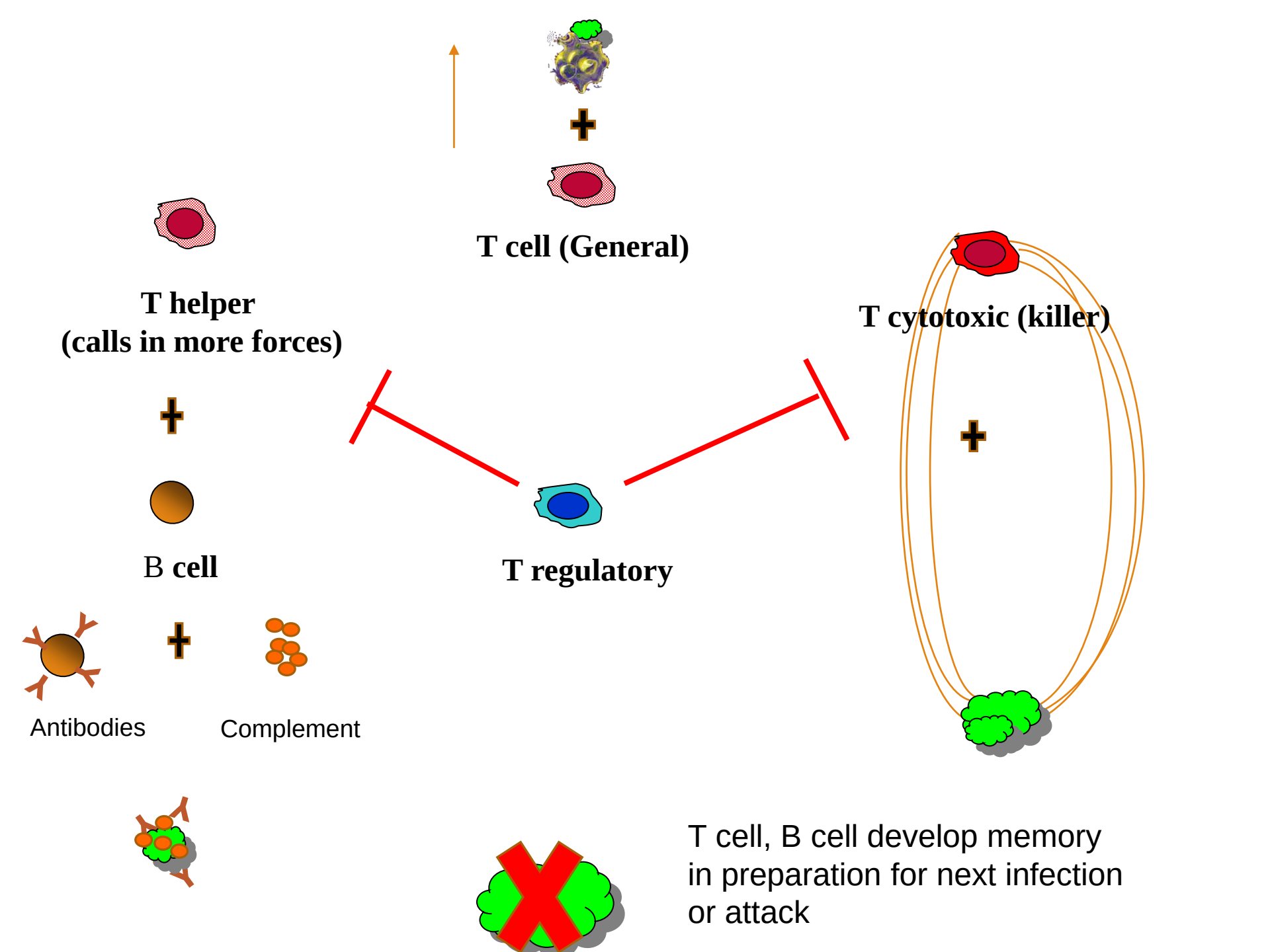


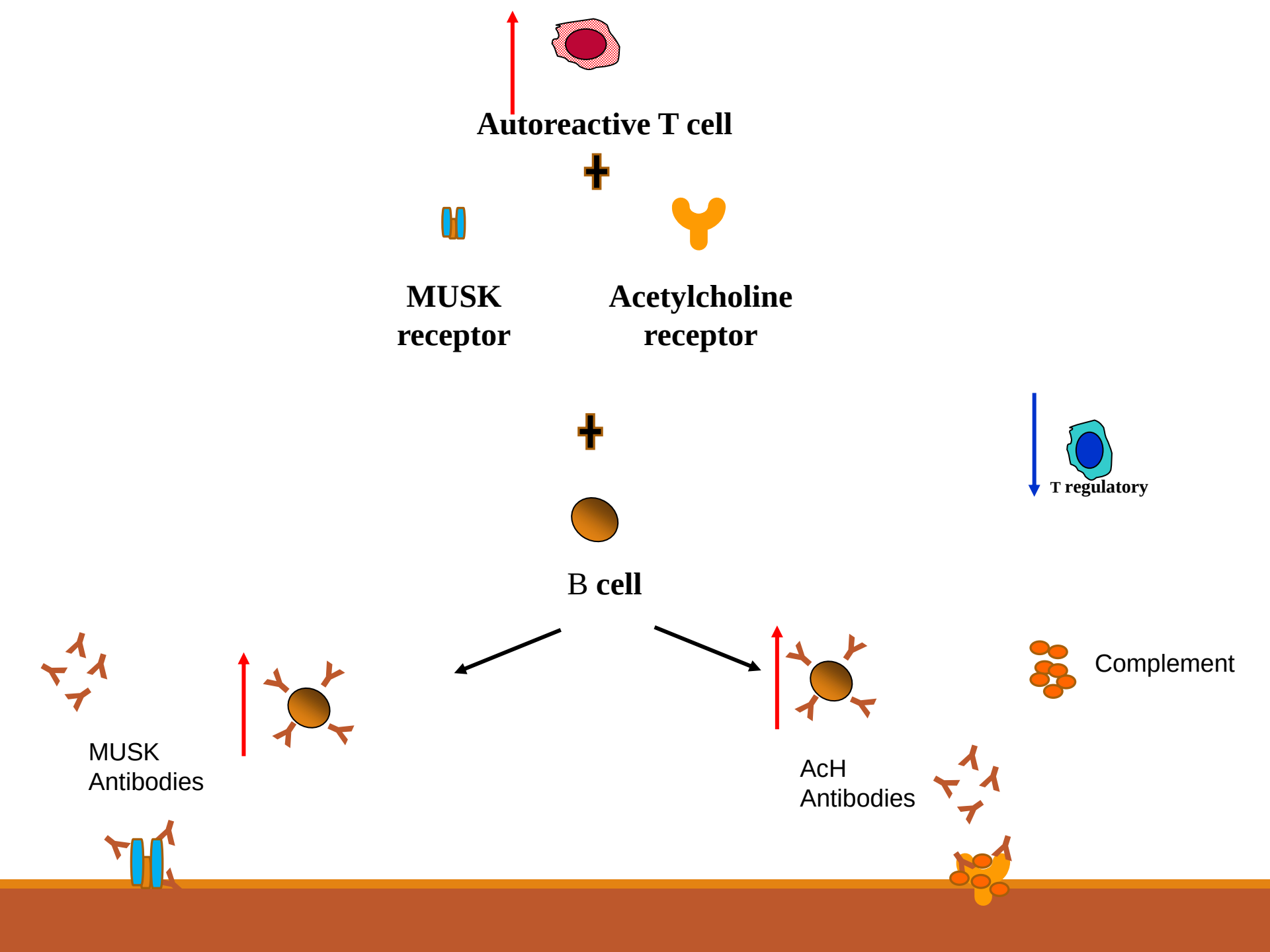
APC-captures the Ag and presents it



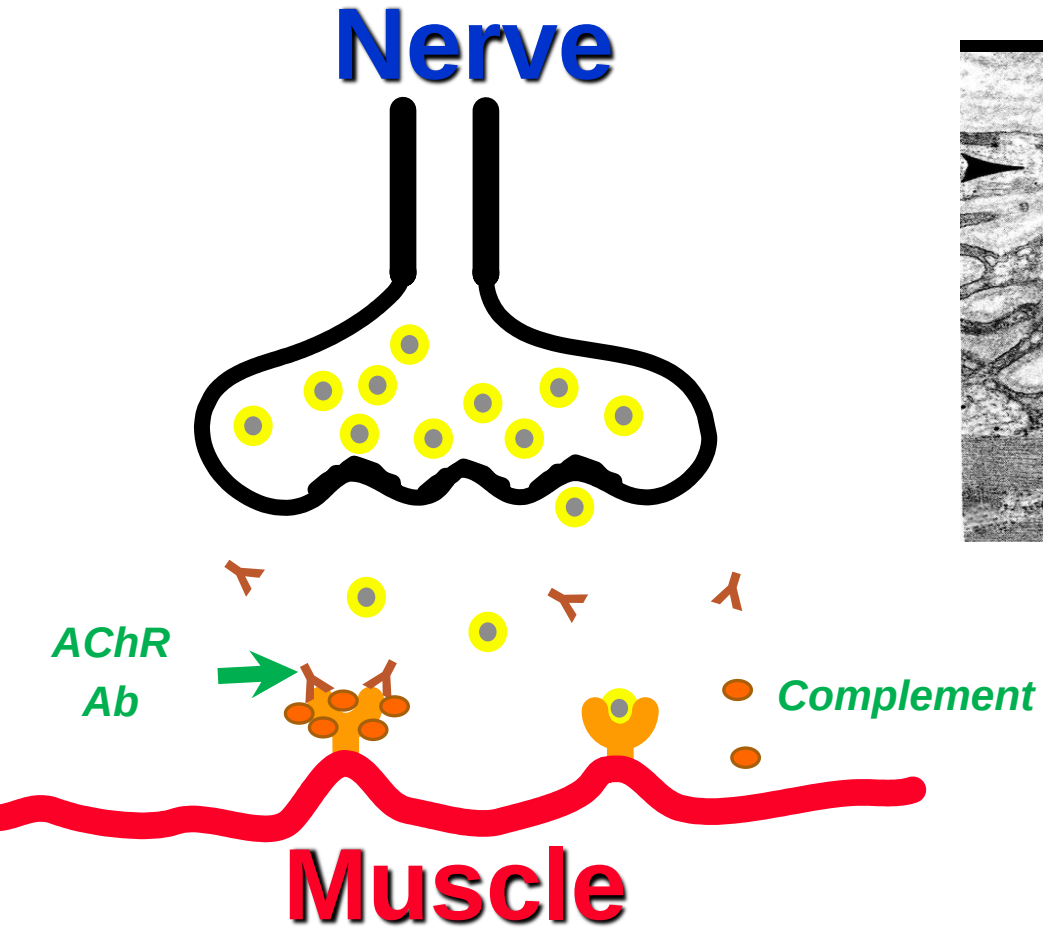


