# C3 Glomerulopathy

Marina Noris

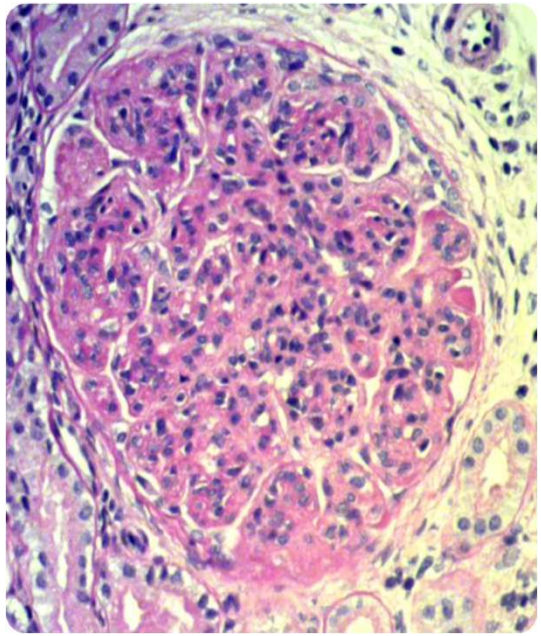
**IPNA teaching course “Complement-Mediated Kidney Diseases**
**11th February 2026**

- **The presenter received grant/research support and/or honoraria from commercial entities:**

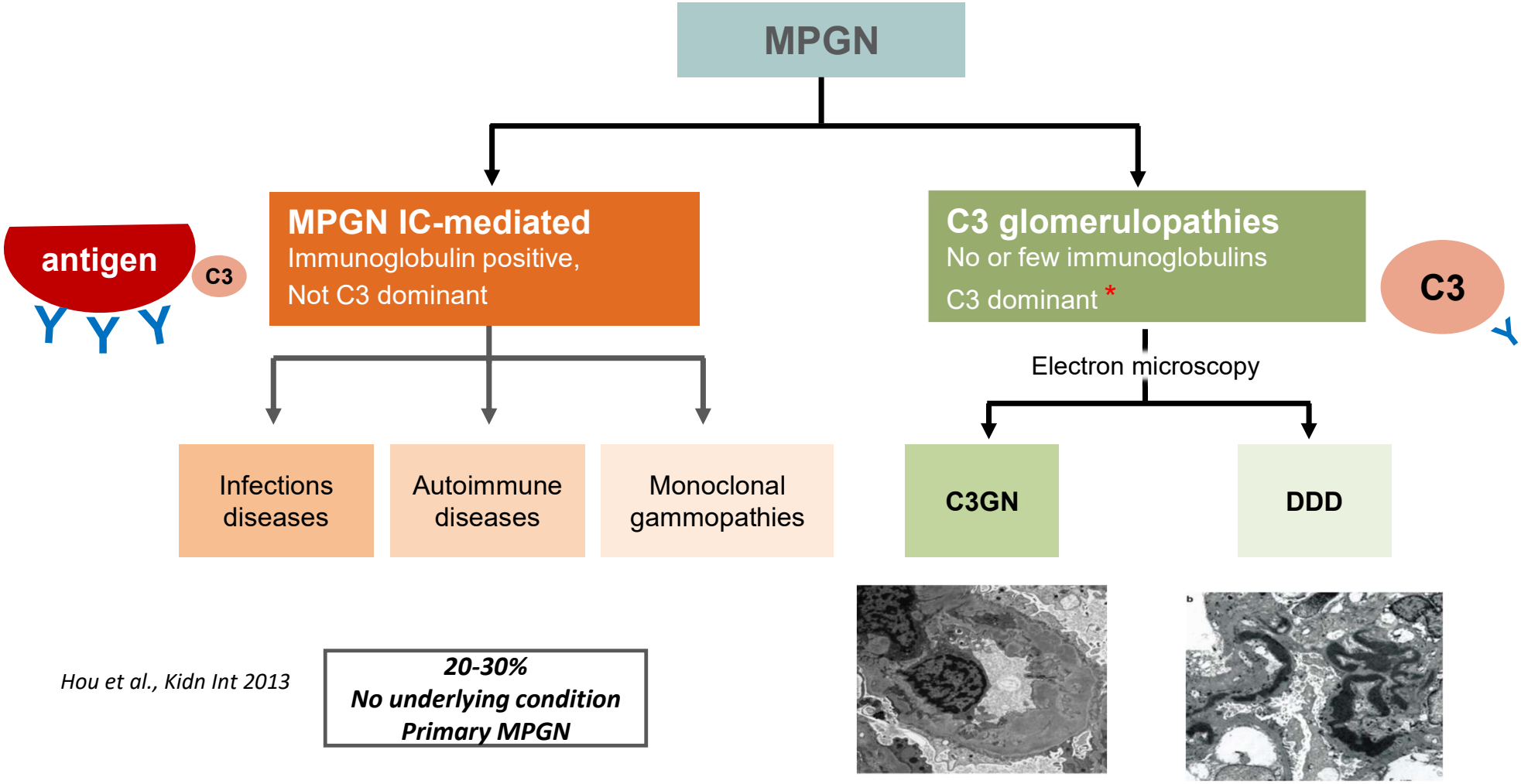
  - *Alexion (research grant and honoraria for educational talks)*
  - *Novartis (research grant and advisory board)*
  - *Sobi (research grant and advisory board)*
  - *Gemini (research and travel grants)*
  - *Eleva (research grant)*

# MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS (MPGN)

- Typical glomerular histopathological pattern of mesangial hypercellularity, endocapillary proliferation and thickening of the glomerular basement membrane
- Predominantly affecting children and young adults
- Variable clinical presentation and outcomes with poor overall prognosis and high rate of progression to end-stage renal disease (ESRD).



Sethi S et al, *N Engl J Med* 2012; Pickering MC, *Kidney Int* 2013; Donadelli R et all, *Front Immunol* 2018; Bomback et al, *Kidney Int* 2018



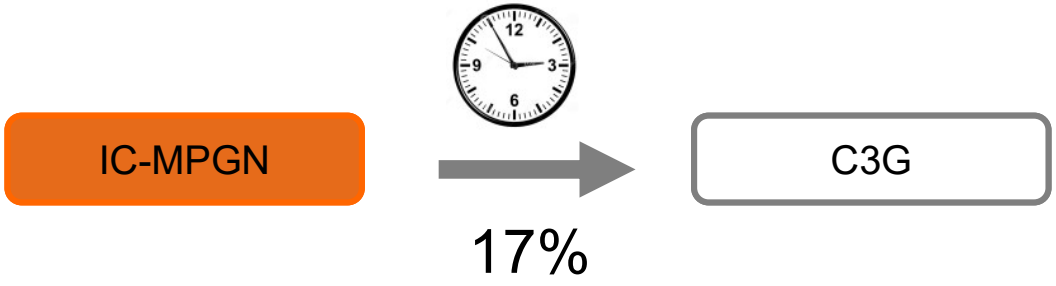

*Hou et al., Kidn Int 2013*

***20-30%***
***No underlying condition***
***Primary MPGN***

***C3 dominant: C3 at least two orders of magnitude stronger than any other common immune reactant**

*Sethi & Fervenza, NEJM 2012*
*Pickering, Kidney Int 2013*

- Up to 20% of patients shift from IC-MPGN to C3G when a kidney biopsy is repeated




*Kerns et al., Ped Nephr 2013*
*Hou J et al., Kidney Int 2013*
*Pickering M et al., Kidney Int 2013*

- Low serum C3 and normal serum C4 levels were found in the large majority of patients with either C3G or primary IC-MPGN, indicating activation of the alternative pathway of complement

