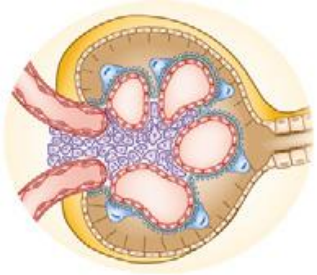
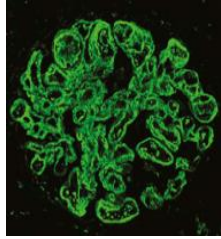
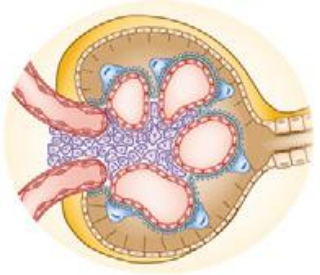


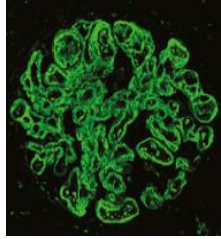


Membranous nephropathy

Dr Esmat Abdollahpour

Assistant professor of TUMS, shariati hospital



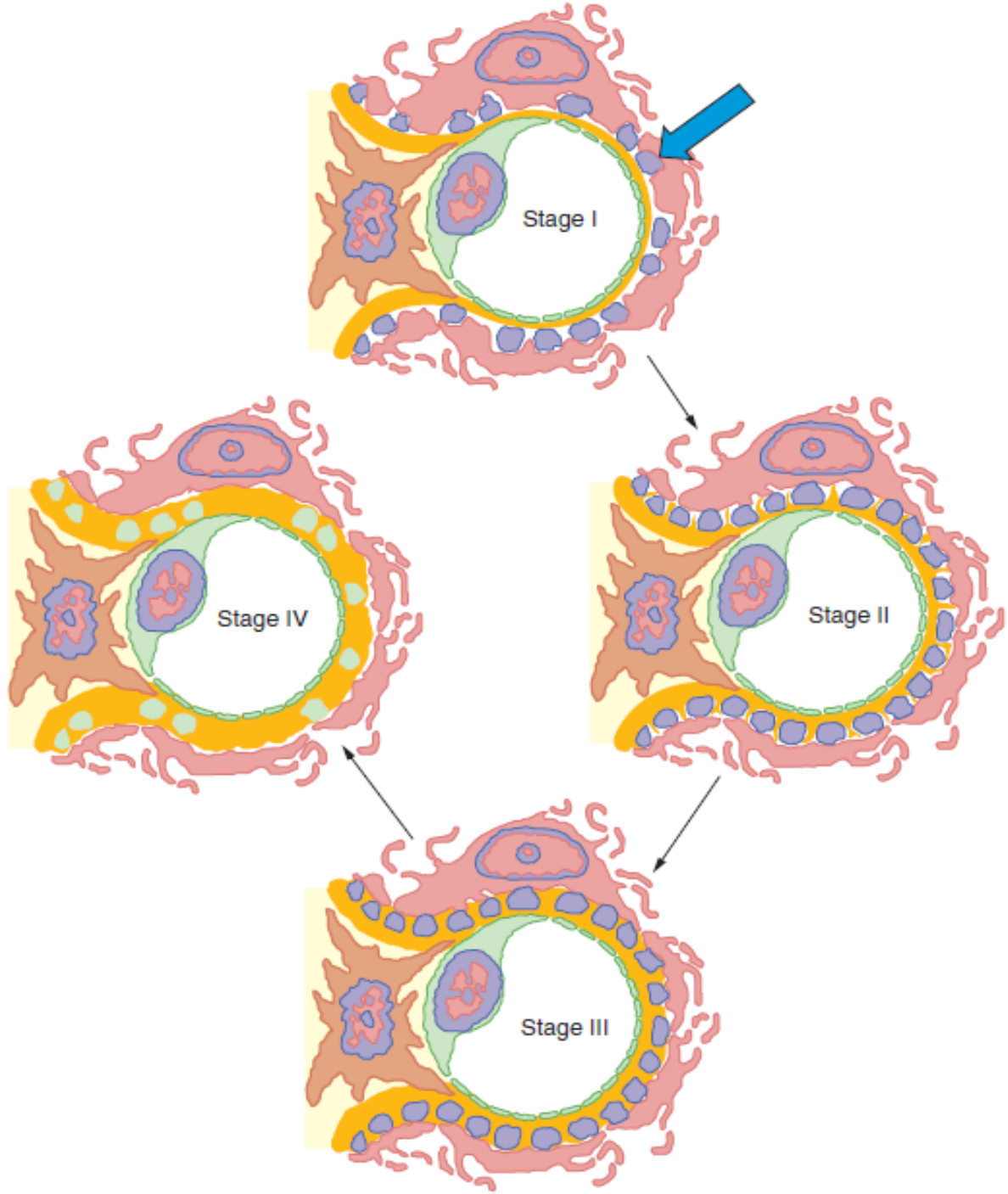


Trends in Toronto Glomerulonephritis Registry: 1975–2015

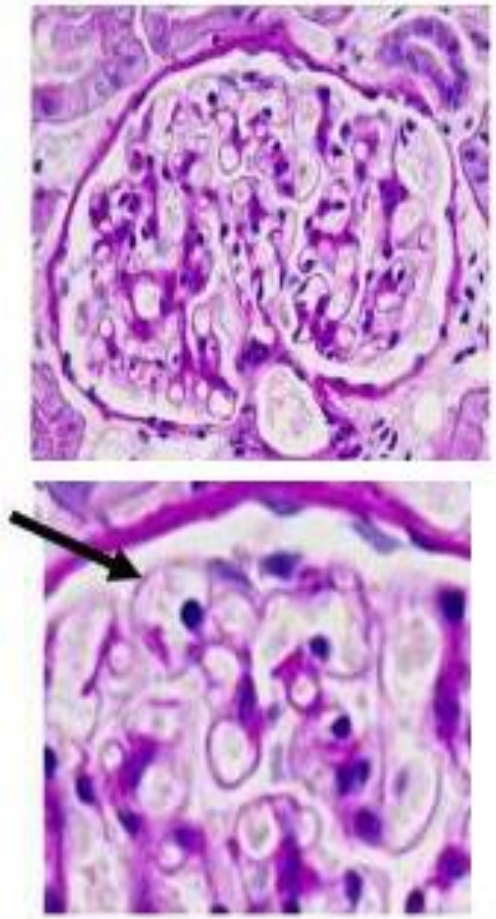
	1975–1979	1980–1984	1985–1989	1990–1994	1995–1999	2000–2004	2005–2011	2012–2015[a]	Total
MN	134	172	171	164	129	138	230	168	1306
MPGN	99	67	33	46	37	22	34	N/A	329
FSGS	141	164	163	239	311	318	338	288	1962
IGA	129	215	227	262	309	299	349	286	2076
LUPUS	170	191	143	174	136	130	262	N/A	1206
Vasculitis	29	66	76	93	76	87	152	N/A	579

Recognized causes of anti-PLA2R/THSD7A–negative secondary membranous nephropathy	
Cause	Examples
Infections	HBV, HCV, HIV, parasites (filariasis, schistosomiasis, malaria), leprosy, syphilis, hydatid disease, sarcoid
Malignancy (20% in patients >57,4% <57)	Solid tumors (lung 26%, prostate 15%, hematologic [plasma cell dyscrasias, non-Hodgkin lymphoma, CLL] 14%, colon 11%), mesothelioma, melanoma, pheochromocytoma; some benign tumors
Autoimmune diseases	SLE (class V), thyroiditis, diabetes, rheumatoid arthritis, Sjogren syndrome, dermatomyositis, mixed connective tissue disease, ankylosing spondylitis, retroperitoneal fibrosis Anti-GBM disease, IgA N, ANCA-associated vasculitis IgG4 disease Membranous-like glomerulopathy with masked IgG k deposits
Alloimmune diseases	Graft versus host disease, autologous stem cell transplants, de novo MN in transplants/transplant glomerulopathy
Drugs/toxins	NSAIDs, COX2 inh, gold, d-penicillamine, captopril, probenecid, sulindac, anti-TNFa, Mercury, lithium, hydrocarbons, formaldehyde, environmental air pollution

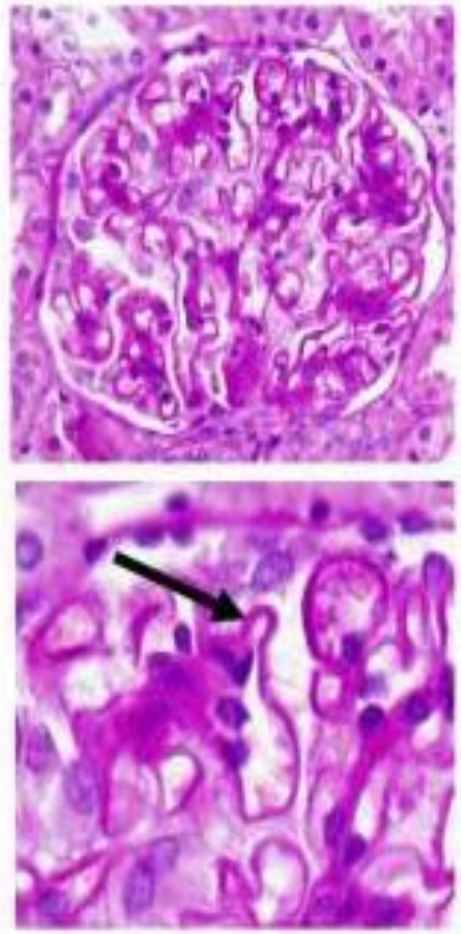
Clinical manifestations of primary membranous nephropathy at presentation and during the course of the disease			
Clinical manifestations	Initially	During course	comments
Nephrotic syndrome			
Proteinuria.3.5 g/d	60% (25-30% subneprotic)	75%	
Edema	60%	75%	
Hypoalbuminuria	60%	75%	Risk increases with serum albumin ,2.8 g/dl
Hyperlipidemia	50%	65%	
Thromboemboli	<1%	7%	
Hematuria	50%	60%	
Reduced GFR	20%	40%	
ESRD	NA	10%–20% (treated) to 33% (untreated)	
Hypertension	30%	Up to 50%	

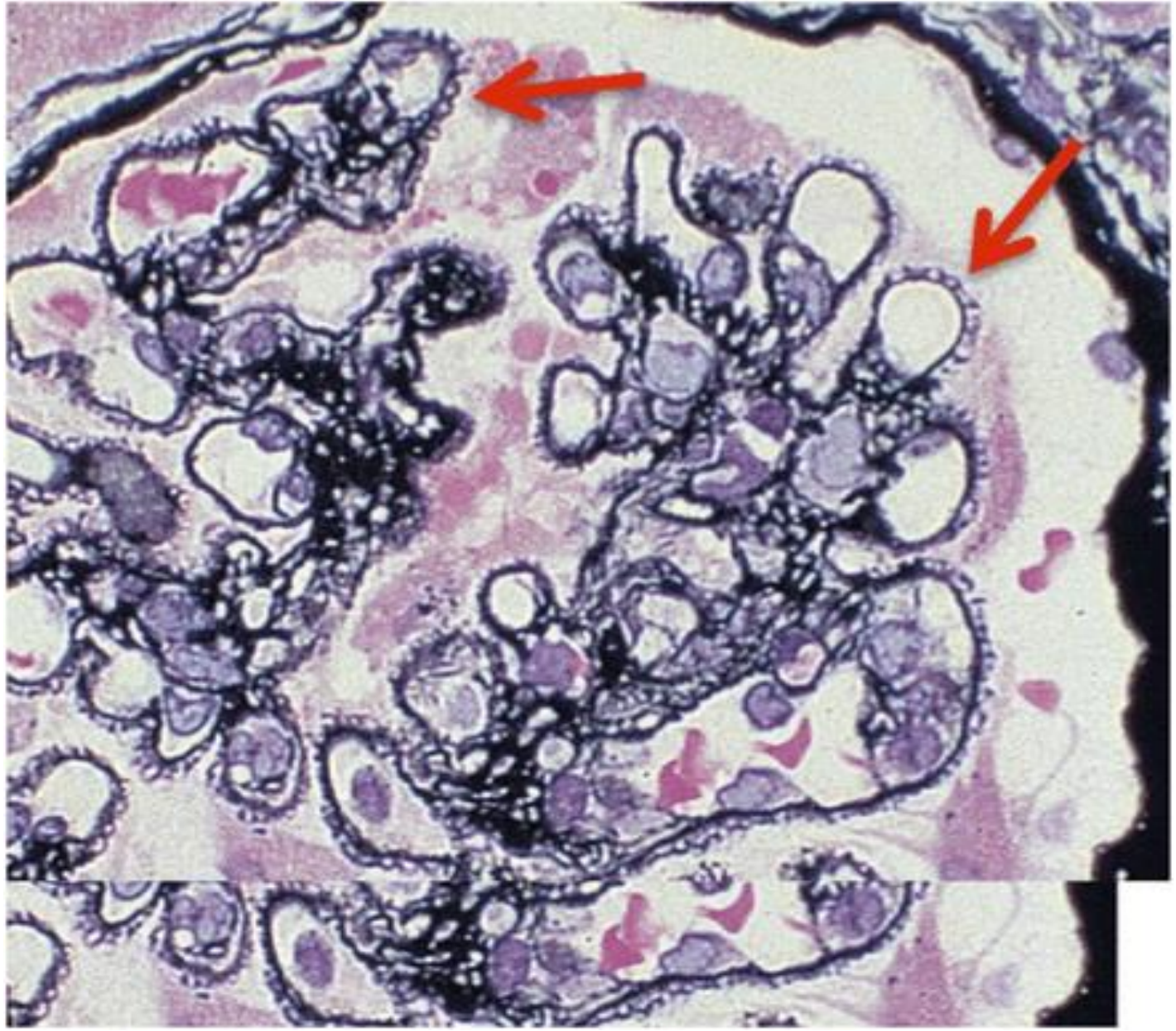

Stage I
Stage II
Stage III
Stage IV

Normal glomerular capillaries with thin walls



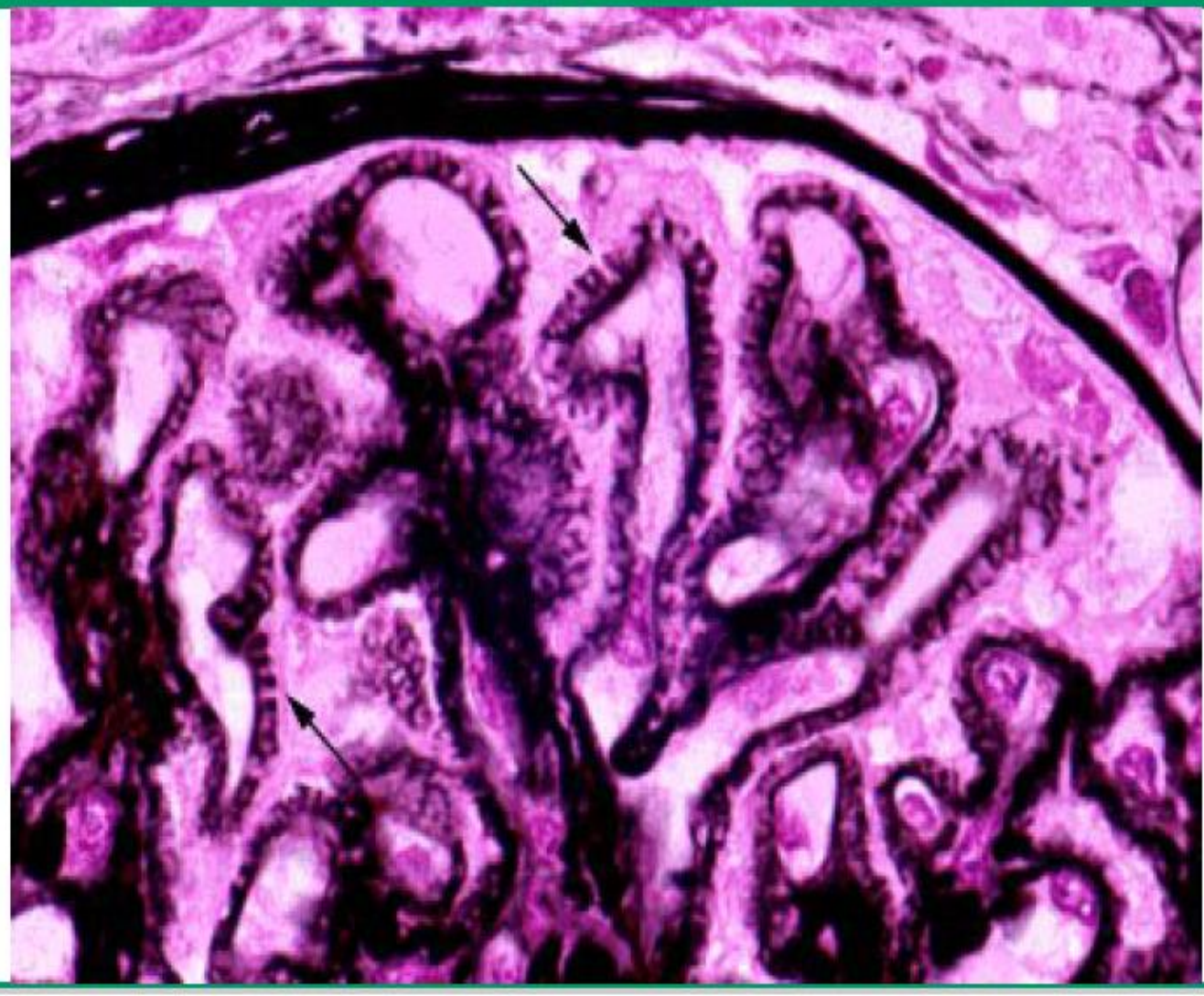
Membranous glomerulopathy with thick capillary walls





