

What is C3 Glomerulopathy or C3G for short?



Learning objectives

- To understand the anatomy of the kidney and glomerulus
- To understand how C3G is **diagnosed**
- To understand the relationship of C3G to post-infectious glomerulonephritis (PIGN) and monoclonal gammopathy of renal significance (MGRS)
- To understand that C3G is caused by **complement dysregulation**
- To understand what the complement system does
- To understand how we study complement in persons with C3G
- To understand that there are **many causes of complement dysregulation** that can give rises to C3G
- To recognize that while there are no disease-specific treatment, the **future is very bright** and multiple new therapies are being tested in clinical trials

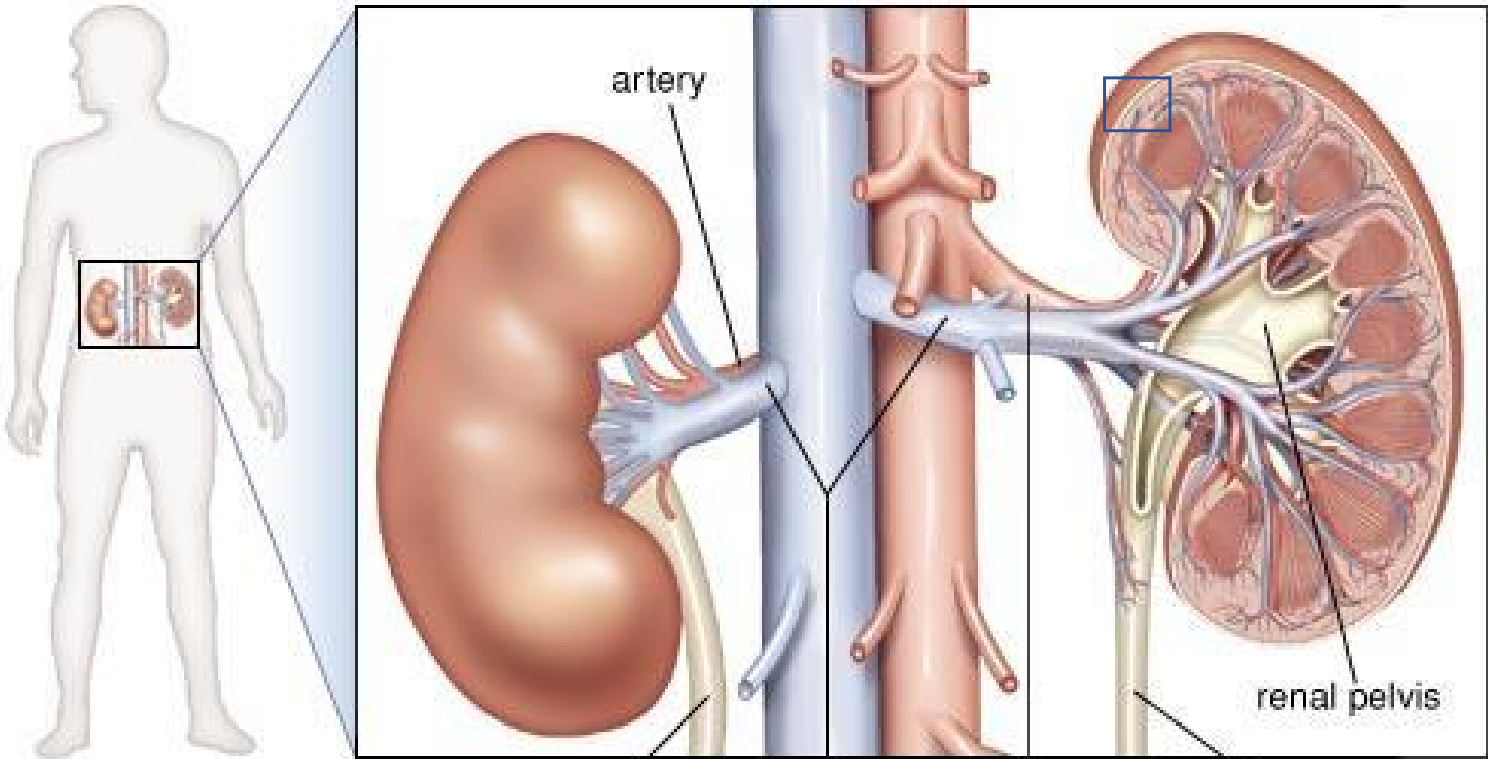
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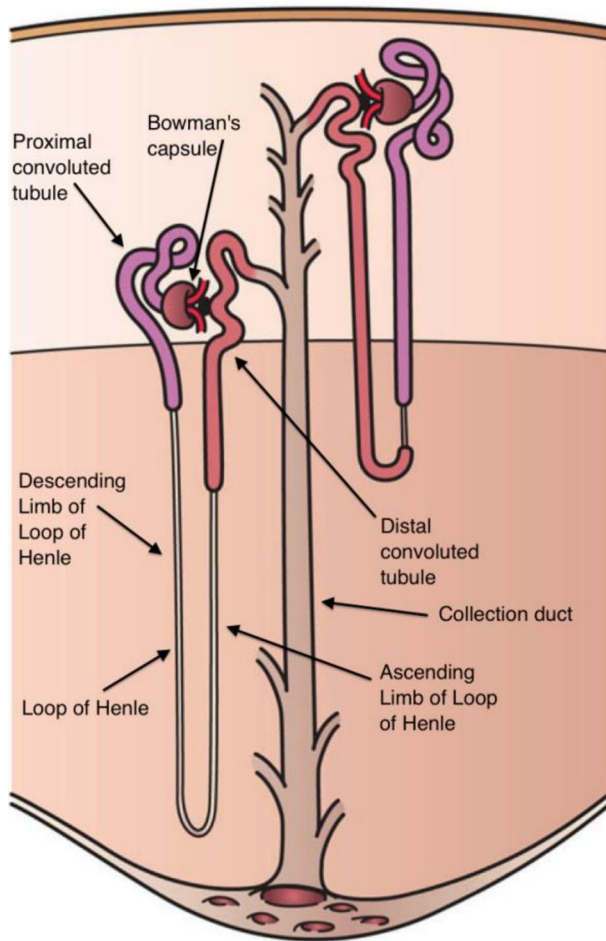
The Kidney

Right Kidney Outside View

Left Kidney Inside View

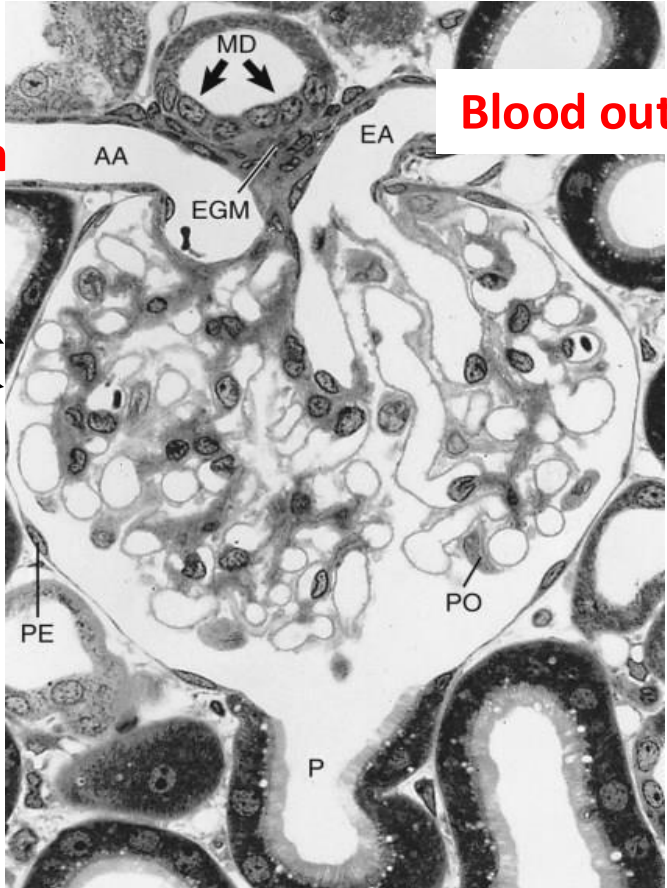
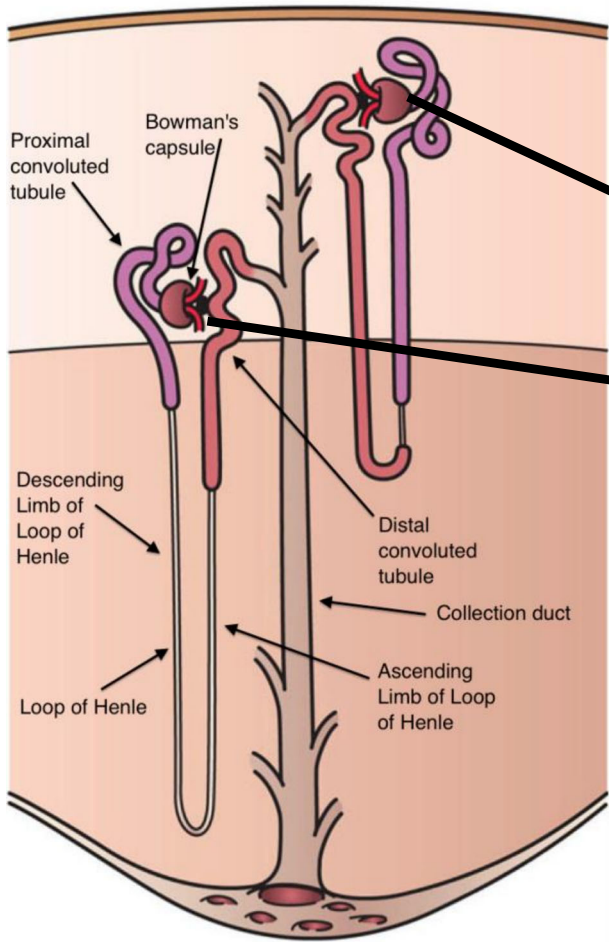


