# C3 Glomerulopathy: role of complement for pathogenesis and treatment

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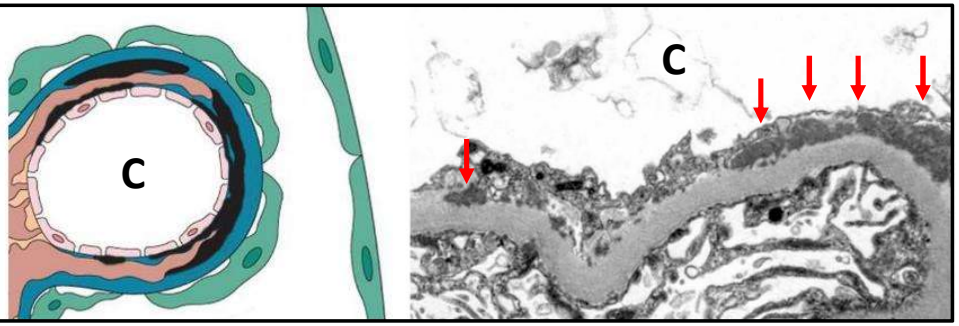
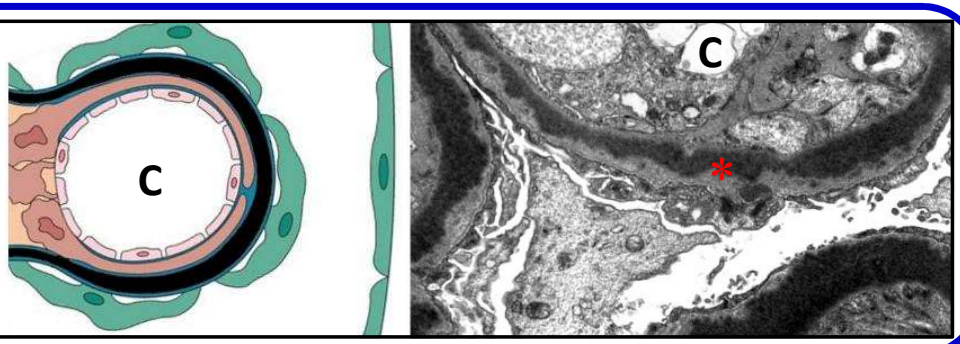
Bambino Gesù
OSPEDALE PEDIATRICO

# MPGN: the old classification…

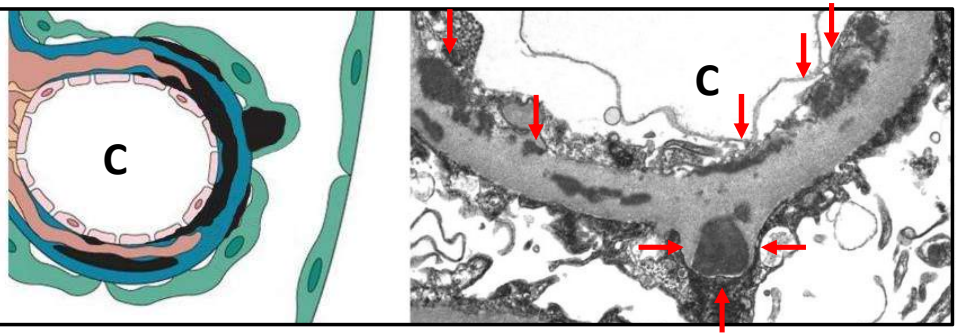
**MPGN Type I**
**Subendothelial deposits**
West et al, J Pediatr 1965




**MPGN Type II / DDD**
**Intramembranous deposits**
Galle, Thesis 1962; Habib et al, Kidney Int 1975




**MPGN Type III**
**Subendothelial and subepithelial deposits**
Burkholder et al, Am J Pathol 1969
Anders et al, Virchows Arch A Pathol Anat Histol 1997
Strife et al, Clin Nephrol 1984



# A new disease entity: C3GN

ORIGINAL ARTICLE

## Primary glomerulonephritis with isolated C3 deposits: a new entity which shares common genetic risk factors with haemolytic uraemic syndrome

Aude Servais, Véronique Frémeaux-Bacchi, Moglie Lequintrec, Rémi Salomon, Jacques Blouin, Bertrand Knebelmann, Jean-Pierre Grünfeld, Philippe Lesavre, Laure-Hélène Noël, Fadi Fakhouri

*J Med Genet* 2007;**44**:193–199. doi: 10.1136/jmg.2006.045328

**19 patients with unusual glomerulonephritis and:**

**- C3NeF positivity (7), CFH (3), CFI (2) or MCP (1) mutations**

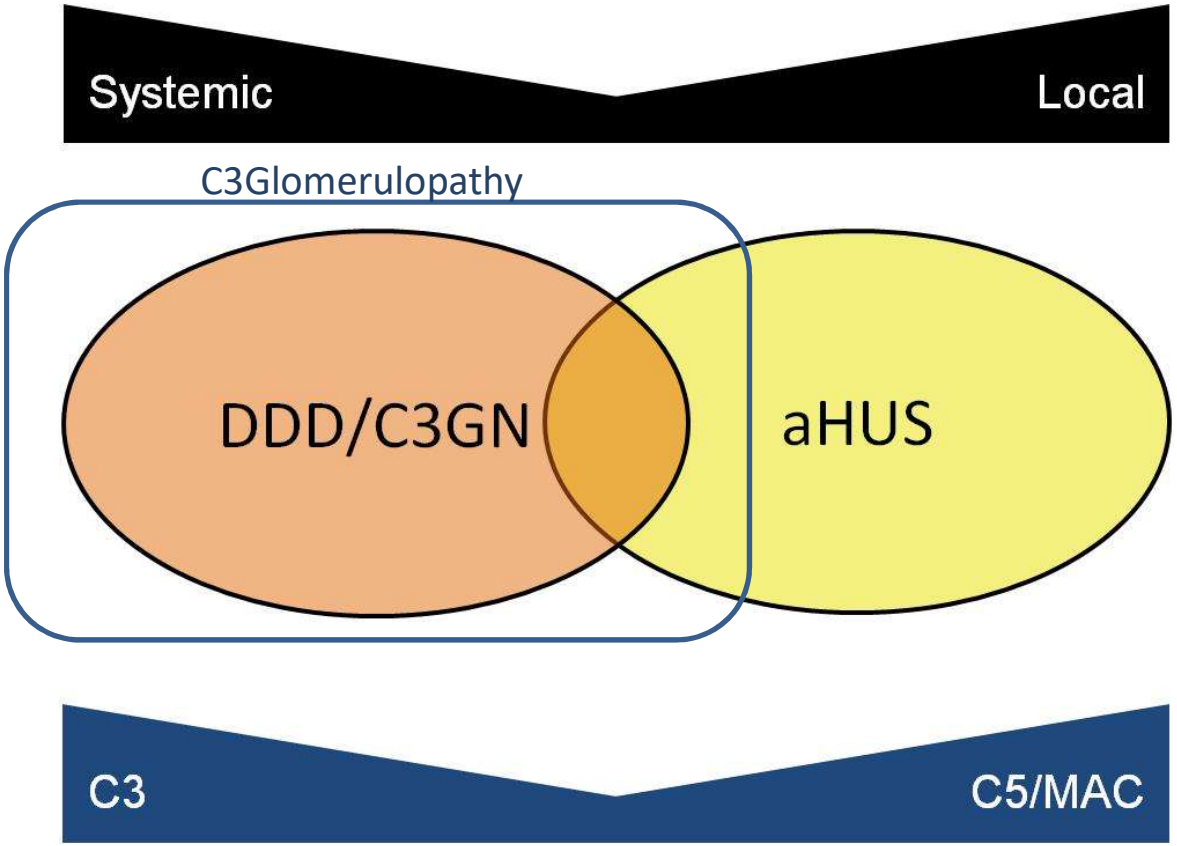
**- overt mesangial and epimembranous C3 deposits**

**- absence of dense intramembranous deposits (no DDD)**

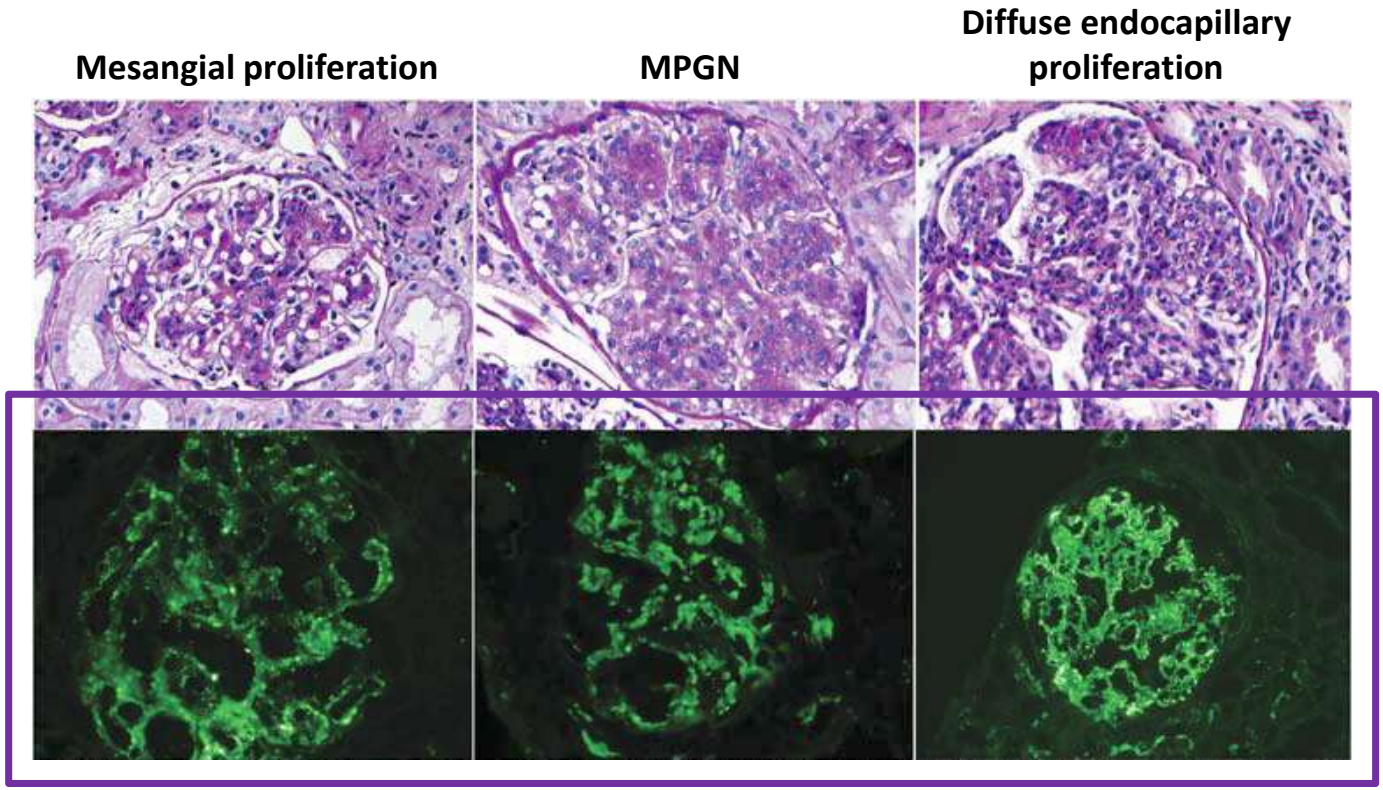
**- no Ig deposition**

**→ C3GN**

# Complement AP dysregulation in kidney diseases



# Renal biopsy in C3G

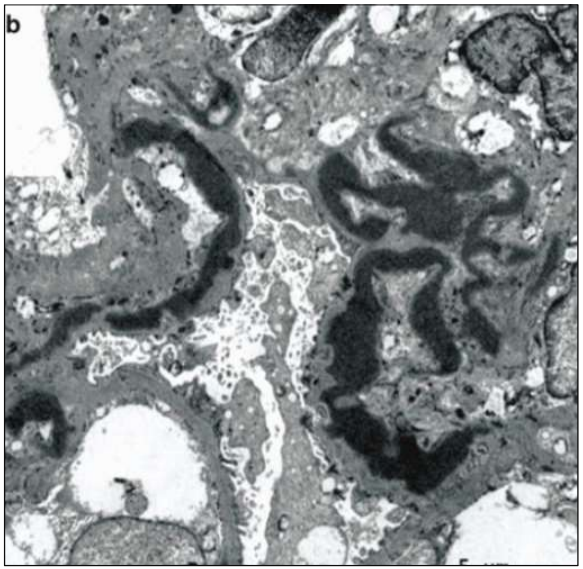



**Pickering et al, KI 2013: C3 at least 2-fold brighter than other IF**

Sethi S, Kidney International (2012) 82, 465–473

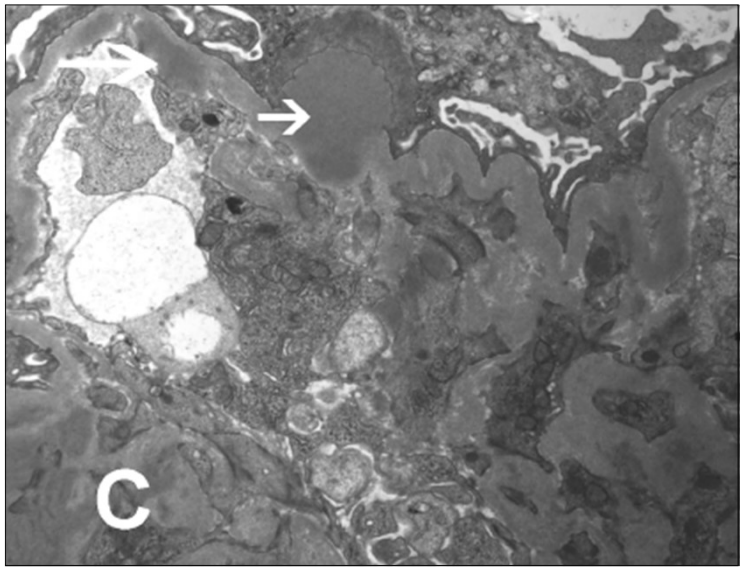
# The distinction C3GN/DDD requires electron microscopy

