the Foundation *for* Peripheral Neuropathy

Welcome!

FPN Webinar:

Anti-MAG Peripheral Neuropathy: An Overview with Richard Lewis, MD

Monday, June 27, 2022

We will begin our presentation shortly.

the Foundation *for* Peripheral Neuropathy

Moderator:

Lindsay Colbert
Executive Director
the Foundation *for* Peripheral Neuropathy

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Before We Begin

This presentation is being recorded. The recording link will be emailed to you so you can view it again later.

Submit your questions anytime via the Questions Box. We will try to answer them during this webinar.

If you are having trouble with the audio using your computer, you can dial in by phone (check your email for dial-in instructions).

the Foundation *for* Peripheral Neuropathy

Presenter:

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Cedars-Sinai Medical Center

PARAPROTEINS AND ANTI-MAG NEUROPATHY

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PROFESSOR OF NEUROLOGY

CEDARS-SINAI MEDICAL CENTER

WHAT WE WILL DISCUSS

- WHAT ARE PARAPROTEINS
- WHAT ARE SOME NEUROPATHIES THAT ARE RELATED TO PARAPROTEINS
- WHAT IS MAG
- HOW DO MAG ANTIBODIES CAUSE DISEASE
- WHAT TREATMENTS ARE AVAILABLE FOR ANTI-MAG NEUROPATHY

PROTEINS IN YOUR BLOOD

- PLASMA IS THE NON-CELLULAR COMPONENT OF BLOOD
- ALBUMIN (EGG WHITES)- OVER 50% OF PLASMA PROTEIN
  - ACT TO CARRY HORMONES, VITAMINS, LIPIDS
- GLOBULINS ~ 40% OF PLASMA PROTEINS
  - ALSO CARRY LIPIDS AND HORMONES
  - IMPORTANT IN IMMUNE FUNCTION
- OTHER PROTEINS
  - FIBRINOGEN FOR CLOTTING
  - ENZYMES
  - HORMONES

Major Types:

Albumin (60%)

Major component of osmotic pressure of plasma

Globulins (35%)

Antibodies (immunoglobulin) and transport proteins

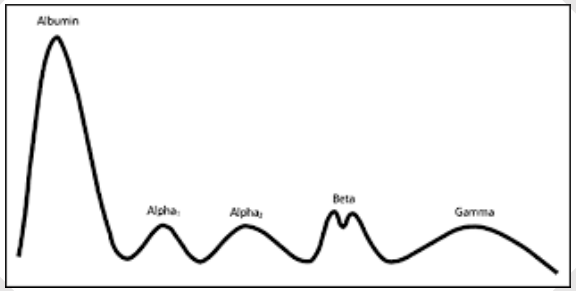
Fibrinogens (4%)

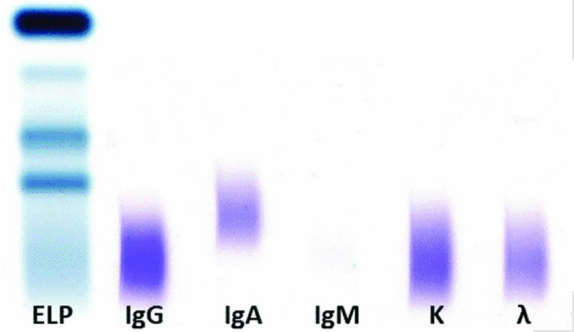
Functions in blood clotting

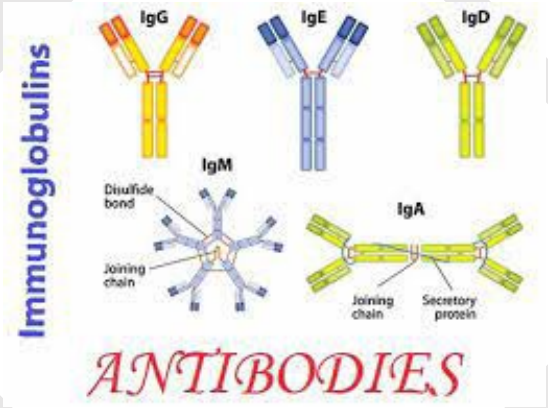
Other (<1%)

Various roles (α-1-antitrypsin, coagulation factors, etc.)