The Nephron



Nephron – the working unit of the kidney

The Nephron



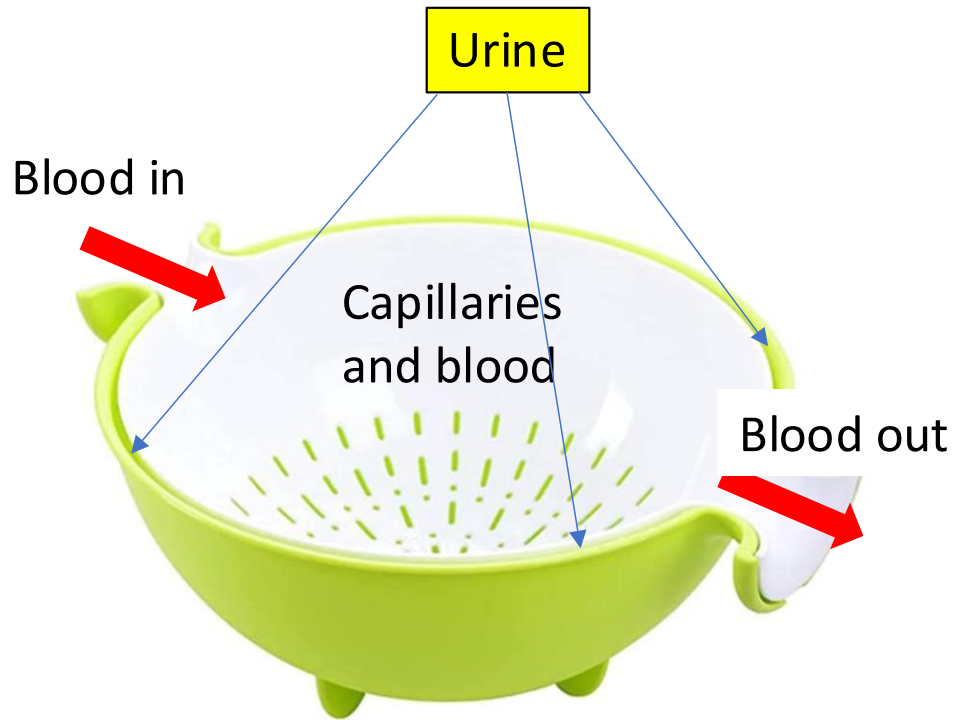
Blood in

Blood out

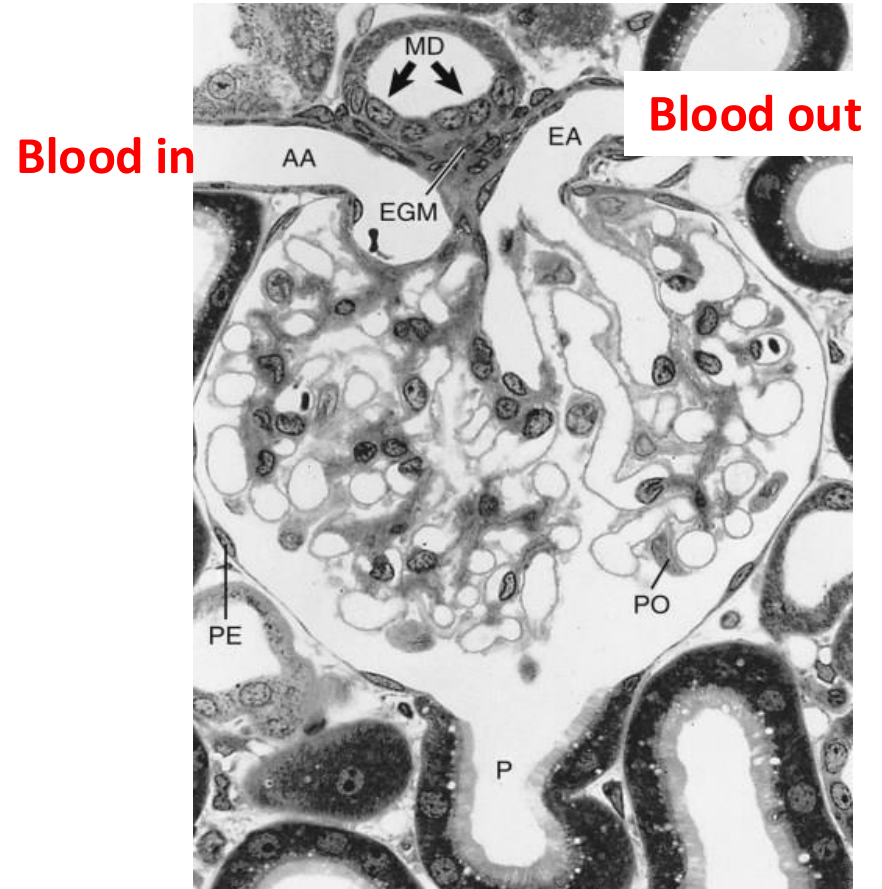
Nephron – the working unit of the kidney

For C3G, we are interested in the glomerulus

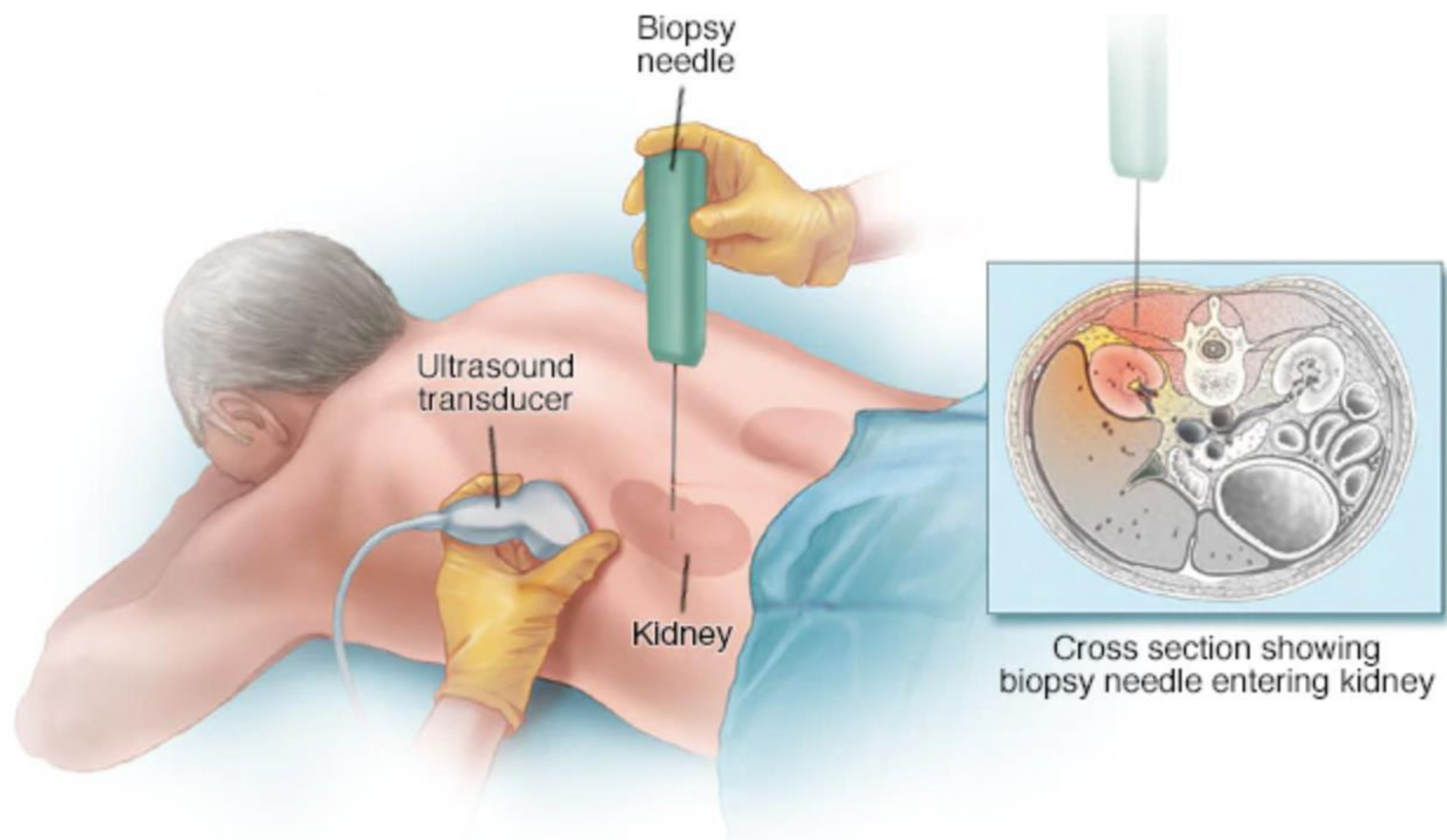
The Nephron



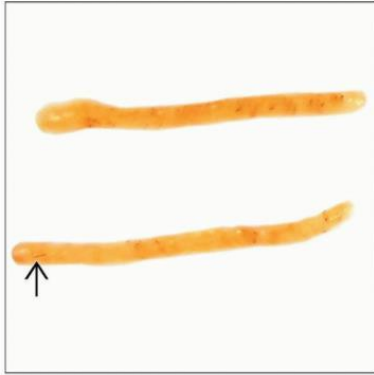
The glomerulus is the filtering unit of the nephron; it's like a colander