**DDD**



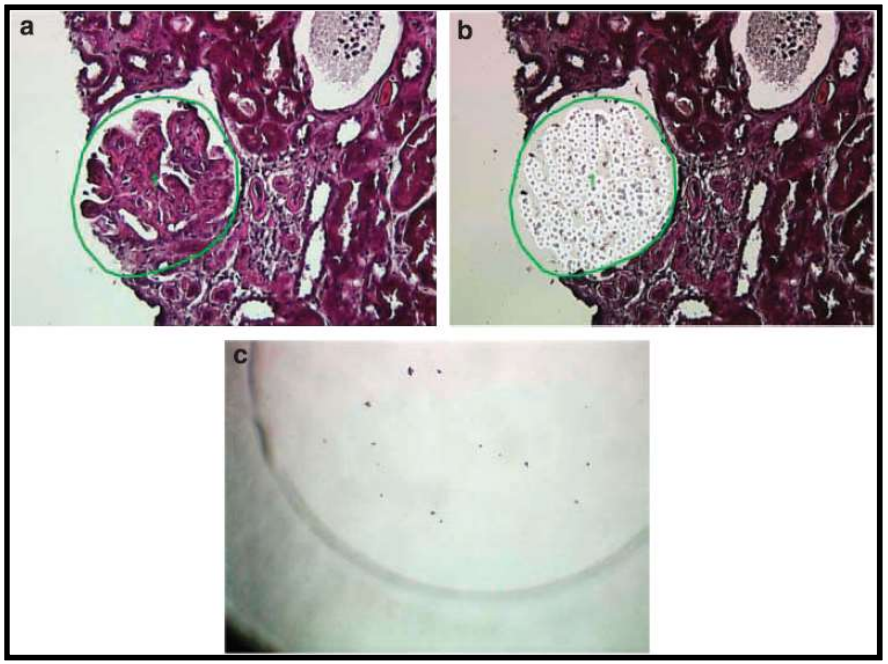

Walker PD et al, Modern Pathol 2007

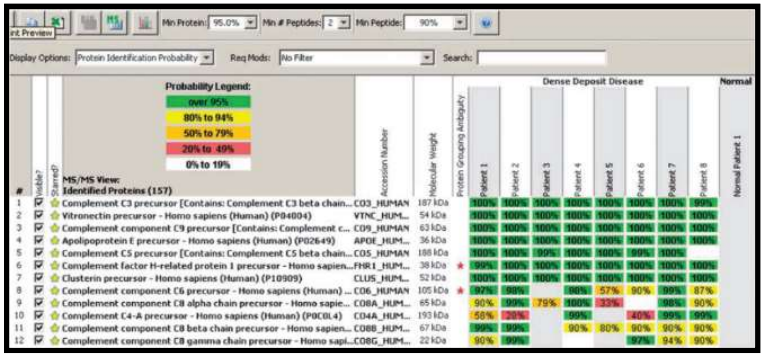
**C3GN**




Sethi S et al, Clin J Am Soc Nephrol 2011

# Evidence for a role of complement in DDD/C3GN in humans

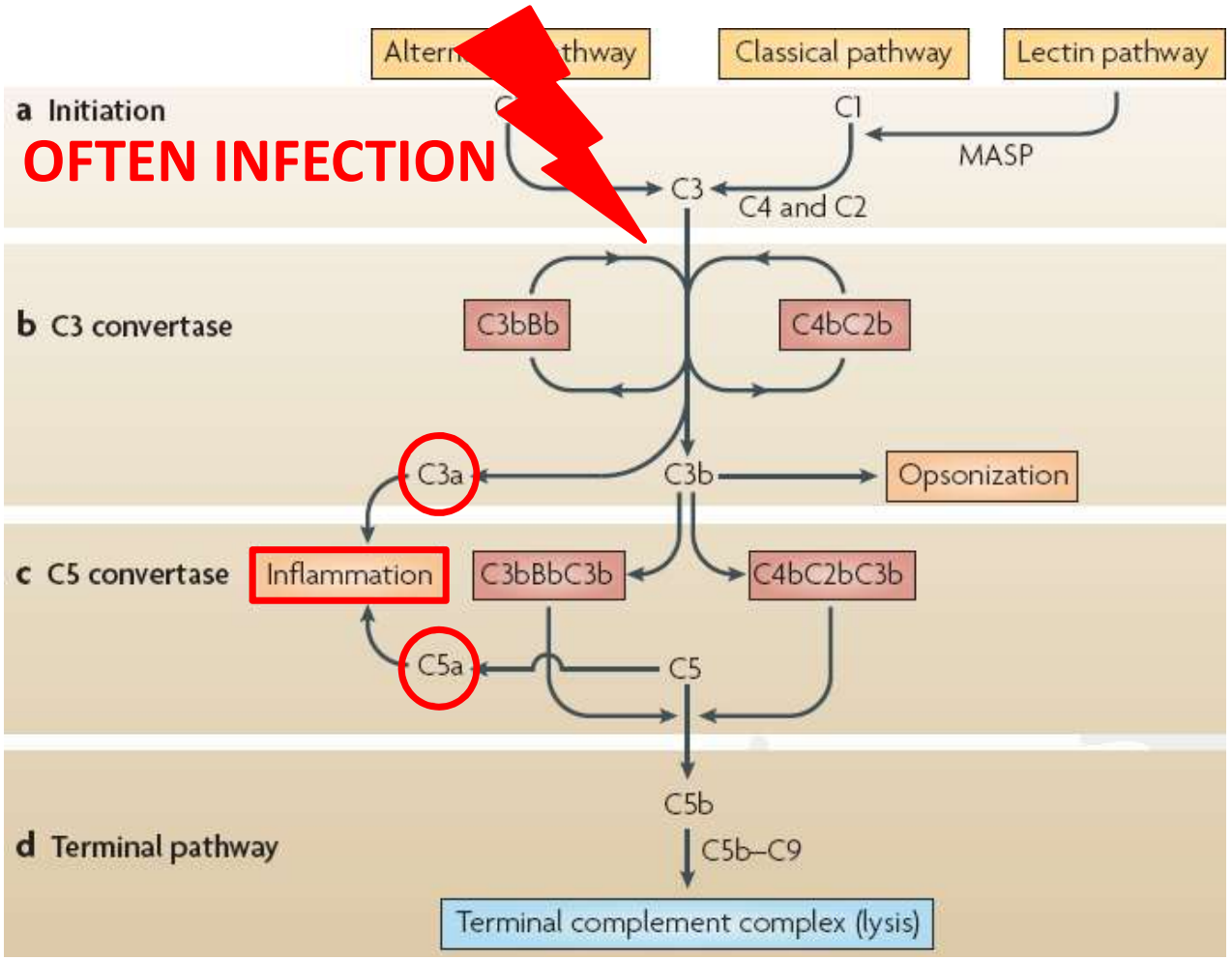



- **Proteomic profile of microdissected glomeruli:**
  ***C3, C4, C5, C6, C7, C8, CFHR1, CFHR5….***
- **Very similar profile between DDD and C3GN**

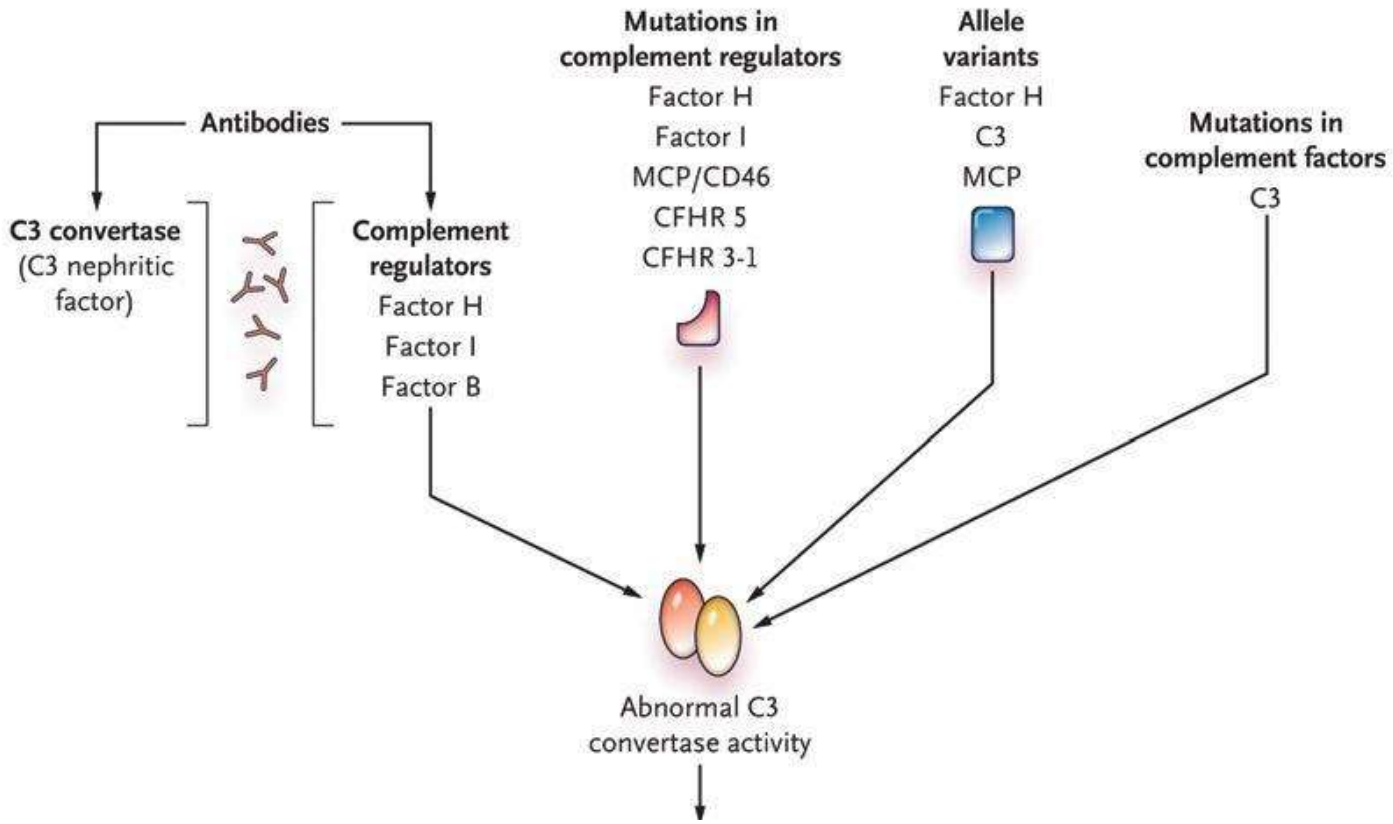
Sethi et al Kidney Int 2009; Sethi S et al Clin J Am Soc Nephrol 2011

# A simplified view of the complement system




Zipfel and Skerka, Nat Rev Immunol 2009

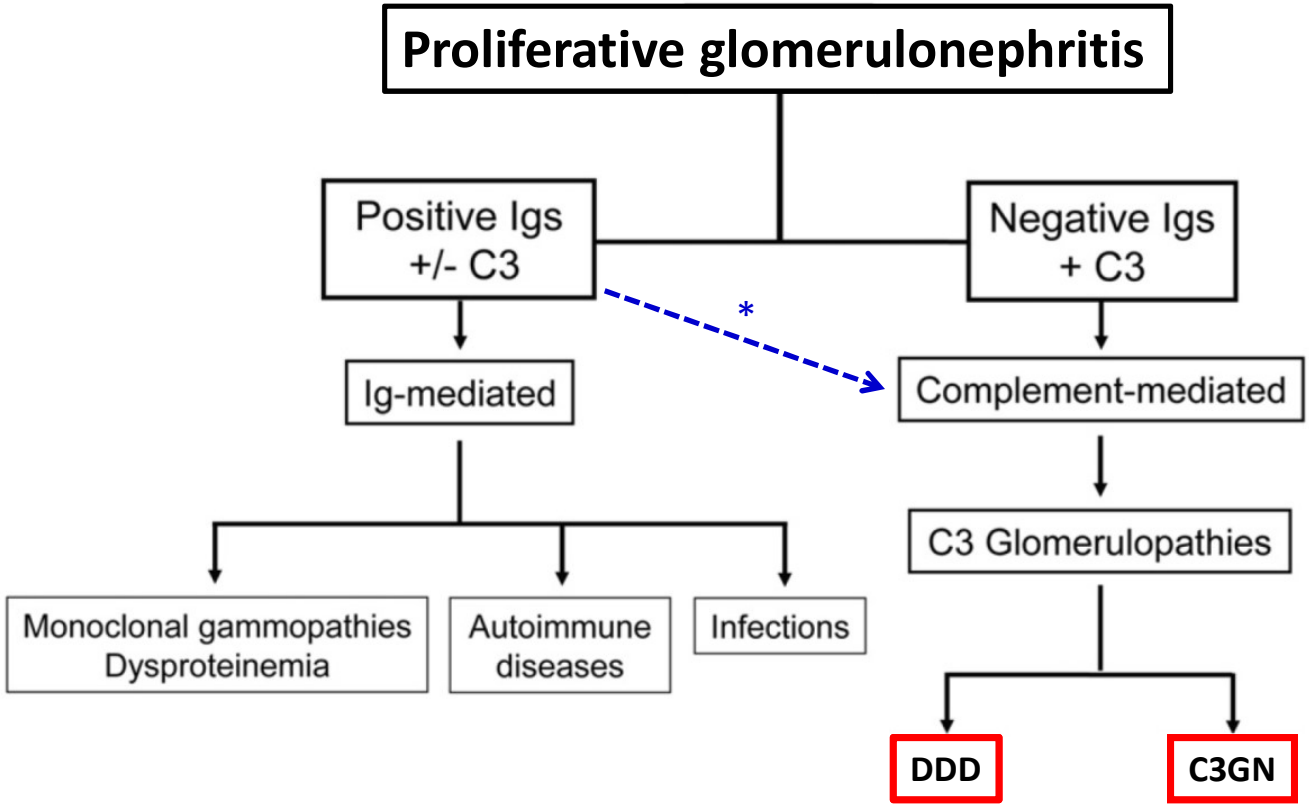
# Different alternative pathway alterations lead to C3 glomerulopathies




C3 glomerulopathies

modified from Sethi S, Fervenza FC NEJM 2012

# New classification of MPGN




Sethi S and Fervenza FC, Semin Nephrol 2011
Sethi S and Fervenza FC, NEJM 2012

*Servais et al, Kidney Int 2012; Dragon-Durey et al. JASN 2004;
Vaziri-Sani et al. Kidney Int 2006; Leroy V et al. Ped Nephrol 2011

# IC-MPGN can also be secondary to dysregulation of the complement alternative pathway: C3Nef

**Table 3 | Complement component analysis and immunofluorescence study of membranoproliferative glomerulonephritis type I cases with positive C3 nephritic factor**

| Patient | C3[a] (660 to 1250 mg/l) | C4[a] (90 to 380 mg/l) | CFB[a] (90 to 320 mg/l) | Histology | Immunofluorescence study |
|---|---|---|---|---|---|
| 25 | 537[b] | 160 | 83 | MPGN I | IgG, IgM, C3 |
| 26 | 512 | 127 | 50 | MPGN I | IgG, IgM, IgA, C3 |
| 27 | 183 | 178 | 225 | MPGN I | IgG, C3 |
| 28 | 701 | 233 | 96 | MPGN I | IgG, C3 |
| 29 | 87 | 202 | 51 | MPGN I | IgG, IgM, C3 |
| 30 | 847 | 222 | 71 | MPGN I | IgG, IgM, C3, C1q |
| 31 | 48 | 126 | 89 | MPGN I | IgG, IgA, C3 |
| 32 | 87 | 309 | 92 | MPGN I | IgG, IgM, C3 |
| 33 | 293 | 209 | 100 | MPGN I | IgG, IgM, C3 |
| 34 | 180 | 248 | 123 | MPGN I | IgG, IgM, C3 |
| 35 | 193 | 95 | 126 | MPGN I | IgG, C3 |
| 36 | 275 | 225 | 159 | MPGN I | IgG, IgM, C3, C1q |
| 37 | 1110 | 162 | 186 | MPGN I | ND[c] |
| 38 | 475 | 175 | 155 | MPGN I | IgG, IgA, C3 |
| 39 | 741 | 169 | 82 | MPGN I | IgG, C3 |
| 40 | 875 | 273 | 124 | MPGN I | IgG, C3, C1q |
| 41 | 135 | 182 | 130 | MPGN I | IgG, IgA, IgM, C3 |
| 42 | 129 | 227 | 64 | MPGN I | IgG, C3 |

Abbreviations: CFB, complement factor B; Ig, immunoglobulin; MPGN I, membranoproliferative glomerulonephritis type I; ND, not done.
[a]Laboratory reference values are indicated in brackets.
[b]Rare variant CFI *IVS 12+5* associated.
[c]Biopsy performed in 1974: lobular MPGN I, no immunofluorescence study available.
Cases with genetic abnormality are presented in Table 2.