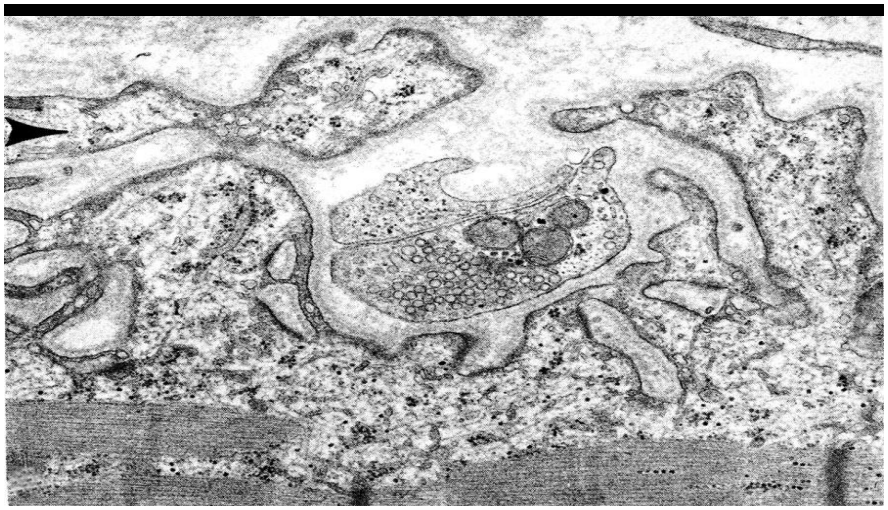
T cell (general)


T cell (General)
T helper
(calls in more forces)
T cytotoxic (killer)
B cell
T regulatory
Antibodies
Complement
T cell, B cell develop memory
in preparation for next infection
or attack


Autoreactive T cell
MUSK receptor
Acetylcholine receptor
T regulatory
B cell
MUSK Antibodies
AcH Antibodies
Complement