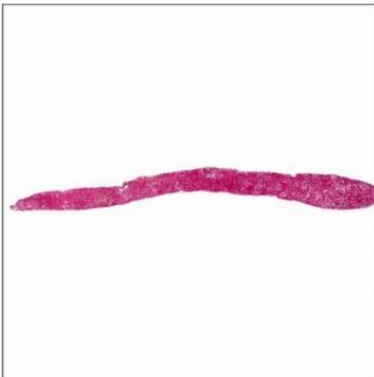
For C3G, we are interested in the glomerulus



About 1 mm x 20 mm

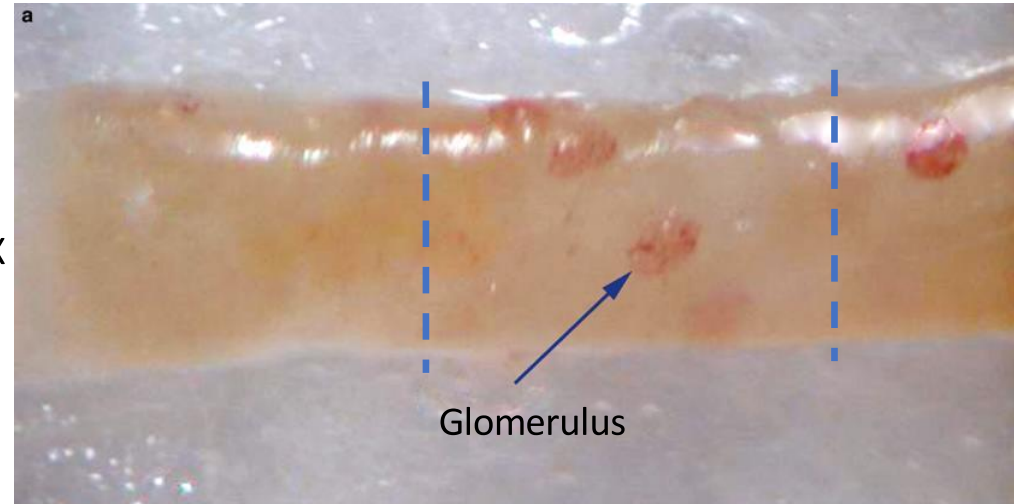


Renal 16-g cores are typically 1 mm in diameter x 10-20 mm long (these are ~13 mm). Glomeruli are pale or congested bulges; red cell casts are brown streaks or dots. (Courtesy C. Swetts, MD.)



The renal biopsy is first examined under low-power magnification to determine the quality of the sample and search for focal lesions. Representative tissue is then allocated for LM, IF, and EM.

CORTEX

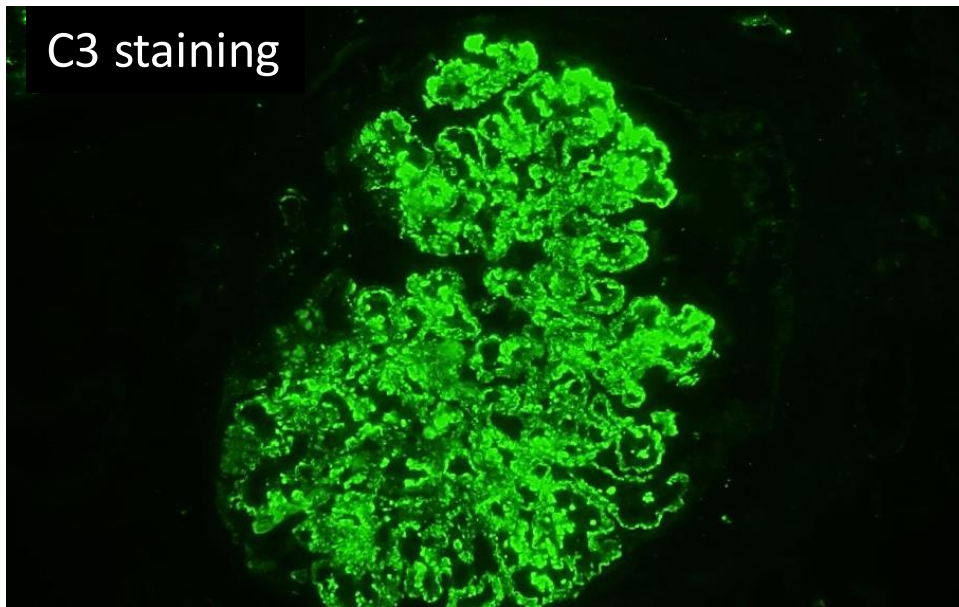


Glomerulus

MEDULLA



C3G is diagnosed by immunofluorescence staining, which **must be positive for C3** by at least two orders of magnitude greater than any other stain.