Servais et al, Kidney Int 2012

# IC-MPGN can also be secondary to dysregulation of the complement alternative pathway: genetic mutations

**Table 2**
Clinical and laboratory findings in different histology groups.

| | Ig-MPGN | C3G | | |
|---|---|---|---|---|
| | | | DDD | C3GN |
| *N* | 67 | 73 | 21 | 52 |
| Gender (% males) | 51% | 41% | 38% | 42% |
| Data at onset | | | | |
| Age (*y*)—mean (SD) | 20.1 (±15.2)[a] | 15.0 (±11.9)[a] | 15.9 (±11.4) | 14.6 (±12.1) |
| Microhematuria | 86% | 86% | 90% | 84% |
| Gross hematuria | 35% | 38% | 38% | 38% |
| Proteinuria | 88% | 90% | 86% | 92% |
| Nephrotic syndrome | 43% | 29% | 29% | 29% |
| Renal impairment | 27%[b] | 14% | 5%[b] | 17% |
| Trigger event | 31% | 42% | 41% | 42% |
| C3NeFs positive | 44%[e] | 54% | 78%[e,f] | 44%[f] |
| Serum C3 (mg/dl)—Median (IQR) | 45 (13–77)[c] | 38 (15–73) | 20 (9–46)[c,d] | 44 (17–87)[d] |
| Serum C4 (mg/dl)—Median (IQR) | 21 (12–29) | 21 (17–27) | 26 (20-29) | 21 (17–25) |
| Low Serum C3 & normal C4 | 67% | 74% | 86% | 69% |
| Plasma SC5b-9 (ng/ml)—Median (IQR) | 515(286–1860) | 417(228–1033) | 353(252–623) | 486(215–1140) |
| Mutation carriers* | 17% | 18% | 14% | 20% |
| Mutation carriers and/or C3NeFs* | 56% | 65% | 83% | 58% |
| Familiarity for nephropathy* | 11% | 14% | 10% | 16% |

Nephrotic syndrome was defined as: 24-h proteinuria exceeding 3.5 g in adults or 40 mg/h/m2 in children together with albuminemia ≤3 g/L. Renal impairment was defined as abnormal serum creatinine levels. Familiarity for nephropathy was defined as the presence of at least one relative (up to 3rd degree) with biopsy-proven Ig-MPGN/C3G, or proteinuria and/or renal impairment without other apparent cause.

Iatropoulos et al, Mol Immunol 2016

# IC-MPGN can also be secondary to dysregulation of the complement alternative pathway: anti-FB and anti-C3b

## Anti-Factor B and Anti-C3b Autoantibodies in C3 Glomerulopathy and Ig-Associated Membranoproliferative GN

Maria Chiara Marinozzi,*† Lubka T. Roumenina,*‡§ Sophie Chauvet,* Alexandre Hertig,‖ Dominique Bertrand,¶ Jérome Olagne,** Marie Frimat,†† Tim Ulinski,‡‡ Georges Deschênes,§§ Stephane Burtey,‖‖ Michel Delahousse,¶¶ Bruno Moulin,** Christophe Legendre,*** Véronique Frémeaux-Bacchi,*† and Moglie Le Quintrec*¶¶

Table 1. Summary of the clinical characteristics of the pat

| Pt | Sex | Age at Onset, yr | Background | Ig-MPGN/C3G | Infectious Trigger |
|---|---|---|---|---|---|
| 1 | M | 31 | Drug/HBV | Ig-MPGN | Yes |
| 2 | F | 34 | Anorexia | Ig-MPGN | Yes |
| 3 | F | 66 | | C3G | No |
| 4 | M | 40 | Myelofibrosis | Ig-MPGN | Yes |
| 5 | M | 49 | | Ig-MPGN | No |
| 6 | M | 32 | | C3G | No |
| 7 | M | 7 | | C3G | Yes |
| 8 | M | 63 | Alcohol/HBV | Ig-MPGN/C3G | Yes |
| 9 | F | 9 | | C3G | No |
| 10 | M | 55 | | Ig-MPGN | Yes |
| 11 | M | 34 | | Ig-MPGN | Na |
| 12 | M | 38 | Drug | Ig-MPGN | Yes |
| 13 | M | 55 | Crohn/B lymphoma | Ig-MPGN | Yes |
| 14 | F | 32 | | Ig-MPGN | Na |
| 15 | M | 18 | | C3G | Na |

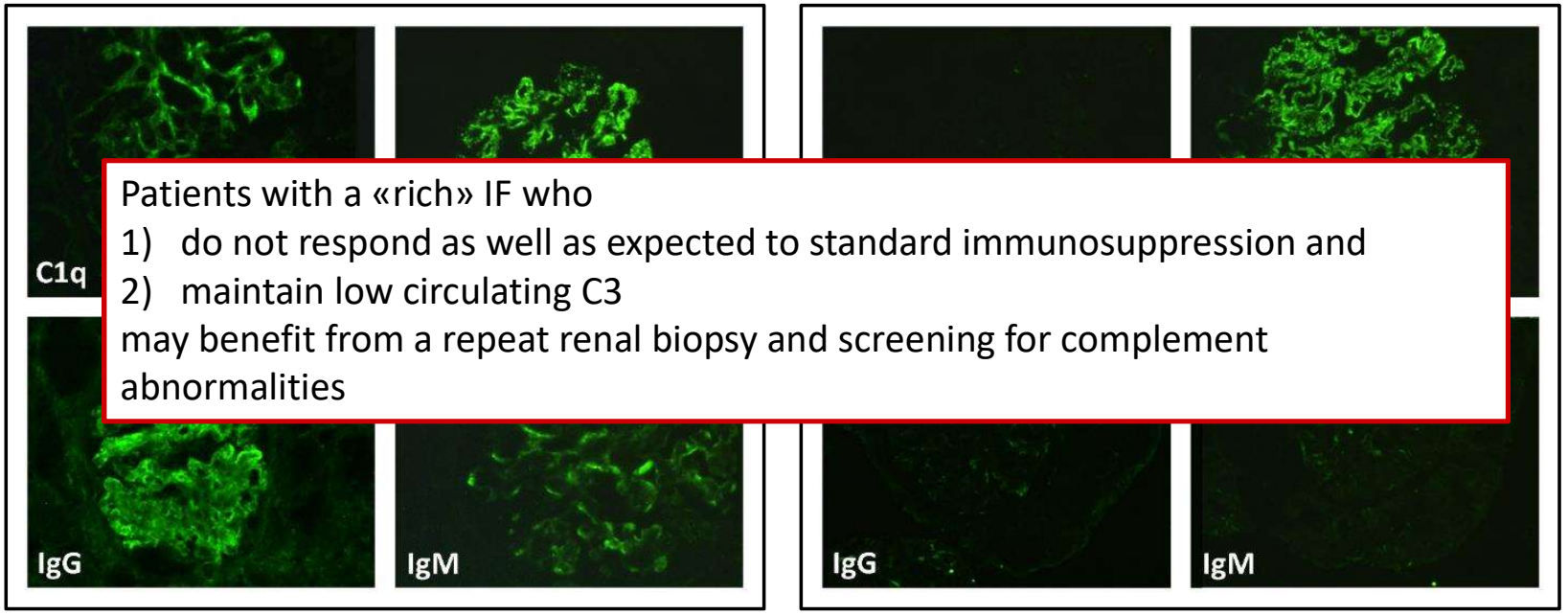
The CKD stages are defined by the level of kidney function according to the Kidne
1.73 $m^2$; stage 3, GFR between 30 and 59 ml/min per 1.73 $m^2$; stage 4, GFR betwee
Pt, patient; NS, nephrotic syndrome; IS, immunosuppressive treatment; M, male;

Marinozzi et al, JASN 2017

# The value of repeat biopsies

First biopsy

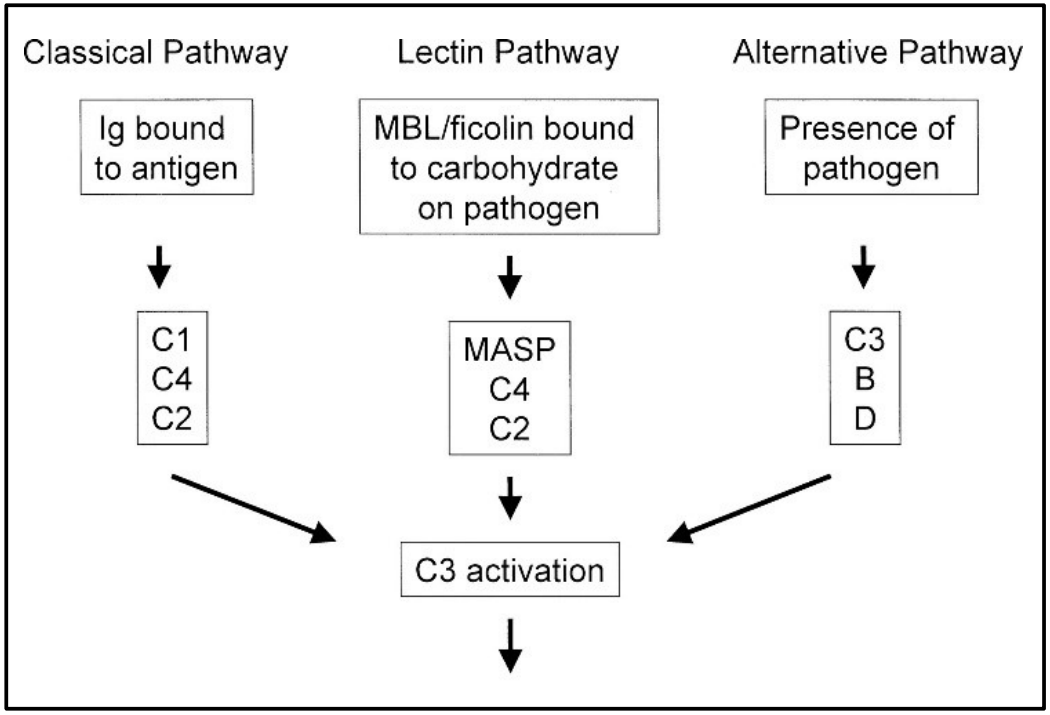
Second biopsy

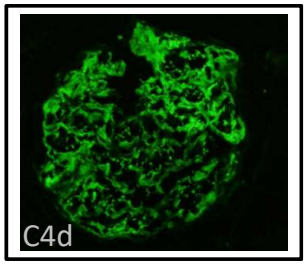


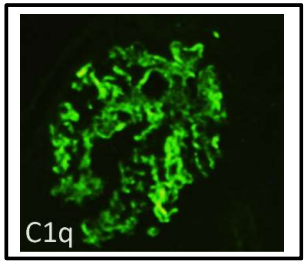

Patients with a «rich» IF who
1) do not respond as well as expected to standard immunosuppression and
2) maintain low circulating C3
may benefit from a repeat renal biopsy and screening for complement abnormalities

**Positive C3Nef**
**Elevated C5b9**
**MCP mutation**

# Does C1q and C4d staining help?



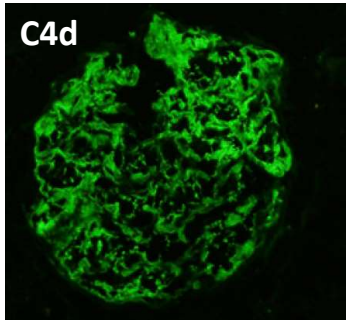



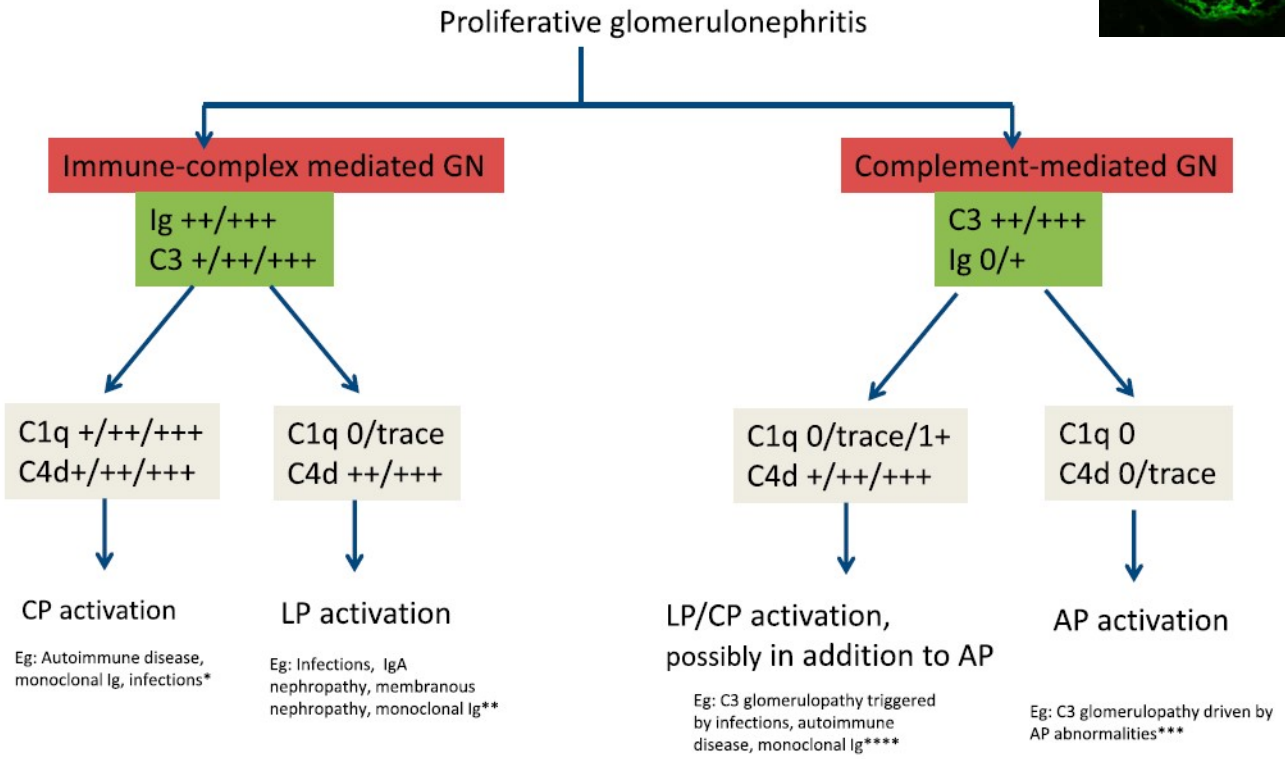
# What can we learn from the renal biopsy?