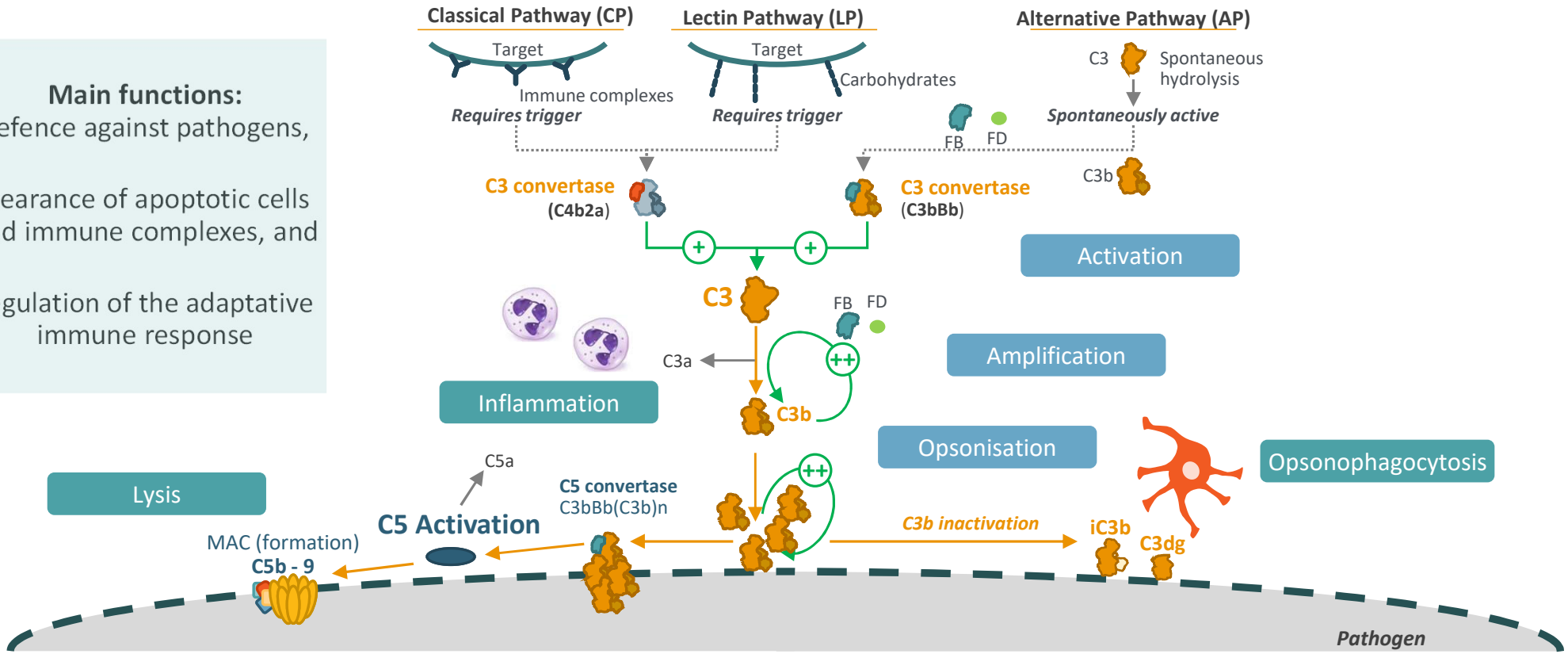
*Servais A et al., Kidney Int 2012*
*Iatropoulos P et al., Mol Immunol 2016*
*Marinozzi MC et al., JASN 2017*

# The complement system is a central component of the innate immune system

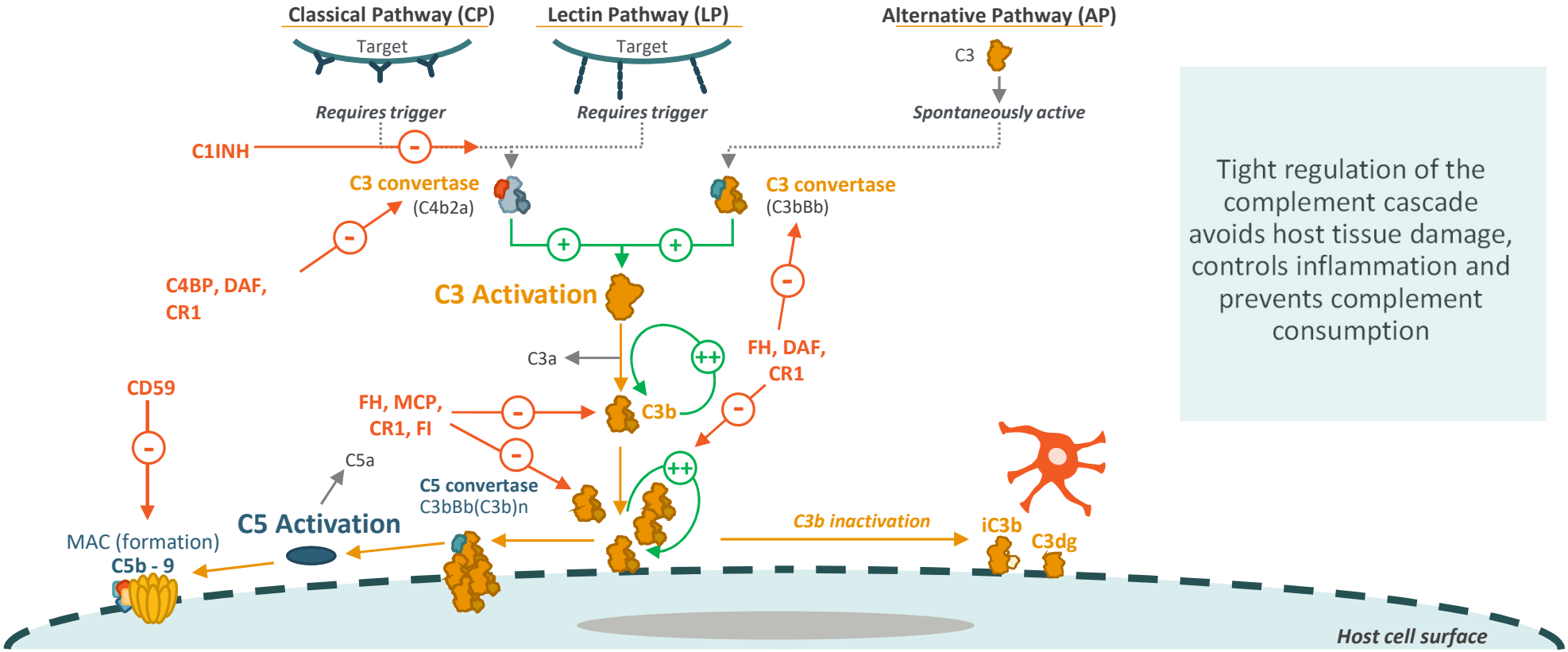
**Main functions:**
defence against pathogens,

clearance of apoptotic cells and immune complexes, and

regulation of the adaptative immune response



# The complement system is tightly regulated




Tight regulation of the complement cascade avoids host tissue damage, controls inflammation and prevents complement consumption

C1INH, C1 inhibitor; C4BP, C4 binding protein; CR1, complement receptor 1; DAF, decay accelerating factor; FH, factor H; FHR, FH-related protein; FI, factor I; MAC, membrane attack complex; MCP, membrane cofactor protein.

1. Noris M & Remuzzi G. *Semin Nephrol* 2013;33:479–92; 2. Smith RJH, *et al. Nat Rev Nephrol* 2019;15:129–43; 3. Józsi M, *et al. Trends Immunol* 2015;36:374–84; 4. Merle NS, *et al. Front Immunol* 2015;6:262.

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# Genetic and acquired complement abnormalities are highly prevalent in patients with C3G

In C3G, abnormalities in **complement genes** are present in **approximately 15-20%** of cases

Such genetic variants in complement genes include:

- **Variations in complement regulators** (*CFH, CFI* and *MCP* genes)
- **Variations in complement activators** (*C3, CFB* and *CFHR* genes)

Acquired factors (**NeFs and autoantibodies**) are present in many patients with C3G

The reported prevalence of NeF and autoantibodies varies widely due to heterogeneity and difficulty in detection:

- **C3G prevalence**: 40–75%

Iatropoulos P, *et al. J Am Soc Nephrol* 2018;29:283–94; 3.

Noris M & Remuzzi G. *Nephrol Dial Transplant* 2024;39:202–14.