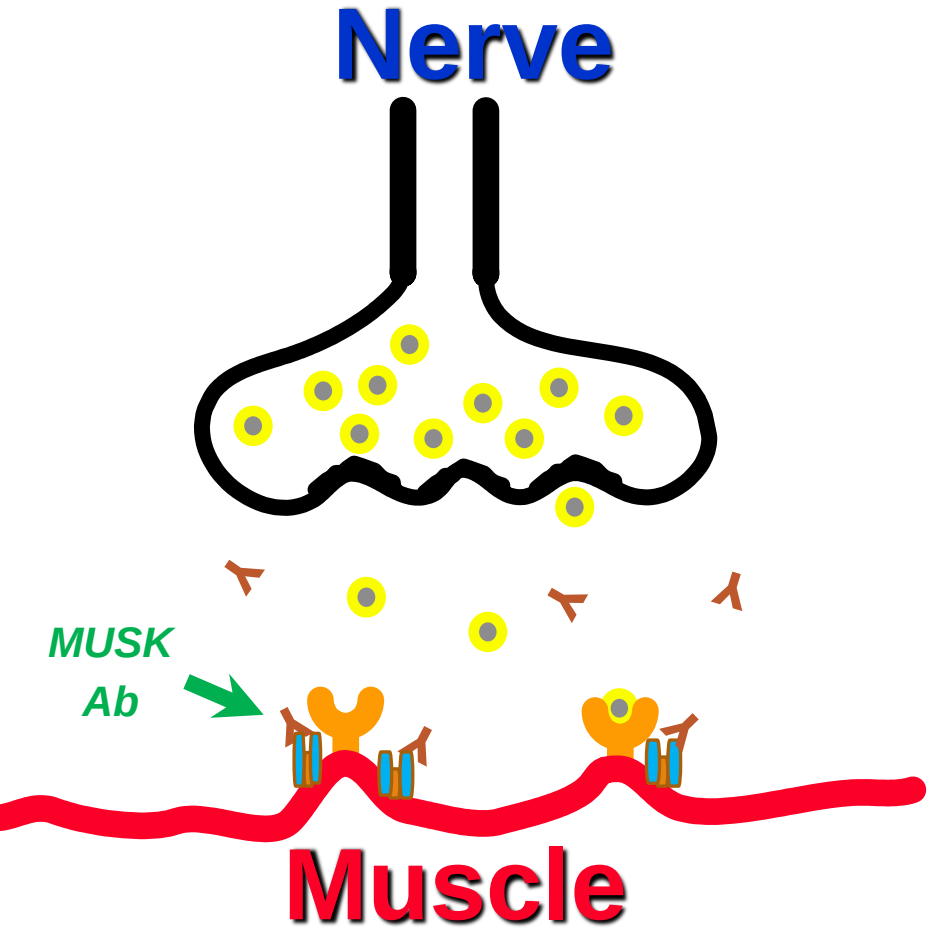
Myasthenia Gravis

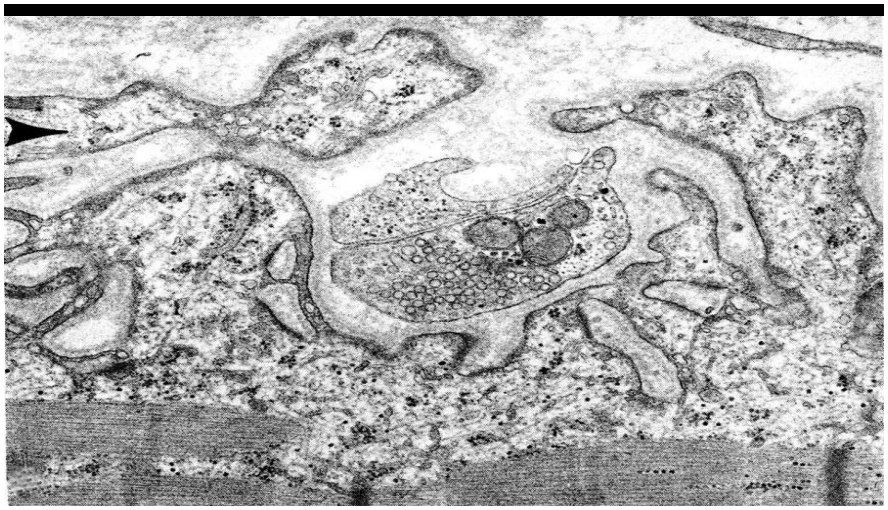




AChRAb+
MG

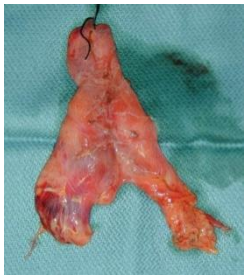
Myasthenia Gravis



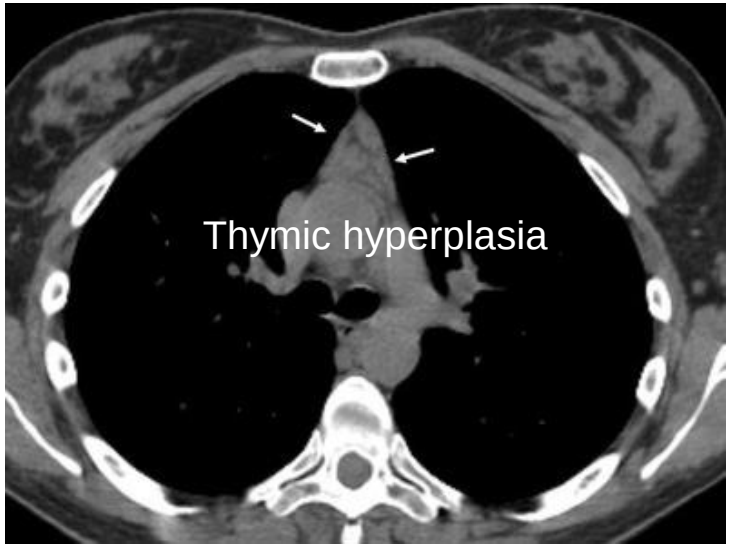


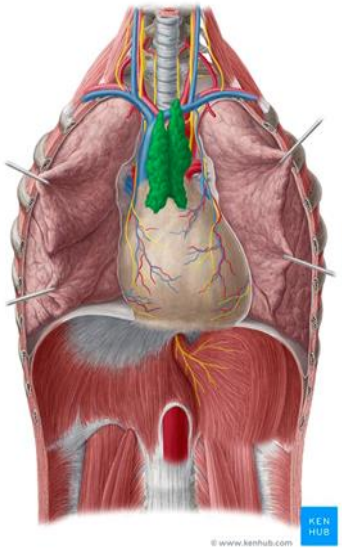
MUSK+
MG

Thymus pathology in MG

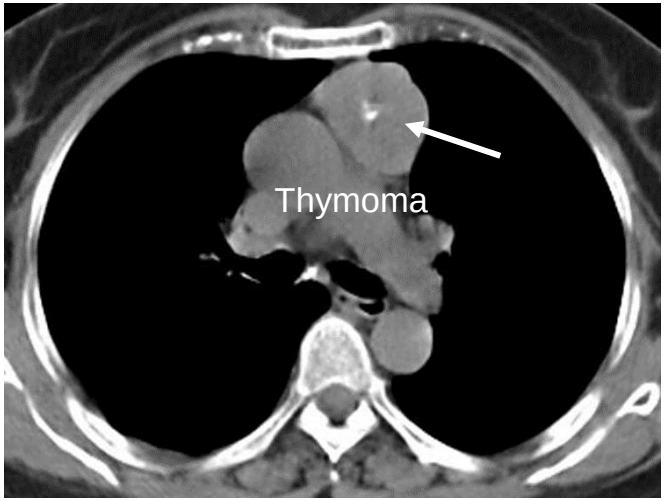


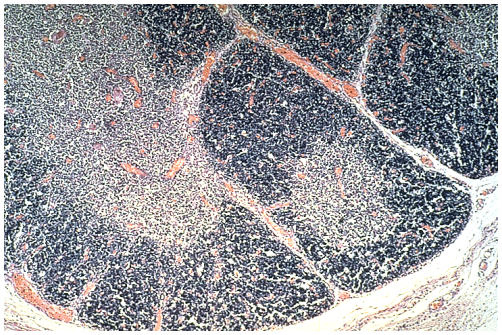
85% activated thymus glands





10% have thymoma, a benign tumor
(most common in males >60 yrs of age)





The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 11, 2016 VOL. 375 NO. 6