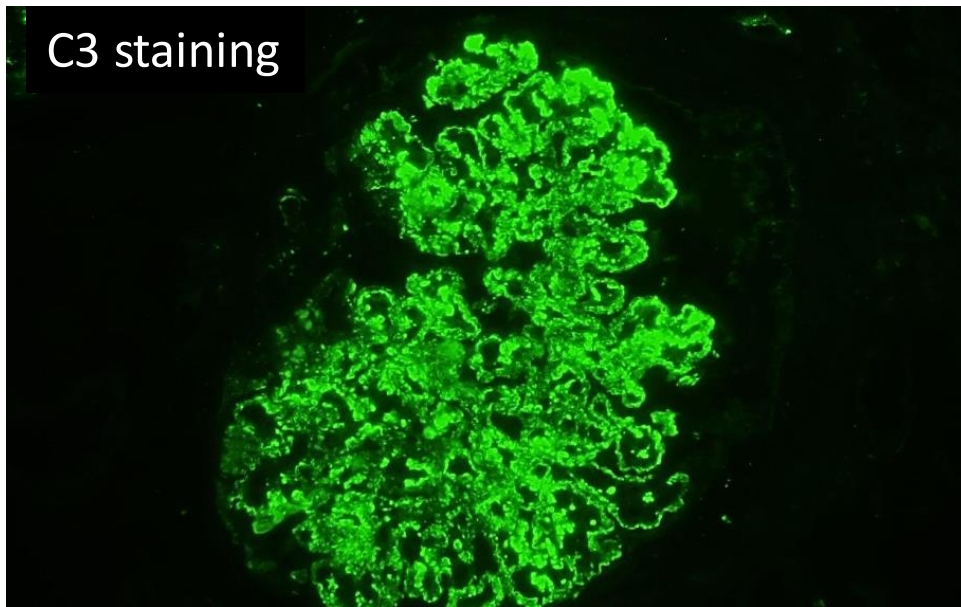


Immunoglobulins (Ig): IgA, IgG, IgM

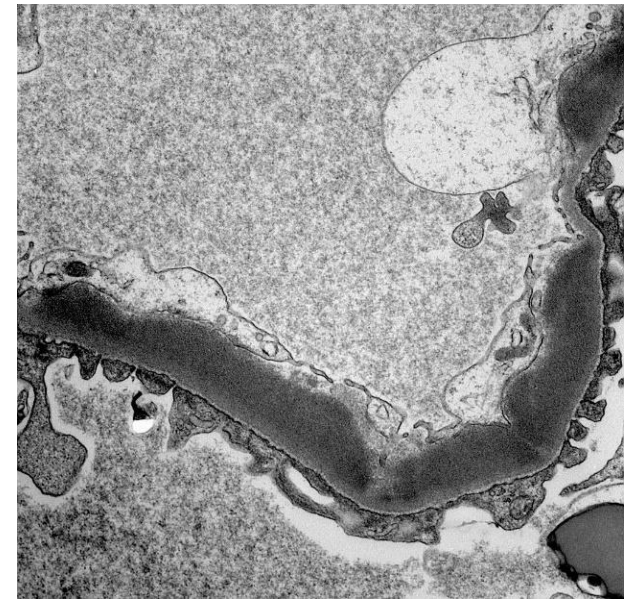
Complement (C): **C3** and C1q

Light chains: Kappa and lambda

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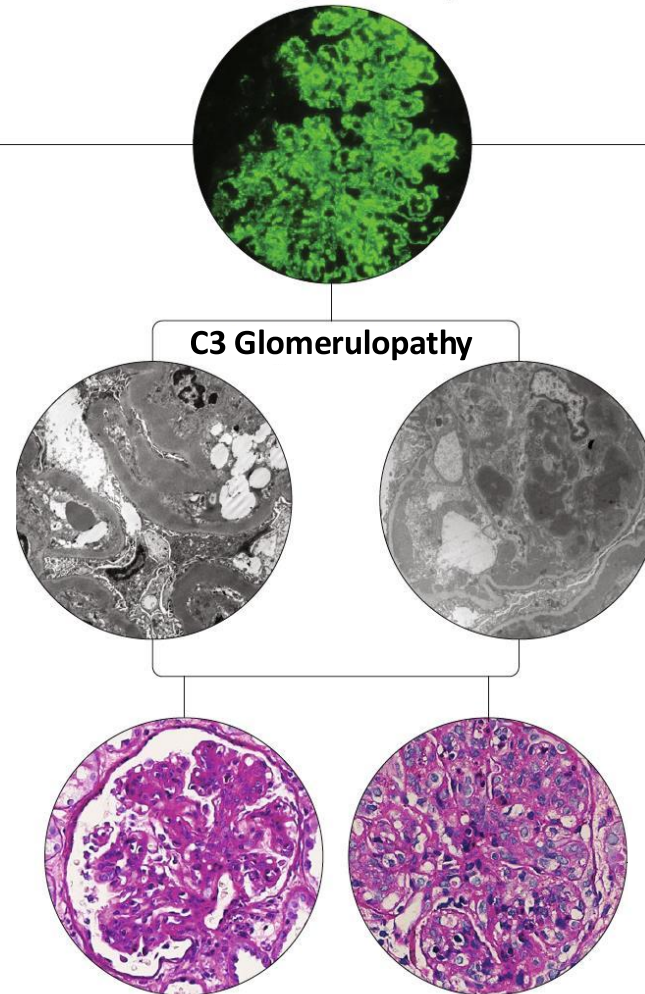


Electron microscopy can then be done to subclassify C3G as Dense Deposit Disease (DDD, shown above) or C3 glomerulonephritis (C3GN)

C3 Dominant Glomerulonephritis

Post-infectious Glomerulonephritis

- 30% of cases are C3 dominant
- **Complement abnormalities resolve within 8-12 weeks**
- Persistent abnormalities = reclassification to C3G



Proliferative glomerulonephritis

MPGN or ICGN

Paraprotein-associated glomerulo-nephritis or monoclonal gammo- pathy of renal signif- icance (MGRS)

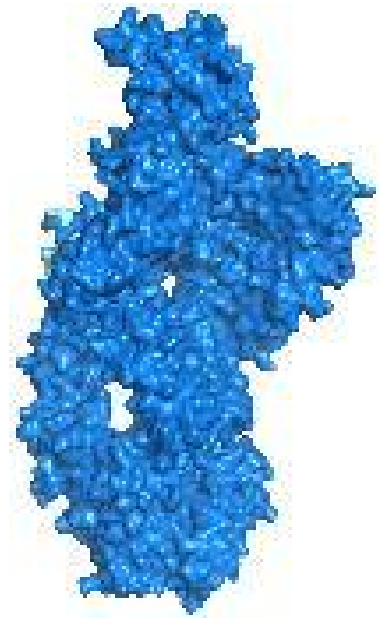
- **Adults > 50 y/o**
- Complement dysregulation driven by paraprotein
- Paraprotein-targeted therapy

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What is C3?

- It is the third component (protein) in the complement cascade
- It is very abundant in blood
- The range of normal values is very broad
- To become active, it undergoes a large change in shape

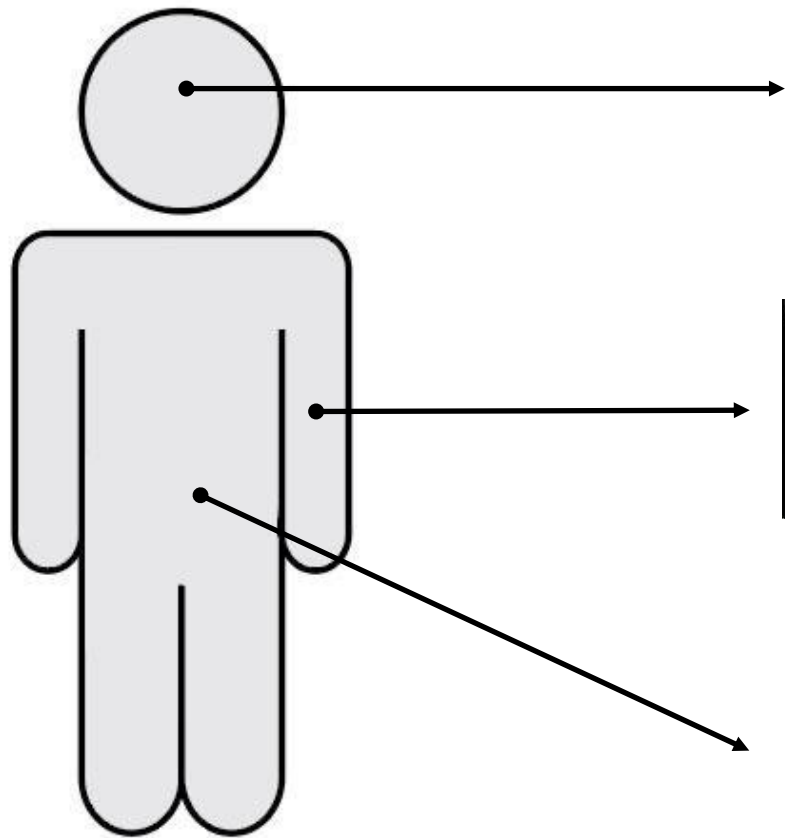


What is C3 Glomerulopathy?

- It is an ultra rare disease
- It is a disease in which C3, its breakdown products, and other complement proteins build up in the glomerulus
- It requires a renal biopsy to make the diagnosis
- Its underlying cause is dysregulation of complement
- Dysregulation of complement can be caused by different things

What is complement?

- It is a defense system in the body
- It is very powerful
- When it is not properly controlled, a variety of diseases can occur in addition to C3G



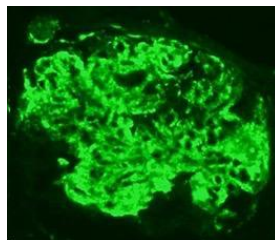
Age Macular Degeneration (AMD)

Complement protein deposition in the macula of the eye



Rheumatoid Arthritis (RA)

Complement protein deposition in the cartilage of joints



C3 Glomerulopathy (C3G)

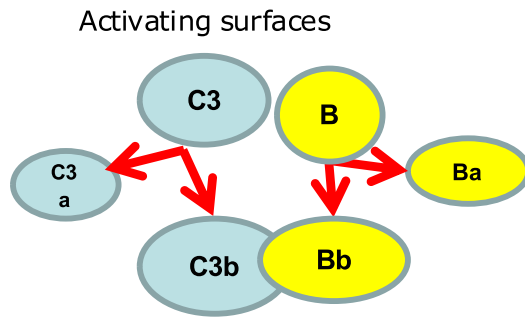
Complement protein deposition in the glomerulus of the kidney

So let's look at the complement system

- There are three phases
 - Initiation – getting it started
 - Amplification – ramping up the process
 - Effector – facing the consequences

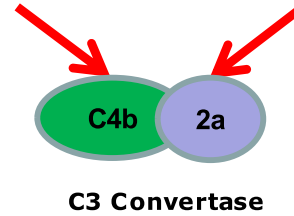
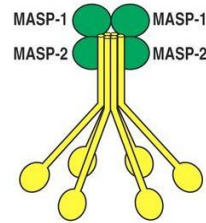
Phase 1 Initiation

Alternative Pathway

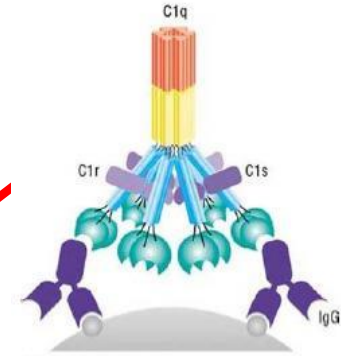


C3 Convertase

Mannose Binding Lectin
Microbial carbohydrates

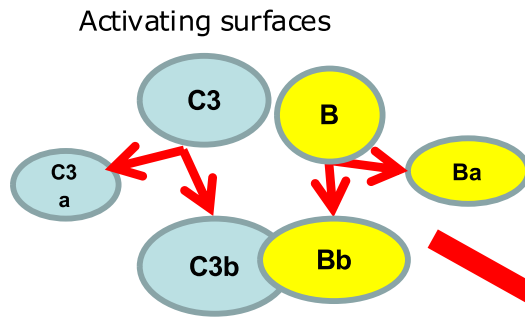


Classical Pathway
Immune complexes

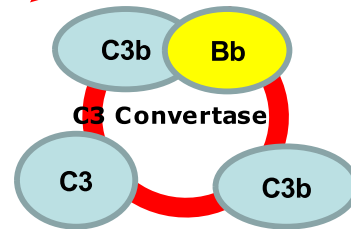


Phase 1 Initiation

Alternative Pathway

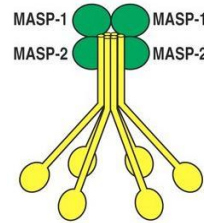


C3 Convertase

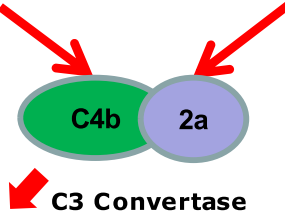
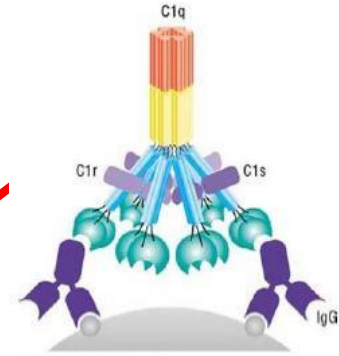