## C4d as a Diagnostic Tool in Proliferative GN

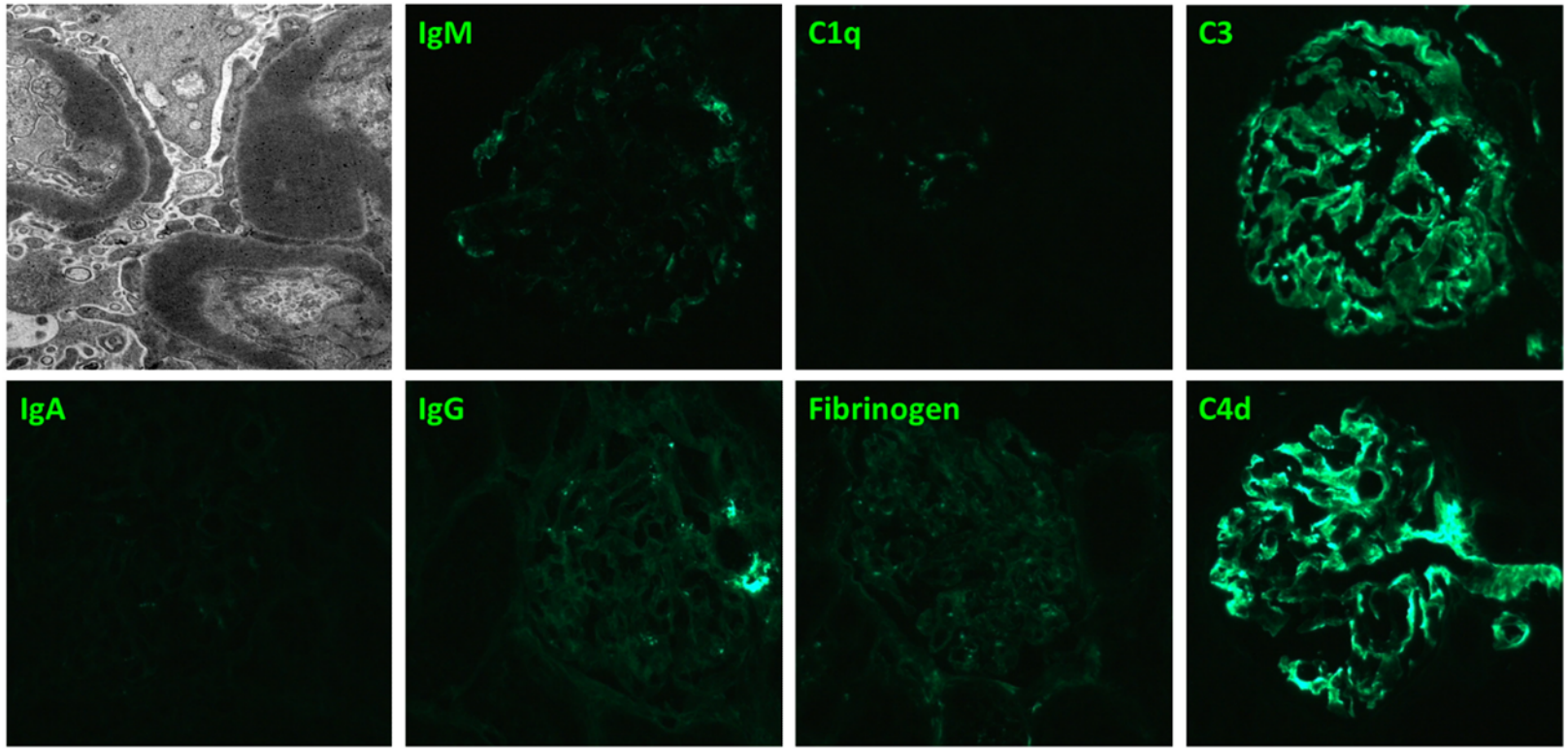
Sanjeev Sethi,* Samih H Nasr,* An S. De Vriese,† and Fernando C. Fervenza‡

*J Am Soc Nephrol* 26: ●●●–●●●, 2015



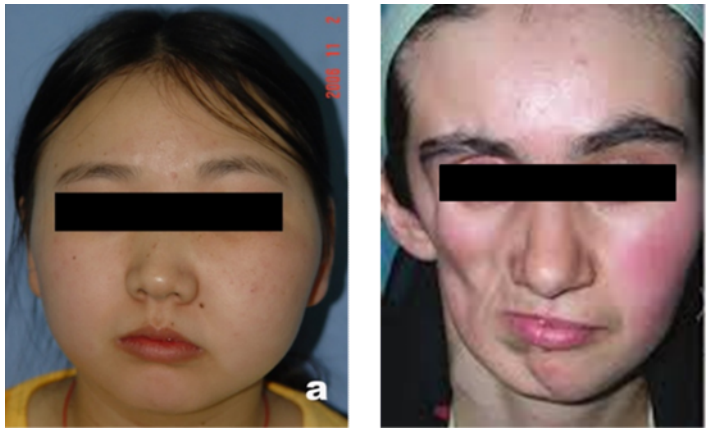
# C4d staining does not exclude C3G



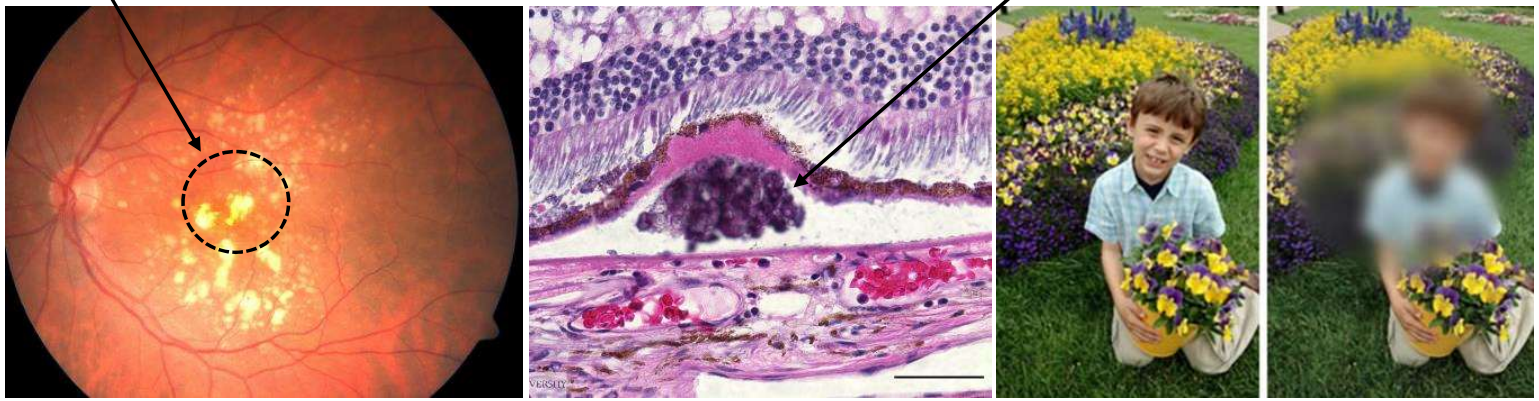

Courtesy of Dr Diomedi-Camassei

# Extrarenal features of C3G

## Partial lipodystrophy




## Drusen



# C3G: clinical presentation is heterogenous

- Post-infectious glomerulonephritis with low C3
- Infection triggering macrohematuria, as in IgA nephropathy
- Nephrotic syndrome
- Accidental finding of non-nephrotic proteinuria, microhematuria
- Atypical

# C3G presenting as acute PIGN

- **Post-infectious glomerulonephritis with**

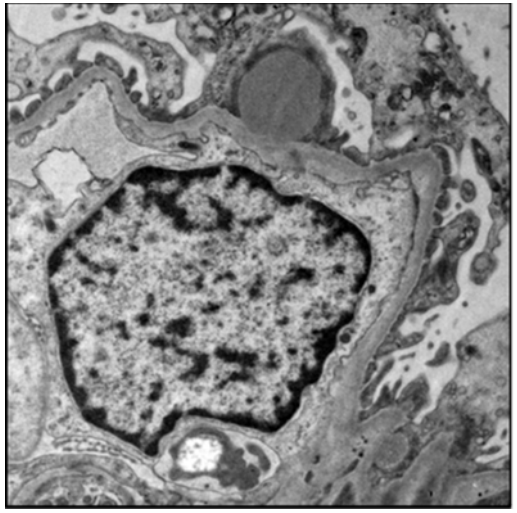
1) **low C3 that persists > 12 weeks or with**
2) **recurrent macrohematuria**

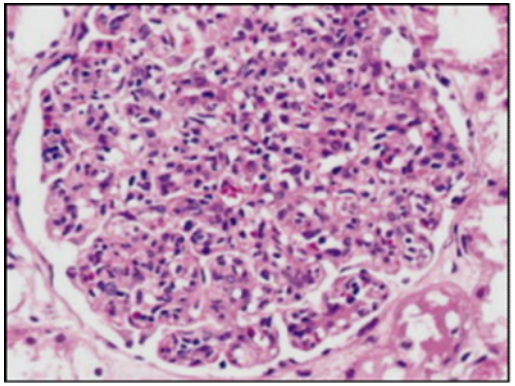
**Table 3 | Complement abnormalities**

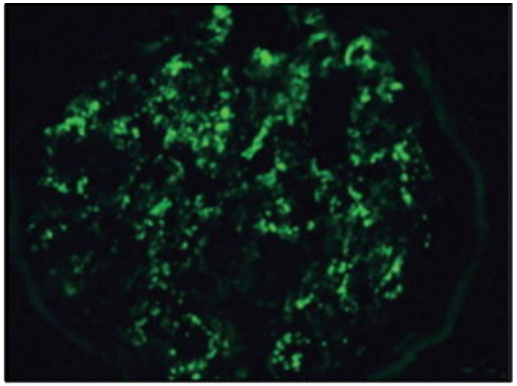
| Patient | *CFH* | *CFHR5* | FH antibodies[a] | Hemolytic assay[b] | APFA[c] | C3NeF | sMAC[d] |
|---|---|---|---|---|---|---|---|
| 1 | c.2171delC, p.Thr724fsX, 725 | No mutations | Negative | ND | ND | Negative | 0.24 mg/l |
| 2 | No mutations | c.646-647, AA>TT, p.Asn216Phe | Negative | 0%, Normal | 63%, Abnormal | Negative | 0.21 mg/l |
| 3 | No mutations | No mutations | Negative | 1%, Normal | 63%, Abnormal | Positive (C3CSAP[e]) | ND |
| 4 | No mutations | No mutations | Negative | 0%, Normal | 1% Abnormal | Positive (IFE) | 1.23 mg/l |
| 5 | No mutations | No mutations | Negative | 12% Abnormal | 34% Abnormal | Positive (IFE) | 0.48 mg/l |
| 6 | No mutations | No mutations | Negative | 0%, Normal | 14% Abnormal | Positive (both assays) | ND |
| 7 | c.3350A>G, p.Asn1117Ser | No mutations | Negative | 0% Normal | 80% | Negative | ND |
| 8 | No mutations | No mutations | Negative | 0% Normal | 123% | Negative | 0.13 mg/l |
| 9 | No mutations | No mutations | Negative | 9% Abnormal | 77% | Positive (both assays) | ND |
| 10 | c.1699A>G, p.Arg567Gly | No mutations | Negative | 0%, Normal | 0% Abnormal | Positive (both assays) | 2.03 mg/l |
| 11 | No mutations | No mutations | Negative | 0%, Normal | 130% | Positive (C3CSAP) | 0.21 mg/l |

Sethi, Kidney International 2012

# Atypical PIGN is a form of C3G







## Light microscopy

| | PIGN | aPIGN | C3GN |
|---|---|---|---|
| Diff. prol. | +++ | +++ | - |
| Mes. prol. | + | + | ++ |
| MPGN | - | - | +++ |
| Crescentic | + | + | - |

## Immunofluorescence

| | PIGN | aPIGN | C3GN |
|---|---|---|---|
| C3 capill. | +++ | +++ | +++ |
| C3 mesang. | +++ | +++ | +++ |
| IgG | ++ | + | +/- |

## Electron microscopy

| | PIGN | aPIGN | C3GN |
|---|---|---|---|
| Humps | +++ | +++ | + |
| Mesangial | +/- | ++ | +++ |
| Sub-endoth. | +/- | ++ | +++ |

Adapted from Sethi et al, Kidney International 2013

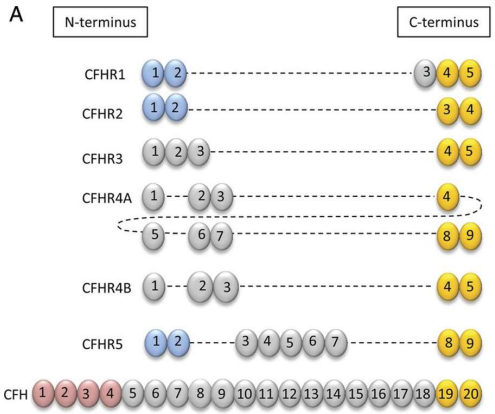
# C3G presenting as “IgA nephropathy”: CFHR glomerulopathy

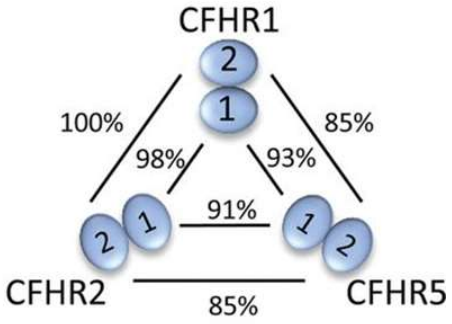
- **Infection-triggered macrohematuria, proteinuria**

## Identification of a mutation in complement factor H-related protein 5 in patients of Cypriot origin with glomerulonephritis