GAMMAGLOBULINS ARE MADE UP OF IMMUNOGLOBULINS

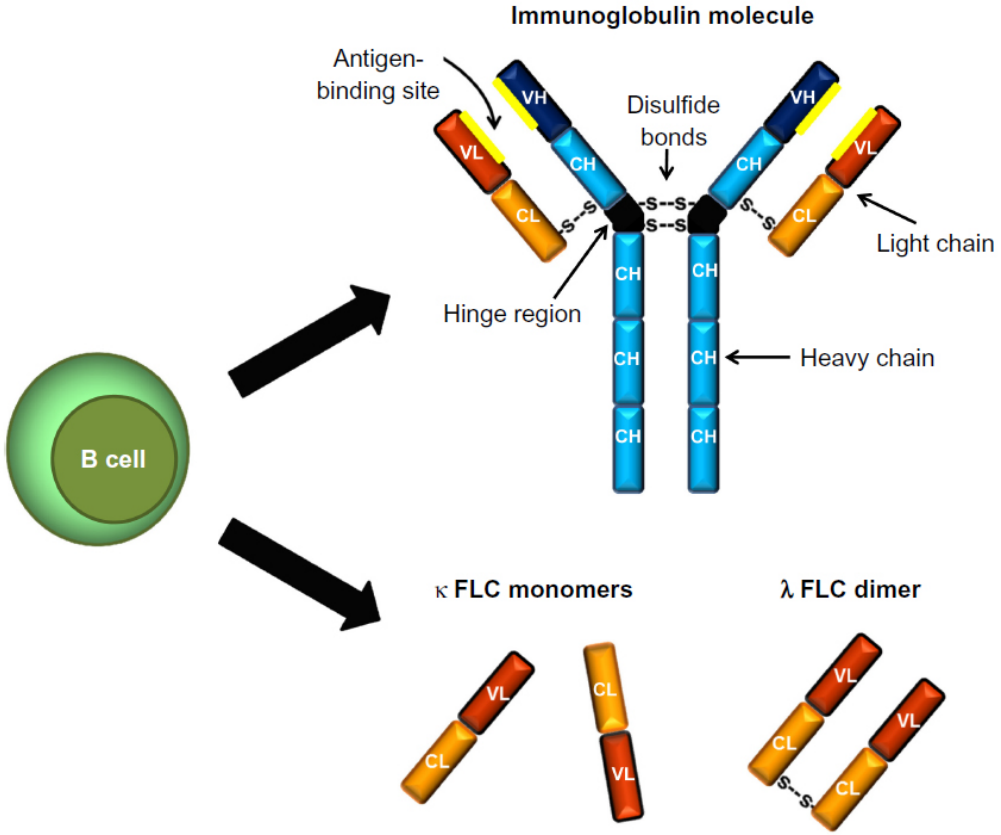


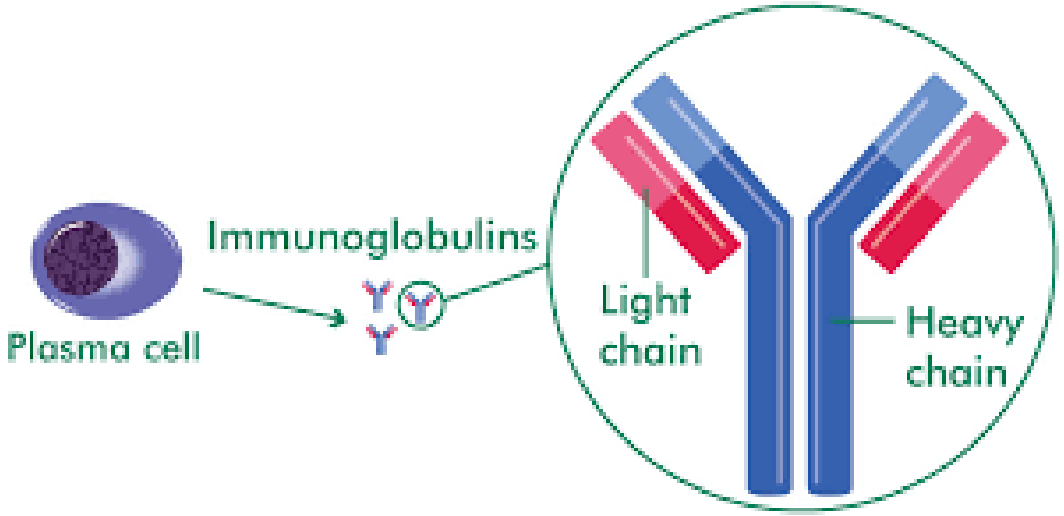




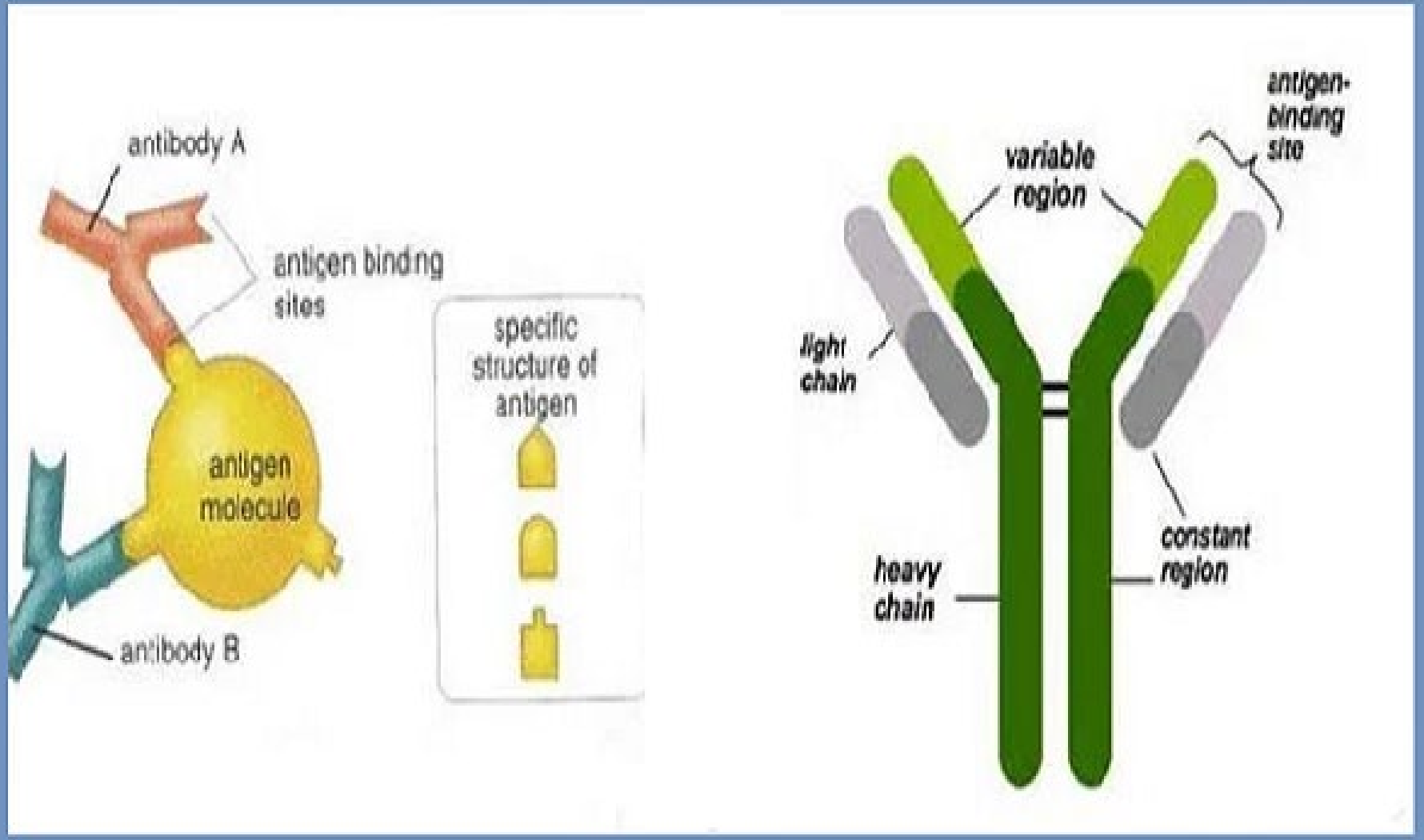
Class of Antibody	Serum levels	Structure	Biological functions
IgM	5%	Monomer Pentamer	Membrane-bound immunoglobulin on the surface of immature and mature B cells First antibody produced in a primary response to an antigen First antibody produced by the fetus Efficient in binding antigens with many repeating epitopes, such as viruses Classical complement activation
IgD	0.3%	Monomer	Membrane-bound immunoglobulin on the surface of mature B cells No biological effector function known
IgA	7-15%	Monomer Dimer	Predominant antibody class in secretions (saliva, tears, breast milk) and mucosa First line of defence against infection by microorganisms
IgG	85%	Monomer	Most abundant class with four isotypes - IgG1, IgG2, IgG3, IgG4 Crosses the placenta Opsonization
IgE	0.02%	Monomer	Defence against parasite infections Associated with hypersensitivity reactions (allergies) Found mainly in tissues