Phase 2 Amplification

Mannose Binding Lectin
Microbial carbohydrates

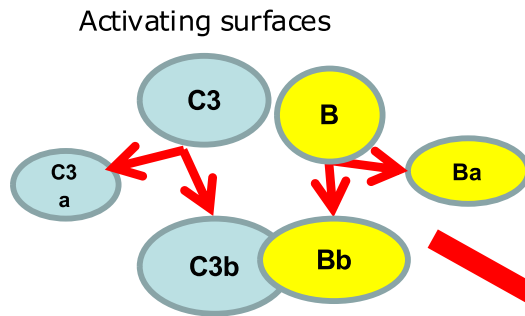


Classical Pathway
Immune complexes

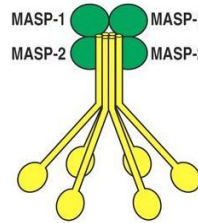


Phase 1 Initiation

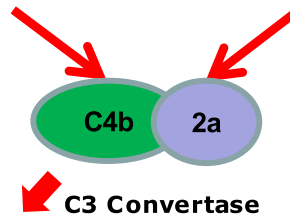
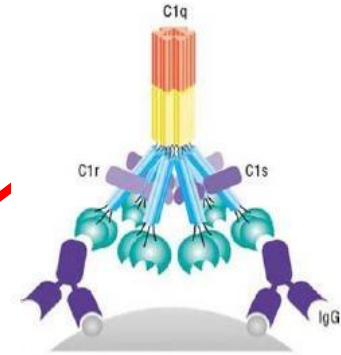
Alternative Pathway



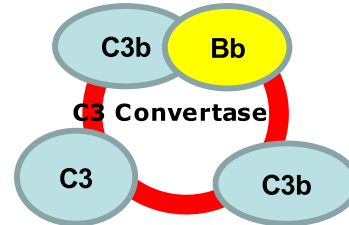
Mannose Binding Lectin
Microbial carbohydrates