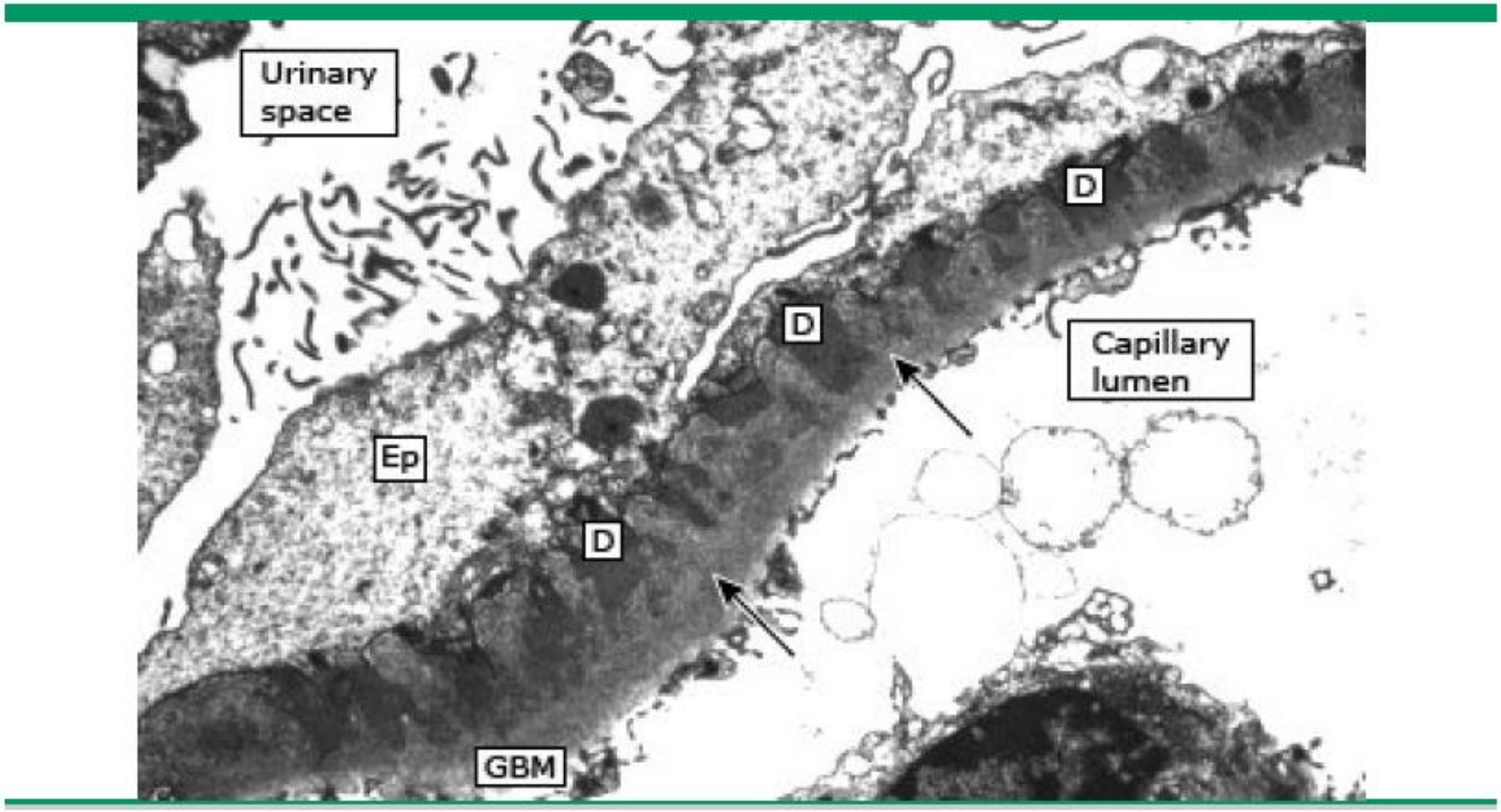
Glomerulus from a patient with primary membranous nephropathy showing the pathognomonic “spikes” of basement membrane projecting from the outer surface of the glomerular basement membrane (arrows) when stained with silver-methenamine

Silver stain in membranous nephropathy



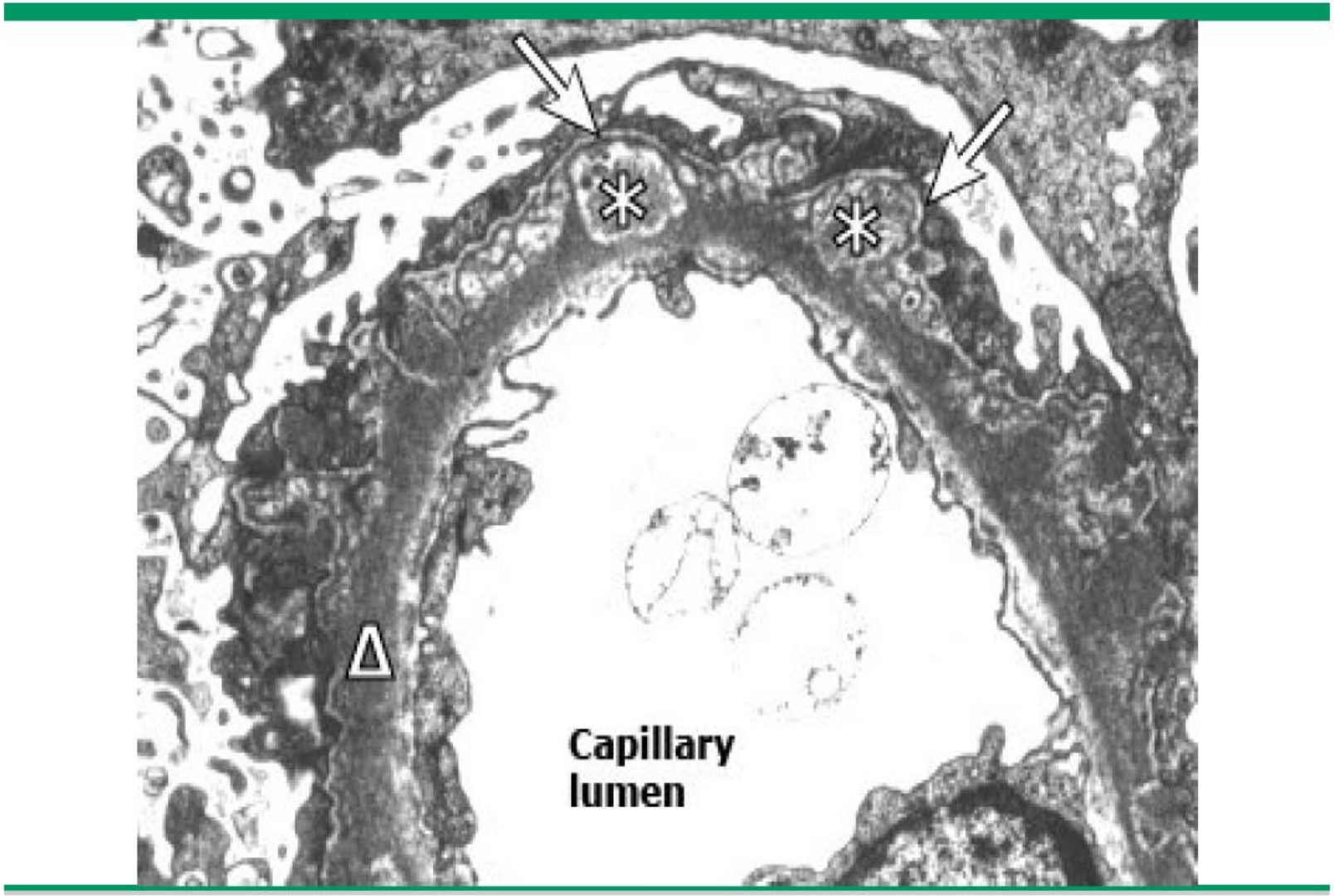
Light micrograph silver stain of membranous nephropathy shows a spike appearance (arrows). The spikes represent new basement membrane growing between the subepithelial immune deposits, which are visible on electron microscopy but not with this stain.

Electron micrograph showing membranous nephropathy

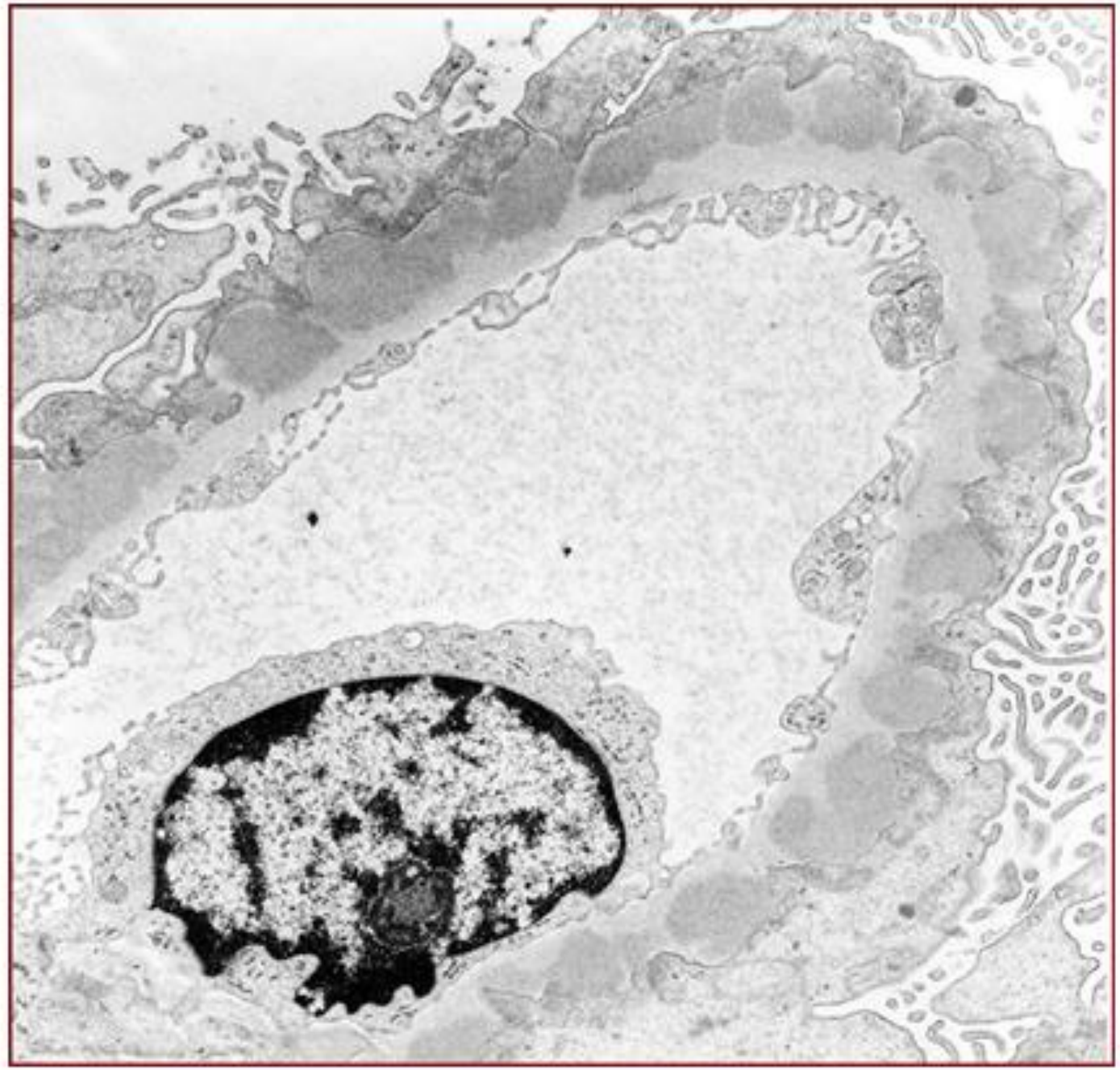


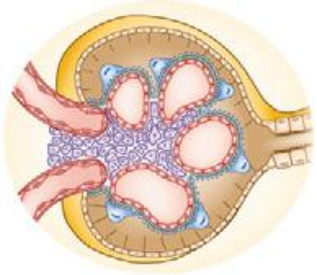
Electron micrograph shows stage II membranous nephropathy. Electron-dense deposits (D) are present in the subepithelial space across the glomerular basement membrane (GBM) and under the epithelial cells (Ep). New basement membrane is growing between the deposits, leading to a spike appearance on silver stain.

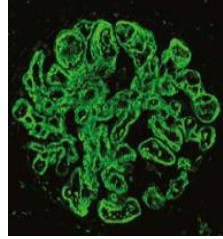
Electron micrograph in stage III membranous nephropathy



Electron micrograph in stage III membranous nephropathy. The subepithelial immune deposits (asterisk) have a lucent, moth-eaten appearance and have been incorporated into the glomerular basement membrane (Δ) as new basement membrane has grown around the deposits (arrows).

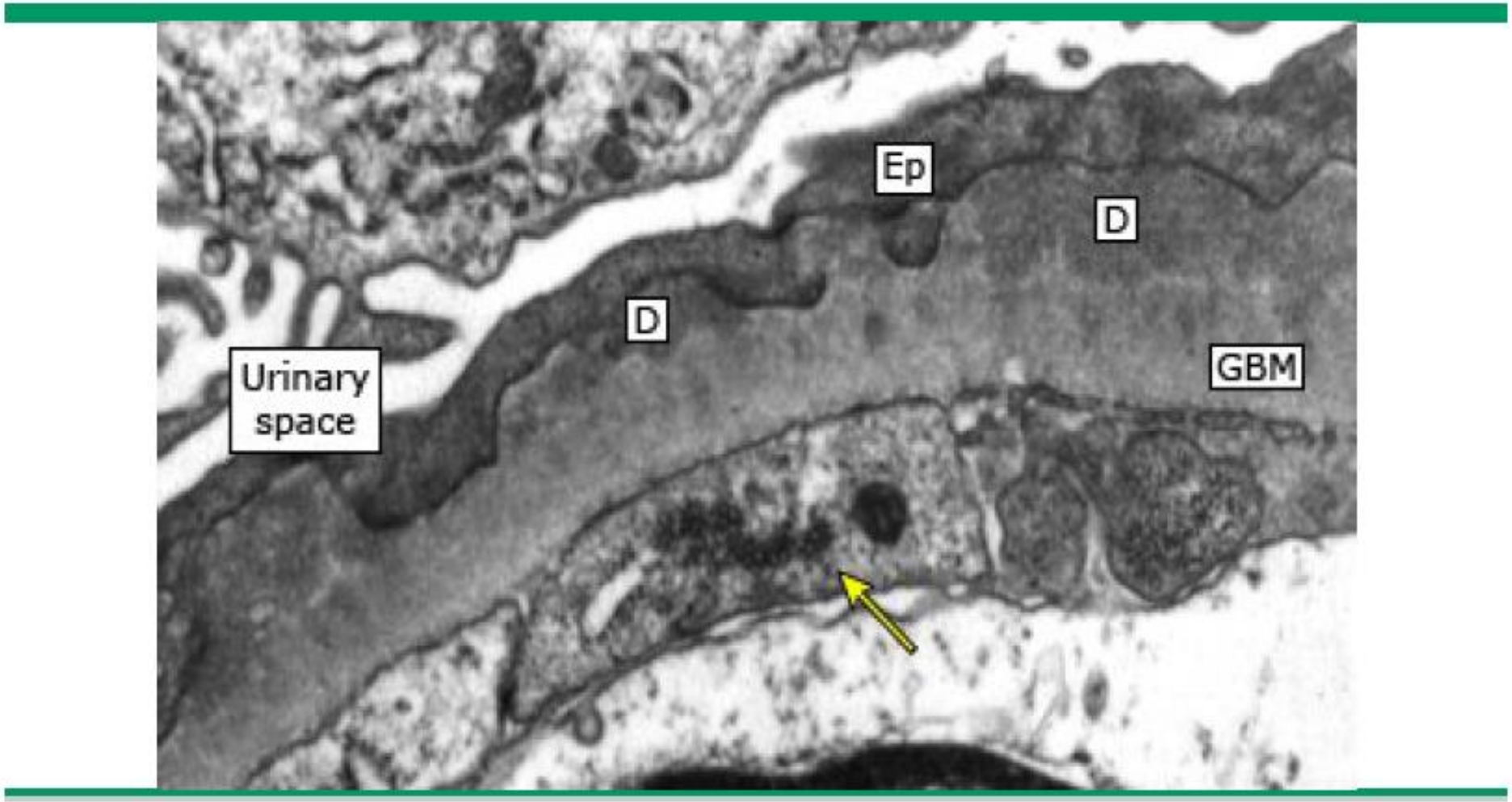




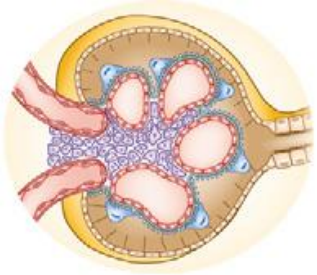


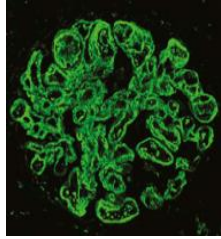
Finding that should prompt careful search for secondary causes of MN
Electron-dense deposits in subendothelial or mesangial locations
Significant mesangial or endothelial cell proliferation
Crescents
Tubular basement membrane staining
Dominant deposition of IgG1/IgG3, IgM, IgA, or C1q
Endothelial tubuloreticular inclusions by electron microscopy
Intraglomerular inflammatory cell infiltrates (cancer)

Electron micrograph showing lupus membranous nephropathy



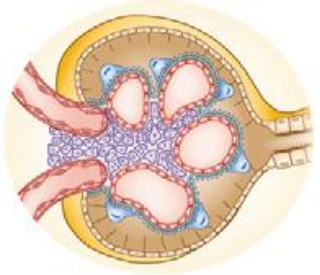
Electron micrograph of lupus membranous nephropathy. The subepithelial immune deposits (D) are characteristic of any form of membranous nephropathy, but the intraendothelial tubuloreticular inclusions (arrow) strongly suggest underlying lupus.