**Diapositiva 8**

**1**

Note to Elena: we have just made the coloured shapes slightly shorter now the sentence on NeFs in the general population has been removed

We have also adjusted 'CFHRs genes' to 'CFHR gene' if this is acceptable.
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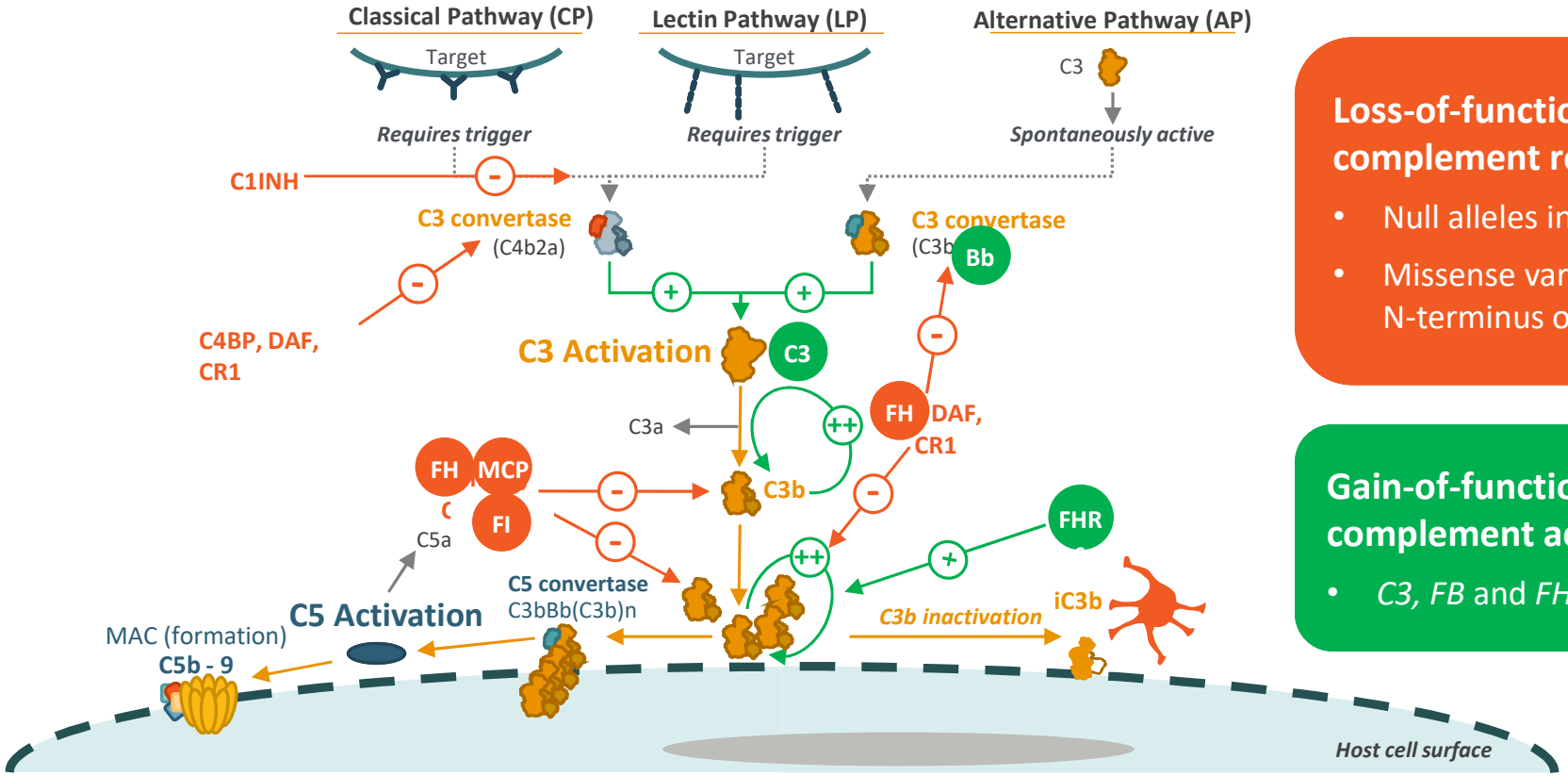
# Mutations lead to excessive complement activation

**The complement cascade**




**Loss-of-function variants in complement regulators:**

- Null alleles in *FH, CFI* and *MCP*
- Missense variants at the N-terminus of *FH*

**Gain-of-function variants in complement activators:**

- *C3, FB* and *FHRs*


Noris M & Remuzzi G. *Semin Nephrol* 2013;33:479–92;

Smith RJH, *et al. Nat Rev Nephrol* 2019;15:129–43; 4.

## Diapositiva 9

1 Note to Elena: Colour or circles now aligned to the red and green boxes.
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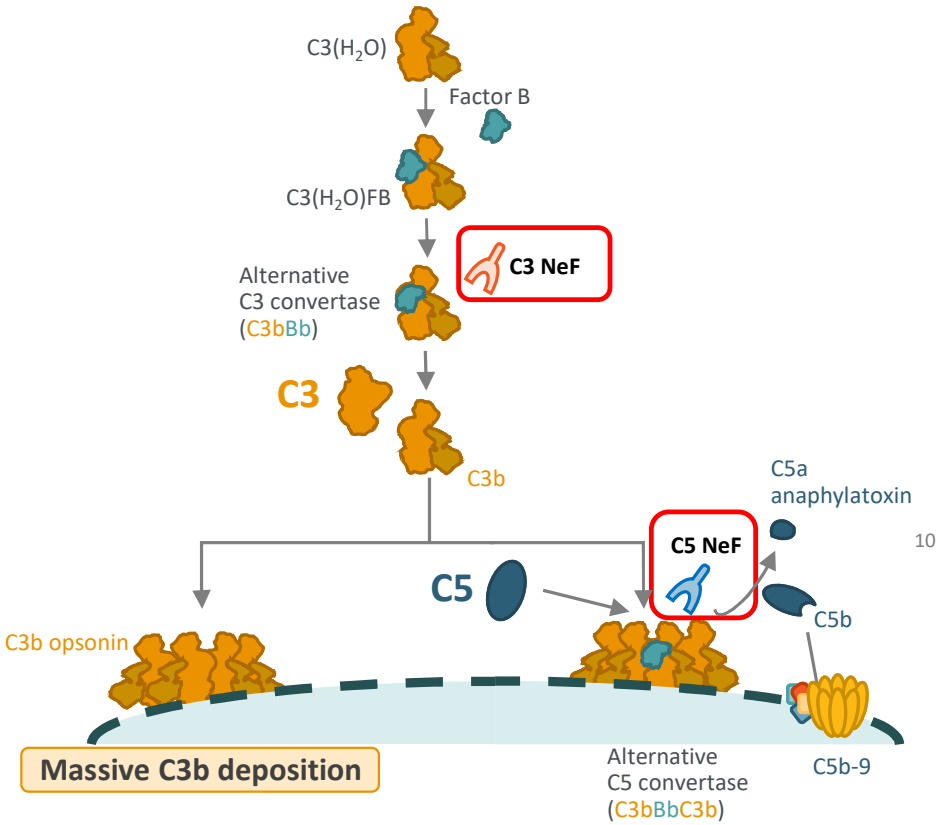
# Immunological drivers in C3G lead to excessive complement activation

| Driver | Frequency in affected patients (%) |
|---|---|
| C3 nephritic factors | 50 |
| C4 nephritic factors | 2.4% |
| C5 nephritic factors | 30-40 |
| Factor H autoantibodies | ~1.0 |
| Factor B autoantibodies | ~2.5 |
| C3b autoantibodies | 1.5 |