Classical Pathway
Immune complexes

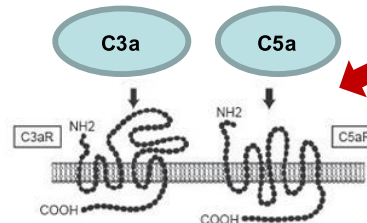


C3 Convertase

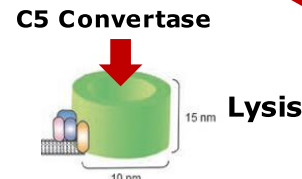


Phase 2 Amplification

Inflammation

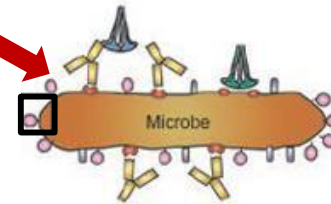


Phase 3 Effector



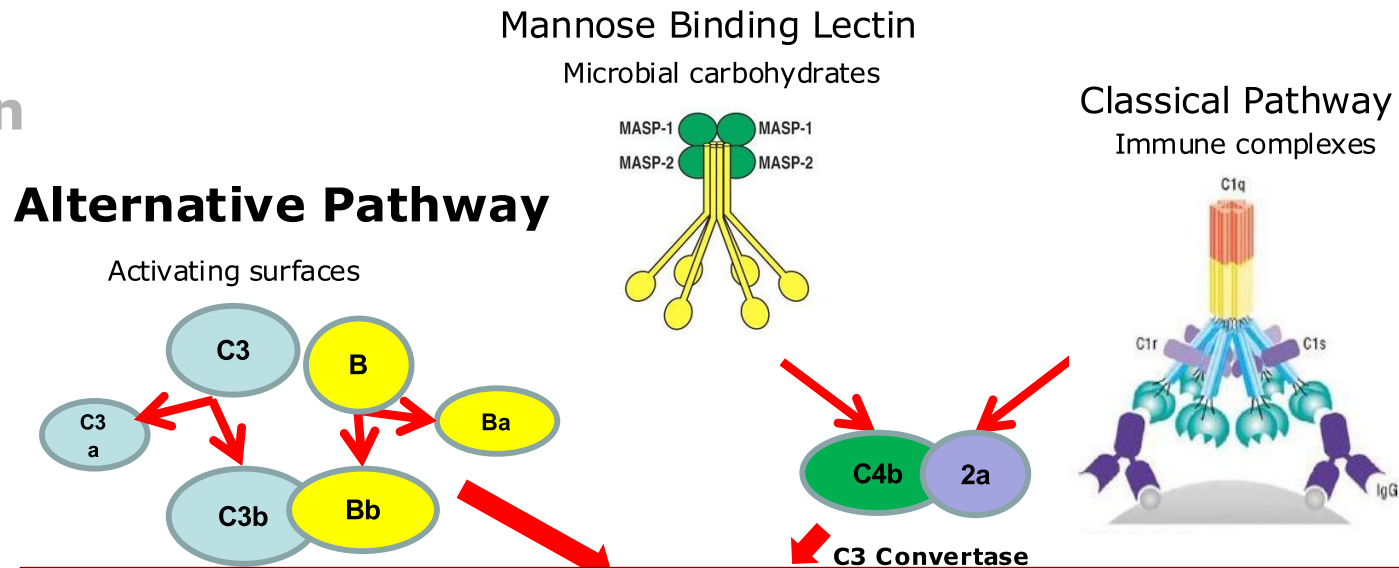
Lysis

Opsonization



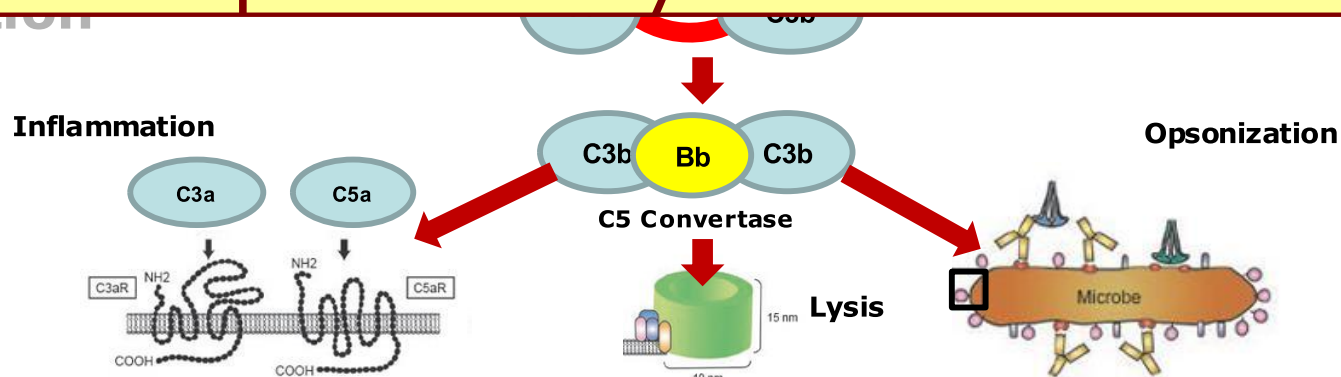
Terminal Pathway

**Phase 1
Initiation**



Exquisite control of the complement system is needed

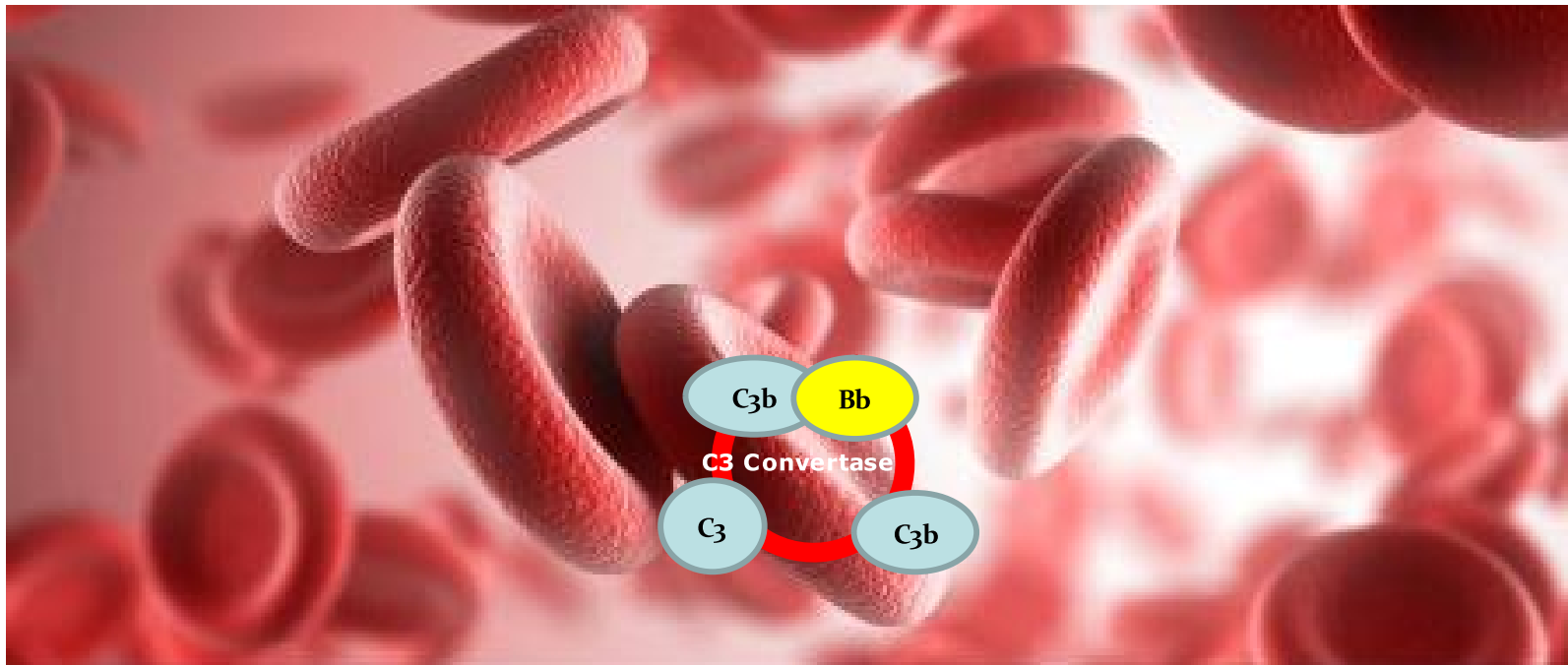
**Phase 2
Amplification**

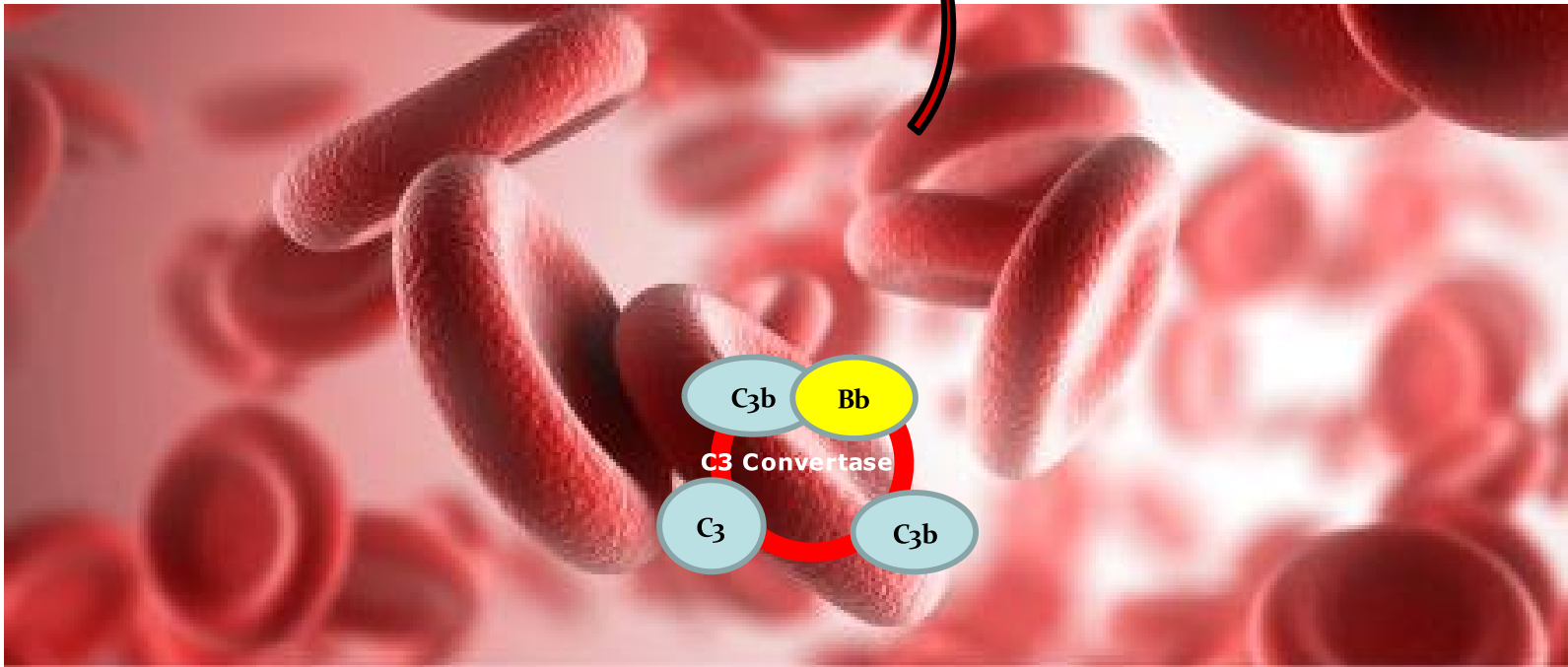
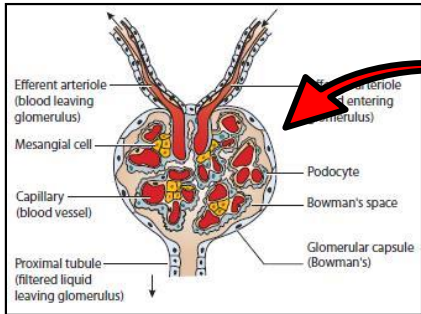


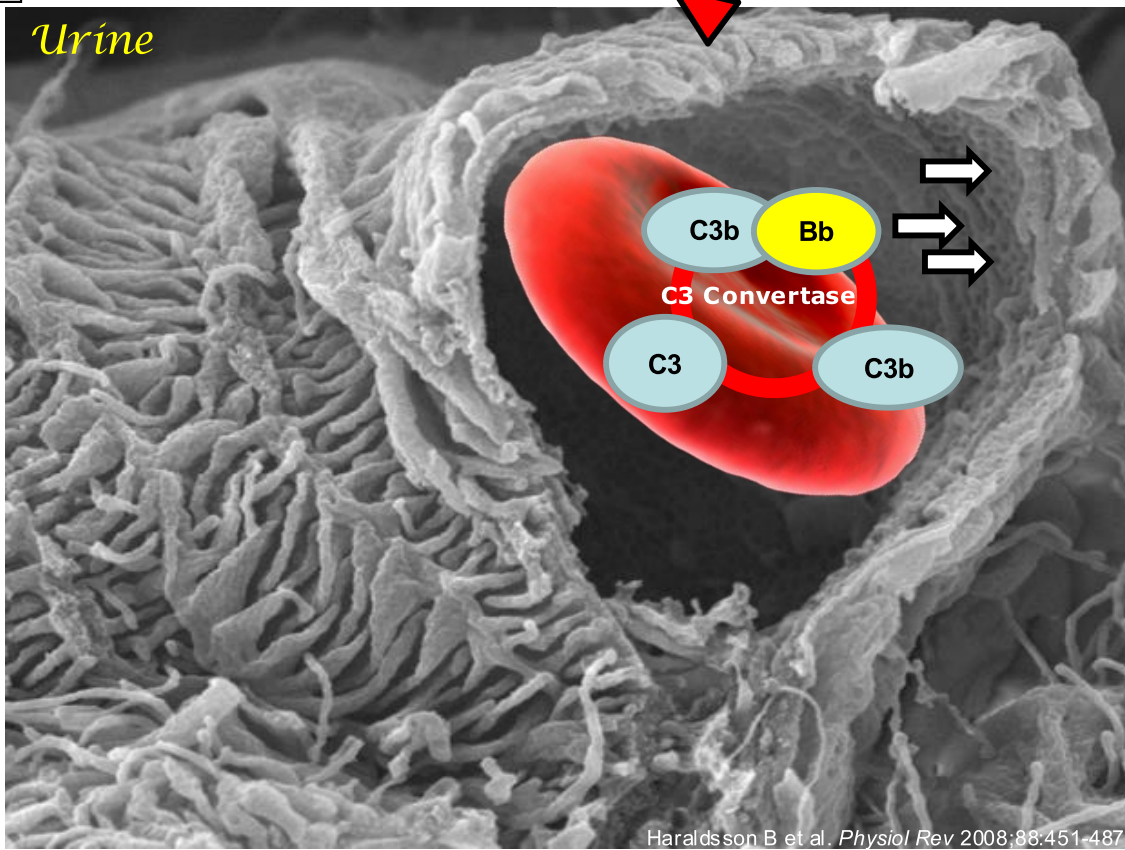
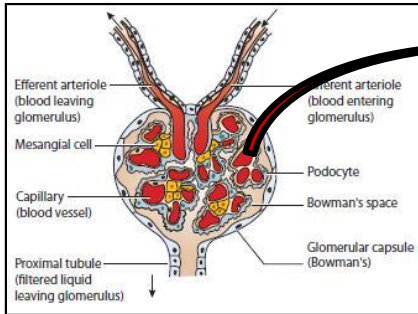
**Phase 3
Effector**