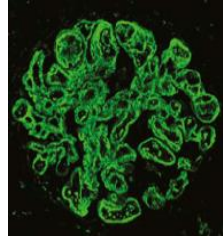


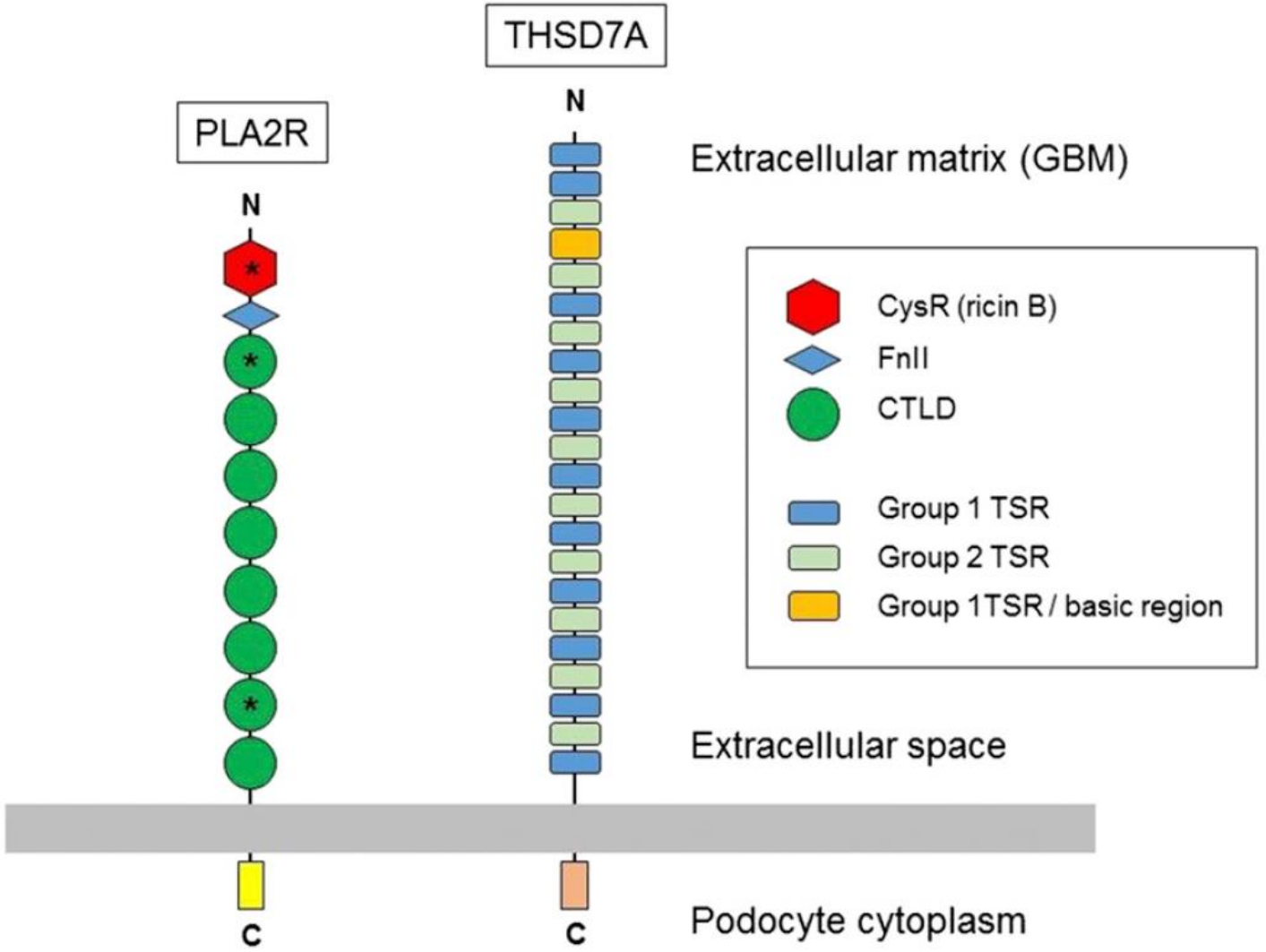


AntiPLA2R
2009

THSD7A
2014







A schematic of the domain structures of PLA2R and THSD7A demonstrates that both proteins are large transmembrane glycoproteins with short cytoplasmic tails

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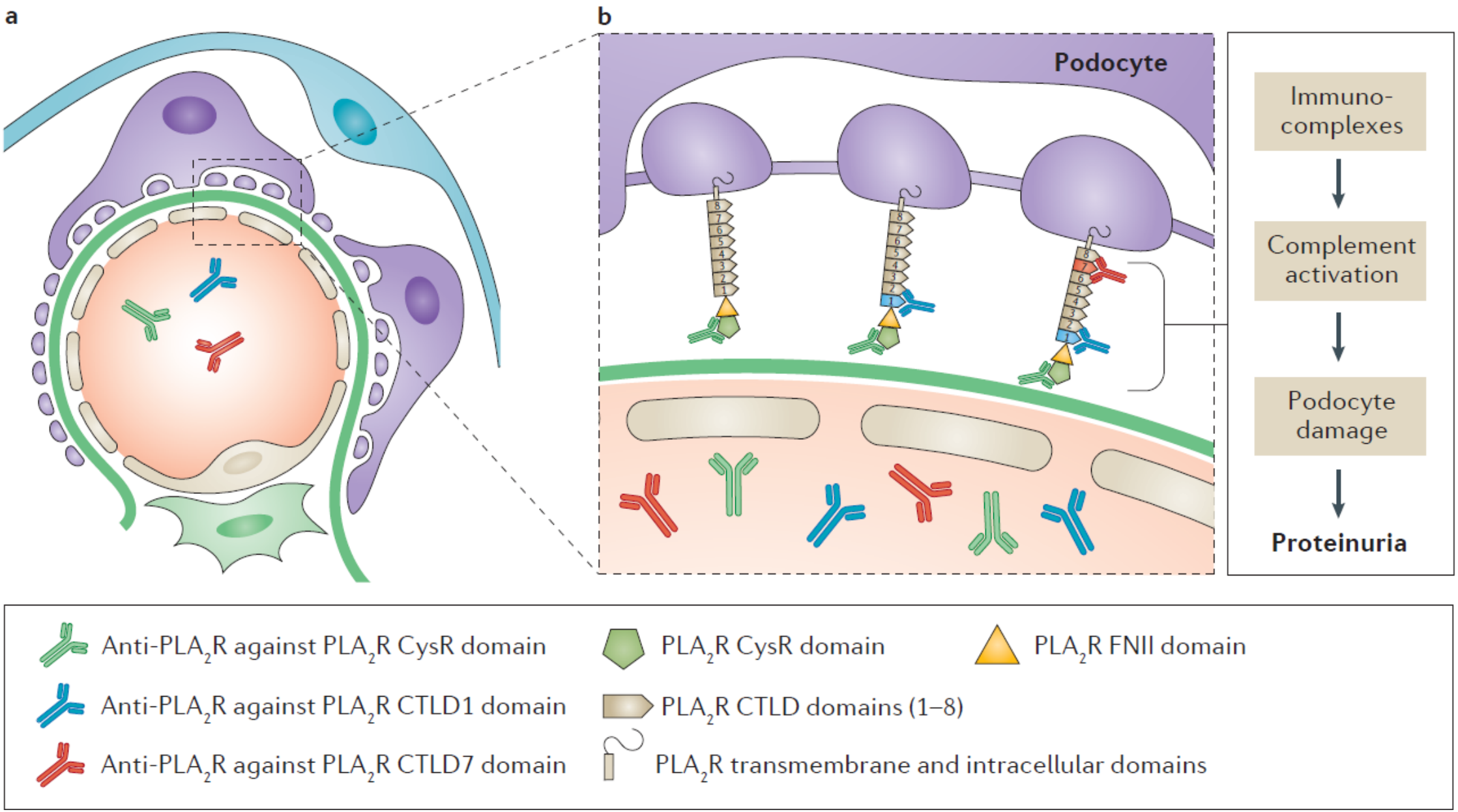
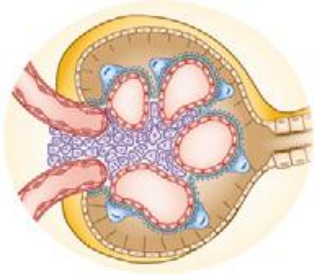
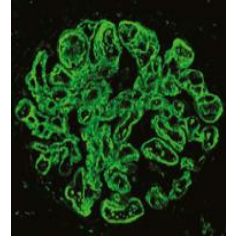
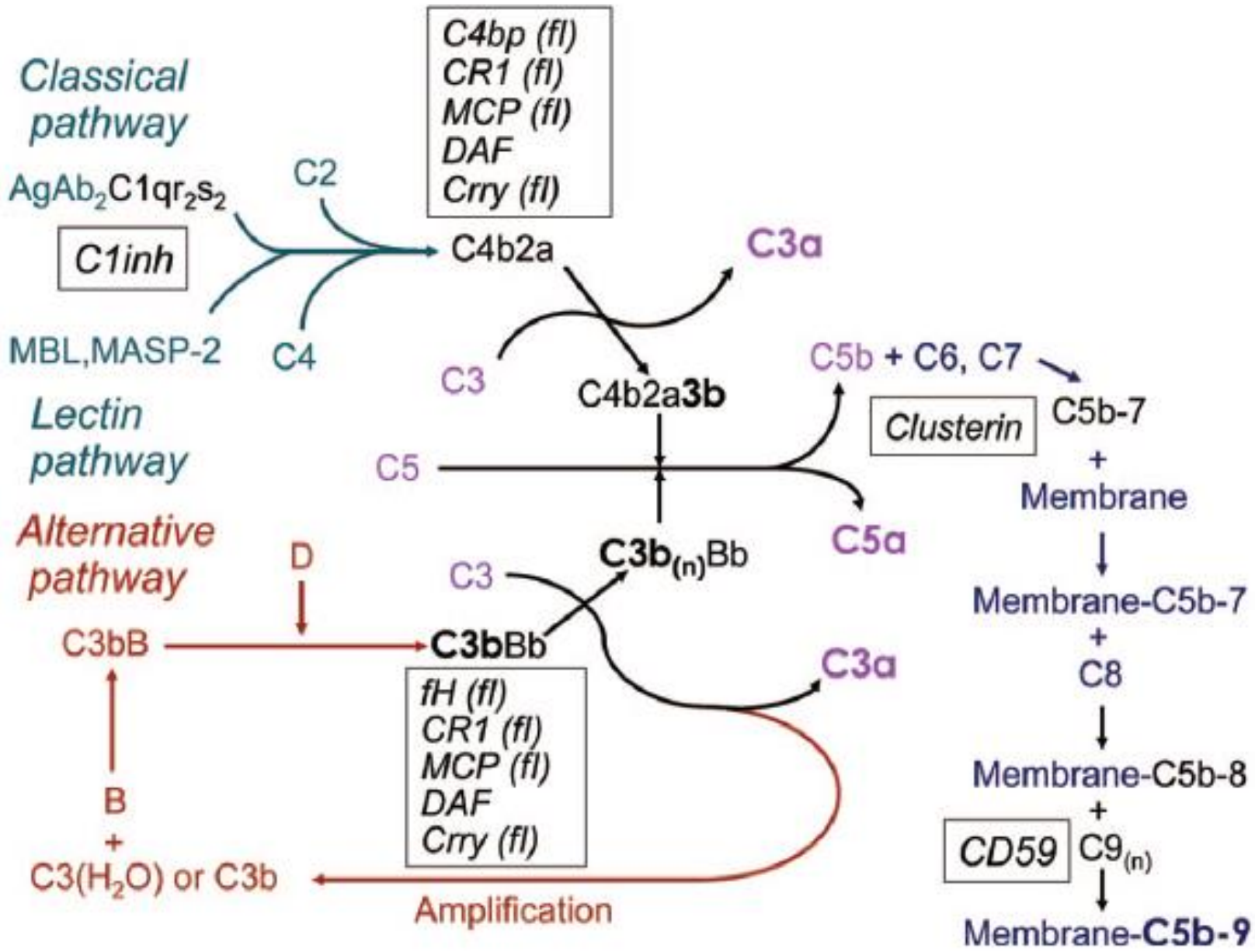
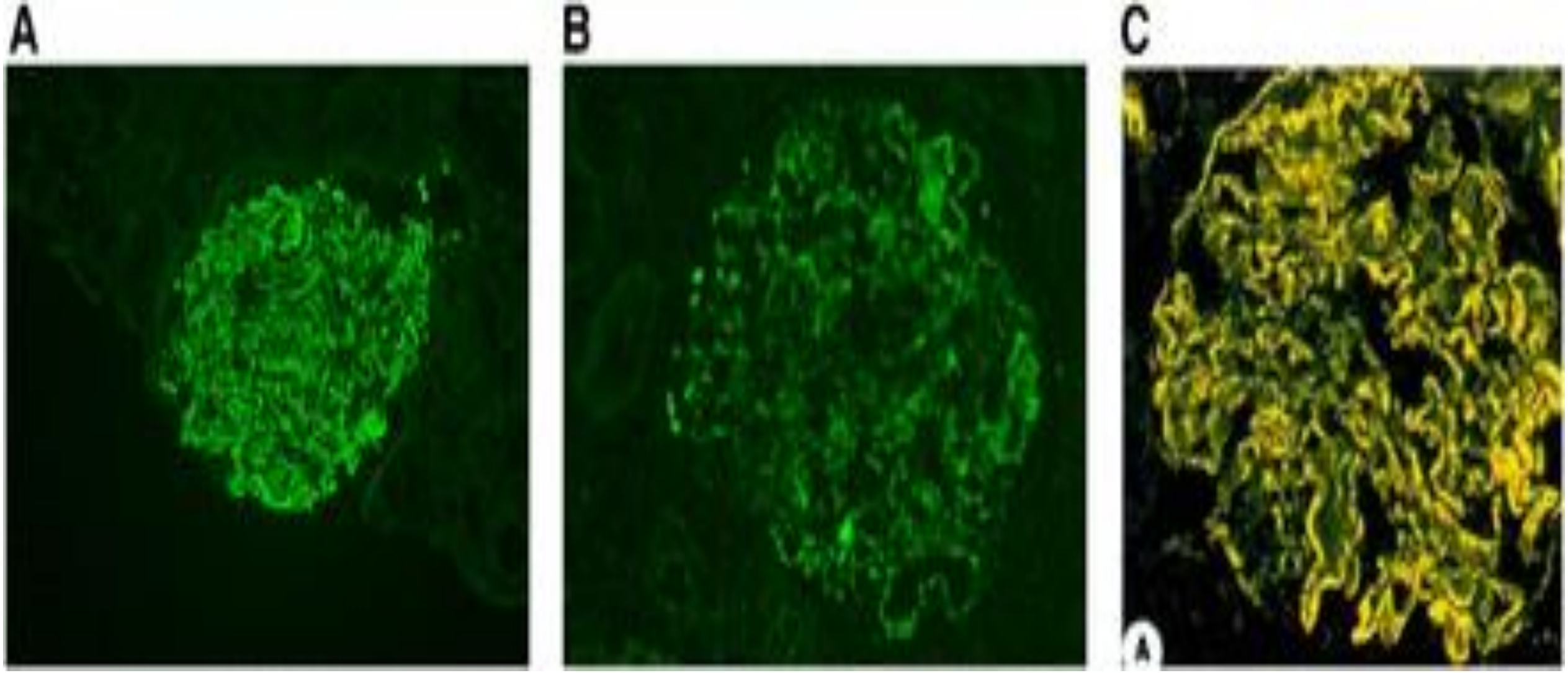

a
b
Podocyte
Immuno-complexes
Complement activation
Podocyte damage
Proteinuria
Anti-PLA2R against PLA2R CysR domain
Anti-PLA2R against PLA2R CTLD1 domain
Anti-PLA2R against PLA2R CTLD7 domain
PLA2R CysR domain
PLA2R CTLD domains (1–8)
PLA2R transmembrane and intracellular domains
PLA2R FNII domain