Daniel P Gale*, Elena Goicoechea de Jorge*, H Terence Cook, Rubén Martinez-Barricarte, Andreas Hadjisavvas, Adam G McLean, Charles D Pusey, Alkis Pierides, Kyriacos Kyriacou, Yiannis Athanasiou, Konstantinos Voskarides, Constantinos Deltas, Andrew Palmer, Véronique Frémeaux-Bacchi, Santiago Rodriguez de Cordoba, Patrick H Maxwell†, and Matthew C Pickering†

Lancet 2010




1) CFHR protein mutation

2) Abnormal dimerization

3) FH deregulation

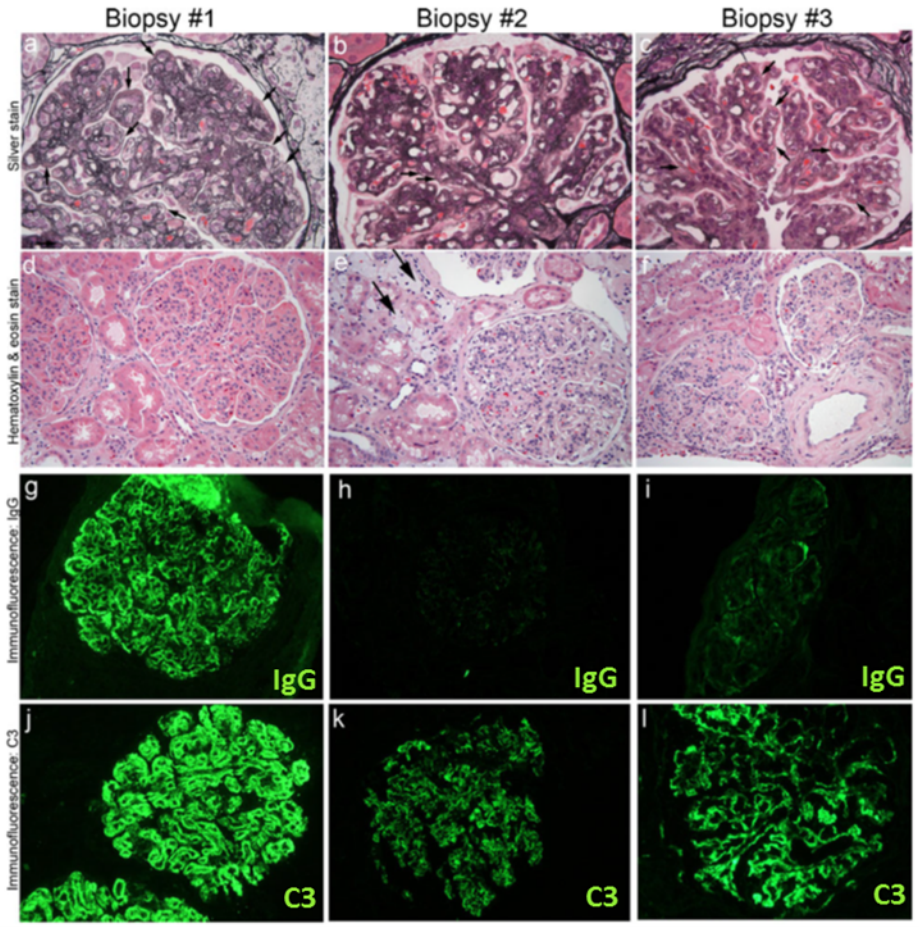
Thomas D. Barbour et al. Nephrol. Dial. Transplant. 2014

# C3G can present as nephrotic syndrome

- Post-infectious glomerulonephritis with low C3
- Infection triggering macrohematuria, as in IgA nephropathy
- **Nephrotic syndrome**

# A difficult case

- 13-year-old boy
- nephrotic syndrome & hematuria
- markedly low C3 and C4
- initial renal biopsy:
  MPGN with strong C3 deposition
  strong immunoglobulin deposition
- follow-up biopsies (1 and 3 years):
  MPGN with strong C3 deposition
  ± no immunoglobulin deposition
- Elevated SC5b-9
  treated with eculizumab:
  decrease in proteinuria




Kerns et al, Ped Nephrol 2013

# C3G can be found on routine urinalysis

- Post-infectious glomerulonephritis with low C3
- Infection triggering macrohematuria, as in IgA nephropathy
- Nephrotic syndrome
- **Accidental finding of non-nephrotic proteinuria, microhematuria**

# C3G can present as aHUS

- Post-infectious glomerulonephritis with low C3
- Infection triggering macrohematuria, as in IgA nephropathy
- Nephrotic syndrome
- Accidental finding of non-nephrotic proteinuria, microhematuria
- **Atypical**

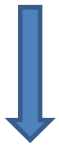
# INITIAL PRESENTATION: aHUS

A 5-year old child was transfered in May 2014 from the Cosenza Pediatric Department with HUS, requiring hemodialysis.

UPON ARRIVAL

He presented with slight confusion, severely hypertensive

- Hb 8.4 g/dl and 66.000 platelets/mmc
- terminal renal failure
- **low C3 (51 mg/dl, normal range 90-180 mg/dl), with normal C4**
- **nephrotic-range proteinuria with red blood cells and casts in the urinary sediment**
- stool culture and serum antibodies were negative for VTEC
- ADAMTS13 levels were slightly reduced (40%)

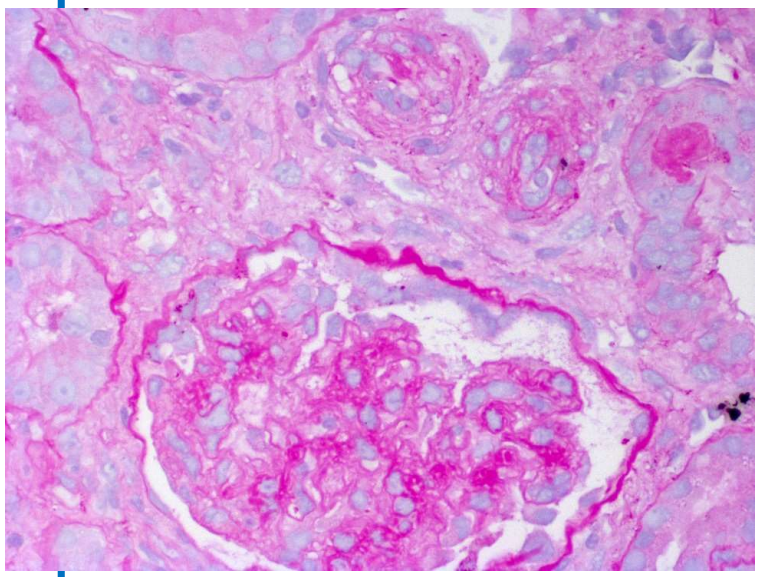


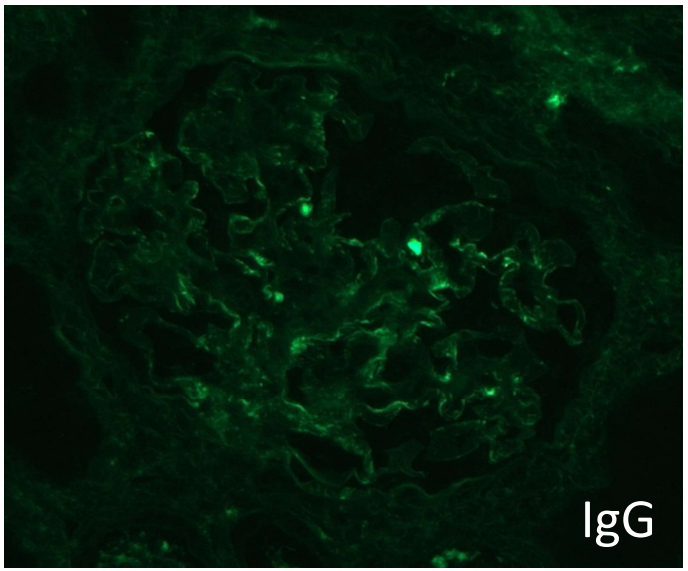
1) a full workup of complement mutations was performed
2) therapy with **eculizumab** was started

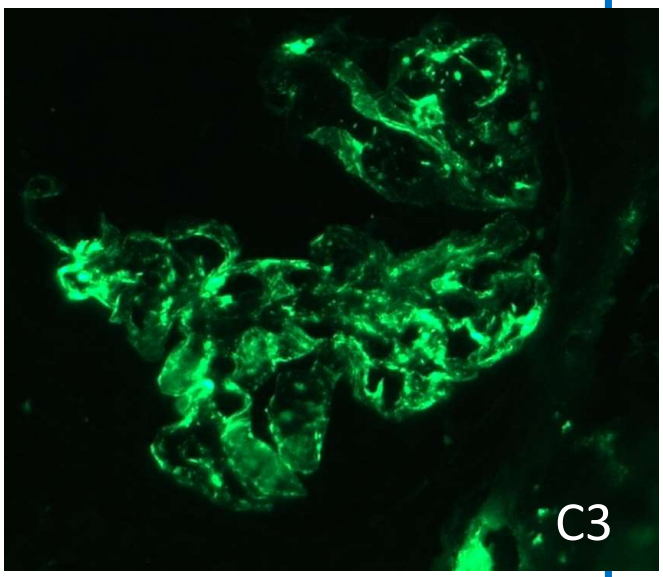
Following start of eculizumab, platelets rapidly increased and after 10 days hemodialysis was discontinued.

However, **renal function remained abnormal with proteinuria in the nephrotic range and persistently low circulating C3**.

Therefore, a renal biopsy was performed, which showed:

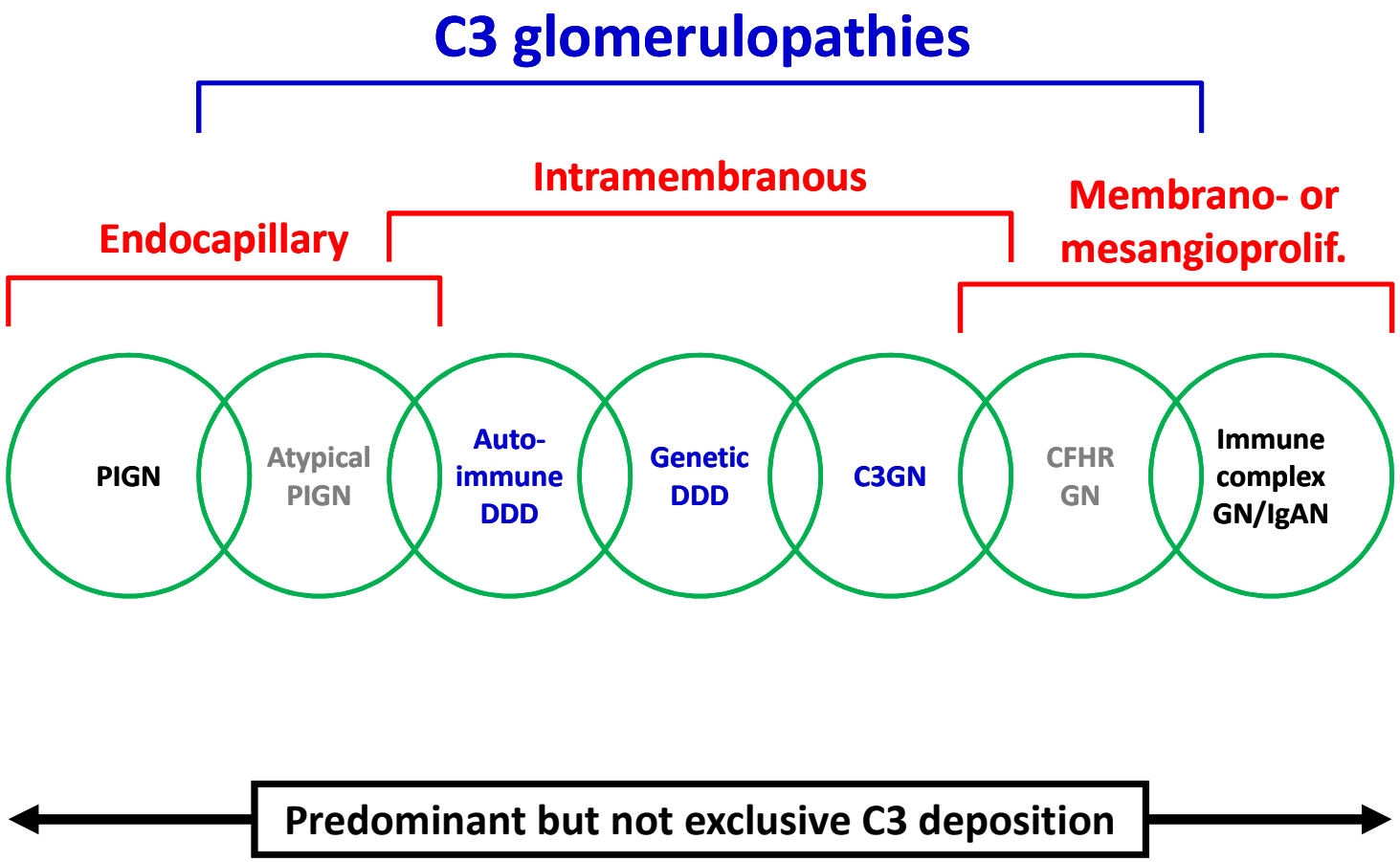





Courtesy of Dr Diomedi-Camassei

# Clinical, histological and molecular overlaps




Adapted from Zipfel et al, Molecular Immunology (2015)

# C3G: OPBG experience on 32 pediatric patients

| Clinical presentation (number of patients) | Urine | Biopsy | | Therapy | | | | | Outcome | |
|---|---|---|---|---|---|---|---|---|---|---|
| | M.E. | C3GN | DDD | None | ACEi | PDN | MMF/CsA | ECUL. | PR NoR | CR |
| Acute PIGN (13) | 100% | 92% | 8% | 31% | 62% | 77% | 0% | 0% | 0% | 100% |
| Nephrotic syndr. (11) | 18% | 91% | 9% | 0% | 100% | 100% | 82% | 18% | 45% | 55% |
| Random urine (8) | 0% | 50% | 50% | 13% | 88% | 50% | 13% | 0% | 13% | 88% |