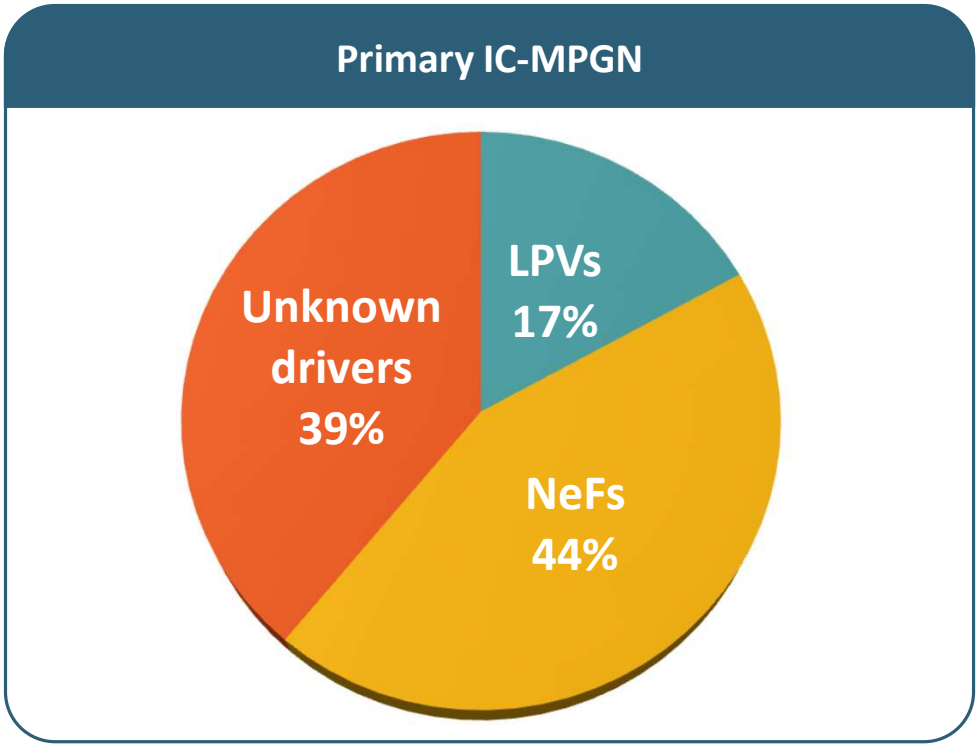
**Nephritic factors (NeFs)** are autoantibodies that stabilise the convertase complexes.
**C3 & C5 NeFs** bind to the assembled C3 and C5 convertase complexes and prevent spontaneous and FH-mediated decay, respectively

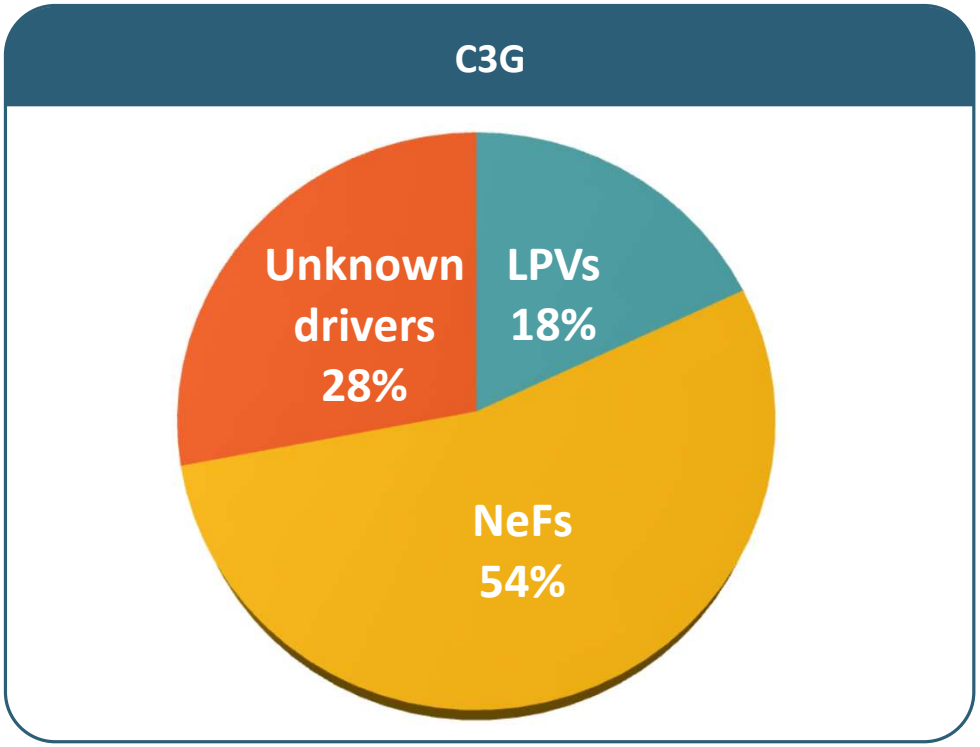





Donadelli R. Et al., Pediatr Nephrol. 2019 ;34:1311-1323
Daha MR *et al. Immunology* 1981;43:33–38
Marinozzi MC *et al. Kidn Int* 2017;92:1232–41

# ALTERNATIVE PATHWAY ABNORMALITIES IN C3G

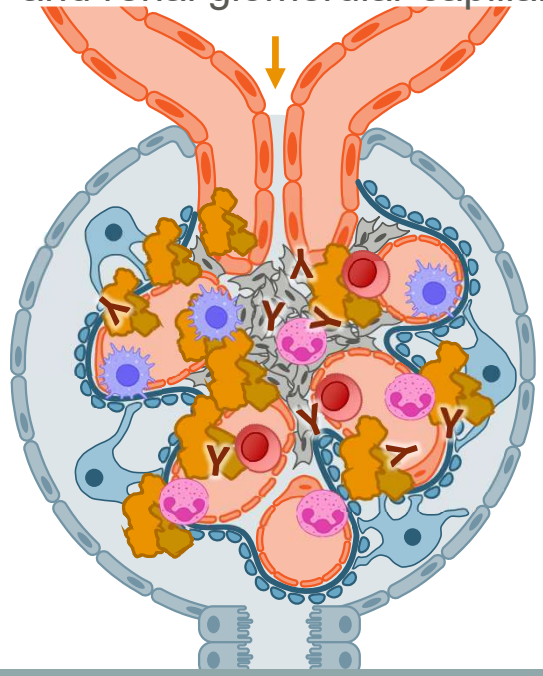


# C3 deposition in the glomeruli results in downstream inflammation and kidney damage

**Complement dysregulation**

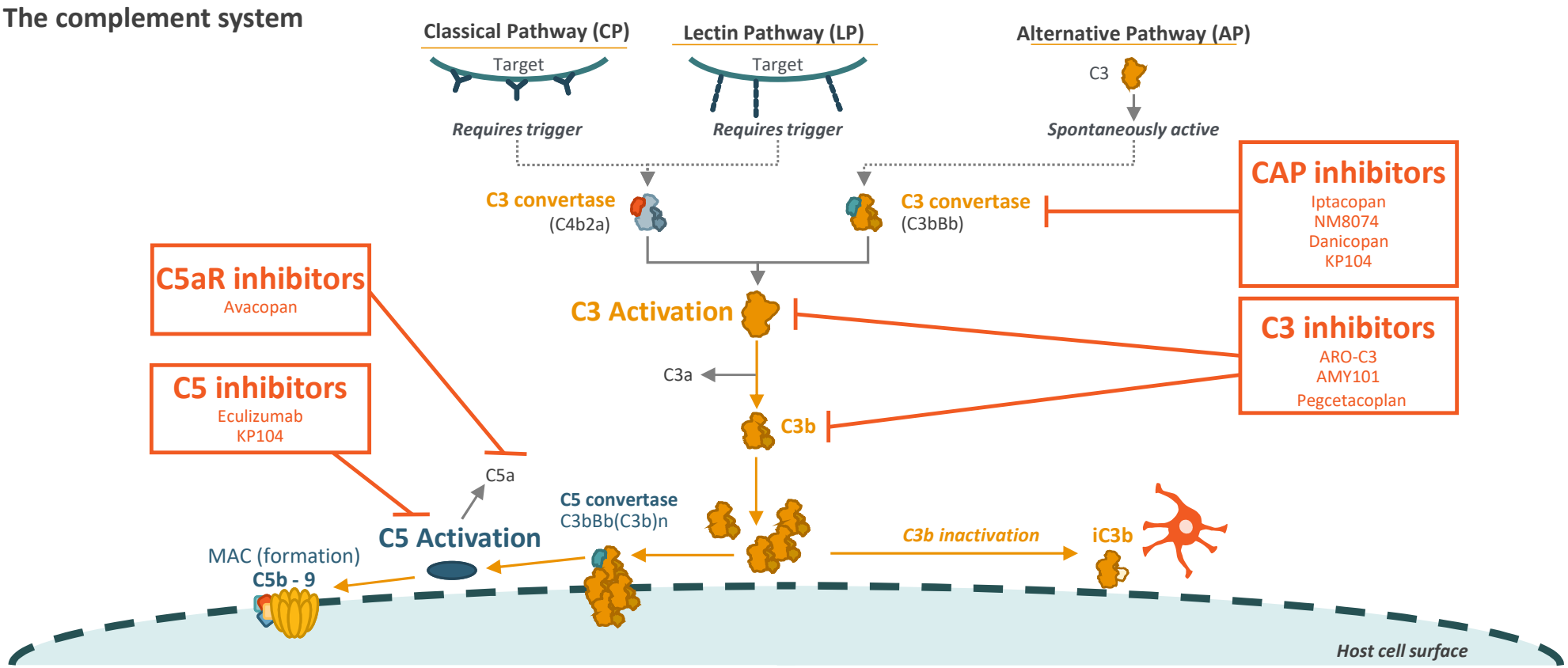
Deposition of **activated C3 and C5 fragments** in the GBM and renal glomerular capillary