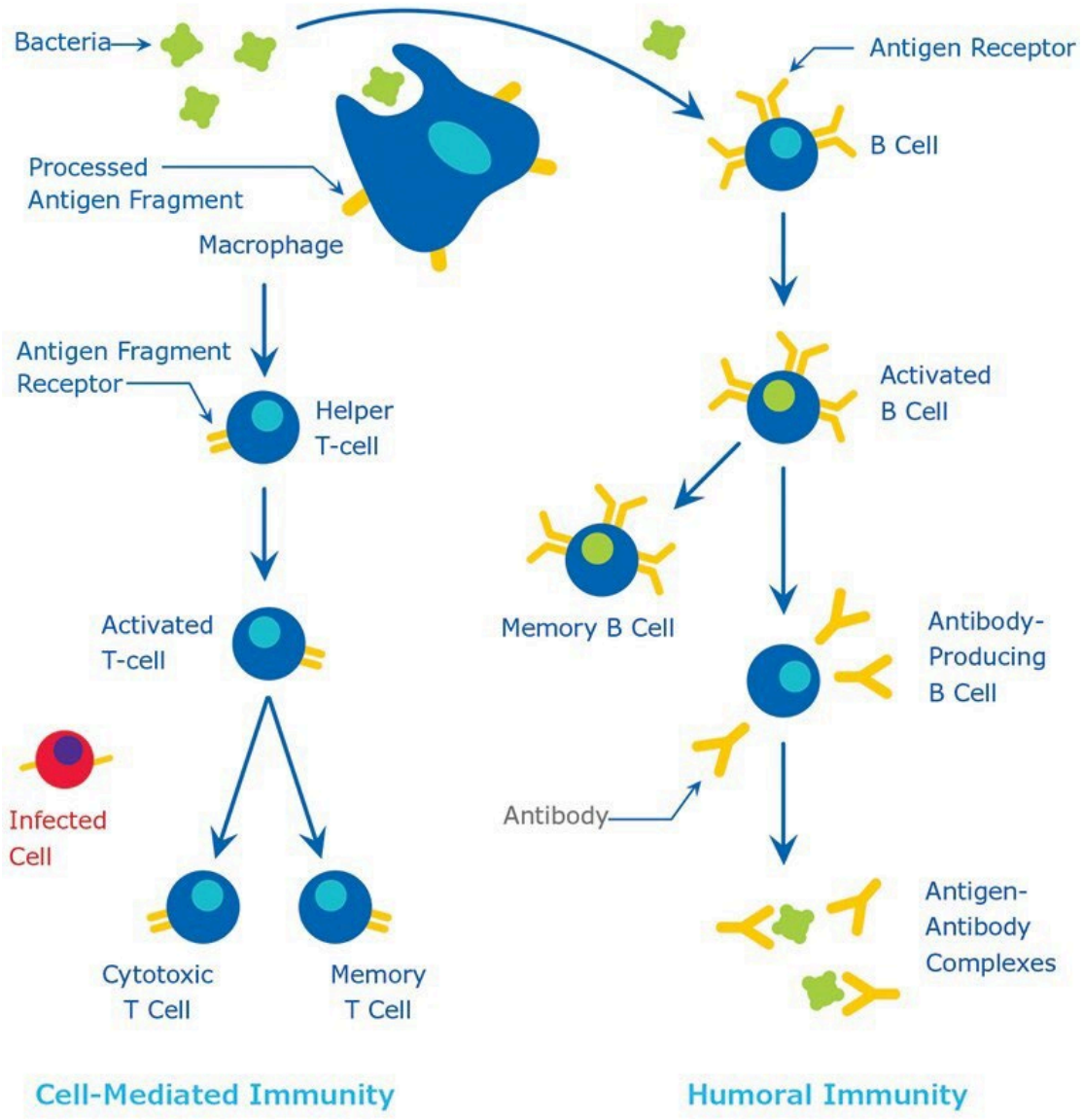
Kappa and Lambda Light Chains



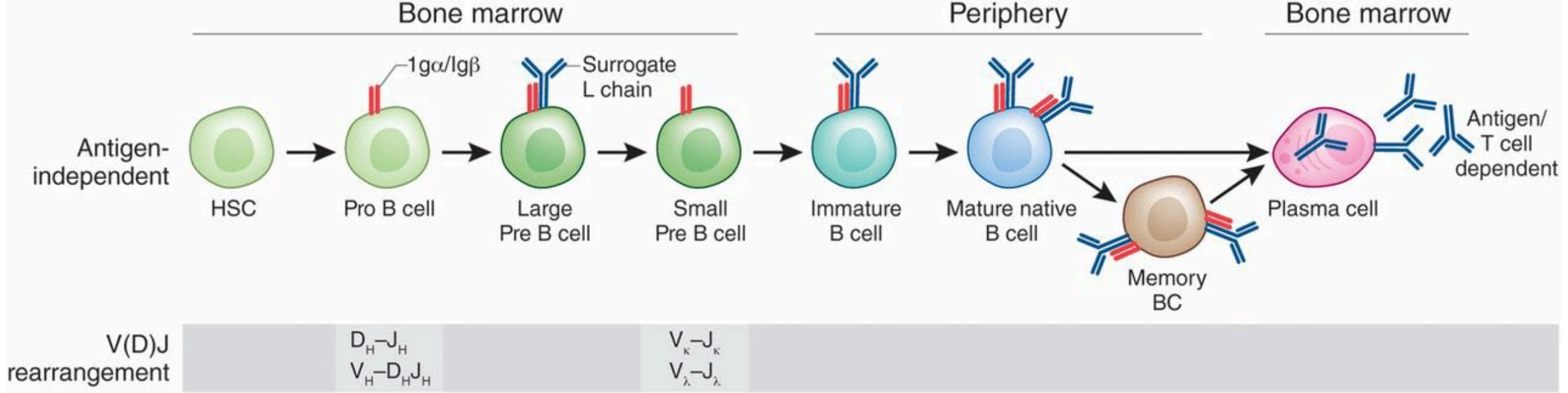


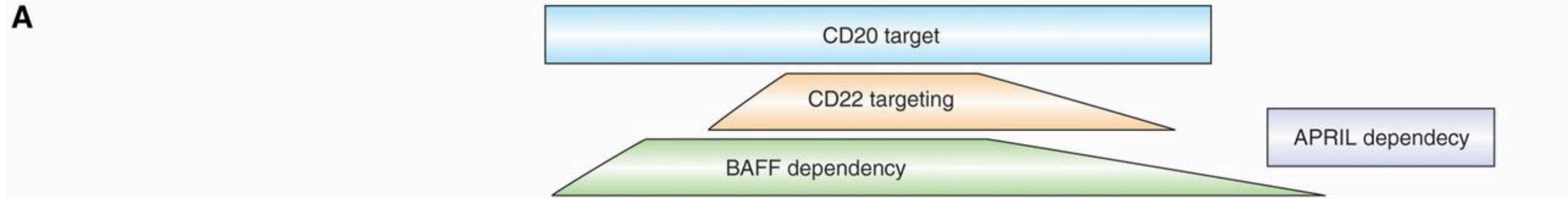
Antigens Vs Antibodies

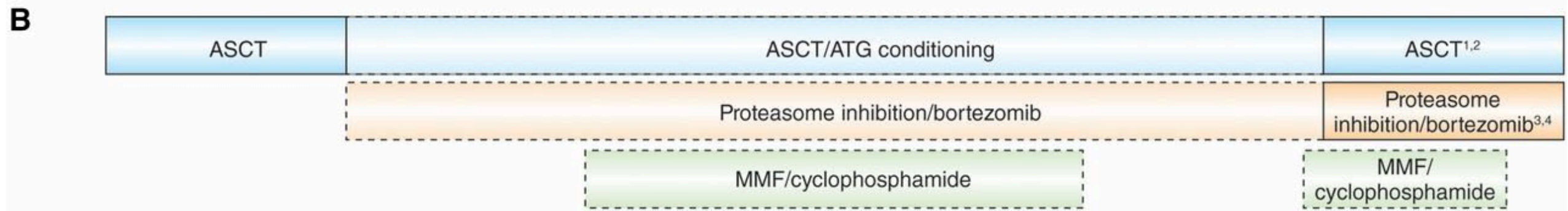




T Cells and B Cells

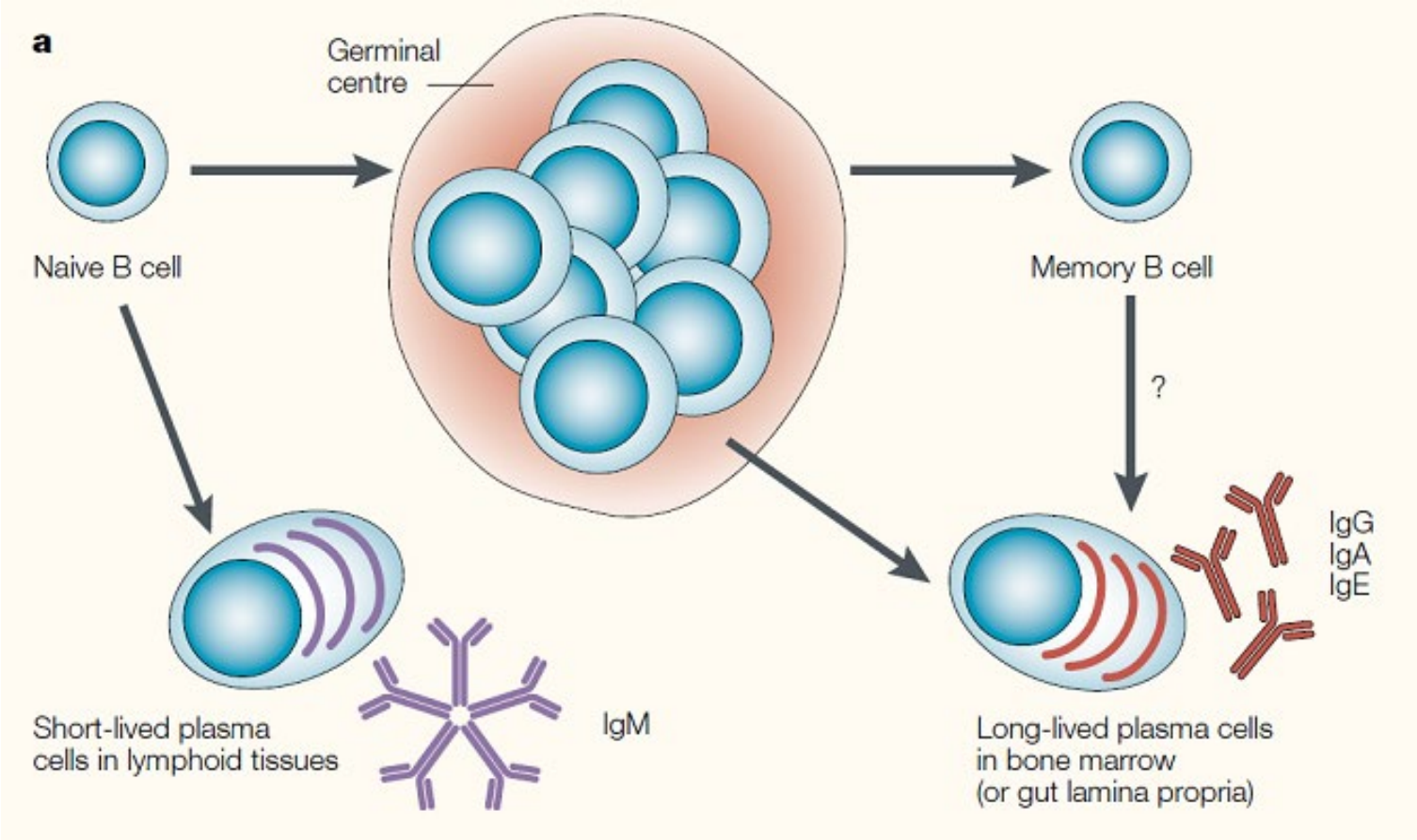

Bone marrow
Periphery
Bone marrow
Antigen-independent
1gα/Igβ
Surrogate L chain
HSC
Pro B cell
Large Pre B cell
Small Pre B cell
Immature B cell
Mature native B cell
Memory BC
Plasma cell
Antigen/ T cell dependent
V(D)J rearrangement
D_H–J_H
V_H–D_HJ_H
$V_κ$–$J_κ$
$V_λ$–$J_λ$


A
CD20 target
CD22 targeting
BAFF dependency
APRIL dependecy


B
ASCT
ASCT/ATG conditioning
ASCT[1,2]
Proteasome inhibition/bortezomib
Proteasome inhibition/bortezomib[3,4]
MMF/cyclophosphamide
MMF/ cyclophosphamide