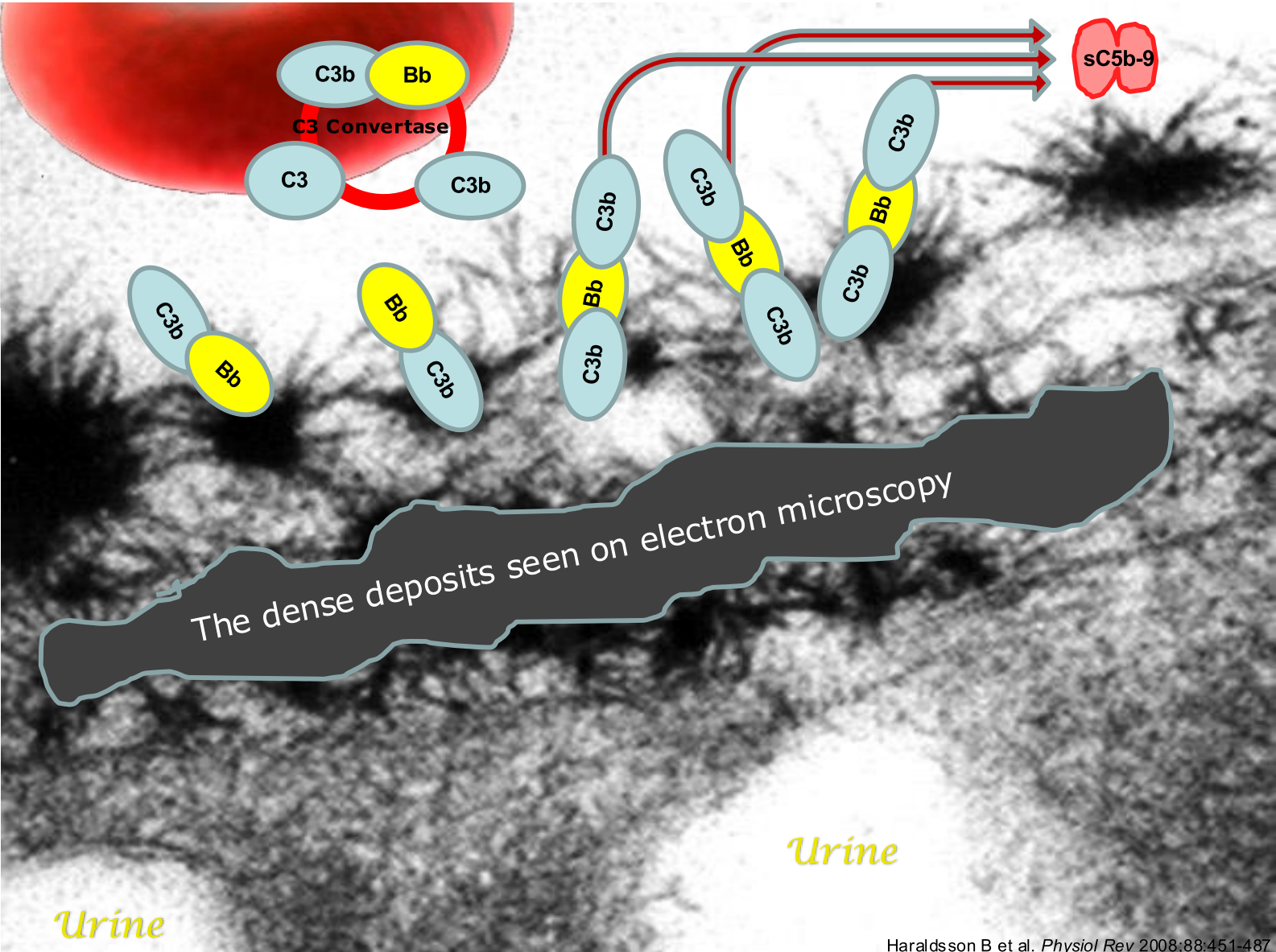
**Terminal
Pathway**

What's happening in the kidney in C3G?









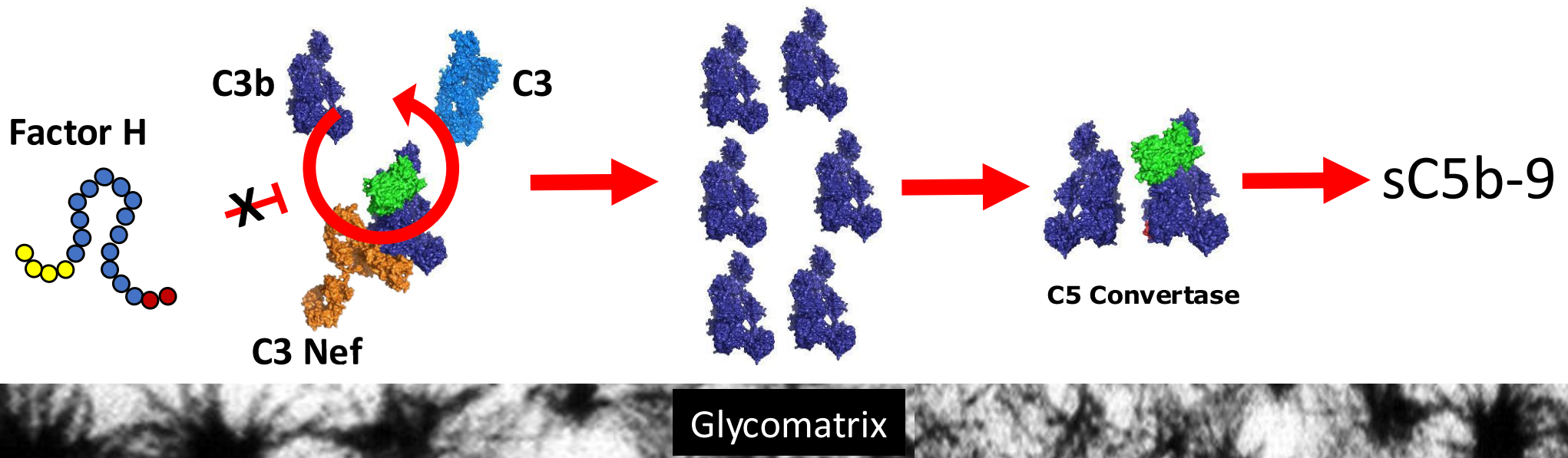
Haraldsson B et al. *Physiol Rev* 2008;88:451-487.

What causes complement dysregulation in C3G?

- Autoantibodies called nephritic factors – 40-60%
- Genetic mutations – 20%
- Unknown – 20-40%

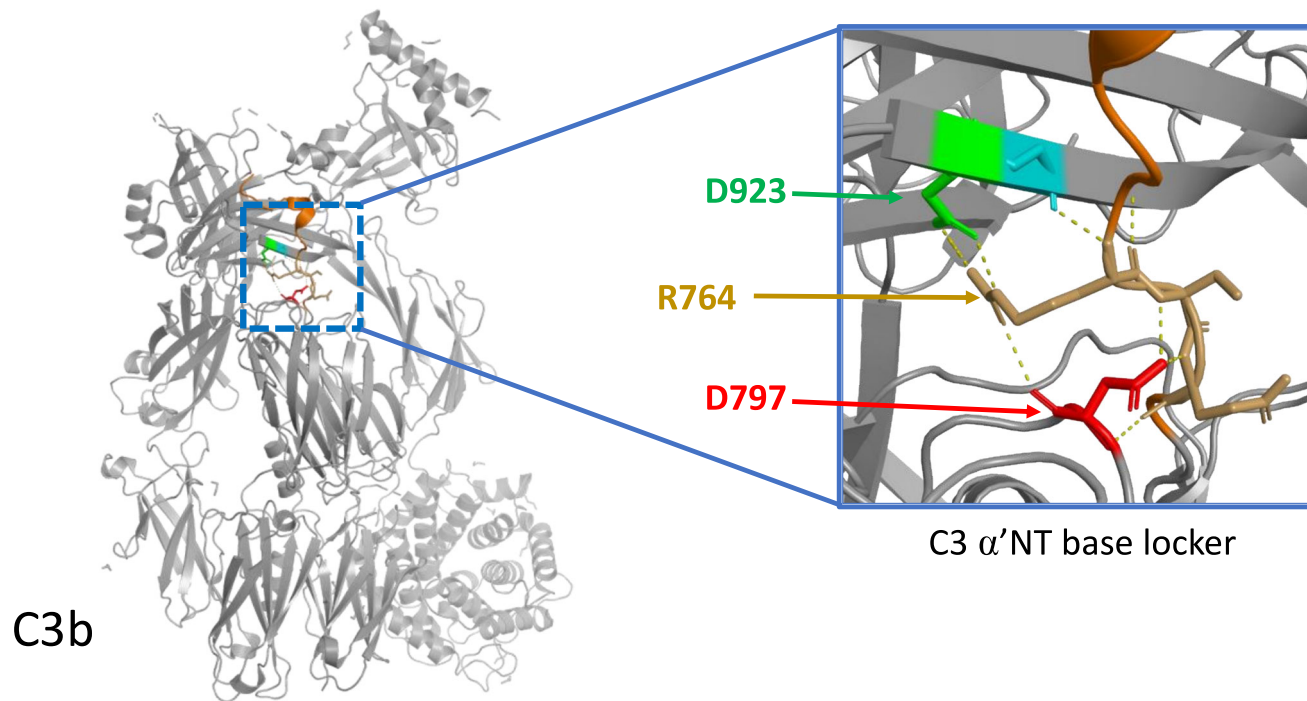
Nephritic factors

- Stabilize C3 convertase so it will not decay as it should
- Prevent regulatory proteins from working properly