- Impairment of GBM structure and function
- Recruitment of inflammatory cells
- Podocyte dysfunction and apoptosis
- Mesangial cell injury

**C3G results in inflammation and damage to the capillary filtration membrane, preventing normal function of the glomerulus**

# Therapeutic targets for C3G regulate complement hyperactivation




Noris M, Remuzzi G. Nephrol Dial Transplant. 2024 ;39:202-214

AJKD 2019

Original Investigation

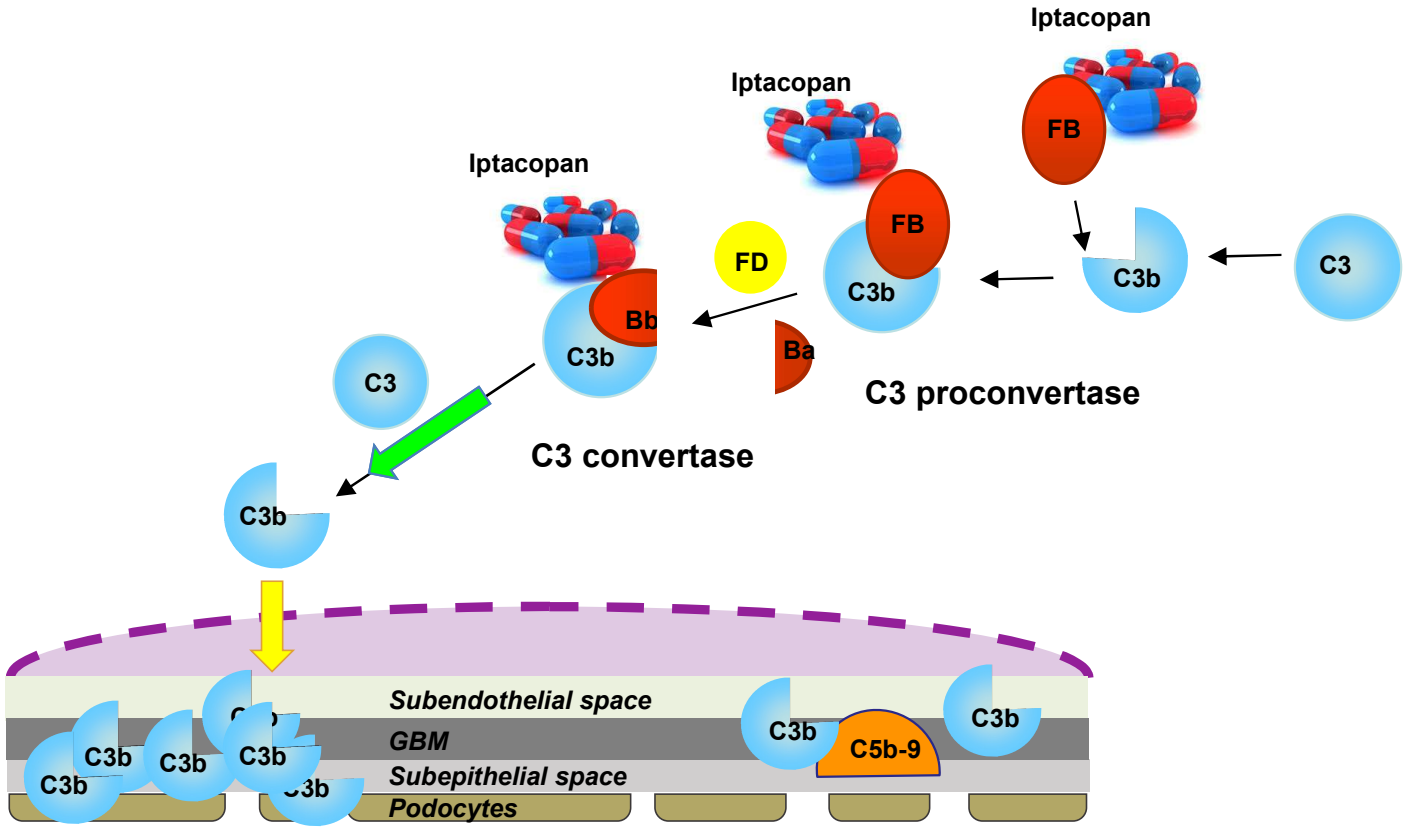
# C5 Convertase Blockade in Membranoproliferative Glomerulonephritis: A Single-Arm Clinical Trial

*Piero Ruggenenti, Erica Daina, Alessia Gennarini, Camillo Carrara, Sara Gamba, Marina Noris, Nadia Rubis, Francesco Peraro, Flavio Gaspari, Andrea Pasini, Angelo Rigotti, Renelda M. Lerchner, Domenico Santoro, Antonio Pisani, Alessandra Pasi, and Giuseppe Remuzzi, on behalf of the EAGLE Study Group*

*sC5b-9 plasma levels were fully normalised by eculizumab in all subjects, whereas proteinuria decreased in only 3 patients*

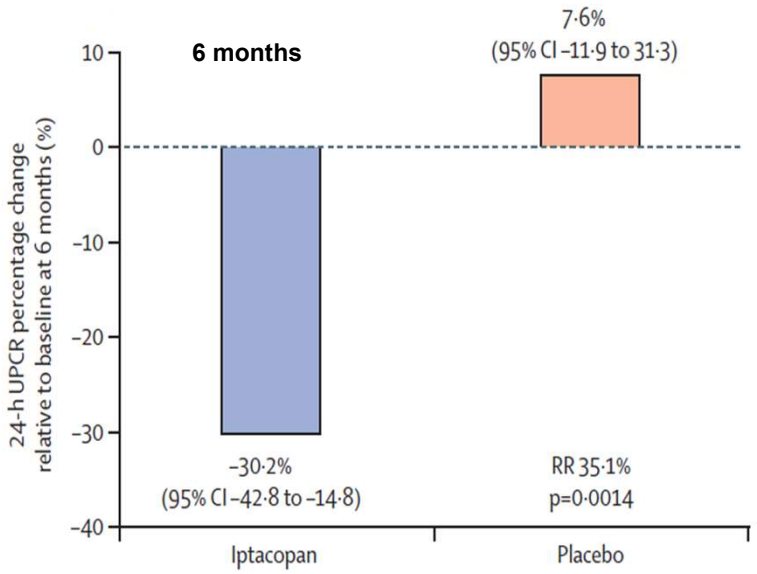
*Even transient treatment withdrawal is associated with a rebound of disease activity that does not appear to fully recover after re-treatment*