IgM made by cells in lymph tissue

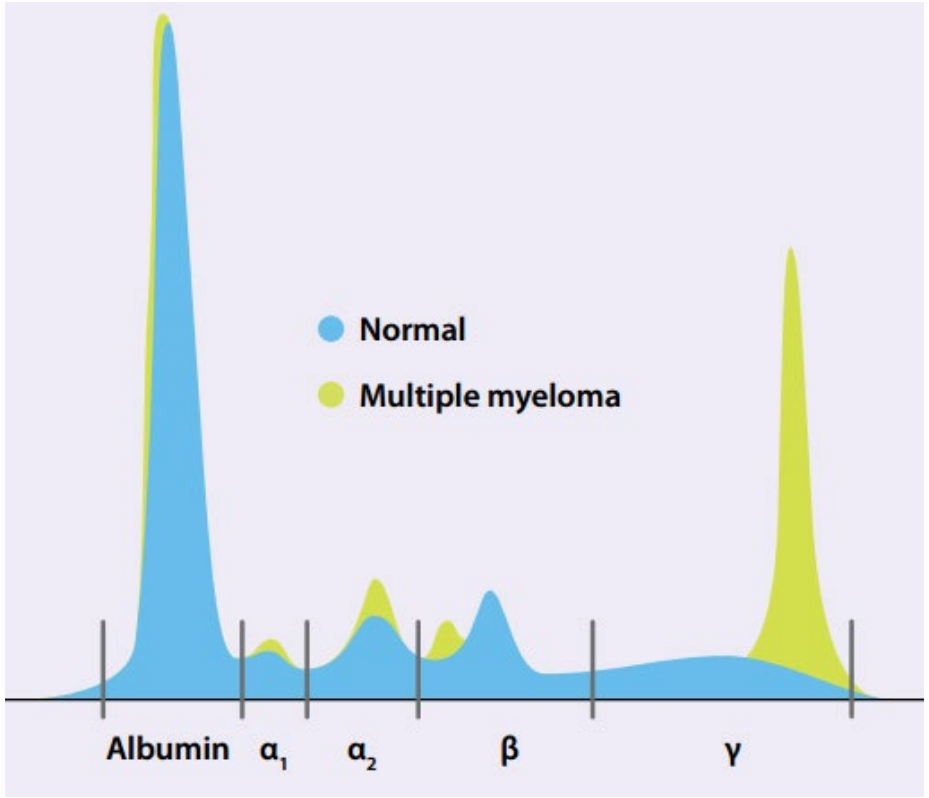
IgG made by plasma cells in bone marrow



Paraproteins

Paraproteins are monoclonal immune globulin fragments or intact immune globulins produced by usually a malignant cone of plasma cells or B cells.

Monoclonal Gammopathy of Uncertain Significance (MGUS) produces small amounts of paraprotein



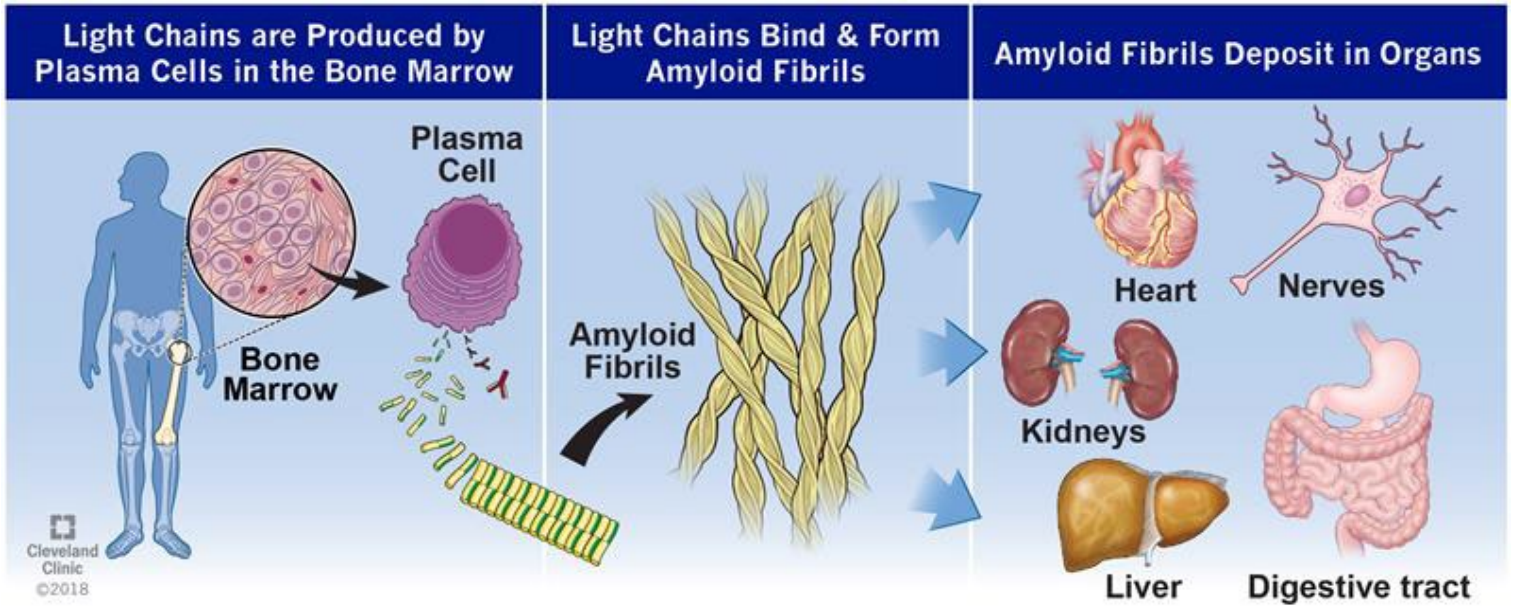
Monoclonal Gammopathy of Undetermined Significance (MGUS) and Myeloma

- MGUS is a benign condition
- MGUS patients have a low level of the paraprotein
- Low level of abnormal plasma cells in the bone marrow,
- No indicators of active or malignant disease.
- All patients with active myeloma once had MGUS.
- **Only 20% of patients with MGUS actually progress to active myeloma.**
- **The risk of a patient's progression from MGUS to active myeloma is only 1% per year.**
- A hematologist/oncologist should monitor patients with MGUS.
- MGUS patients may not need to be treated

IgG and IgM Paraproteins

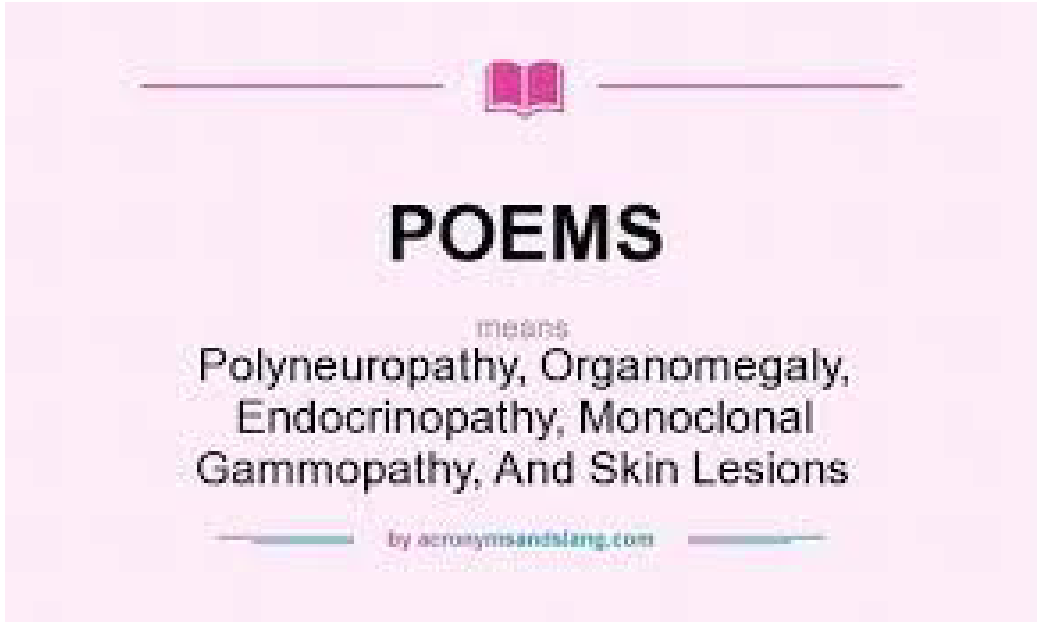
- IgG and IgA Paraproteins in Myeloma
- IgM Malignancy is Waldenstrom's Macroglobulinemia
- IgG MGUS can be seen in 5% of people over the age of 60
- IgG most common but has weak association with neuropathy
- IgM in only 5% of MGUS but over 50% have neuropathy