# C3 glomerulopathy outcome: Servais

**Table 1 | Clinical and biological data according to histological type**

| | All | MPGN 1 | DDD | GNC3 | *P*-value |
|---|---|---|---|---|---|
| *N* | 134 | 49 | 29 | 56 | |
| Sex (M/F) | 81/53 (60.4%) | 32/17 (65.3%) | 17/12 (58.6%) | 33/24 (58.9%) | NS |
| Children[a]/adults | 52/82 (38.8%) | 21/28 (42.8%) | 17/12 (58.6%) | 14/42 (25.0%) | NS |
| Age at diagnosis (years) | 24.3 ± 18.6 | 20.7 ± 16.8 | 18.9 ± 17.7 | 30.3 ± 19.3 | <0.05[c] and <0.01[d] |
| Proteinuria (g/day) | 4.9 ± 4.1 | 6.9 ± 4.4 | 5.6 ± 4.5 | 3.6 ± 3.3 | <0.05[c] |
| Nephrotic syndrome | 58 (41.1%) | 32 (65.3%) | 11 (37.9%) | 15 (26.8%) | <0.0001[c] and 0.02[e] |
| Microhematuria | 83 (58.8%) | 25 (51.0%) | 22 (75.8%) | 36 (64.3%) | NS |
| HBP | 43 (30.5%) | 16 (32.6%) | 6 (20.7%) | 21 (37.5%) | NS |
| eGFR (ml/min per 1.73 $m^2$) | 69.3 ± 36.6 | 73.7 ± 33.7 | 75.5 ± 38.8 | 65.9 ± 37.4 | NS |
| ACE inhibitor/ARB treatment | 64 (45.4%) | 27 (55.1%) | 10 (34.5%) | 27 (48.2%) | NS |
| Immunosuppressive treatment | 61 (43.2%) | 28 (57.1%) | 14 (48.3%) | 19 (33.9%) | 0.02[c] |
| Follow-up (years) | 11.2 ± 11.2 | 11.7 ± 12.0 | 12.0 ± 12.1 | 10.2 ± 10.1 | NS |
| *At last follow-up* | | | | | |
| eGFR (ml/min per 1.73 $m^2$) | 50.4 ± 39.5 | 47.7 ± 40.3 | 53.8 ± 40.3 | 50.9 ± 37.1 | NS |
| Proteinuria (g/day) | 2.2 ± 2.7 | 2.4 ± 3.5 | 1.4 ± 1.6 | 2.1 ± 2.4 | NS |
| Nephrotic syndrome | 19 (14.1%) | 8 (16.3%) | 2 (6.9%) | 9 (16.1%) | NS |
| Duration of evolution until ESRD[b] (years) | 10.3 ± 10.2 | 10.1 ± 9.8 | 9.8 ± 11.6 | 10.8 ± 10.0 | NS |
| Dialysis | 49 (36.6%) | 20 (40.8%) | 12 (41.4%) | 17 (30.3%) | NS |
| Age at dialysis (years) | 35.6 ± 17.6 | 30.3 ± 17.2 | 36.9 ± 18.1 | 40.8 ± 16.9 | NS |
| Renal transplantation | 35 (26.1%) | 14 (28.6%) | 11 (37.9%) | 10 (17.8%) | NS |
| • Recurrence | 18 (51.4%) | 6 (42.8%) | 6 (54.5%) | 6 (60%) | NS |
| • Thrombotic microangiopathy | 6 (17.1%) | 2 (14.3%) | 3 (27.3%) | 1 (10.0%) | NS |
| • Vascular rejection | 2 (5.8%) | 1 (7.1%) | 0 (0%) | 1 (10.0%) | NS |

**Servais A, KI 2012**

# Risk factors of poor long-term outcome in C3G

Multivariate analysis of the association of long-term renal outcome with clinical, laboratory and genetic features.

| | All patients | | |
|---|---|---|---|
| | HR | HR 95%CI | *p* |
| Absence of mutations or C3NeFs | 7.1 | 1.9–26.3 | 0.004 |
| Sclerotic glomeruli (% of glomeruli) | 69.3 | 3.1–1553 | 0.008 |
| Crescents (% of glomeruli) | 39.7 | 3.3–481 | 0.004 |
| Nephrotic syndrome at onset | 10.9 | 2.5–47 | 0.002 |

HR: hazard ratio calculated by Multivariate Cox proportional-Hazards analysis. CI: confidence Interval.nc: not calculable. Nephrotic syndrome was defined as: 24-h proteinuria exceeding 3.5 g in adults or 40 mg/h/m2 in children together with albuminemia $\leq$3 g/dL. Intensified immunosuppression was also included in multivariate Cox Regression analysis but was not significantly associated with progress to ESRD (HR = 3.9, 95%CI 0.65–23.9, $p = 0.138$).

Iatropoulos et al, Mol Immunol 2016

# Autoimmune forms of C3G

**C3 nephritic factor (C3NeF):**

- Differences in the stabilization of the C3 convertase
- May disappear spontaneously

**CFH (mini-)antibody**

**CFB autoantibody**

**C3b autoantibody**

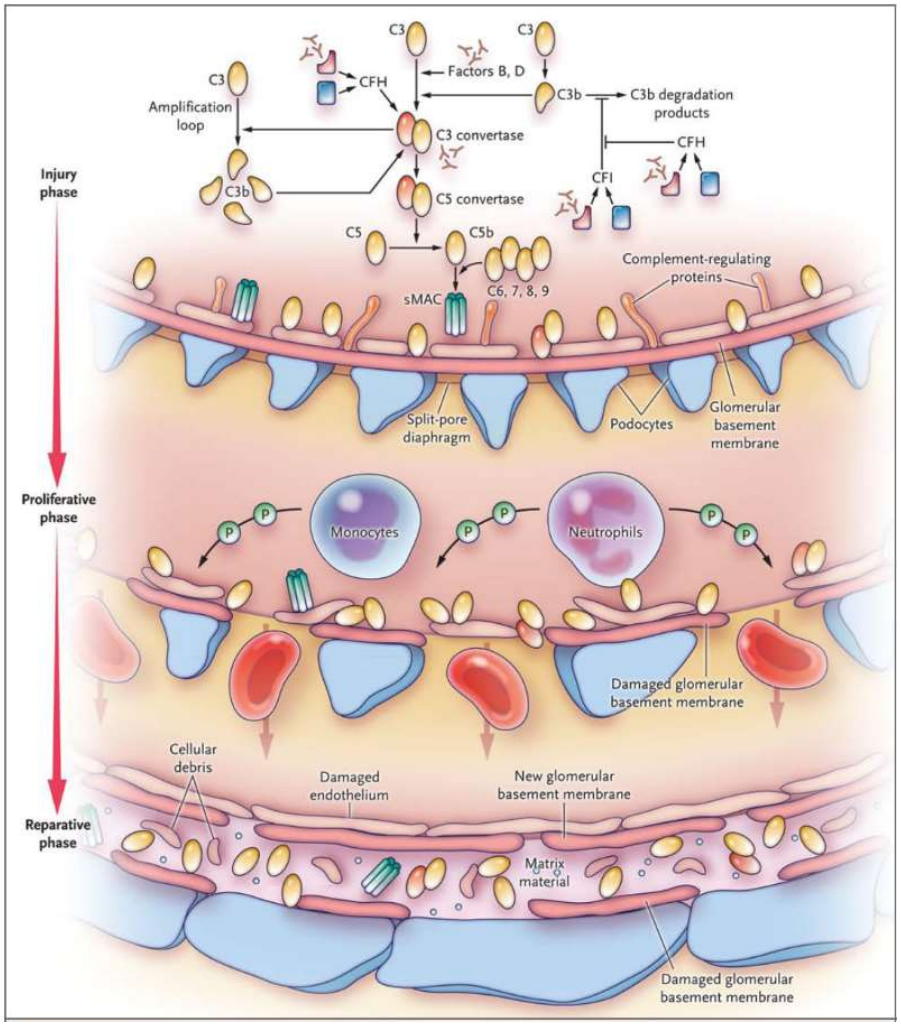
# Genetic forms of C3G

Courtesy of Christoph Licht

| Gene / Protein | Mutation / Variant | Function | Phenotype | Reference |
|---|---|---|---|---|
| CFH | Mutations:<br>- homo- / compound heterozygous<br>- SCRs 1-4 (regulatory domain)<br>- Cys residues (tertiary structure) | - Intact surface binding<br>- Reduced C3b binding<br>- Loss of CFH cofactor and decay accelerating activity | DDD<br>C3GN | Levy, Kidney Int 1986<br>Meri, J Exp Med 1992<br>Vogt, Pediatr Nephrol 1995<br>Ault, J Biol Chem 1997<br>Dragon-Durey, J Am Soc Nephrol 2004<br>Licht, Kidney Int 2006<br>Habbig, Kidney Int 2009 |
| CFH | Polymorphisms:<br>- Y402H (SCR 7) | - Impaired C3b / heparin binding<br>- Impaired CFH cofactor activity | DDD | Hageman, Proc Nat Acad Sci 2005<br>Abrera-Abeleda, J Med Genet 2006<br>Abrera-Abeleda, J Am Soc Nephrol 2011 |
| CFHR3-1 | CNV:<br>- CFHR3-1 hybrid gene | - Not tested<br>- ?Dominant negative effect | C3GN | Malik, J Am Soc Nephrol 2012 |
| CFHR5 | CNV:<br>- Duplication within CFHR5 exons 2/3 | - Not tested<br>- ?Dominant negative effect | CHFR-GN | Gale, The Lancet 2010 |
| CFHR5 | Polymorphisms | - Not tested | DDD | Abrera-Abeleda, J Med Genet 2006<br>Abrera-Abeleda, J Am Soc Nephrol 2011 |
| C3 | Mutations:<br>- Heterozygous deletion | - $C3_{mut}$ resistant to cleavage by C3bBb<br>- $C3_{mut}$ convertase – resistant to CFH inactivation | DDD | Martinez-Barricarte, J Clin Invest 2010 |
| C3 | Polymorphisms | - Not tested | DDD | Smith, J Am Soc Nephrol 2007<br>Abrera-Abeleda, J Am Soc Nephrol 2011 |

# How to treat C3G?

**Inflammation !**



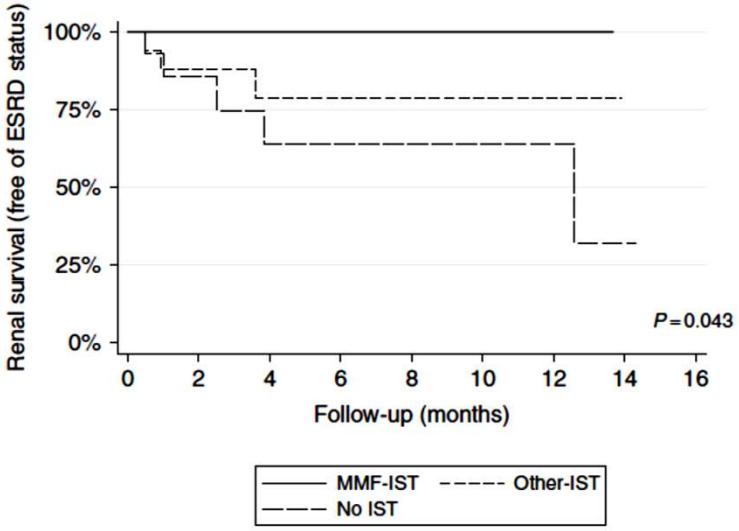

Sethi S, Fervenza FC NEJM 2012

# Treatment of C3G: mycophenolate

## Effectiveness of mycophenolate mofetil in C3 glomerulonephritis

Cristina Rabasco[1], Teresa Cavero[1], Elena Román[2], Jorge Rojas-Rivera[3], Teresa Olea[4], Mario Espinosa[5], Virginia Cabello[6], Gema Fernández-Juarez[7], Fayna González[8], Ana Ávila[9], José María Baltar[10], Montserrat Díaz[11], Raquel Alegre[3], Sandra Elías[12], Monserrat Antón[13], Miguel Angel Frutos[14], Alfonso Pobes[15], Miguel Blasco[16], Francisco Martín[17], Carmen Bernis[18], Manuel Macías[19], Sergio Barroso[20], Alberto de Lorenzo[21], Gema Ariceta[22], Manuel López-Mendoza[6], Begoña Rivas[4], Katia López-Revuelta[7], José María Campistol[16], Santiago Mendizábal[2], Santiago Rodríguez de Córdoba[23] and Manuel Praga[1,24] for the Spanish Group for the Study of Glomerular Diseases (GLOSEN)

KI 2015; 88(5):1153-60




| | Patients at risk according to months of follow-up | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group of treatment | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 |
| MMF-IST | 22 | 15 | 10 | 5 | 4 | 4 | 2 | 1 | 1 |
| Other-IST | 18 | 13 | 10 | 6 | 4 | 2 | 2 | 1 | 1 |
| No IST | 20 | 14 | 11 | 7 | 6 | 6 | 5 | 4 | 3 |

**Figure 1 | Renal survival (defined by a status free of end-stage renal disease) in patients treated with MMF (MMF-IST), other IST (other-IST), and no IST (non-IST).** ESRD, end-stage renal disease; IST, immunosuppressive treatments; MMF, mycophenolate mofetil.

# Treatment of C3G: KDIGO guidelines

www.kidney-international.org meeting report

## Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference

OPEN

Timothy H.J. Goodship[1], H. Terence Cook[2], Fadi Fakhouri[3], Fernando C. Fervenza[4], Véronique Frémeaux-Bacchi[5], David Kavanagh[1], Carla M. Nester[6,7], Marina Noris[8], Matthew C. Pickering[2], Santiago Rodríguez de Córdoba[9], Lubka T. Roumenina[10,11,12], Sanjeev Sethi[13] and Richard J.H. Smith[6,7]; for Conference Participants[14]