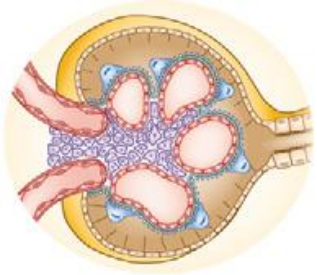


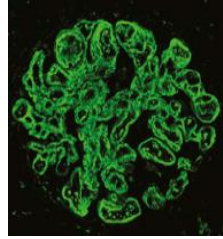



Classical pathway
AgAb2C1qr2s2
C1inh
MBL,MASP-2
Lectin pathway
Alternative pathway
C2
C4
C4bp (fl)
CR1 (fl)
MCP (fl)
DAF
Crry (fl)
C4b2a
C3
C3a
C4b2a3b
C5
C5b + C6, C7
Clusterin
C5b-7
+
Membrane
C5a
C3b(n)Bb
D
C3
C3bB
C3bBb
fH (fl)
CR1 (fl)
MCP (fl)
DAF
Crry (fl)
C3a
B
+
C3(H2O) or C3b
Amplification
Membrane-C5b-7
+
C8
Membrane-C5b-8
+
CD59
C9(n)
Membrane-C5b-9

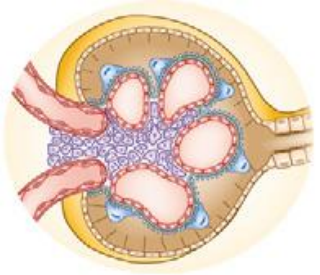


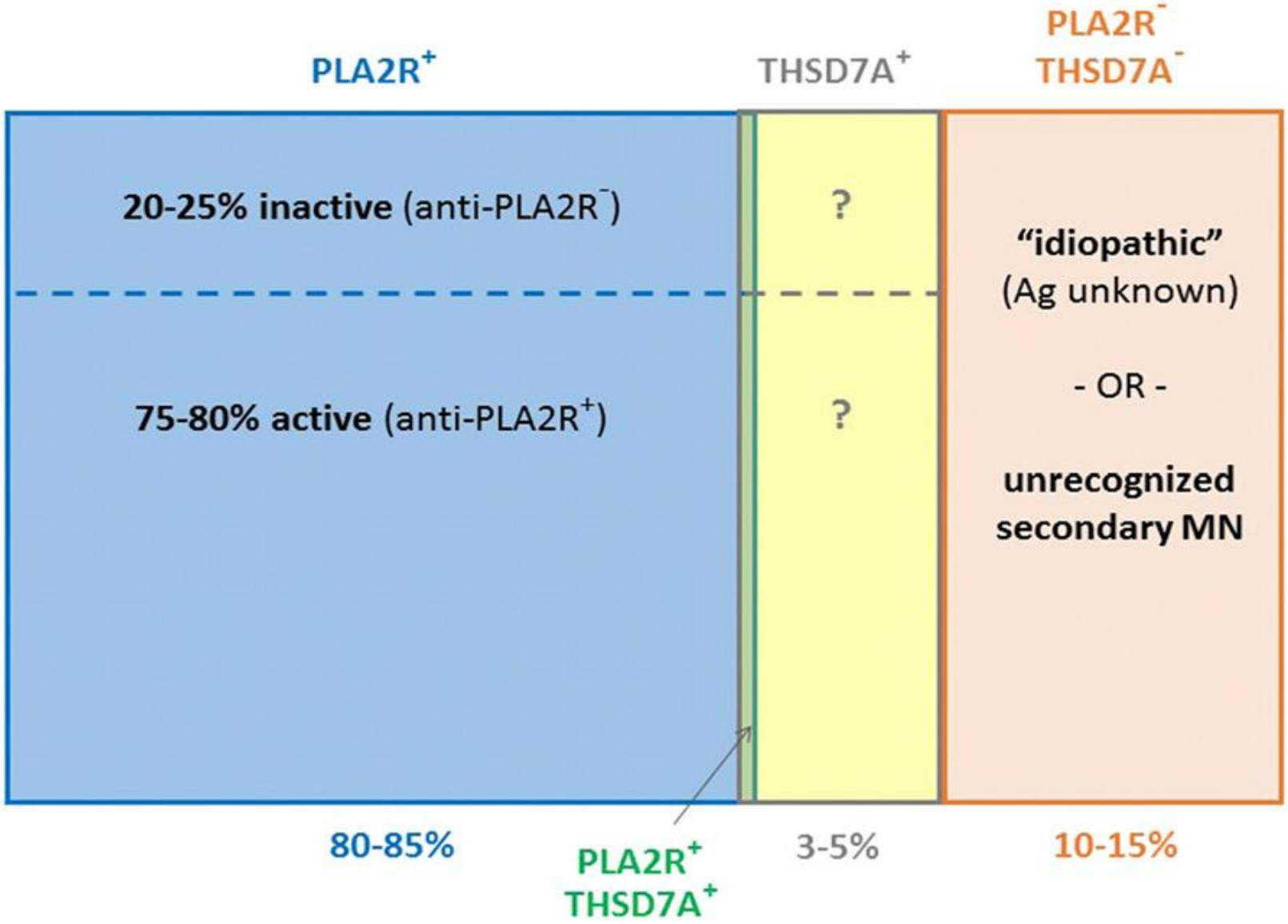
Immunofluorescence microscopy in primary membranous nephropathy (PMN). (A) Finely granular staining for IgG, predominately IgG4, present uniformly in a subepithelial distribution in all glomeruli in a patient with PLA2R-associated PMN. (B) Finely granular staining for PLA2R antigen that colocalizes with IgG4 in a patient with PMN. (C) Finely granular staining for the complement membrane attack complex, C5b-9, in a patient with active PMN

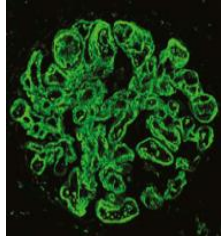




Interpretation of serum anti-podocyte antibody and glomerular antigen staining in primary membranous nephropathy			
Serum Antibody (+/-)	Glomerular Antigen(+/-)	Percent of Patients Who Underwent Biopsy, %	Diagnosis
Anti-PLA2R (+)	PLA2R (+)	70	PLA2R-mediated PMN (active)
Anti-PLA2R (-)	PLA2R (+)	15	PLA2R-mediated PMN (inactive)
Anti-THSD7A (+)	THSD7A (+)	3-5	THSD7A-mediated PMN (active)
Anti-THSD7A (-)	THSD7A (+)	unknown	THSD7A-mediated PMN (inactive)
Anti-PLA2R/THSD7A (-)	PLA2R/THSD7A (-)	10	Non-PLA2R/THSD7A–mediated anti podocyte Ab (pathogenesis Unknown)







This schematic (not to scale) presents a categorization of primary MN into subgroups on the basis of association with the two known antigens, PLA2R and THSD7A

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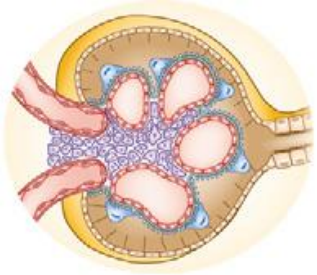
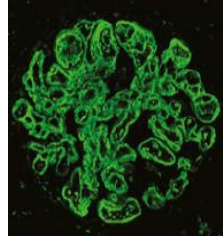
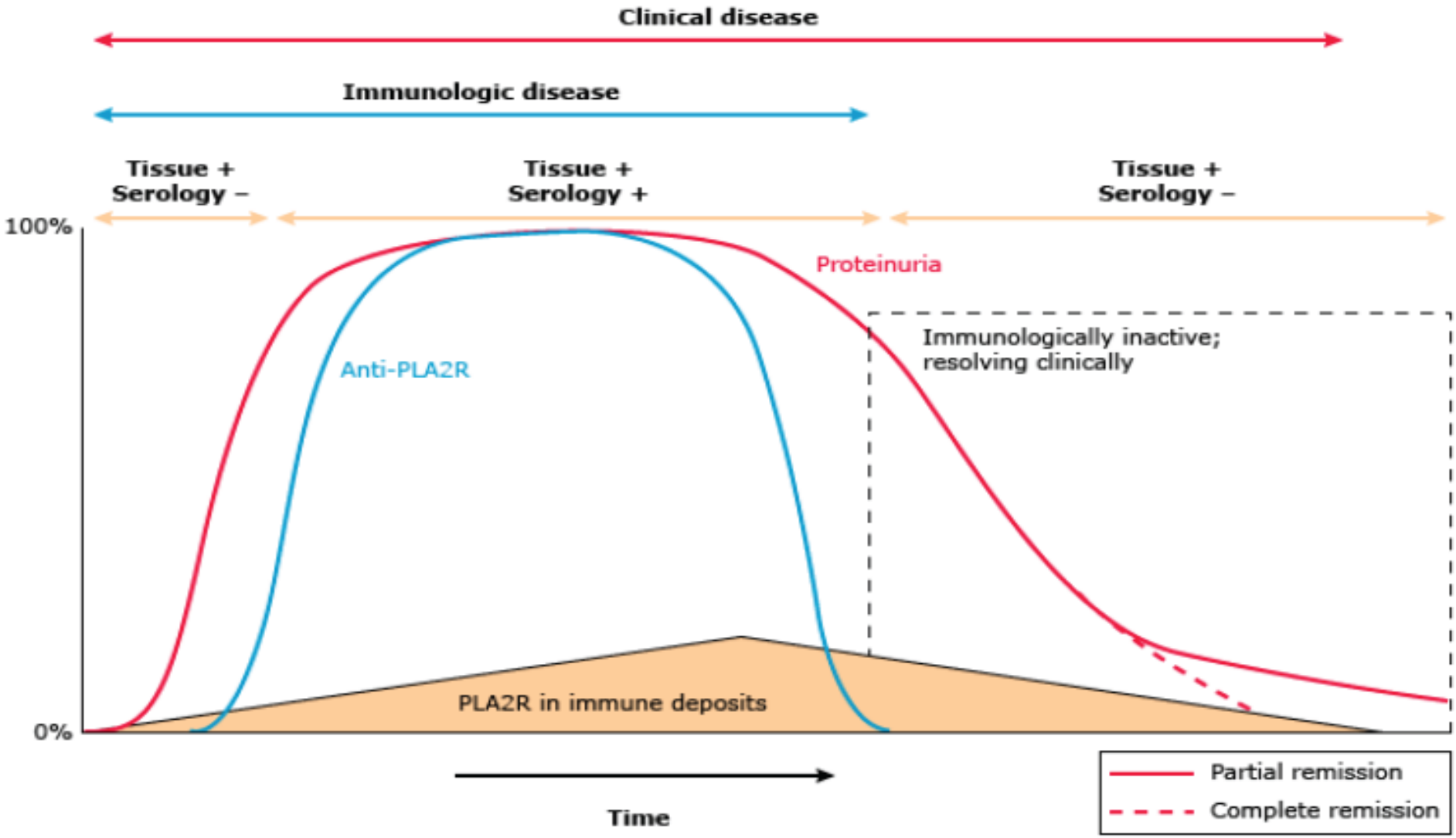


PLA2R staining versus anti-PLA2R versus proteinuria schematic





Schematic representation of the temporal association of serological tests for anti-PLA2R, tissue staining for PLA2R, and clinical activity represented by proteinuria. Note that tissue staining for PLA2R may precede the appearance of circulating anti-PLA2R and persist after the antibodies disappear from circulation. Resolution of proteinuria lags behind immunological remission.

Clinical and translational correlates of circulating levels of anti-PLA2R

Anti-PLA2R antibody is about 80% sensitive and 100%specific for PMN(although rare patients with sarcoid, HBV, HCV, HIV, and cancer have been reported)

Anti-PLA2R antibody can be present for many months before proteinuria appears

In non-nephrotic patients, low, or declining, anti-PLA2R levels predict spontaneous remission and high levels predict progression to nephrotic syndrome

Anti-PLA2R–negative patients can become positive later

High antibody levels (before and after treatment) correlate with proteinuria, response to therapy, and (after therapy) long-term outcomes

Patients with higher antibody levels require more prolonged immunosuppression to achieve remission rates comparable to those with lower levels

Expansion of the specificity of anti-PLA2R antibody to include additional epitopes (epitope spreading) correlates with a worse prognosis

Patients with IgG4 antibody directed only at the cysteine-rich epitope of PLA2R have a higher rate of spontaneous remission

Anti-PLA2R levels go down in remission and return with relapse

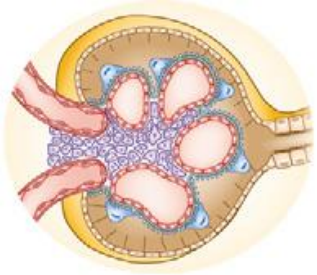
Elevated anti-PLA2R levels after treatment predict relapse

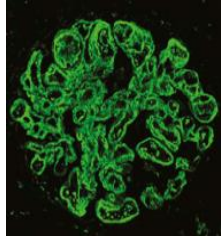
Elevated anti-PLA2R levels at the time of transplantation predict recurrence (especially if DQA1a05:01/05 positive)

Disappearance of anti-PLA2R antibodies (immunologic remission) precedes renal remission (disappearance of proteinuria) by weeks to months

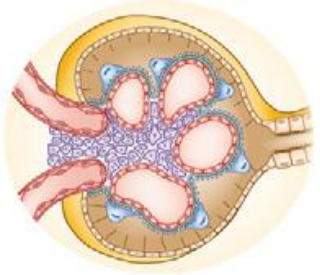
Patients previously positive for anti-PLA2R/THSD7A who become negative will exhibit positive glomerular staining for weeks to months

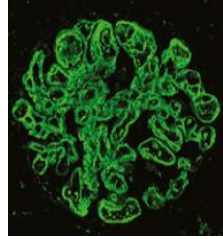
>50% of cases of pediatric PMN are PLA2R-positive

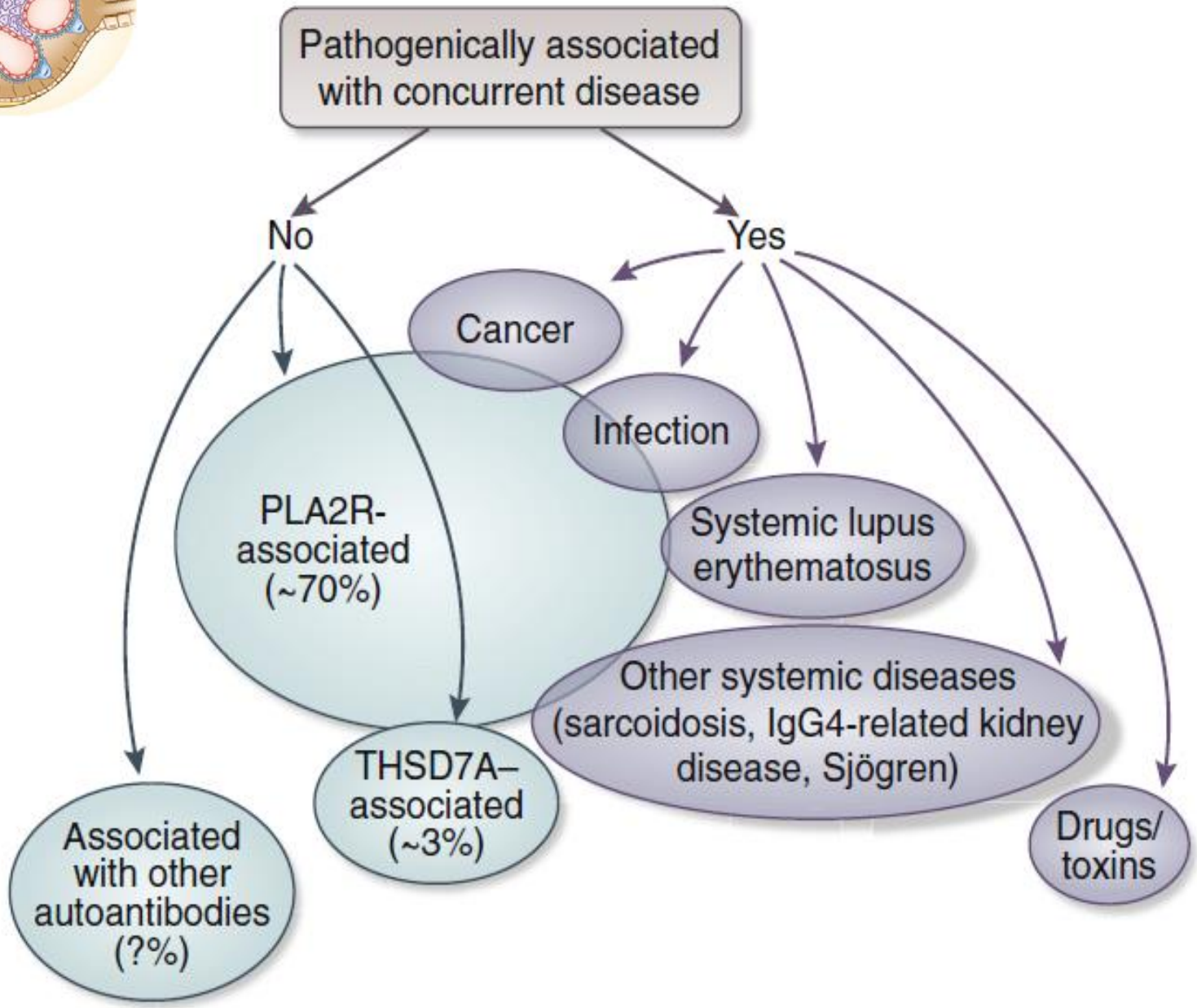




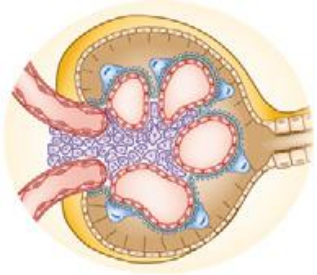
THSD7A, Anti PLA2R and malignancies
Cause or coincident?