Light Chains are Significant



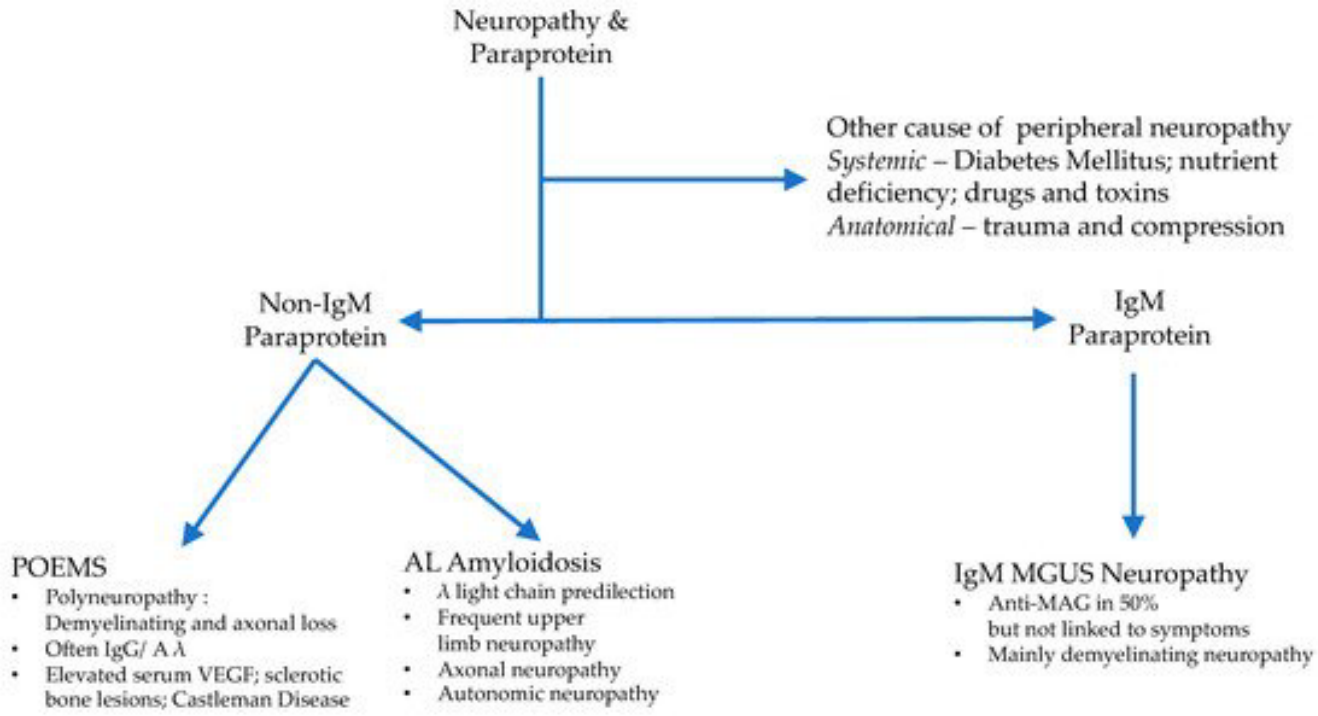
- Some people have high levels of free light chains
  - Usually have paraprotein as well
- Lambda light chains
  - Raise concern for amyloidosis
  - AL Amyloid can be related to myeloma
  - Genetic TTR amyloid now treatable

Lambda Light Chains and POEMS



Mandatory Criteria -Polyneuropathy -Monoclonal plasma cell proliferative disorder		
Major Criteria -Sclerotic bone lesion -Castleman disease -Vascular endothelial growth factor [VEGF] elevation	**Minor Criteria** -Organomegaly -Extravascular Volume overload -Endocrinopathy -Skin Changes -Papilledema -Thrombocytosis/ Polycythemia	**Common Sign/Symptoms** -Clubbing -Weight loss -Hyperhidrosis -Pulmonary hypertension/restrictive lung disease -Thrombotic diatheses -Diarrhea -Low vitamin B12 values