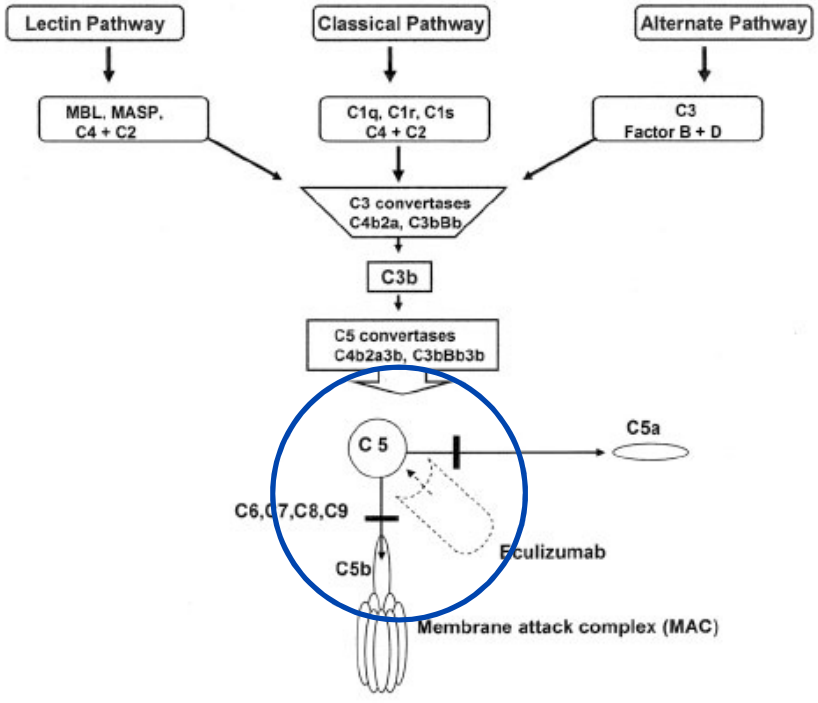
Goodship KI 2017

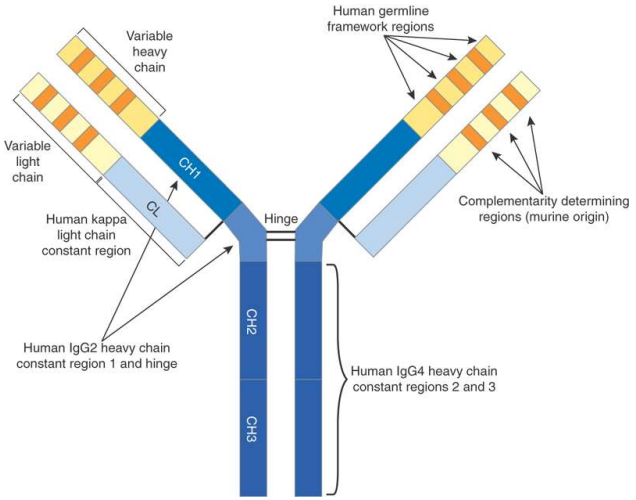
**Table 5 | Recommended treatment approach for C3G[a]**

| | |
|---|---|
| **All patients** | • Optimal blood pressure control (suggested blood pressure below the 90% in children and ≤120/80 mm Hg in adults)<br>○ Priority agents include angiotensin converting enzyme inhibitors and angiotensin receptor blockers<br>• Optimal nutrition for both normal growth in children and healthy weight in adults<br>• Lipid control |
| **Moderate disease** | **Description**<br>• Urine protein over 500 mg/24 h despite supportive therapy<br>*or*<br>• Moderate inflammation on renal biopsy<br>*or*<br>• Recent increase in serum creatinine suggesting risk for progressive disease<br>**Recommendation**<br>• Prednisone<br>• Mycophenolate mofetil |
| **Severe disease** | **Description**<br>• Urine protein over 2000 mg/24 h despite immunosuppression and supportive therapy<br>*or*<br>• Severe inflammation represented by marked endo- or extracapillary proliferation with or without crescent formation despite immunosuppression and supportive therapy<br>*or*<br>• Increased serum creatinine suggesting risk for progressive disease at onset despite immunosuppression and supportive therapy<br>**Recommendation**<br>• Methylprednisolone pulse dosing as well as other anti-cellular immune suppressants have had limited success in rapidly progressive disease<br>• Data are insufficient to recommend eculizumab as a first-line agent for the treatment of rapidly progressive disease |

C3G, C3 glomerulopathy.
[a]Based on a single, small prospective trial, case reports, and expert opinion.

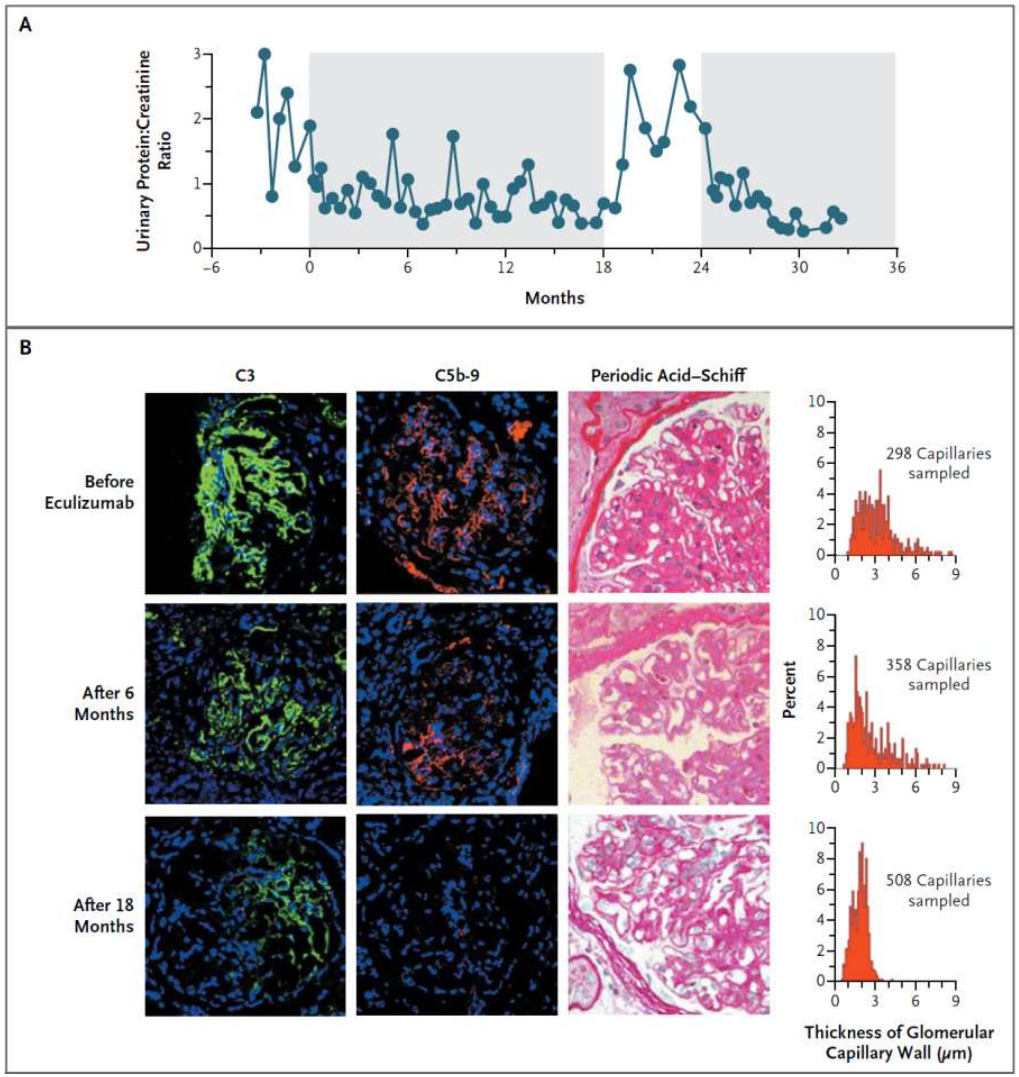
# Complement-targeting therapies: anti-C5 blocks the terminal complement pathway




Rother et al. Nature Biotechnology 2007

# Treatment of DDD with anti-C5 (eculizumab)




**ATTENTION:**

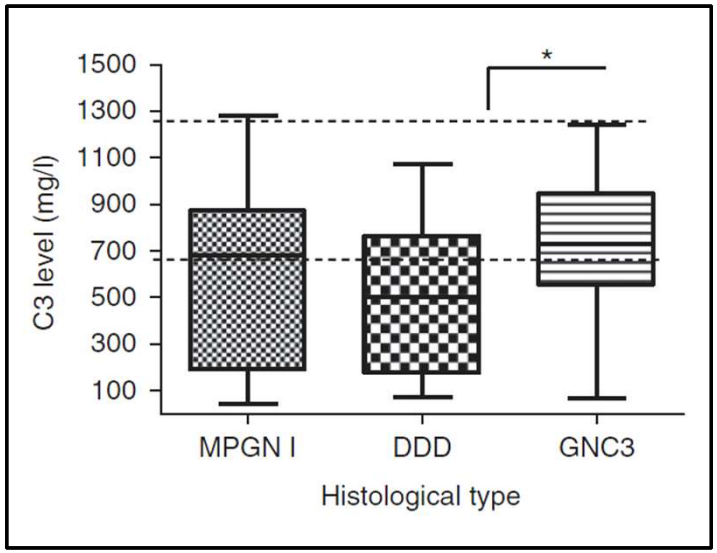
- **not all patients respond so well**
- **it may work better in those with elevated sC5b9**
- **expensive and there is a risk of meningococcal infection**

**Figure 1. Change in the Patient's Urinary Protein:Creatinine Ratio, the Glomerular Deposition of C3 and C5b-9, and the Thickness of Glomerular Capillary Walls before Treatment and after 6 and 18 Months of Treatment.**

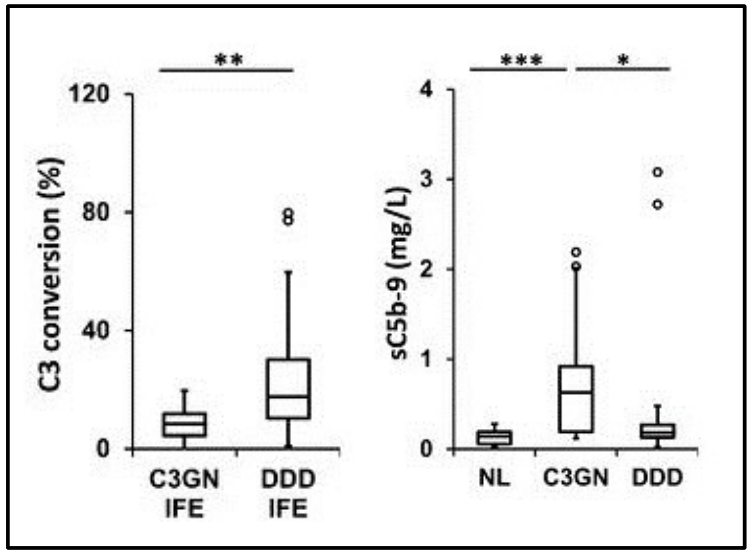
Panel A shows the changes in the patient's urinary protein:creatinine ratio (mg/mg), starting 6 weeks before the first eculizumab infusion. The shaded areas represent the time during which the patient was undergoing treatment with eculizumab and the white areas the time before therapy began and the period during which therapy was discontinued. Panel B shows stained specimens from renal biopsies performed before treatment with eculizumab and at 6 and 18 months during the first treatment period. During this period, the clearance of C3 and C5b-9 deposition is nearly complete (C3 is shown in green fluorescence and C5b-9 in red fluorescence; nuclei are stained in blue); histologic improvement is revealed with periodic acid–Schiff staining. The far right column shows the progressive reduction in the thickness of the glomerular capillary walls in response to treatment. Capillary thickness was estimated by observing the width of positive periodic acid–Schiff staining in all peripheral capillary loops of analyzed glomeruli; the number of capillaries sampled at the time of each biopsy is provided.

Vivarelli et al, New England J Med 2012

# Circulating C3 and C5b-9 according to renal histology




Servais et al, Kidney Int 2012

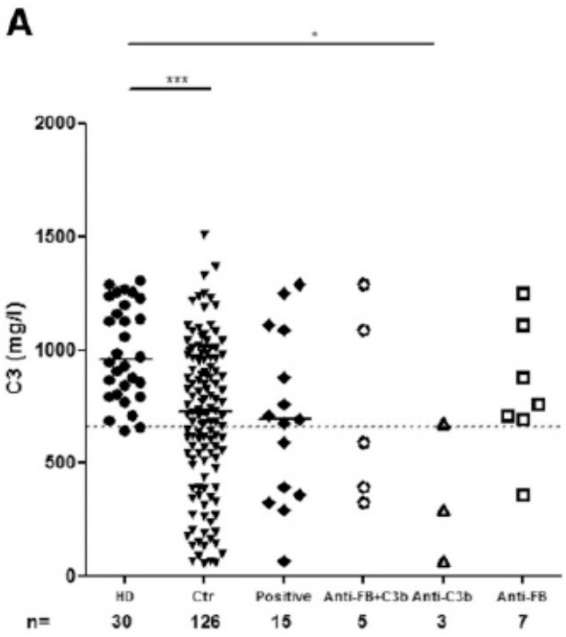


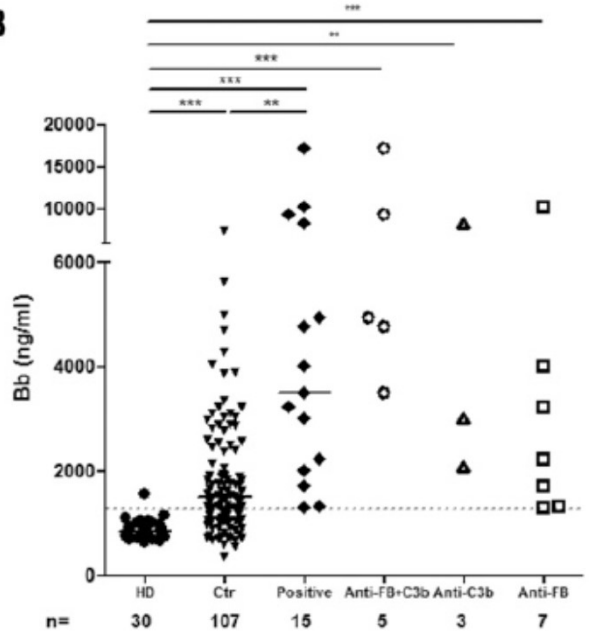

Yuzhou Zhang et al. CJASN 2014

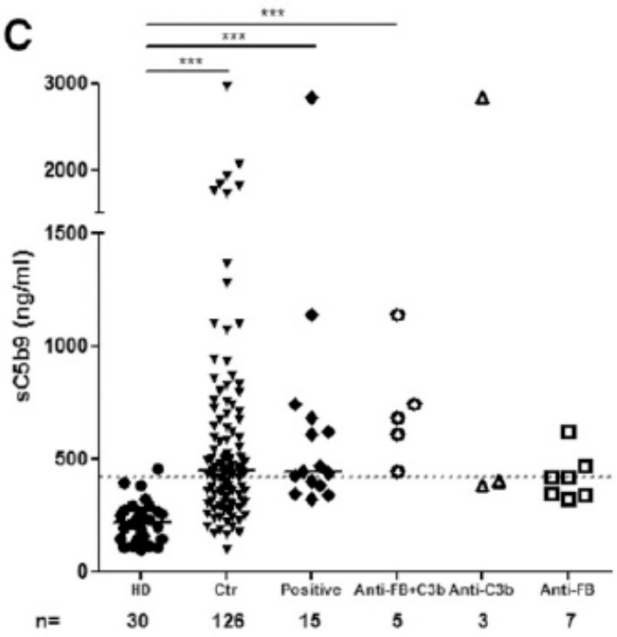
**C3 convertase dysregulation:**
**DDD>C3GN**