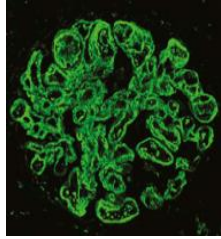






- Presence of such antibodies does not rule out the concurrence of infection, malignancy and does not obviate the need for an infectious work-up and age-appropriate cancer screening
- Detection of anti-PLA2R antibodies in a substantial minority of patients with hepatitis infection or with sarcoidosis
- possible association between THSD7A antibodies and cancer.



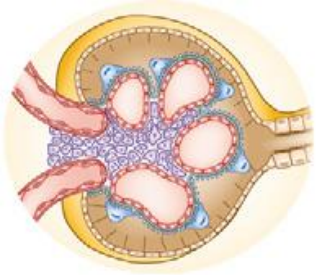


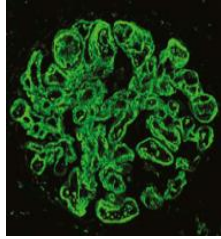
IMMUNOLOGICAL REMISSION IN PLA2R-ANTIBODY– ASSOCIATED MEMBRANOUS NEPHROPATHY IN A KIDNEY TRANSPLANT PATIENT AFTER EXCISION OF BREAST CANCER

Ali Al Azzawi1, Aldo Torres-Ortiz1, Youssef Al hmada1, Wisit Wisit Cheungpasitporn1. 1University of Mississippi Medical Center, Jackson, MS, United States

a case of coexistent PLA2R-positive MN and breast cancer after kidney transplant (KTx), who had immunological remission in PLA2R-Ab and reduction of proteinuria after excision of breast cancer

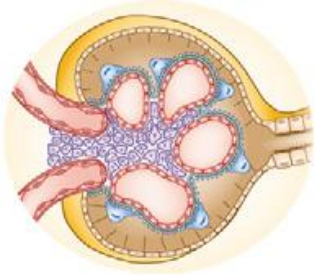
NKF 2019 Spring Clinical Meetings, AJKD Vol 73 | Iss 5 | May 2019

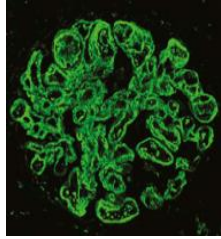




Is serial monitoring of Anti PLA2R antibodies during treatment recommended?

Measuring PLA2R antibodies in patients with a recurrence or worsening of proteinuria should help distinguish between relapse and other causes of proteinuria





Risk factors for progression	Good prognosis
Age	Complete remission of proteinuria
Male sex	Partial remission of proteinuria
Decreased GFR on presentation	Long duration of remission
Increased excretion of some LMW markers such as β2 microglobulin	
Persistent elevated anti-PLA2R or THSD7A levels after therapy	Low anti-PLA2R or THSD7A levels or decreased levels
Anti-PLA2R against CTLD1, CTLD7 domain*	Anti-PLA2R against CysR domain
C3 staining in the biopsy sample	
Increased urinary excretion of C3dg and C5b-9	
Risk alleles*: HLA-DQR1; PLA2R1 HLA-DRB	

*Presence of risk alleles for both HLA and PLA2R raises the risk for PMN up to 79-fold

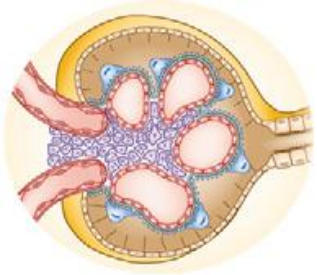
ORIGINAL RESEARCH ARTICLE

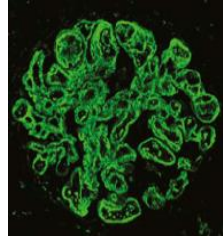
WILEY Journal of Cellular Physiology

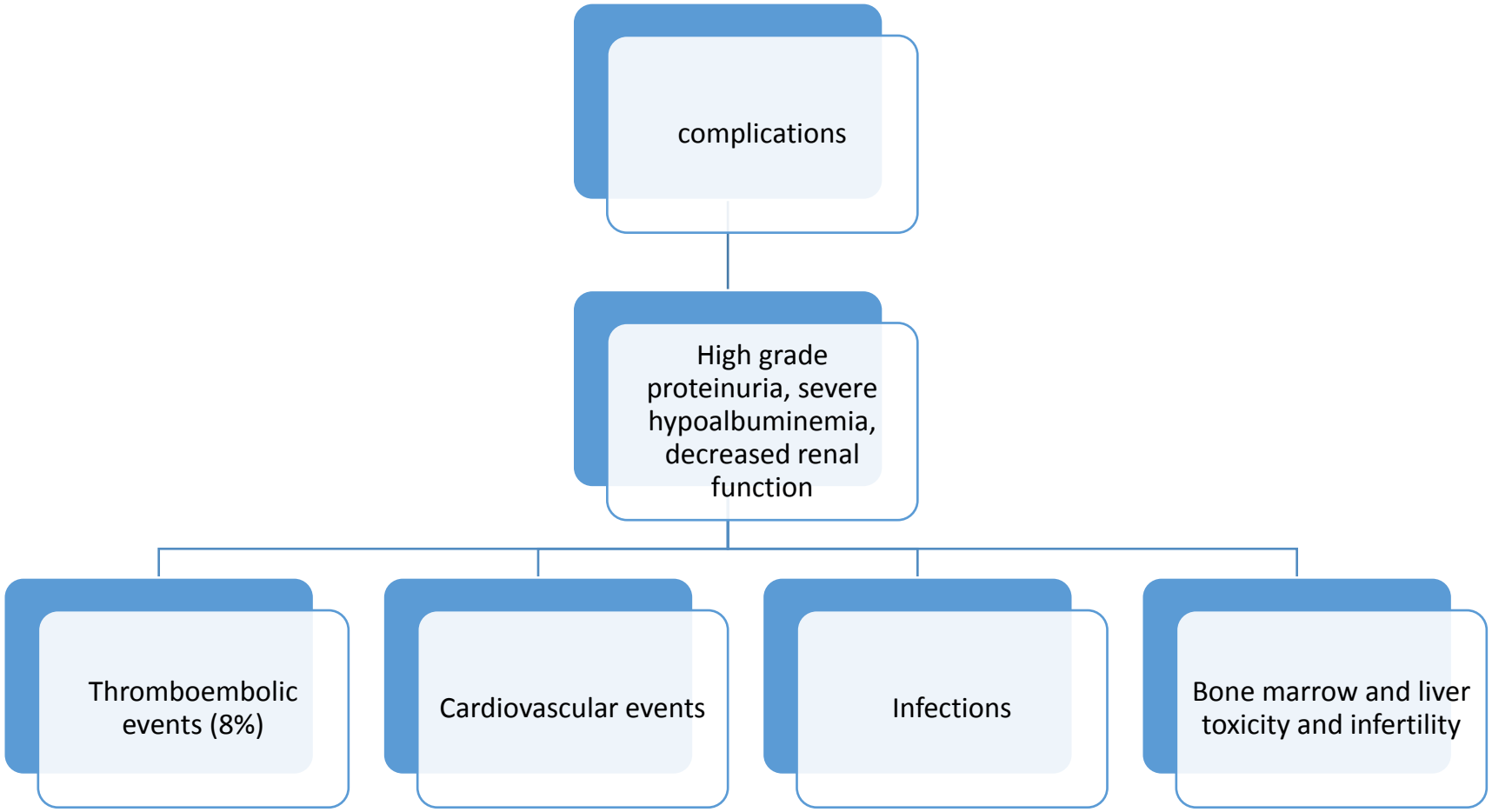
Upregulated microRNAs in membranous glomerulonephropathy are associated with significant downregulation of IL6 and MYC mRNAs

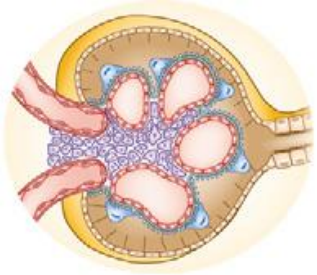
Cristina Barbagallo[1*] | Roberta Passanisi[1,2*] | Federica Mirabella[1] | Matilde Cirnigliaro[1] | Arianna Costanzo[3] | Giovanni Lauretta[1] | Davide Barbagallo[1] | Cristina Bianchi[4] | Fabio Pagni[5] | Sergio Castorina[2,6] | Antonio Granata[7†] | Cinzia Di Pietro[1†] | Marco Ragusa[1,8†] | Lorenzo S. Malatino[3†] | Michele Purrello[1†]

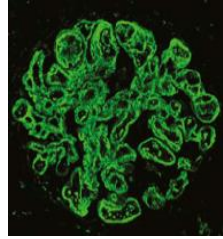
Ten miRNAs (let-7a-5p, let-7b-5p, let-7c-5p, let-7d-5p, miR-107, miR-129-3p, miR-423-5p, miR-516-3p, miR-532-3p, and miR-1275) were differentially expressed (DE) in MGN biopsies compared to unaffected controls

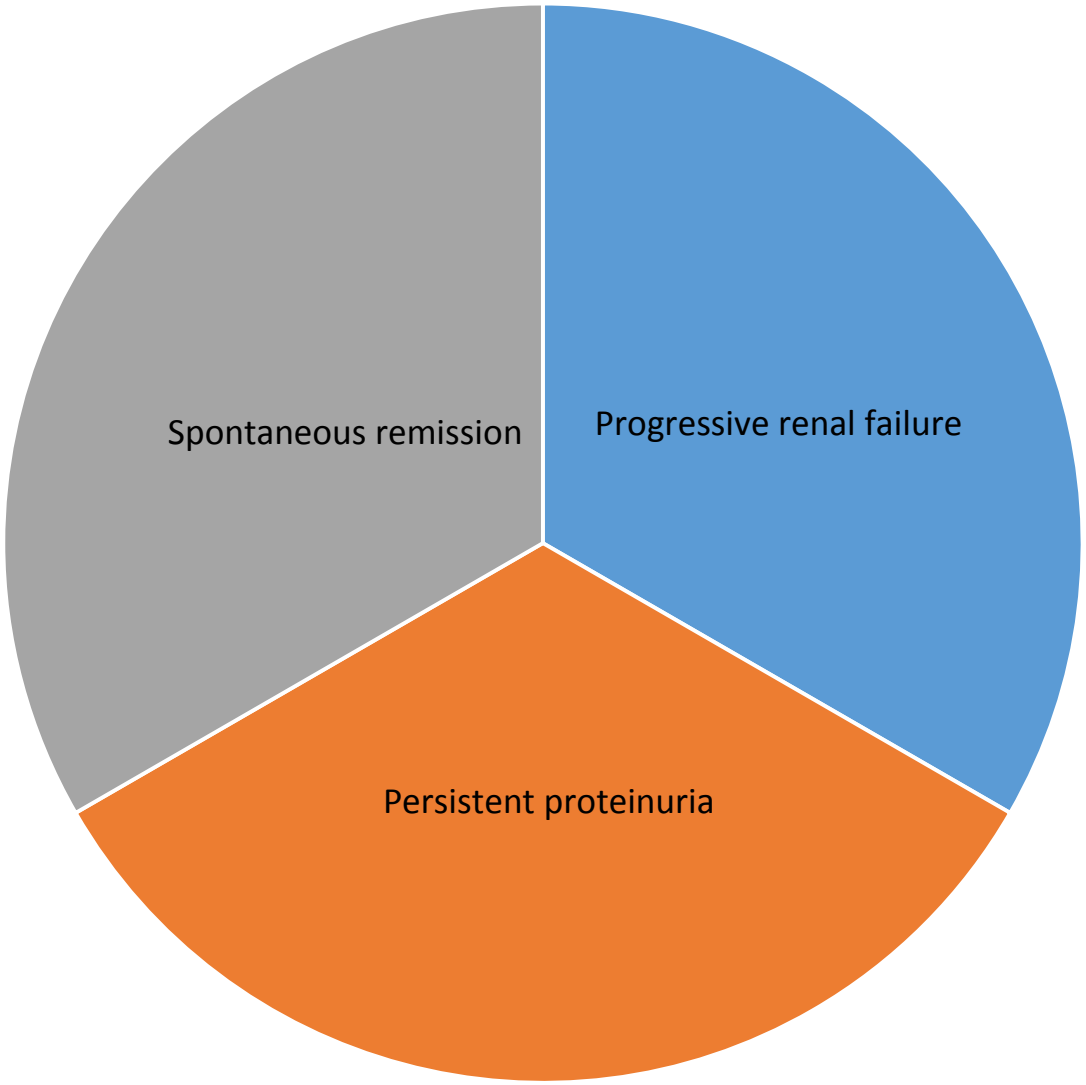




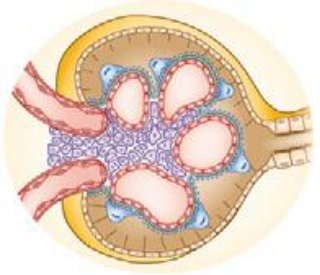

complications
High grade proteinuria, severe hypoalbuminemia, decreased renal function
Thromboembolic events (8%)
Cardiovascular events
Infections
Bone marrow and liver toxicity and infertility

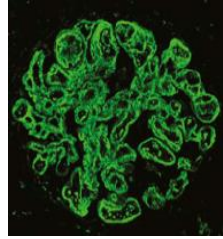




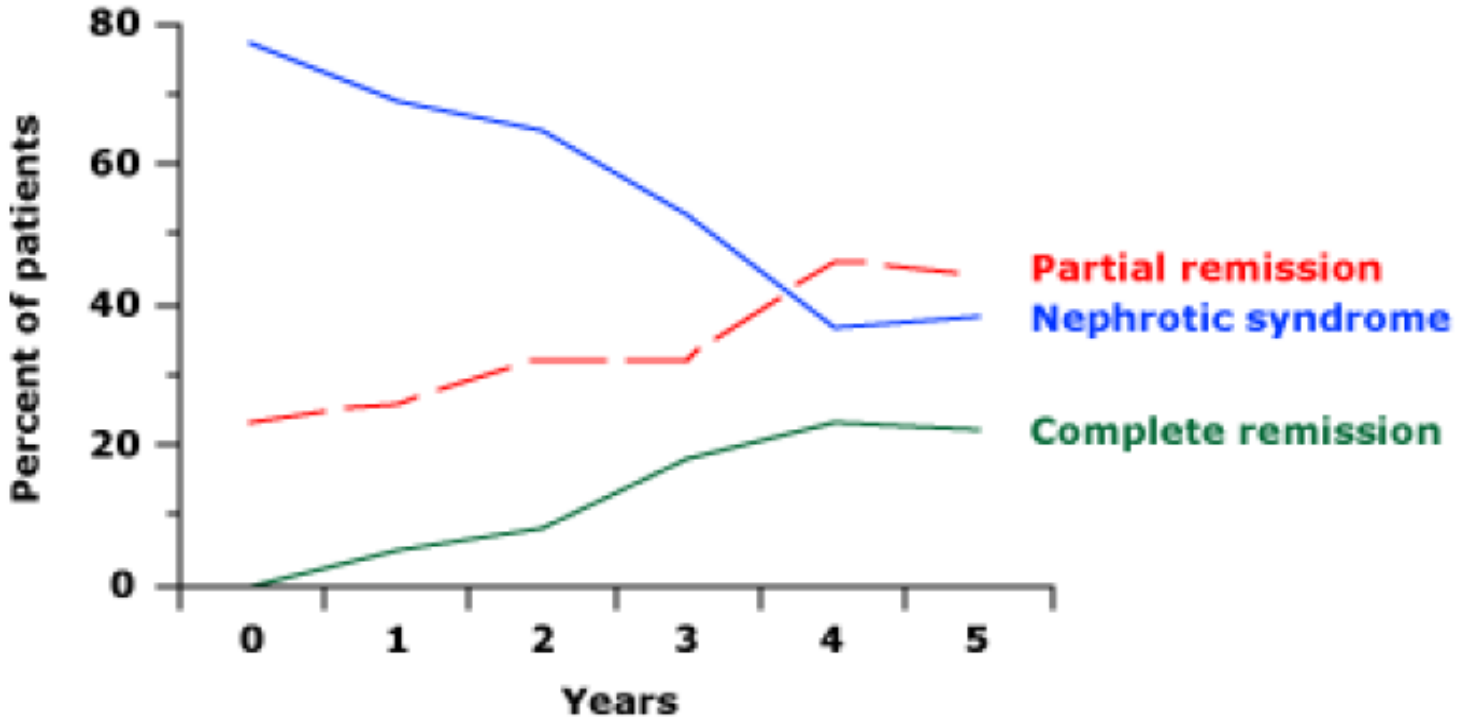


Rule of thirds

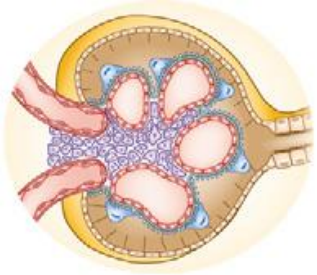




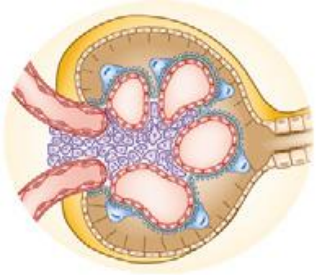
High incidence of remission in untreated membranous nephropathy

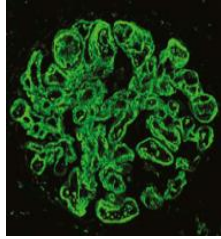


Course of 100 consecutive untreated patients with idiopathic membranous nephropathy. Over a five-year period, there was a progressive increase in the incidence of partial or complete remission, while the incidence of the nephrotic syndrome fell.