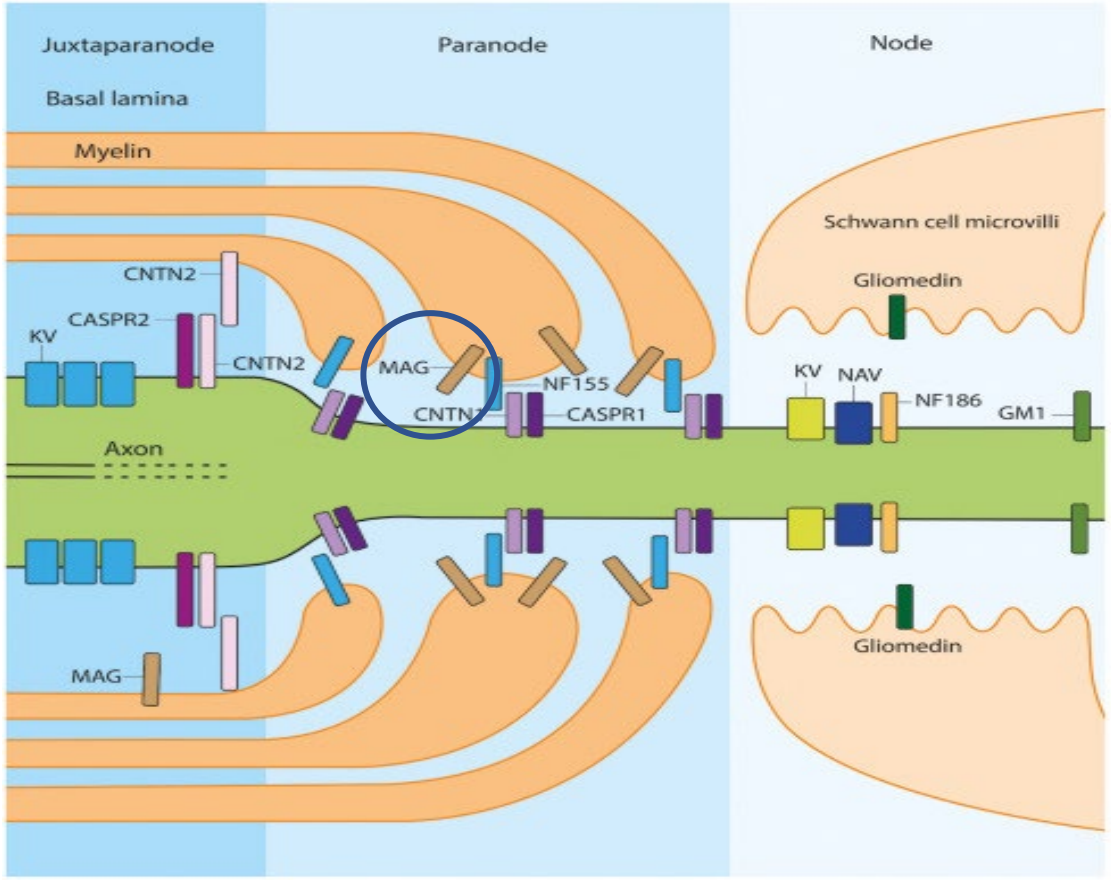
IgM and Peripheral Neuropathy



- 50% of IgM MGUS associated with neuropathy
- IgM kappa more associated than lambda
- 50% of the IgM kappa neuropathies are with slow nerve conduction
- Most of these have anti-MAG antibodies

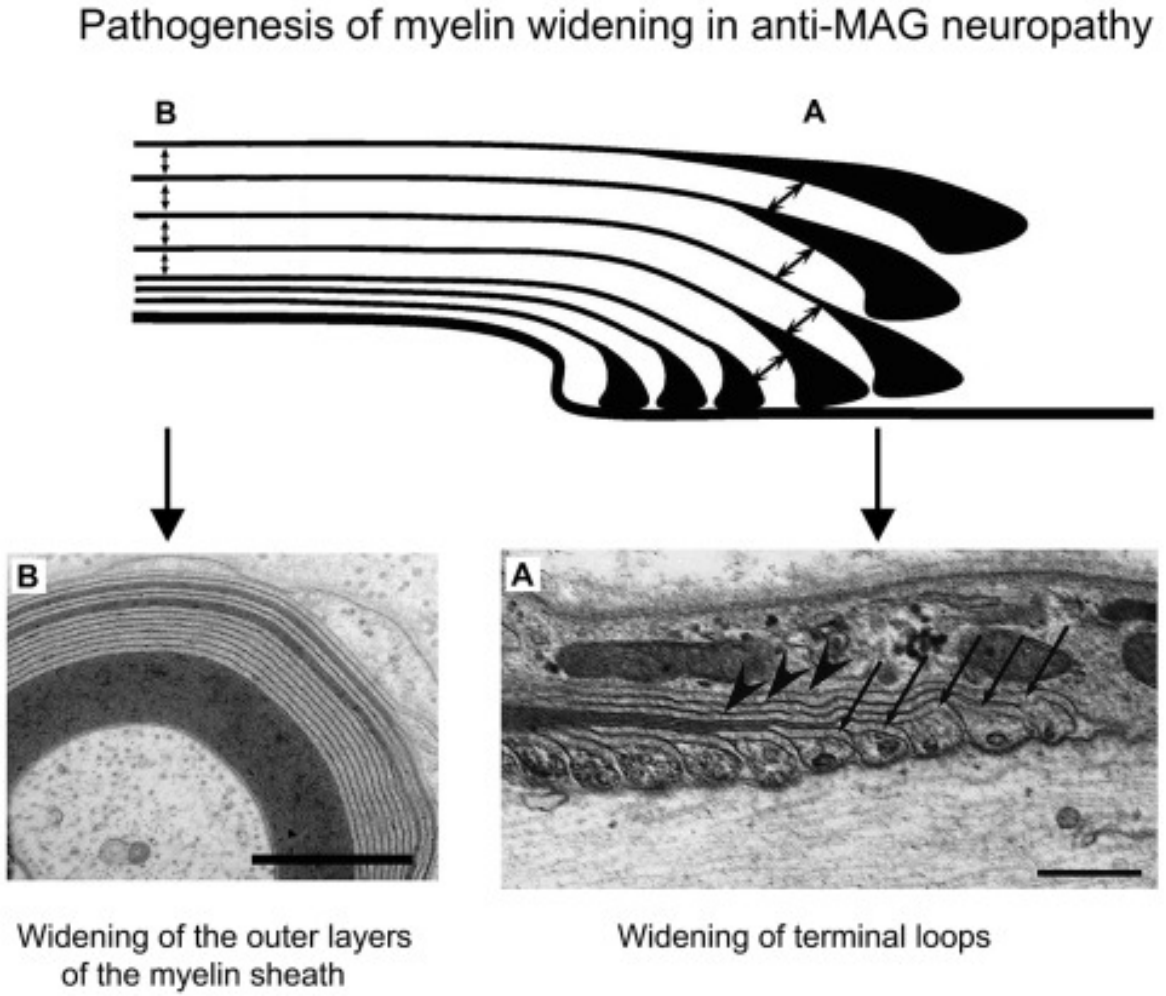
What is MAG?
Myelin Associated Glycoprotein

- MAG is a glycoprotein that is found within the myelin sheath and in Schwann cells.
- thought that MAG plays a role in a signaling cascade that “turns on” the Schwann cells, leading to normal myelin production and healthy peripheral nerve activity.



What Do MAG antibodies do?

- Antibodies attack MAG on Schwann Cells and Myelin
- Damage myelin and attachments to axon
- Cause conduction changes
- Cause axons to be destroyed



What Does Anti-MAG Neuropathy Do to People?