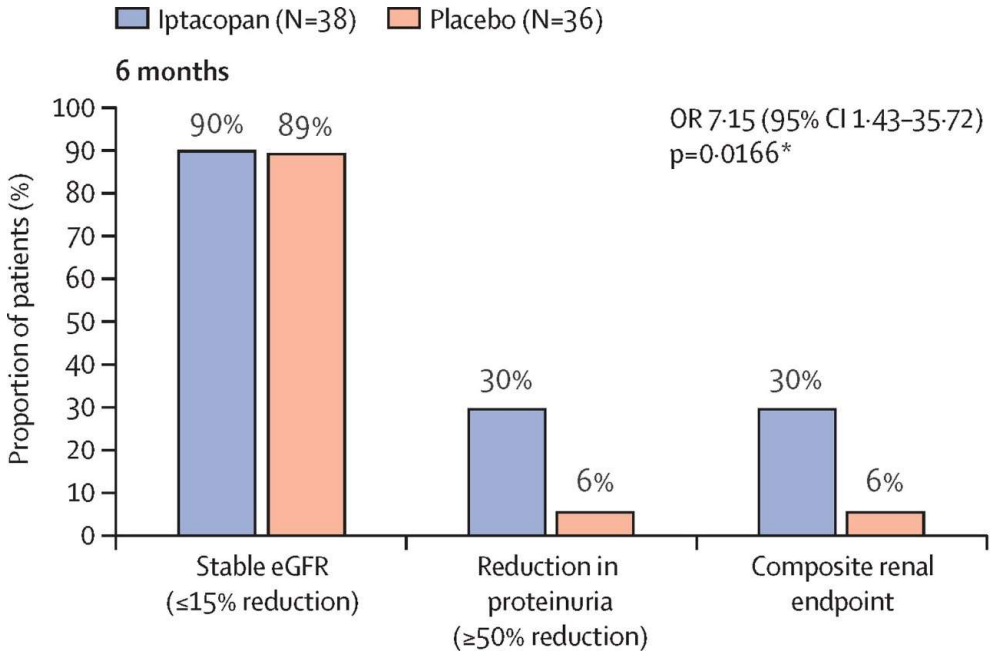
# ORALLY ACTIVE SELECTIVE INHIBITOR OF THE ALTERNATIVE PATHWAY C3 CONVERTASE




Iptacopan (LNP-023) binds to Factor B. It does not prevent the formation of the C3 convertase, but it specifically inhibits C3 convertase enzymatic activity, blocking the conversion of C3 to C3b

## APPEAR-C3G : multicentre, randomised, double-blind, placebo-controlled, phase 3 study of iptacopan versus placebo in 74 patients with C3G



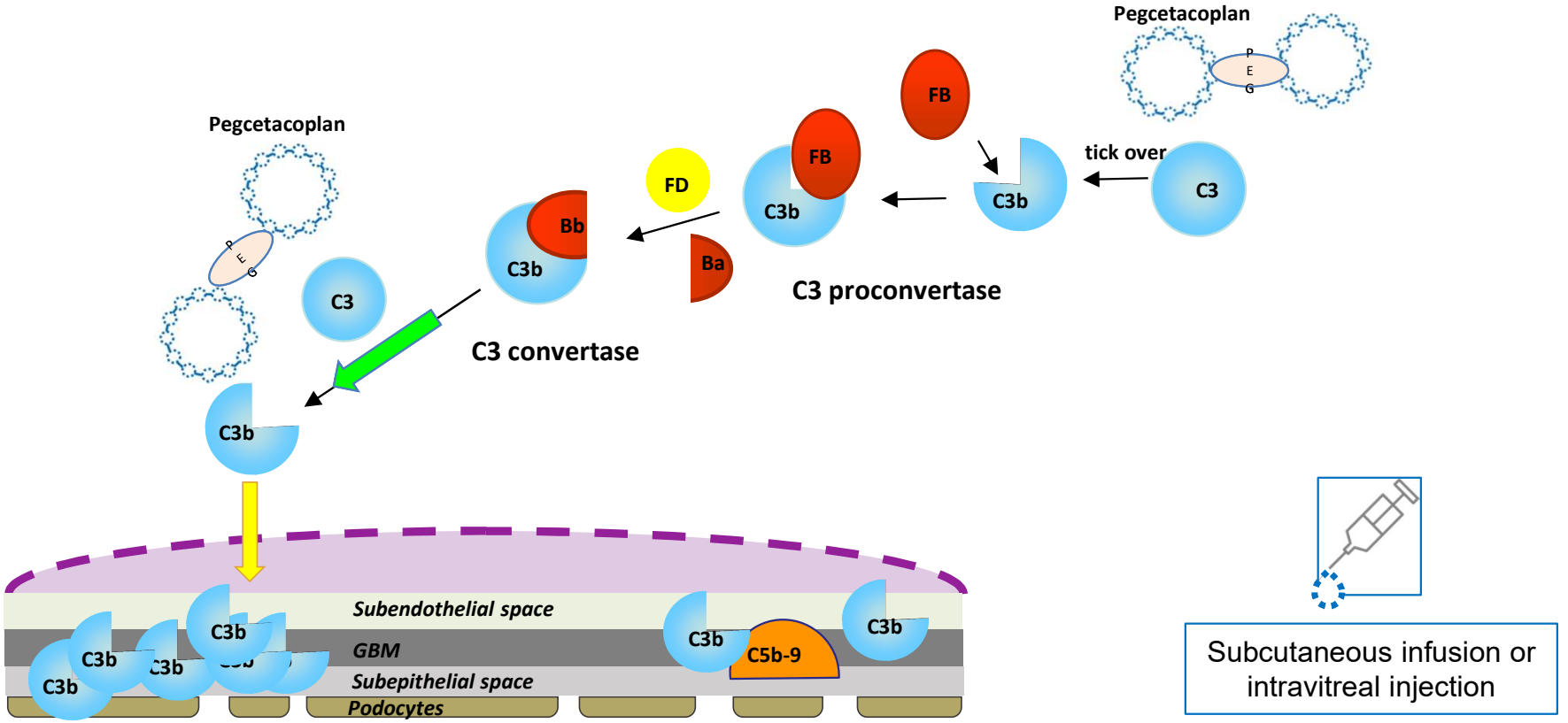




Primary end-point: percentage change in proteinuria following six months of treatment with iptacopan or placebo

Proportion of patients reaching the composite renal endpoint: ≥50% reduction UPCR and stable eGFR: 30%

*Kavanagh D et al., Lancet, 2025*

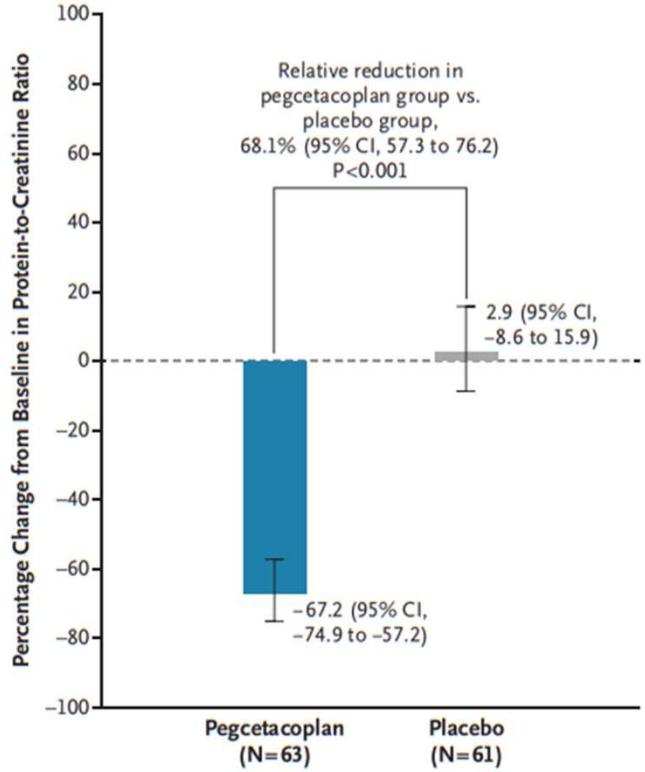
# A CYCLIC PEGYLATED PEPTIDE THAT BINDS TO A POCKET OF C3 AND C3b AND INHIBITS ACTIVATION