Complete remission	• Proteinuria <0.3 g/d
Partial remission	• >50% reduction from baseline • and between 0.3 and 3.5 g/d • stable GFR
No remission	• <50% reduction • Or >3.5 g/d
relapse	Recurrence of >3.5 g/d after remission

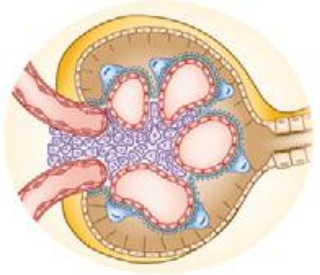




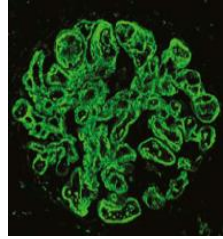
Factors associated with the risk of progressive loss of kidney function in patients with membranous nephropathy

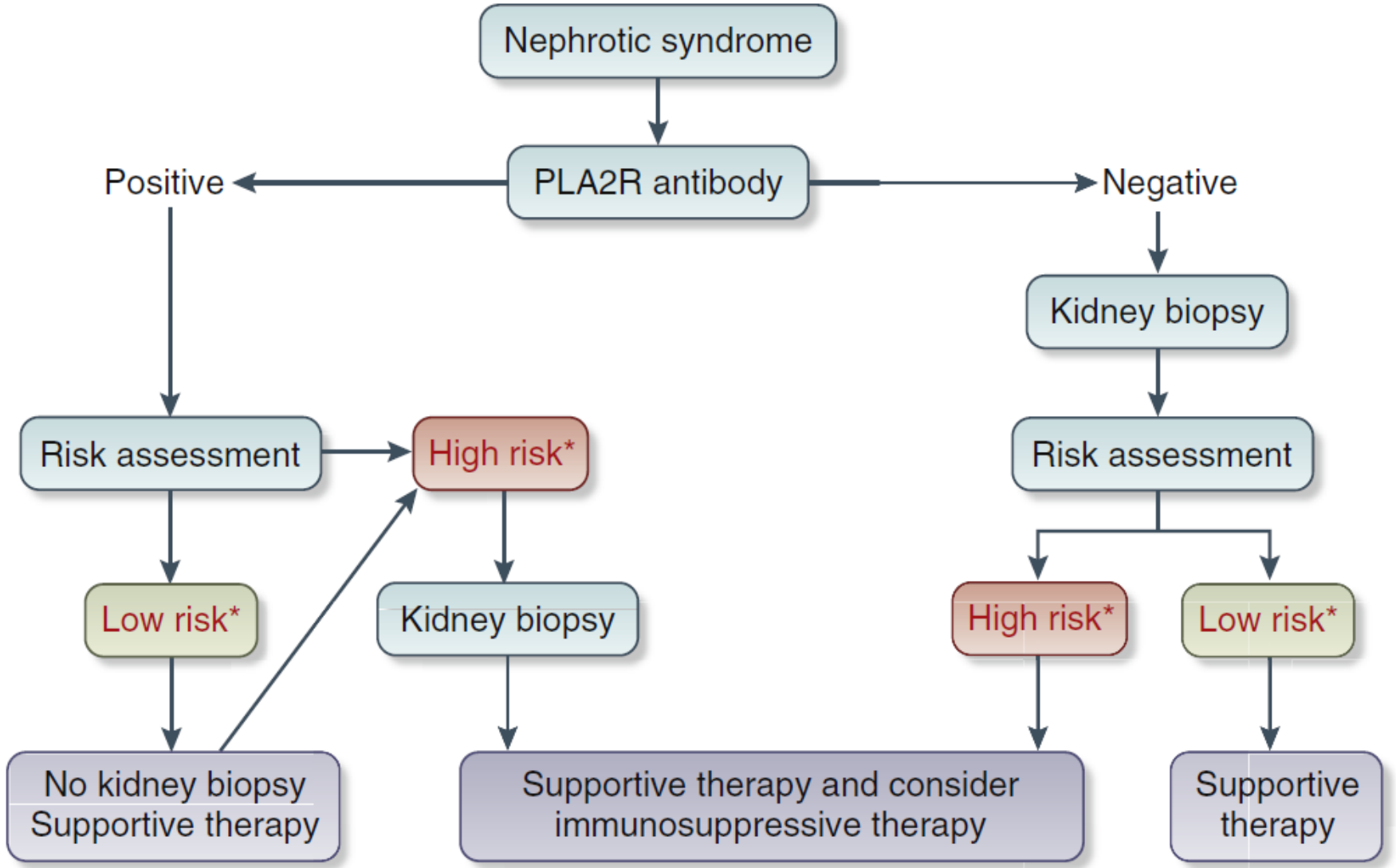
Low risk	High risk
Proteinuria <3.5 g/d	• Serum creatinine >1.5 mg/dl (133 µmol/l) • Decrease in eGFR by ≥ 20% over any time period during the preceding 12 months not explained otherwise[a] • Proteinuria >8 g/d for > 6 mo • Presence of low-molecular-weight proteinuria • Urine IgG > 250 mg/24 h • PLA2R antibody levels and evolution[b]

Kidney International (2019) 95, 268–280



Proposed algorithm for the diagnosis of membranous nephropathy





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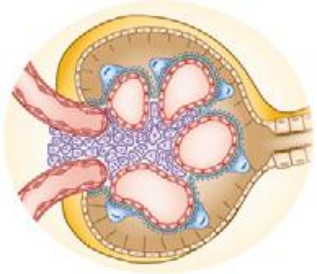
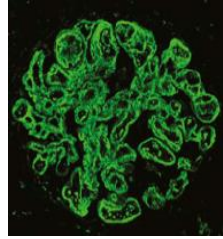


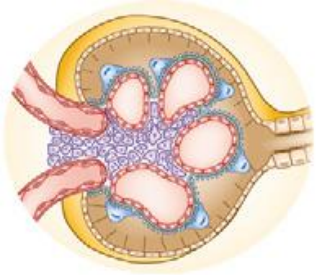


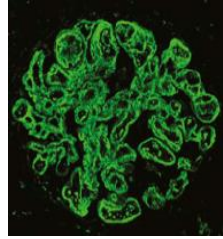
Diagnostic evaluation and treatment of primary membranous nephropathy

Urine protein, GFR, ANA, C3/C4, HBV, HCV, HIV
Serum anti-PLA2R/THSD7A level[1]
Renal biopsy to confirm MN

- Serum anti-PLA2R/THSD7A negative
  - Biopsy stained for PLA2R/THSD7A *negative*
    - Secondary MN[1] (Table 1)
      - Supportive care Treat underlying systemic disease
  - Biopsy stained for PLA2R/THSD7A *positive*
    - Inactive PMN
      - Supportive care Monitor anti-PLA2R and proteinuria monthly
        - Anti-PLA2R turns positive, proteinuria > 3.5 g/day or GFR decreasing
- Serum anti-PLA2R/THSD7A positive
  - Active PMN
    - Proteinuria < 3.5 g/day
      - Supportive care Monitor anti-PLA2R and proteinuria monthly
    - Proteinuria > 3.5 g/day
      - Initiate IST Monitor anti-PLA2R/THSD7A
        - Anti-PLA2R negative
          - Discontinue or taper IST
        - Anti-PLA2R positive (6 months)
          - If decreasing, maintain IST. If stable or rising, change IST

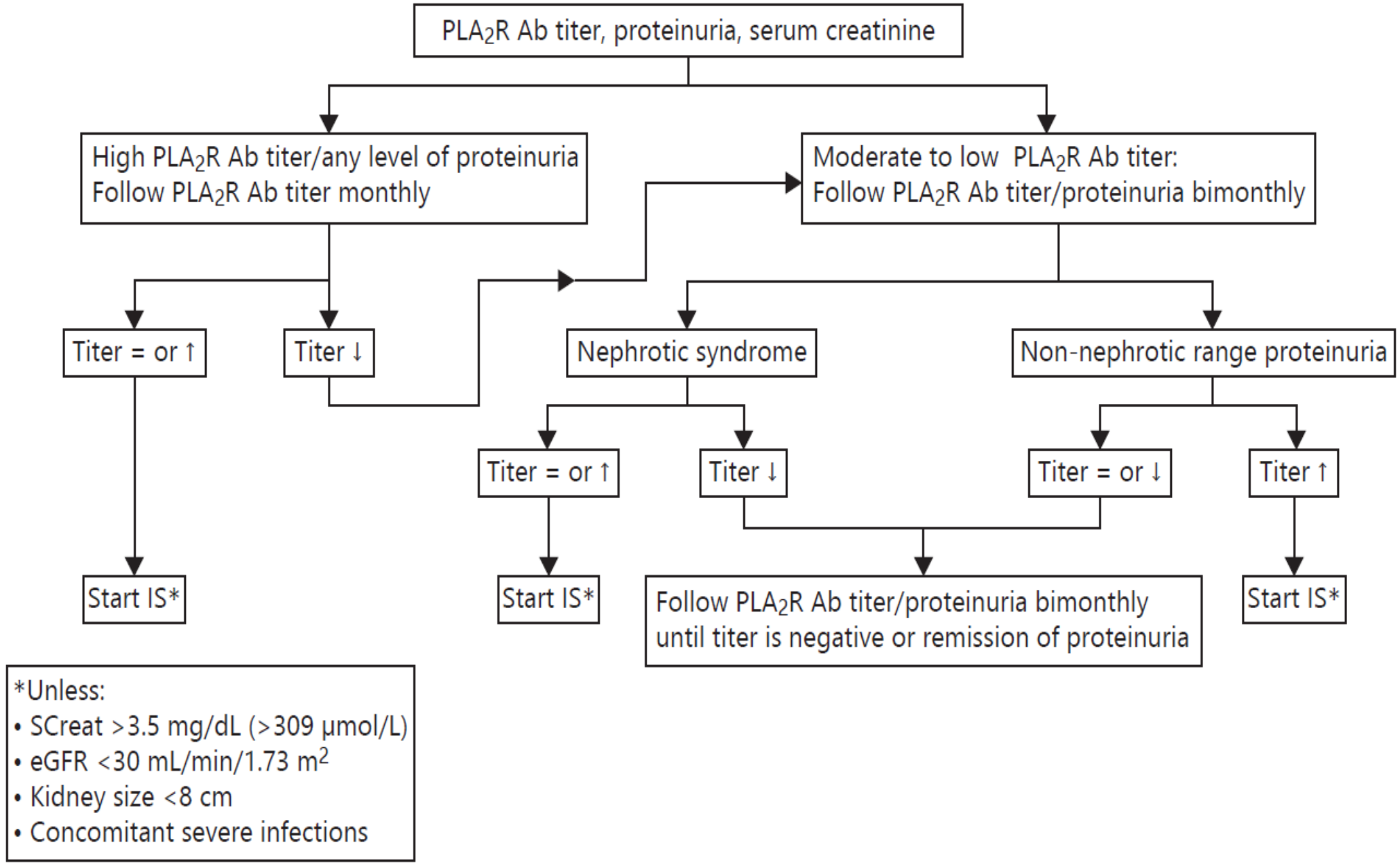
Clin J Am Soc Nephrol 12: 983–997, June, 2017

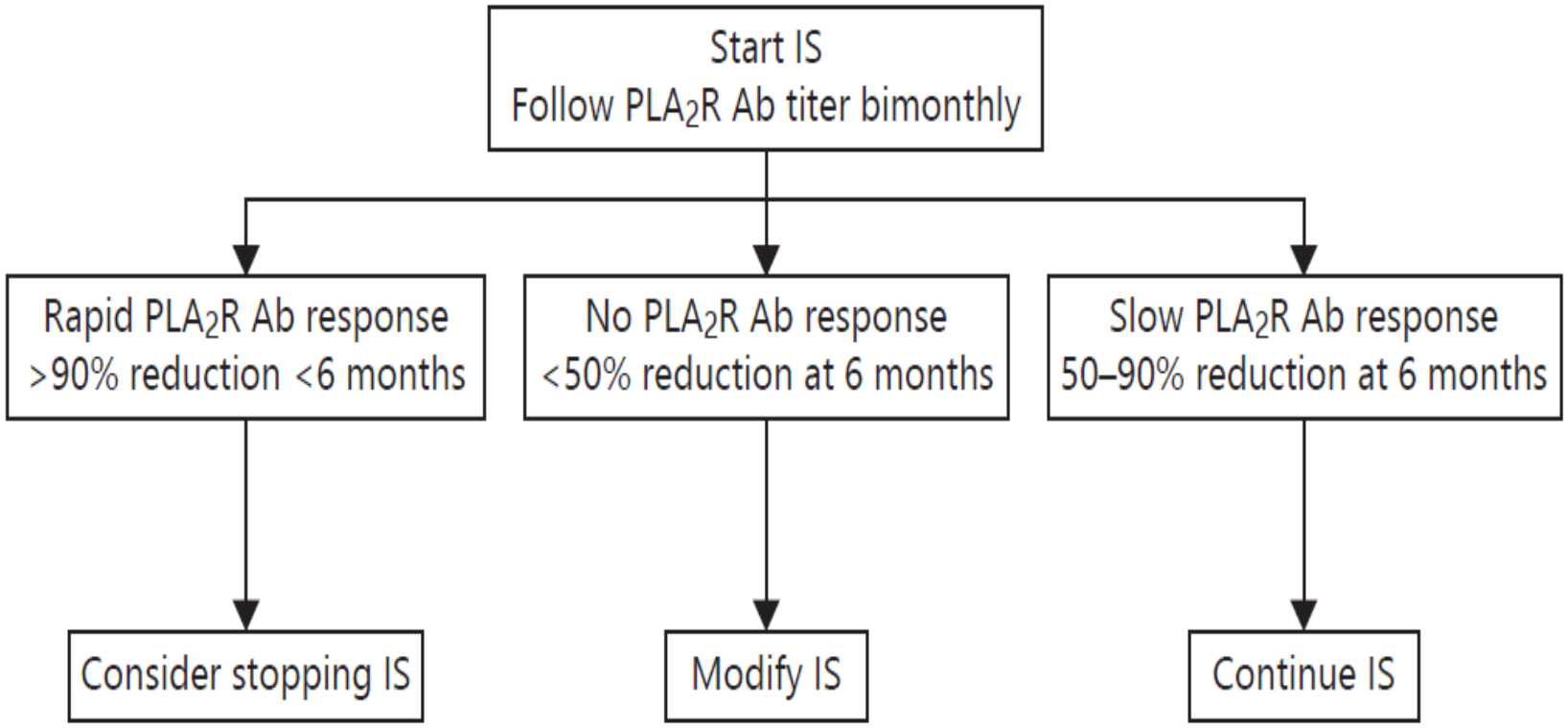




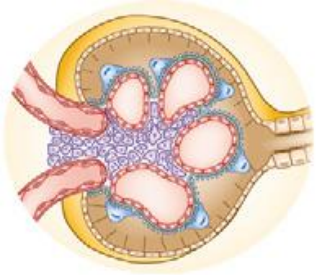
Treatment of MN

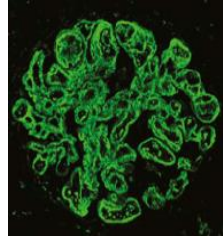
Upr<4 g/day Nl RF Low PLA2R Ab	Upr 4-8 g/day more than Nl or near nl RF Mild PLA2R Ab No symptom	Low RF or decrease RF High PLA2R Ab Nephrotic syndrome and sign
Supportive care Assessment of Upr and Cr every 3 month then twice a year	Supportive care Immunosuppressive therapy (Upr >4 gr/day after 6 months)	Supportive care Immunosuppressive therapy (Upr>8 g/day after 3 month)


PLA2R Ab titer, proteinuria, serum creatinine
High PLA2R Ab titer/any level of proteinuria
Follow PLA2R Ab titer monthly
Moderate to low PLA2R Ab titer:
Follow PLA2R Ab titer/proteinuria bimonthly
Titer = or ↑
Titer ↓
Nephrotic syndrome
Non-nephrotic range proteinuria
Titer = or ↑
Titer ↓
Titer = or ↓
Titer ↑
Start IS*
Start IS*
Follow PLA2R Ab titer/proteinuria bimonthly
until titer is negative or remission of proteinuria
Start IS*
*Unless:
• SCreat >3.5 mg/dL (>309 µmol/L)
• eGFR <30 mL/min/1.73 m2
• Kidney size <8 cm
• Concomitant severe infections