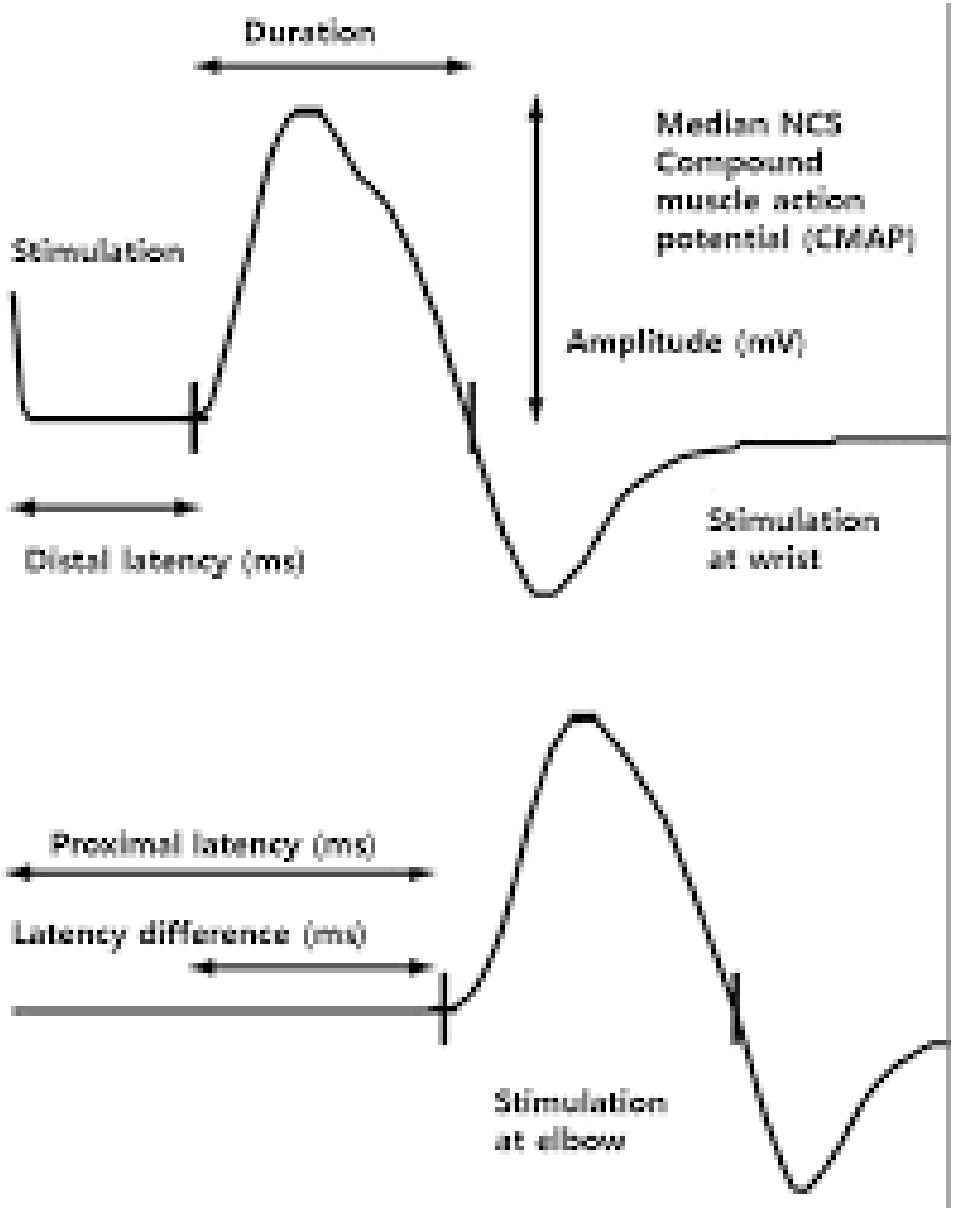
- Variable manifestations
- Most people have a very slow, insidious, primarily sensory neuropathy which begins in toes and feet and over many years progresses going up the legs and involving fingers and hands
- The symptoms are numbness and tingling with or without buzzing, stinging pain
- Causes imbalance and difficulty walking
- Weakness of hands and ankles can occur

What Does the Neurologist Find on Exam?

- Ataxic gait (as if drunk)
- Falls when closes eyes
- Vibration and position sense abnormal – large diameter fiber
- Reflexes absent in ankles and reduced elsewhere
- Strength may be reduced

Diagnosis: Role of Nerve Conduction Testing

- EMG has characteristic pattern of conduction changes
  - Distal segments of motor nerves conduct slower than proximal segments
- Sensory responses absent or very reduced



Diagnosis: Testing for anti-MAG antibodies

Serum Immunofixation will find IgM kappa paraprotein

Anti- MAG testing done with screening test but this is not specific

Specific test then done

Quantitative IgM levels

(normal < 200; MGUS < 500; Malignant > 800)

Serum Protein Electropheresis can quantify the mini-monoclonal spike

- These are the bad actors

Refer to Hematology/Oncology

TREATMENT

- Treatment of anti-MAG neuropathy is essentially the treatment of the paraprotein.
  - Heme/Onc needs to determine if MGUS or Malignancy
- Sometimes the heme/onc issues drive treatment; Sometimes the neuropathy
- Malignant disorders require more aggressive treatment
- Goals of treatment is to reduce the MGUS spike by reducing the total IgM levels

Treatment Considerations

- Mild neuropathy may not need treatment
- Low levels of IgM may not need treatment.
- Discussion of benefits and risks
- Can treat neuropathic pain with meds
- Usual treatments for inflammatory neuropathies (CIDP) are not effective
- No proven treatment
- No specific anti-MAG treatment
    - Research approach was encouraging but had to be stopped

Rituximab and B Cell Depletion

Intravenous treatment that needs to be repeated

Different regimens but all reduce circulating B cells to < 1%

B cells are also sequestered in lymph nodes, bone marrow etc

So never completely reduce B cells

Monitor total IgM levels and mini-monoclonal spike

Repeat dosing depends on clinical condition

- Most commonly every 6 months
- Some treat every 3 months initially if IgM levels very high

How Do We Know if Treatment is Working?

- IgM levels tell us that the treatment is effective in the blood
- Anti-MAG level drop helpful
- But is it doing anything to the neuropathy?
  - Neurologic exam
  - EMG not usually considered useful but may show improvement
- Is the patient seeing a benefit in their function and quality of life?
  - Outcome measures should be used
  - Functional rating scales
  - QoL scales
  - Timed walking tests- 10 meter walk; Timed Up and Go
  - Others

Why Did Clinical Trials Not Work When Small Series Showed Benefit?

- Slow, insidious disease may take time to show improvement
  - Studies did not go long enough
- Sensory disorders difficult to show effect
- Outcome measures used were not sensitive to change
- May need significant lowering of IgM to have benefit
  - Multiple treatments over time may be needed
- Some deficits may not be fixable
  - Recruitment did not take this into account
- May not work in enough patients to be statistically significant

Patients and Their Doctors Need to Work Together

Doctors and Patients Don't Always Speak the Same Language

Patient Responsibility

Let your doctor know the degree of your dysfunction

What are your fears and concerns?

- "Will I have to be in a wheelchair?"
- "Will this shorten my life?"
- "Will I need to be on treatment forever?"

What you want the treatment to do

" I don't understand"

Physician Responsibility

- Realistic prognosis
- Realistic expectations of treatment
  - Short Term Goals
  - Long Term Goals
- Should treatment start now or wait?
- Risks and Benefits
  - Side effects ≠ Risks
- How Effect Will Be Determined

The Future

- Need to better understand the variability of the problems in Paraprotein Neuropathies
- Develop outcome measures that can be used in practice and clinical trials
- Develop new treatments that are specific for anti-MAG and other antibody mediated neuropathies
- Develop new treatments for the paraprotein that are less risky and more effective

Thanks for Listening Hope That Was Helpful

Time for Questions and Comments

the Foundation *for* Peripheral Neuropathy

Thank You for Watching!

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