Randomized Trial of Thymectomy in Myasthenia Gravis

G.I. Wolfe, H.J. Kaminski, I.B. Aban, G. Minisman, H.-C. Kuo, A. Marx, P. Ströbel, C. Mazia, J. Oger, J.G. Cea, J.M. Heckmann, A. Evoli, W. Nix, E. Ciafaloni, G. Antonini, R. Witoonpanich, J.O. King, S.R. Beydoun, C.H. Chalk, A.C. Barboi, A.A. Amato, A.I. Shaibani, B. Katirji, B.R.F. Lecky, C. Buckley, A. Vincent, E. Dias-Tosta, H. Yoshikawa, M. Waddington-Cruz, M.T. Pulley, M.H. Rivner, A. Kostera-Pruszczyk, R.M. Pascuzzi, C.E. Jackson, G.S. Garcia Ramos, J.J.G.M. Verschuuren, J.M. Massey, J.T. Kissel, L.C. Werneck, M. Benatar, R.J. Barohn, for the MGTX Study Group*

Treatment

Thymectomy Trial

- 126 patients (2006 – 2012)
- Prednisone alone *vs*. Thymectomy + Prednisone
- Measuring disability and average prednisone dose

RESULTS

- Disability was less in Thymectomy + Prednisone group
- Average prednisone, dose at year 3 years was less in thymectomy group
- Less crisis, hospitalizations, rescue therapy
- Side effects similar in both groups

Wolfe GI et al. N Engl J Med 2016;375:511-522