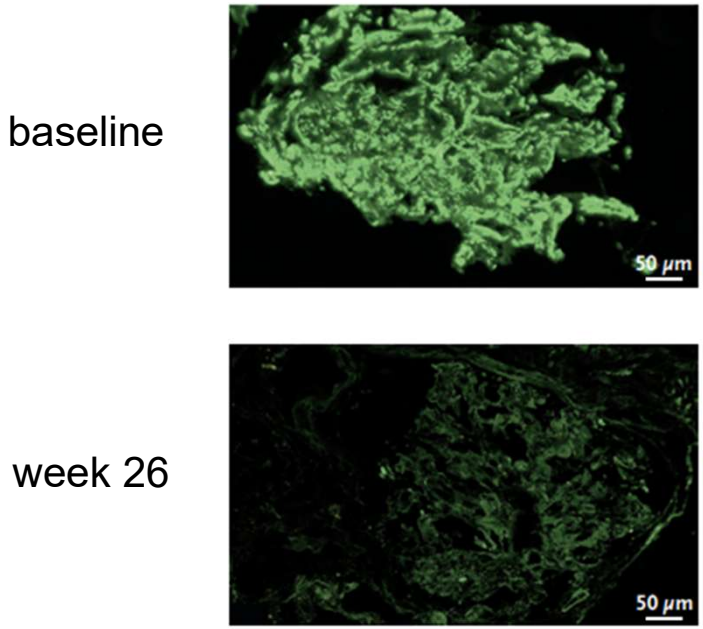



Two dentical cyclic peptides covalently bound to a PEG molecule. It prevents the activation of C3 to C3b either by spontaneous hydrolysis and by the C3 convertases of the three complement pathways

# VALIANT : multicentre, phase 3, double-blind, placebo-controlled trial in 124 adolescents and adults with C3G or primary IC- MPGN

*Improved Urinary Protein-to-Creatinine Ratio and decreased C3 staining in the biopsy at Week 26*




*Higher % of patients in the pegcetacoplan than in the placebo group met the composite renal end-point criteria (stabilization of eGFR and ≥50% reduction in urinary protein-to-creatinine ratio) (49% vs. 3%).*

Fakhouri F et al., *NEJM* 2025

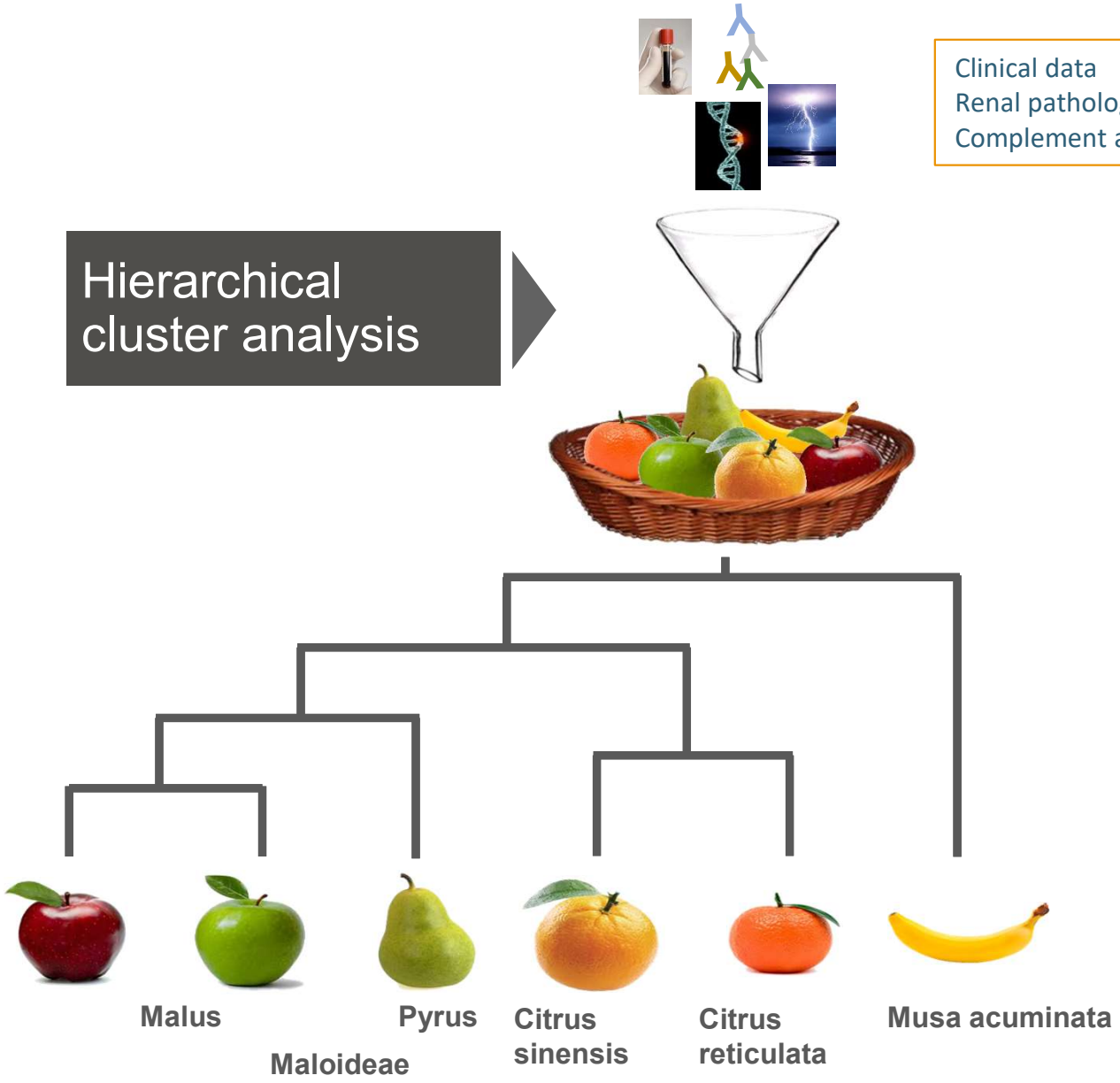
# C3G: TOWARD PRECISION MEDICINE

C3G is **complex multifactorial disease** that results from the concurrence of **genetic, acquired and environmental factors**

The heterogeneous response could be related to the **mechanisms of complement activation**, which **may vary substantially from patient to patient**

Because each **drug may act only in specific subgroups of patients**, its effect in the overall population will likely **be diluted**

The choice of drug should be tailored to each **patient's individual characteristics**


Clinical data
Renal pathology data
Complement abnormalities
Hierarchical cluster analysis
Malus
Pyrus
Maloideae
Citrus sinensis
Citrus reticulata
Musa acuminata