Am J Nephrol 2018;47(suppl 1):30–42



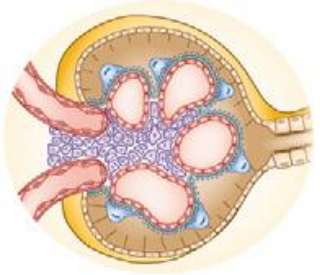


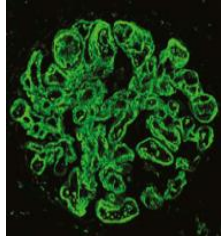
The Remission Clinic protocol

- Low sodium diet with or without diuretics and protein intake 0.8–1.0 mg/kg per day
- Dual renin–angiotensin system blockade with maximum tolerated doses of ACEIs and ARBs

  Start and up-titrate an ACEI (or ARB)

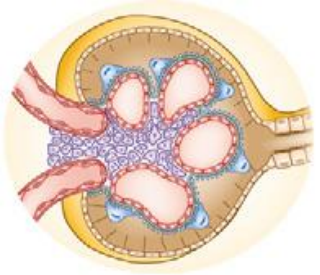
  Start and up-titrate an ARB (or ACEI)
- Start and up-titrate other antihypertensive agents to achieve the maximum tolerated reduction in blood pressure (consider dihydropyridine calcium-channel blockers as a last resort)
- Add a lipid-lowering agent

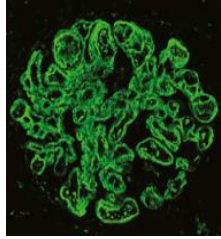




Treatment of membranous nephropathy, conventional immunosuppressive protocol

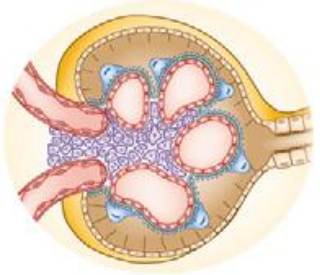
Regimen	Drug	Dose	Schedule
Alkylating agents plus steroid combination therapy[‡]			
Chlorambucil cyclical therapy	Chlorambucil	0.2 mg/kg per day	Months 2, 4, and 6
	Prednisolone	0.5 mg/kg per day	Months 1, 3, and 5
	Methylprednisolone	1 g IV	Three consecutive days at start of months 1, 3, and 5
Cyclophosphamide cyclical therapy	Cyclophosphamide	2.5 mg/kg per day[§]	Months 2, 4, and 6
	Prednisolone	0.5 mg/kg per day	Months 1, 3, and 5
	Methylprednisolone	1 g IV	Three consecutive days at start of months 1, 3, and 5
Cyclophosphamide daily therapy	Cyclophosphamide	1.5 mg/kg per day	Months 1–6[‖]
	Prednisolone	0.5 mg/kg every second day	Months 1–5, then taper dose to stop in 6–8 weeks
	Methylprednisolone	1 g IV	Three consecutive days at start of months 1, 3, and 5

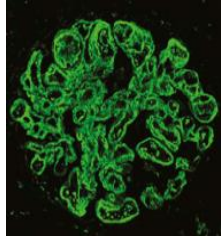




Calcineurin inhibition therapy[¶]			
Ciclosporin regimen	Ciclosporin	Initial dose 3.5 mg/kg per day, trough level 125–225 µg/l	Months 1–6, then taper dose by 25% each month; continue treatment at 50% of dose until 12 months, then taper to lowest possible maintenance dose[#]
	Prednisolone**	0.15 mg/kg per day	Months 1–6, then taper dose (maximum of 15 mg)
Tacrolimus regimen	Tacrolimus	Initial dose 0.05 mg/kg per day, achieve trough level 3–5 ng/l; if remission is not achieved after 2 months, increase to 5–8 ng/l	Months 1–12, then taper to lowest possible maintenance dose[‖]
	Prednisolone**	0.15 mg/kg per day	Months 1–6, then taper dose (maximum of 15 mg)

Nature review, nephrology, 13(563-579), September 2017

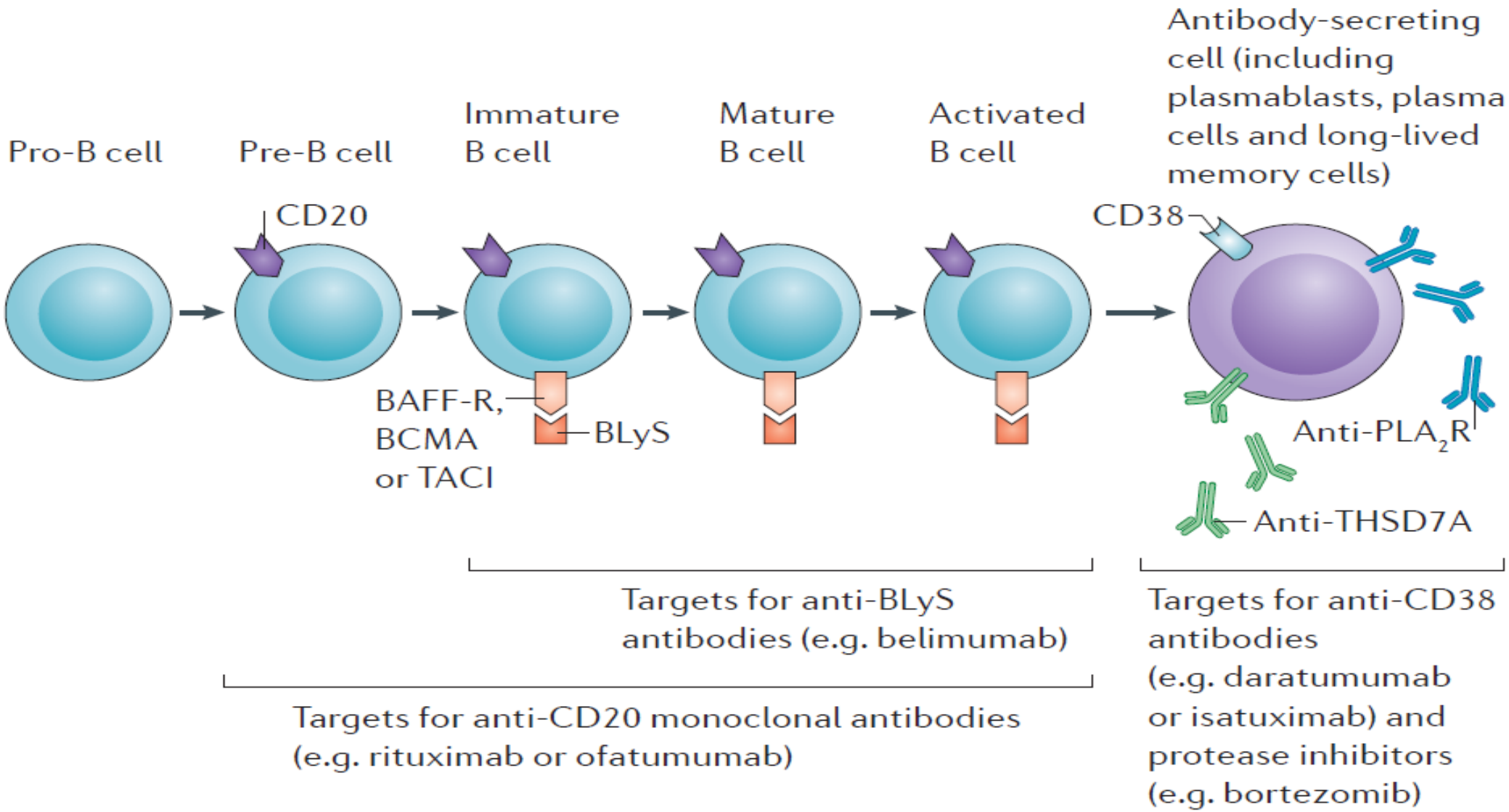




Target	Drug	Dose	Schedule
Anti-CD20 monoclonal antibodies*	Rituximab	• 375 mg/m² intravenously • 375 mg/m² intravenously • 1,000 mg intravenously	• Every week for 4 weeks • B cell-driven treatment‡ • Days 1 and 15
	Ofatumumab	300 mg intravenously	B cell-driven treatment‡
Anti-BLyS monoclonal antibodies§	Belimumab	10 mg/kg intravenously	• Every 4 weeks (if urinary protein:creatinine ratio <1,000 mg/mmol) • Every 2 weeks (if urinary protein:creatinine ratio >1,000 mg/mmol)
Plasma cell-targeted protocols (proteasome inhibitors‖)	Bortezomib	1.3 mg/m² subcutaneously	Four doses over 2 weeks

A second 375 mg/m2 dose of rituximab or a second dose of 300 mg of ofatumumab are administered 1 week after the first infusion if >5 circulating B cells per mm3 remain

Nature review, nephrology, 13(563-579), September 2017



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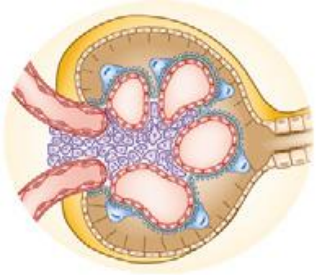
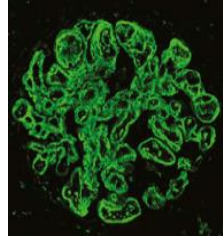
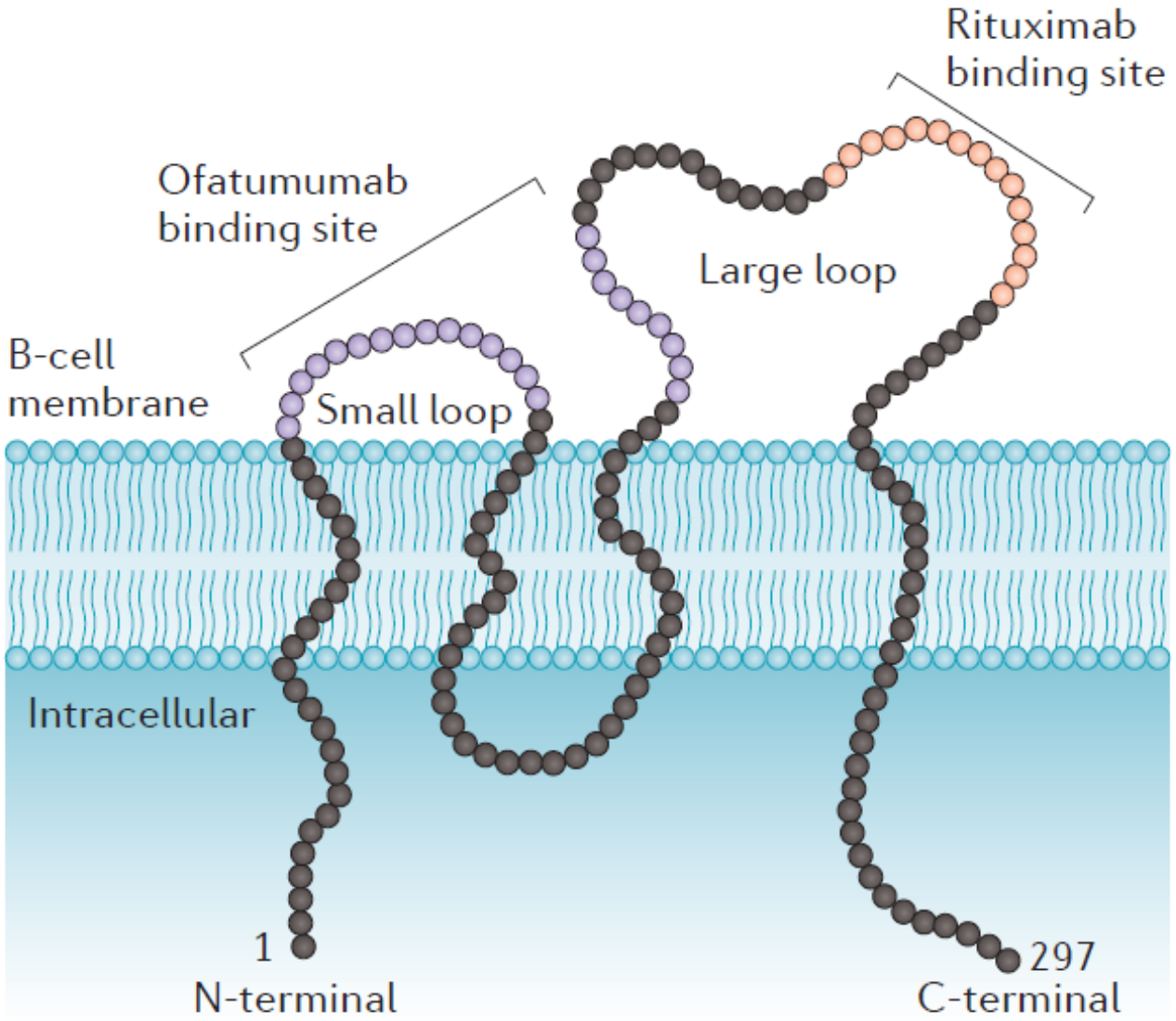




The molecular configuration of the CD20 molecule



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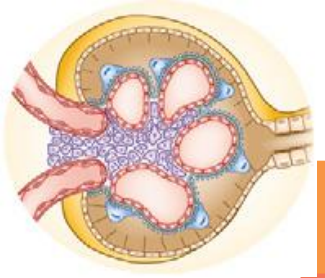
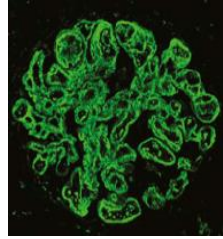




NEPHROLOGY

APSN

Nephrology **21** (2016) 139–146

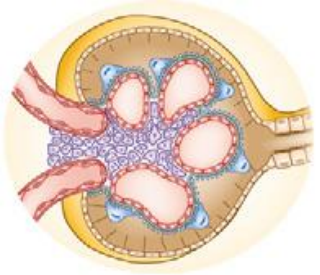
Original Article

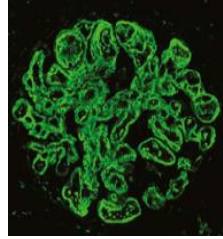
Tacrolimus combined with corticosteroids versus Modified Ponticelli regimen in treatment of idiopathic membranous nephropathy: Randomized control trial

RAJA RAMACHANDRAN,[1] HARSHA KUMAR HN,[1] VINOD KUMAR,[1] RITAMBHRA NADA,[2] ASHOK KUMAR YADAV,[1] AJAY GOYAL,[1] VIVEK KUMAR,[1] MANISH RATHI,[1] VIVEKANAND JHA,[1] KRISHAN LAL GUPTA,[1] VINAY SAKHUJA[1] and HARBIR SINGH KOHLI[1]

Departments of [1]Nephrology and [2]Histopathology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Both TAC and MPR are comparable in induction remission, but with different adverse effect profile and with higher relapse rate





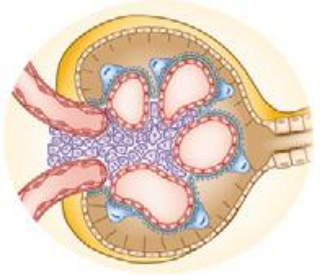
Safety of Rituximab Compared with Steroids and Cyclophosphamide for Idiopathic Membranous Nephropathy

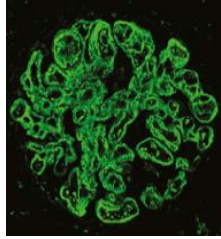
Jan A.J.G. van den Brand,* Piero Ruggenenti,[†‡] Antonietta Chianca,[‡] Julia M. Hofstra,* Annalisa Perna,[‡] Barbara Ruggiero,[‡] Jack F.M. Wetzels,* and Giuseppe Remuzzi[†‡]

*Department of Nephrology, Radboud University Medical Center, Nijmegen, The Netherlands; [†]Unit of Nephrology, Azienda Socio Sanitaria Territoriale Ospedale Papa Giovanni XXIII, Bergamo, Italy; and [‡]IRCCS - Instituto di Ricerche Farmacologiche "Mario Negri", Department of Renal Medicine, Clinical Research Center for Rare Diseases "Ado e Cele Daccò", Ranica, Bergamo, Italy

Rituximab (RTX) may be a safer alternative, lower partial remission rates with rituximab versus cyclophosphamide, rates of complete remission and the composite renal end point did not differ significantly between groups

J Am Soc Nephrol 28: 2729–2737, 2017



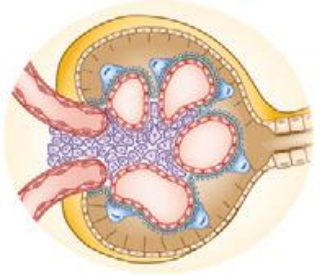


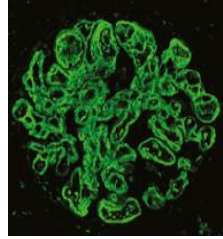
Rituximab for Severe Membranous Nephropathy: A 6-Month Trial with Extended Follow-Up

Karine Dahan,* Hanna Debiec,[†‡] Emmanuelle Plaisier,*[†‡] Marine Cachanado,[§] Alexandra Rousseau,[§] Laura Wakselman,[§] Pierre-Antoine Michel,* Fabrice Mihout,* Bertrand Dussol,[‖] Marie Matignon,[¶] Christiane Mousson,** Tabassome Simon,[§] and Pierre Ronco,*[†‡] on behalf of the GEMRITUX Study Group