Genetic mutations

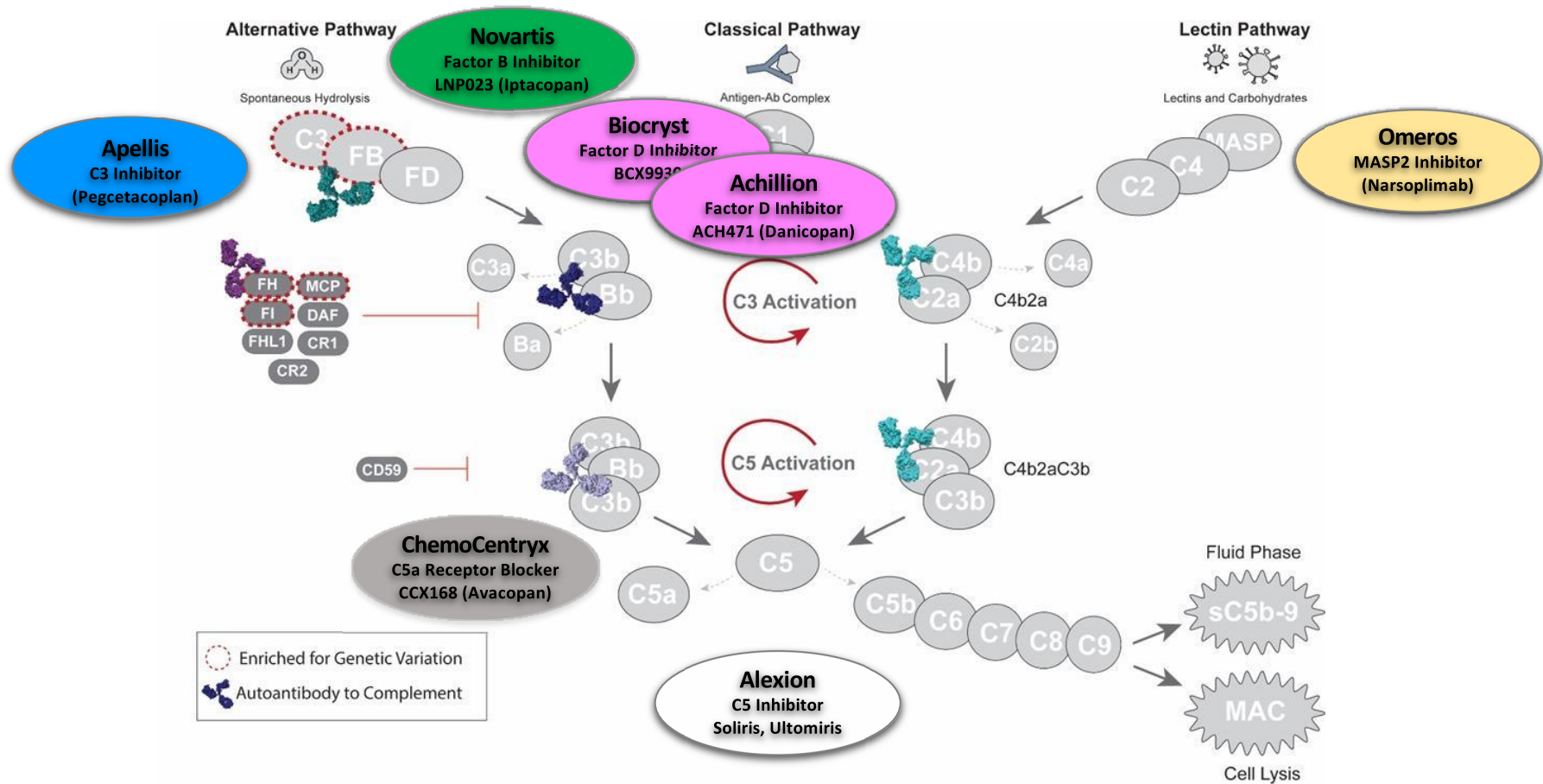
- A mutational hotspot in C3 accounts for about 2% of cases



How do we stop this mess?

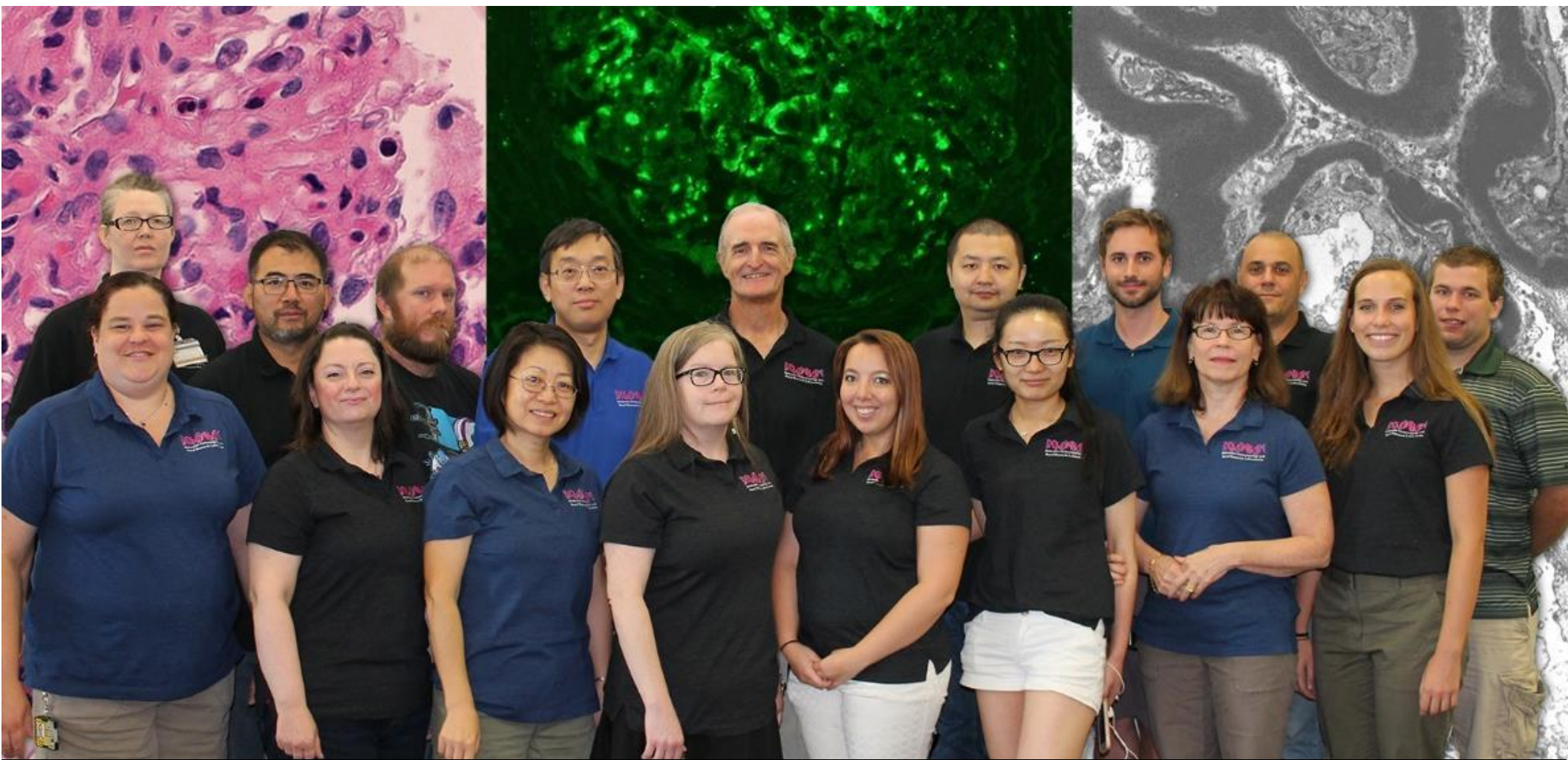
- Current therapy is supportive
- There are a large number of clinical trials to test new anticomplement drugs
- Iowa is the leading center worldwide for these trials

How do we stop this mess?



Take home points

- C3G is an ultra rare disease
- It CANNOT be diagnosed without a kidney biopsy
- It is caused by dysregulation of the alternative pathway of complement
- Dysregulation can be caused by genetic and acquired factors
- Each patient should have a thorough genetic and complement functional evaluation
- Numerous anti-complement drugs are in clinical trials making the future bright for persons with C3G



We thank the NIH for its support and the patients who entrust us with their care.