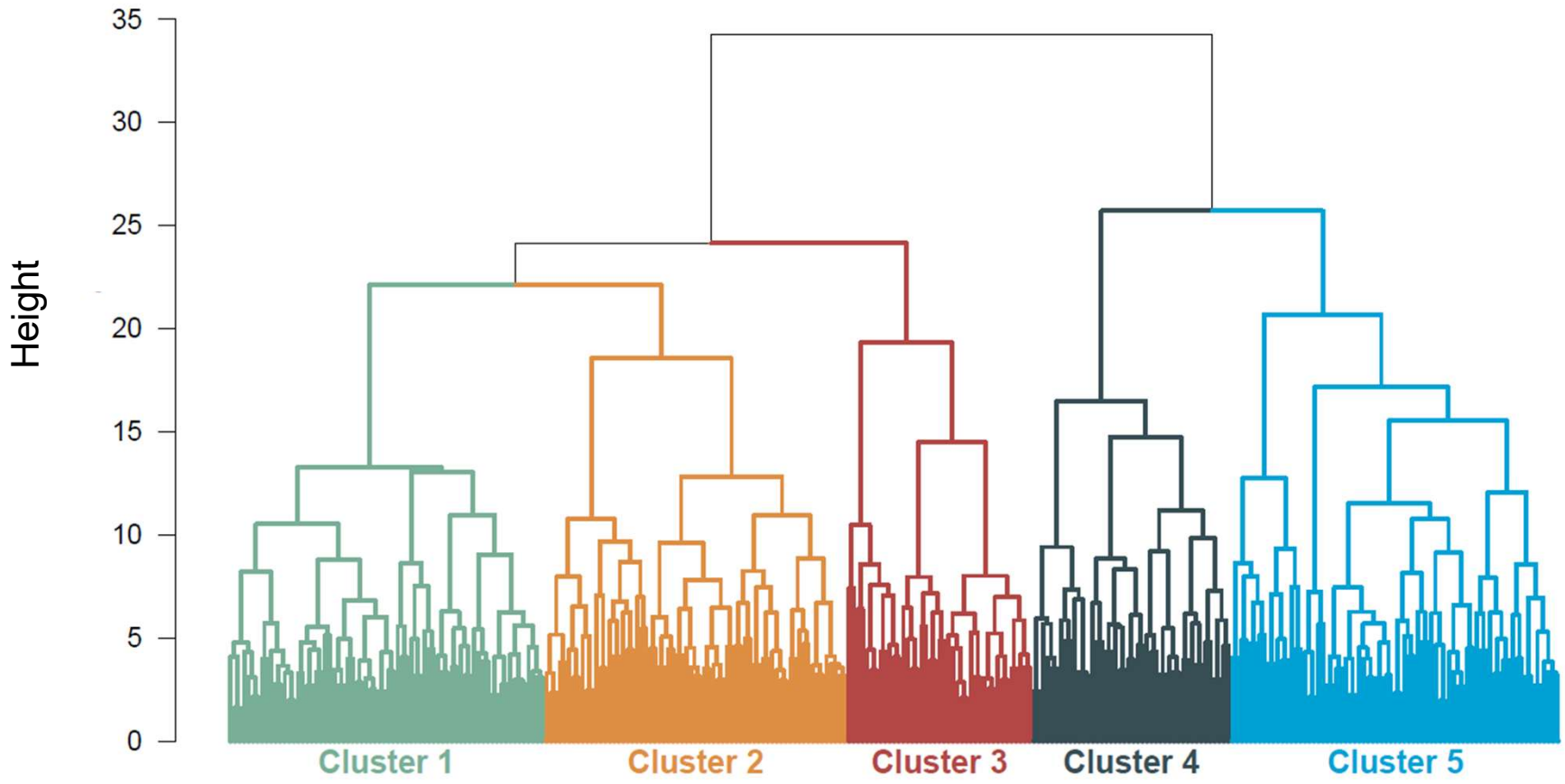
# TWENTY-NINE HISTOLOGIC, BIOCHEMICAL, GENETIC AND CLINICAL VARIABLES AT ONSET IN 295 PATIENTS

*Examples of variables included in cluster analysis*

| **Clinical features** *(n=7)* | **Histology findings** *(n=17)* | **Complement profile** *(n=5)* |
|---|---|---|
| Age (onset) | C3 staining on IF | Serum C3 |
| Familiarity for nephropathy | IgG staining on IF | Serum C4 |
| Micro-/Gross hematuria at onset | Intramembranous electron dense deposits | Plasma sC5b-9 |
| Proteinuria/Nephrotic syndrome at onset | Subendothelial deposits | NeF positivity |
| Renal impairment/ESRD at onset | % of sclerotic glomeruli | Carrier of LPV or rare CNV |
| ... | ... | |

Benigni et al, *Kidney Int,* 2025

# CLUSTER ANALYSIS IN PATIENTS DEMONSTRATES THE PRESENCE OF FIVE GROUPS




Benigni et al, Kidney Int, 2025

Benigni et al, *Kidney Int,* 2025

# CLUSTER ANALYSIS IDENTIFIED FIVE DISTINCT GROUPS OF PATIENTS

***Clusters 1-3**:*
*Fluid–phase complement activation*

***Cluster 1***
Low serum C3 and high plasma sC5b-9 levels
*Fluid-phase AP C3 and C5 convertase activation*

***Cluster 2:***
Low serum C3 and high plasma sC5b-9 levels
Ig and C1q staining on IF
*Fluid-phase AP C3 and C5 convertase activation + classical pathway activation*

***Cluster 3:***
Low serum C3 and mostly normal plasma sC5b-9 levels
Very dense deposits on EM
*Fluid-phase AP C3 convertase activation only*

***Cluster 4 and 5:***
*Solid–phase AP complement activation*
Normal serum C3 levels, normal plasma C5b-9 , Intense C3 staining on IF

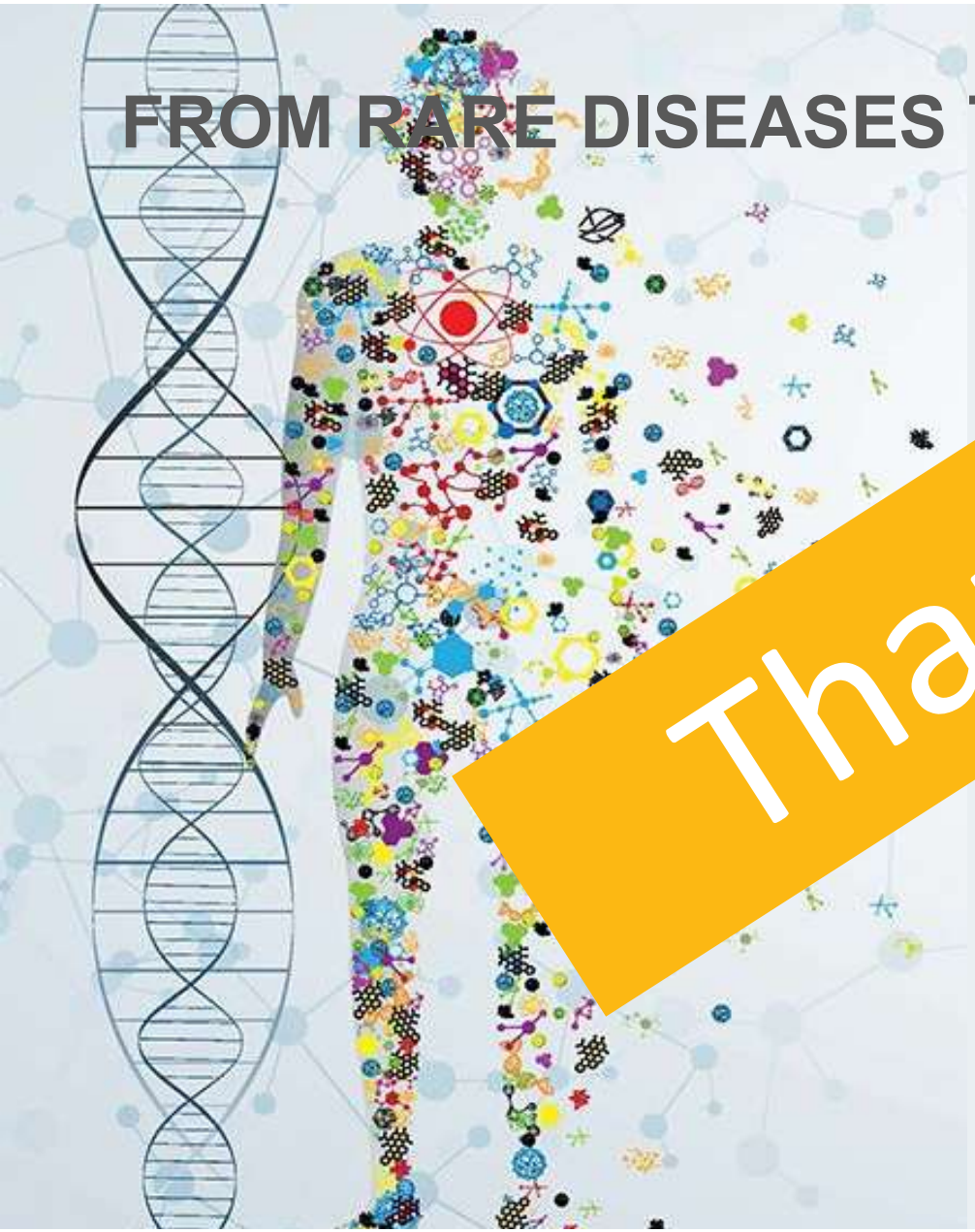
***Cluster 4***
No genetic abnormalities, late onset

***Cluster 5***
Complement gene abnormalities, early onset



Benigni et al, *Kidney Int,* 2025

# FROM RARE DISEASES THE FUTURE O DICINE



Thank you!