**C5 convertase dysregulation:**
**C3GN>DDD**

# Circulating C3, C5b-9 and Bb according to anti-C3b and anti-FB



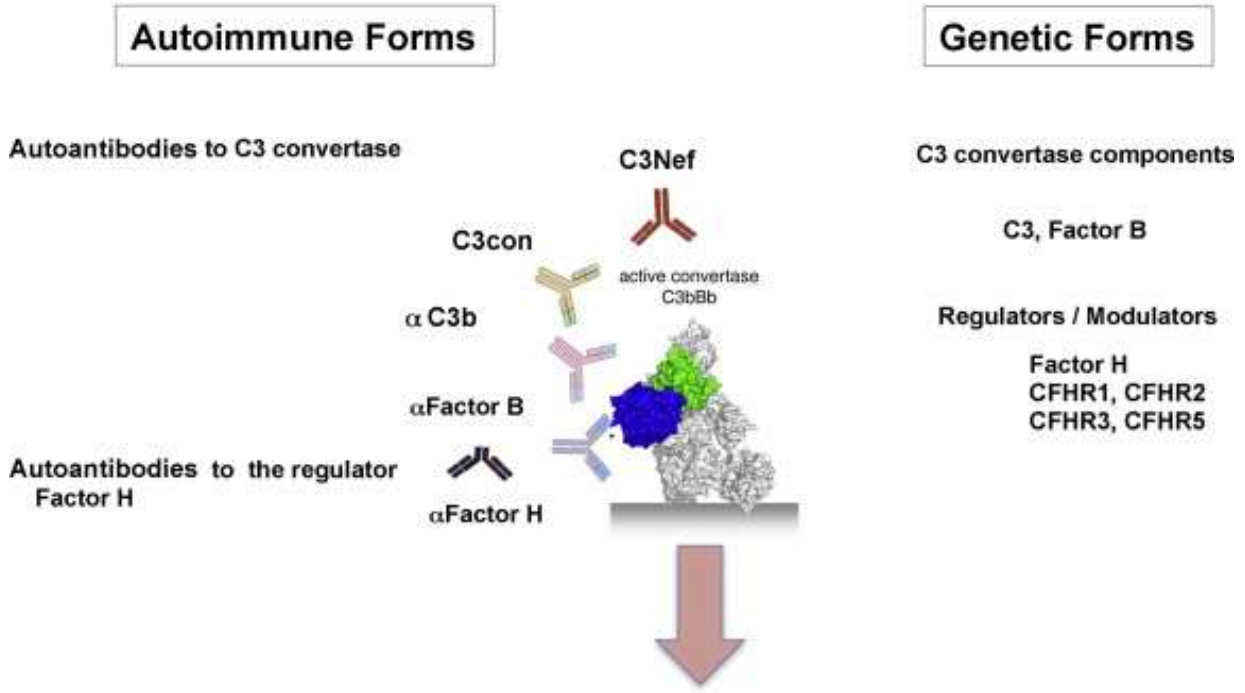

**C3 convertase dysregulation: elevated Bb**

**C5 convertase dysregulation: elevated C5b9**

Marinozzi et al, JASN 2017

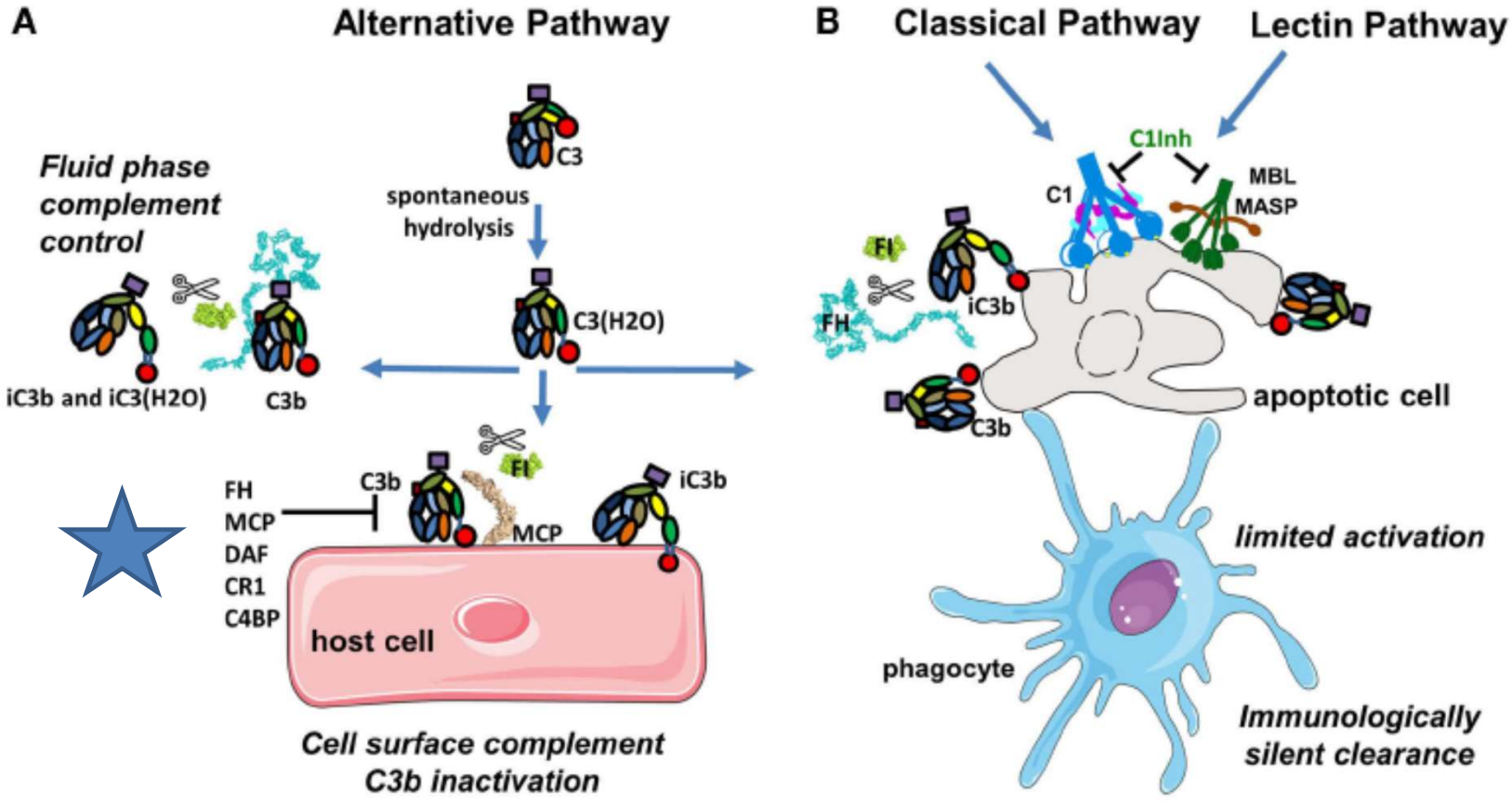
# Different mechanisms of disease in different patients with C3G

Zipfel PF Molecular Immunology, 2015

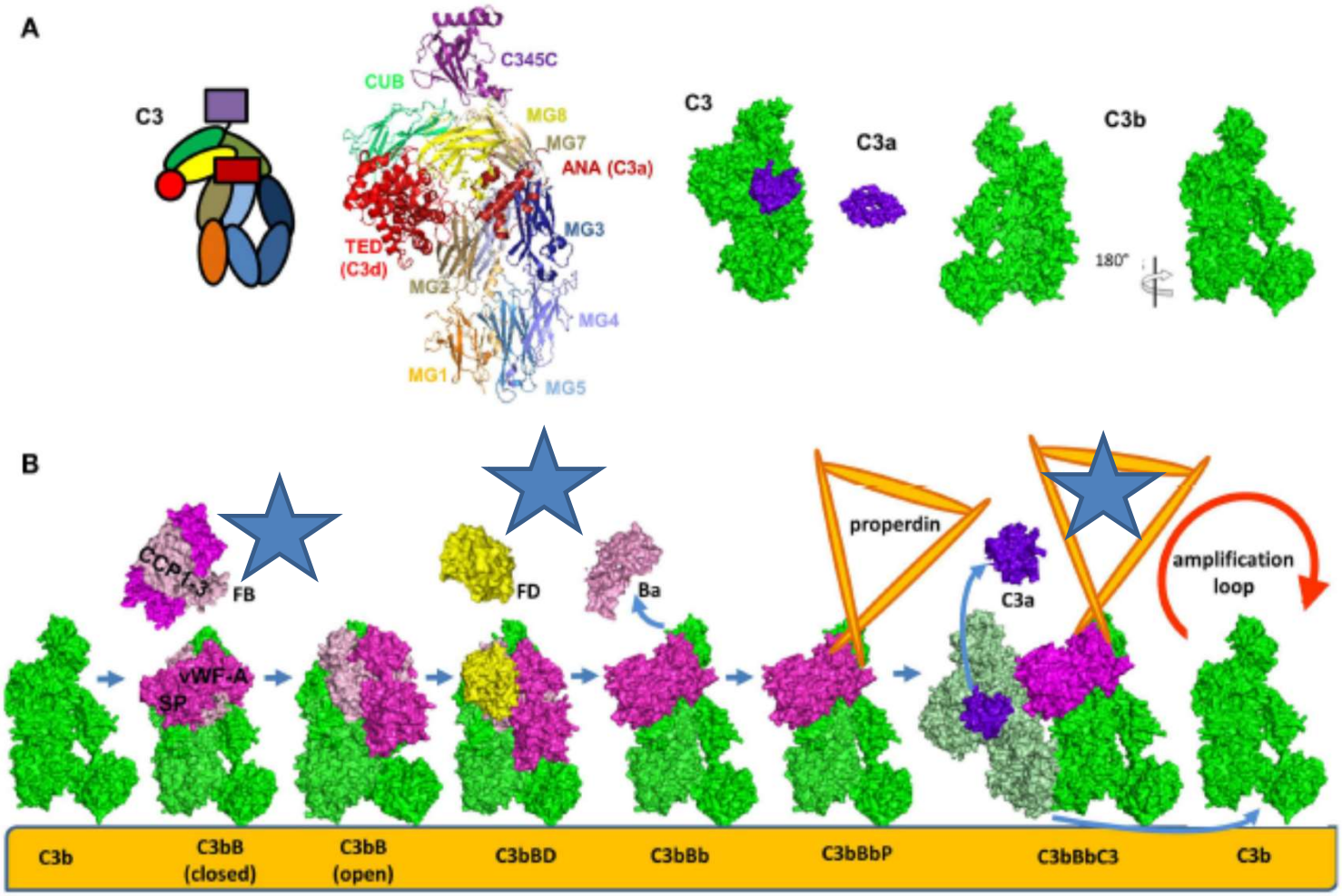



**Alternative pathway of complement dysregulation**

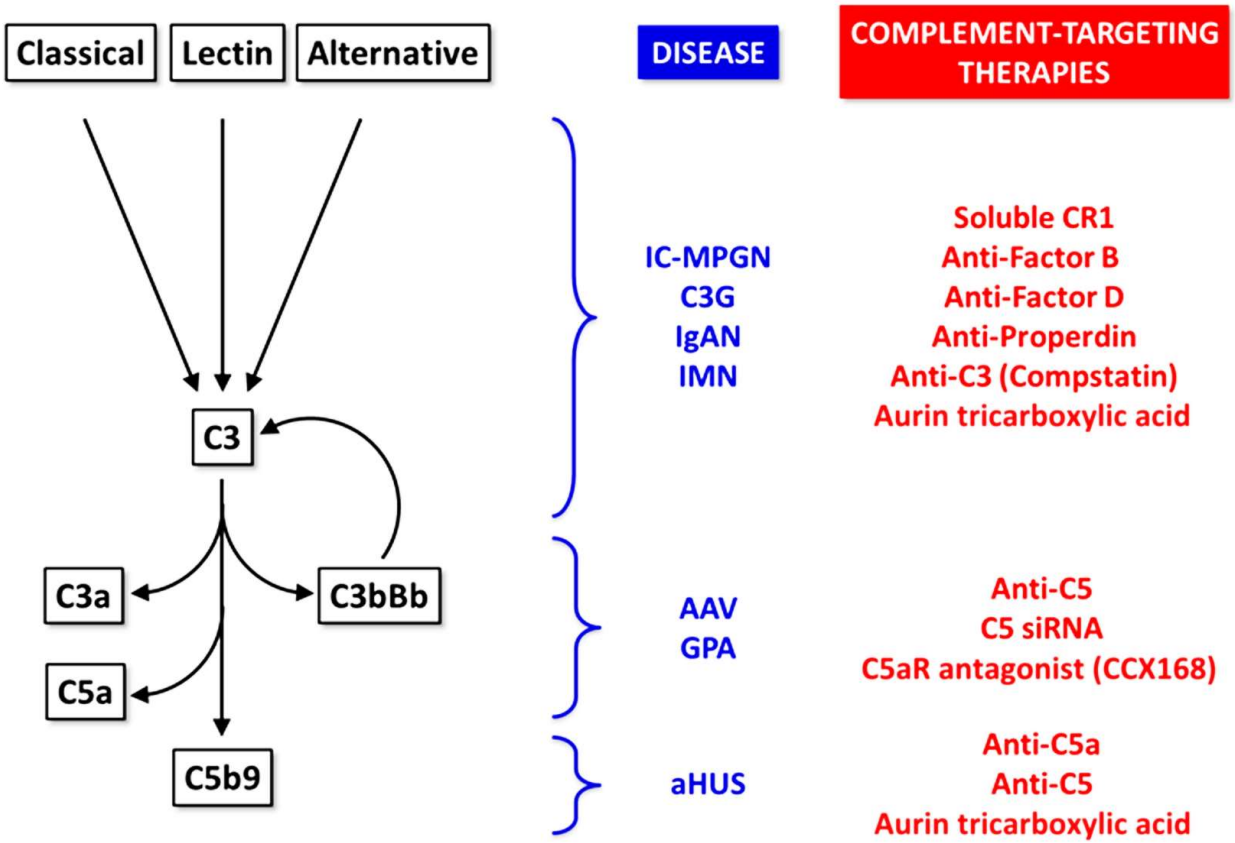
# Targeting the alternative pathway



# Targeting the alternative pathway



# Complement-targeting therapies on the horizon




Courtesy Christoph Licht

# Take-home messages

**1) C3 glomerulopathy is not a single disease entity but rather a disease spectrum due to AP dysregulated activation which may be**

- **Permanent (genetic) as in genetic C3G**
- **Transitory (infectious trigger) as in atypical PIGN**
- **Concomitant to an immune-mediated mechanism such as in antibody-mediated C3G, IC – MPGN**

**2) C3G is extremely heterogenous and less rare than we thought. Some cases may spontaneously improve. Some patients have a relapsing course.**

**3) Treatment of C3G should be tailored on a pathogenetic basis to target the involved mediator. Immunosuppressive drugs (PDN, MMF) may be beneficial both to treat the immune-mediated mechanism, if present, and if there is evidence of renal inflammation**

**4) Anti-C5 therapy may be beneficial in some, but not in all patients**

# THANK YOU


- Prof Joshua Thurman
- Prof Carla Nester
- Prof Christoph Licht
- Prof Matthew Pickering

- Dr Marina Noris
- Dr Elena Bresin
- Dr Veronique Fremeaux-Bacchi

- Dr Andrea Pasini
- Dr Domenico Sperlì

- Prof Francesco Emma

**The patients and their families**


Bambino Gesù
OSPEDALE PEDIATRICO