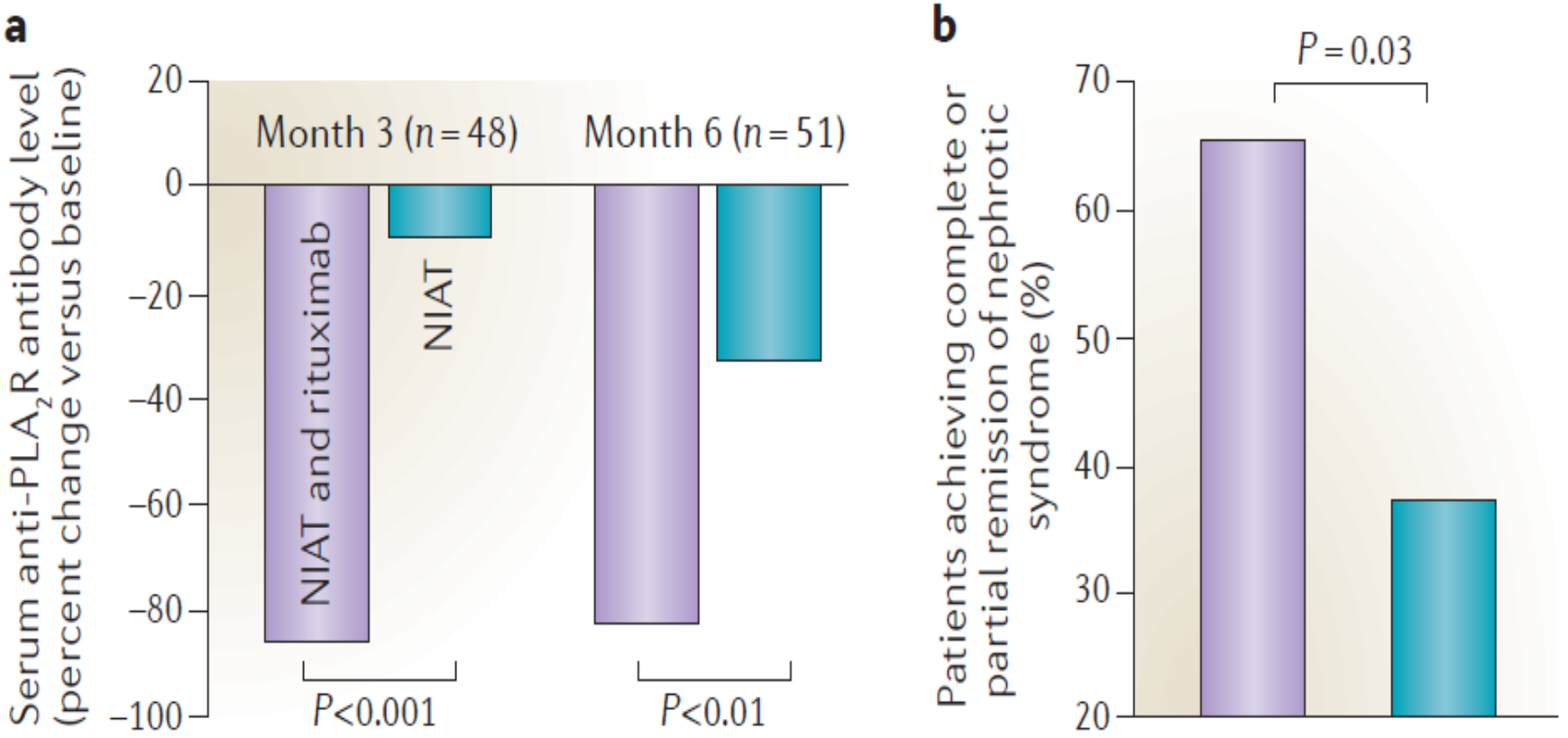
*Department of Nephrology and Dialysis, Assistance Publique Hôpitaux de Paris, Hôpital Tenon, Paris, France; [†]Sorbonne Universités, Université Pierre et Marie Curie Paris 06, Paris, France; [‡]Institut National de la Santé et de la Recherche Médicale, Unité Mixte de Recherche 1155, Paris, France; [§]Department of Clinical Pharmacology and Unité de Recherche Clinique, Assistance Publique Hôpitaux de Paris, Hôpital Saint Antoine, Paris, France; [‖]Department of Nephrology and Transplantation, Assistance Publique-Hôpitaux de Marseille, Hôpital de la Timone, Marseille, France; [¶]Department of Nephrology and Transplantation, Assistance Publique Hôpitaux de Paris, Hôpital Henri Mondor, Creteil, France; and **Department of Nephrology and Transplantation, Centre Hospitalier Universitaire, Dijon, France

J Am Soc Nephrol 28: 348–358, 2017

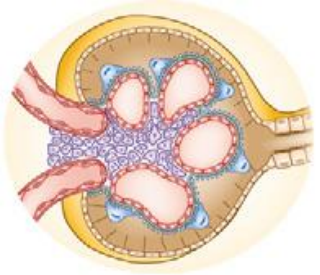


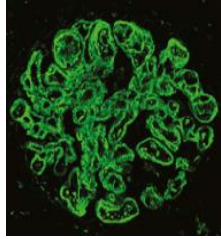


Key findings from the GEMRITUX trial



Nature review, nephrology, 13(563-579), September 2017

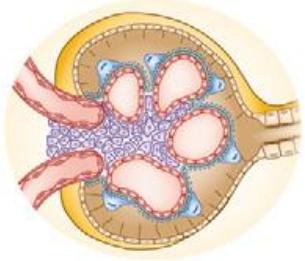


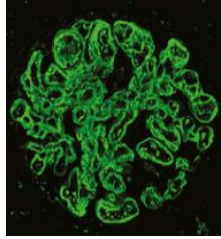


A European multicentre and open-label controlled randomized trial to evaluate the efficacy of Sequential treatment with TAcrolimus–Rituximab versus steroids plus cyclophosphamide in patients with primary MEmbranous Nephropathy: the STARMEN study

Jorge Rojas-Rivera[1,2], Gema Fernández-Juárez[2,3], Alberto Ortiz[1,2], Julia Hofstra[4], Loreto Gesualdo[5], Vladimir Tesar[6], Jack Wetzels[4], Alfons Segarra[2,7], Jesus Egido[1], and Manuel Praga[2,8], on behalf of the STARMEN Investigators

Clinical Kidney Journal, 2015, vol. 8, no. 5, 503–510

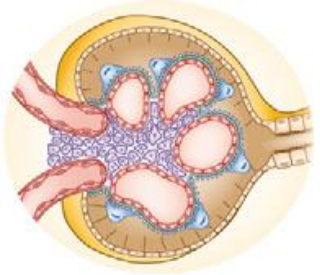


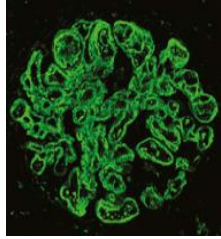


A Multicenter Randomized Controlled Trial of Rituximab versus Cyclosporine in the Treatment of Idiopathic Membranous Nephropathy (MENTOR)

Fernando C. Fervenza[a] Pietro A. Canetta[b] Sean J. Barbour[c] Richard A. Lafayette[d]
Brad H. Rovin[e] Nabeel Aslam[f] Michelle A. Hladunewich[g] Maria V. Irazabal[a]
Sanjeev Sethi[h] Debbie S. Gipson[i] Heather N. Reich[g] Paul Brenchley[j]
Matthias Kretzler[k] Jai Radhakrishnan[b] Lee A. Hebert[e] Patrick E. Gipson[i]
Leslie F. Thomas[l] Ellen T. McCarthy[m] Gerald B. Appel[b] J. Ashley Jefferson[n]
Alfonso Eirin[a] John C. Lieske[a] Marie C. Hogan[a] Eddie L. Greene[a] John J. Dillon[a]
Nelson Leung[a] John R. Sedor[o] Dana V. Rizk[p] Samuel S. Blumenthal[q] Lada B. Lasic[r]
Luis A. Juncos[s] Dollie F. Green[t] James Simon[u] Amy N. Sussman[v] David Philibert[w]
Daniel C. Cattran[g] for the Mentor Consortium group

Nephron 2015;130:159–168





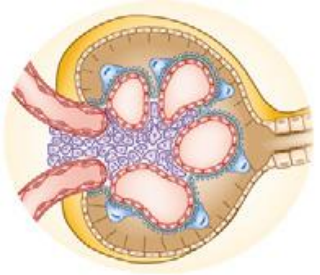
ORIGINAL ARTICLE

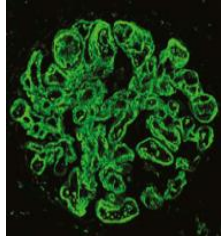
Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy

F.C. Fervenza, G.B. Appel, S.J. Barbour, B.H. Rovin, R.A. Lafayette, N. Aslam, J.A. Jefferson, P.E. Gipson, D.V. Rizk, J.R. Sedor, J.F. Simon, E.T. McCarthy, P. Brenchley, S. Sethi, C. Avila-Casado, H. Beanlands, J.C. Lieske, D. Philibert, T. Li, L.F. Thomas, D.F. Green, L.A. Juncos, L. Beara-Lasic, S.S. Blumenthal, A.N. Sussman, S.B. Erickson, M. Hladunewich, P.A. Canetta, L.A. Hebert, N. Leung, J. Radhakrishnan, H.N. Reich, S.V. Parikh, D.S. Gipson, D.K. Lee, B.R. da Costa, P. Jüni, and D.C. Cattran, for the MENTOR Investigators

Rituximab was non inferior to cyclosporine in inducing complete or partial remission of proteinuria at 12 months and was superior in maintaining proteinuria remission up to 24 months.

n engl j med 381;1 nejm.org July 4, 2019





Evaluation Time Point	Rituximab (N=65)	Cyclosporine (N=65)	Risk Difference (95% CI)	P Value for Noninferiority	P Value for Superiority
	no. with complete or partial remission (%)		*percentage points*		
End of treatment period at 12 mo	39 (60)	34 (52)	8 (−9 to 25)	0.004	—
End of follow-up at 24 mo	39 (60)	13 (20)	40 (25 to 55)	<0.001	<0.001

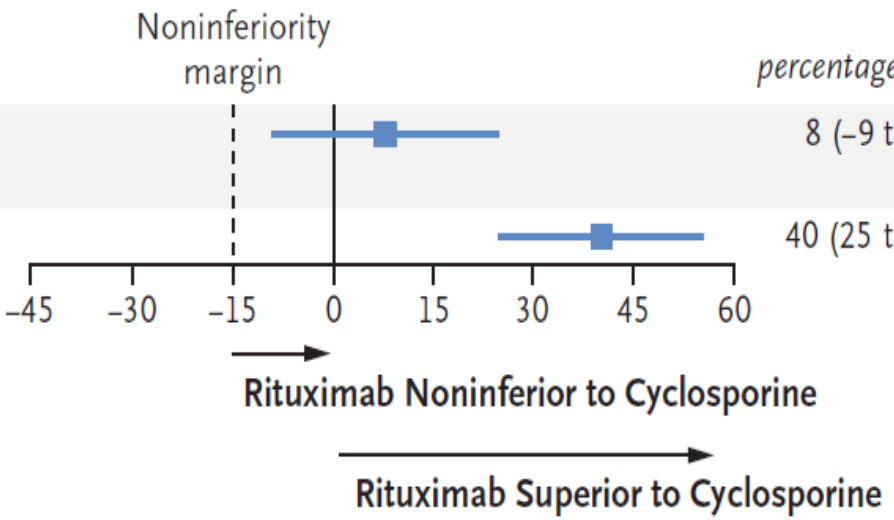
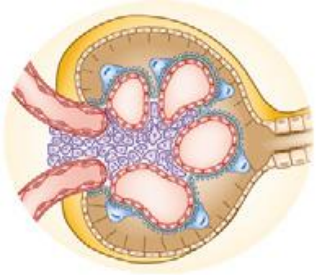
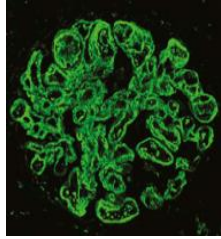


Figure 1. Composite Outcome of Complete or Partial Remission at 12 and 24 Months.



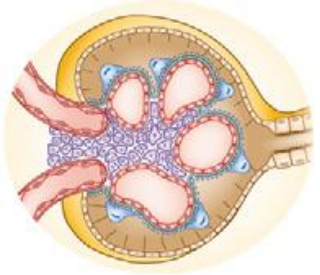


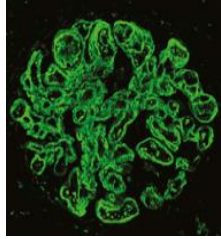
A pilot study to determine the dose and effectiveness of adrenocorticotrophic hormone (H.P. Acthar® Gel) in nephrotic syndrome due to idiopathic membranous nephropathy

Michelle A. Hladunewich[1], Daniel Cattran[1], Laurence H. Beck[2], Ayodele Odutayo[1], Sanjeev Sethi[3], Rivka Ayalon[2], Nelson Leung[4], Heather Reich[1] and Fernando C. Fervenza[4]

[1]Division of Nephrology, University of Toronto for the Toronto Glomerulonephritis Registry, Toronto, ON, Canada, [2]Division of Nephrology, Boston University School of Medicine, Boston, MA, USA, [3]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA and [4]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA

Nephrol Dial Transplant (2014) 29: 1570–1577



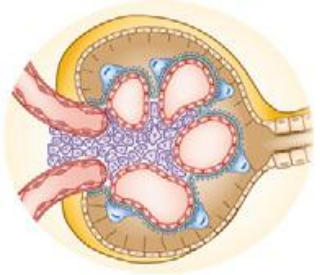


Synthetic ACTH in High Risk Patients with Idiopathic Membranous Nephropathy: A Prospective, Open Label Cohort Study

Anne-Els van de Logt[1] *, Charles H. Beerenhout[2], Hans S. Brink[3], Jos J. van de Kerkhof[4], Jack F. Wetzels[1], Julia M. Hofstra[1]

1 Radboud university medical center, Radboud Institute for Health Sciences, Department of Nephrology, Nijmegen, The Netherlands, **2** Maxima medical center, Department of Internal Medicine, Veldhoven, The Netherlands, **3** Medisch Spectrum Twente, Department of Internal Medicine, Enschede, The Netherlands, **4** Bernhoven Hospital, Department of Internal Medicine, Uden, The Netherlands

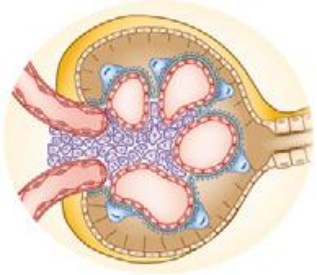
PLOS ONE | journal.pone.0142033 November 12, 2015

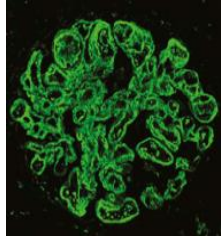


ACTH (corticotrophin) therapy in resistant primary membranous nephropathy

- ACTH therapy to 11 patients who had failed treatment with other IS treatments
- corticotrophin 40 IU subcutaneous twice a week for 6 months
- >50% reduction in proteinuria
- 2 patients who developed excessive fluid retention and infection

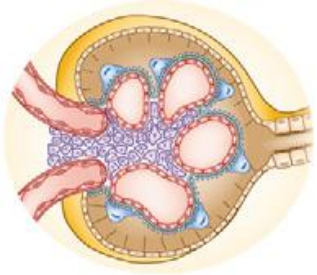
Kidney International (2019) 96, 245–251 251

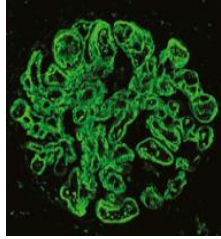




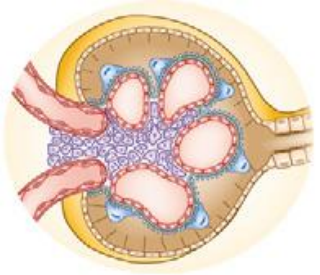
When to stop IS therapy?

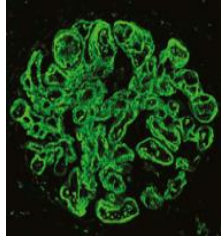
Apart from small kidney size there is no other threshold for which treatment is deemed futile even patients with eGFR <30 ml/min/1.73 m2





MN after kidney transplantation
Cumulative risk of disease recurrence: 50-60% over 6 years , 30-35% during first year
If proteinuria > 1000 mg, treatment with rituximab
Persistent anti-PLA2R antibodies prior to kidney transplantation are associated with an increased risk of recurrence of membranous nephropathy in the allograft
Giving rituximab several months before transplantation: could prevent recurrence
Early diagnosis and early B-cell targeting therapy
Anti-PLA2R–negative de novo MN, affecting about 2% of all renal transplant recipients





EARLY TREATMENT WITH RITUXIMAB IN RECURRENT MEMBRANOUS NEPHROPATHY AFTER KIDNEY TRANSPLANT:

Nikhil Agrawal1, Sreedhar Adapa2, Venu Madhav Konala3, Hemant Dhingra2, Martha Pavlakis1. 1Beth Israel Deaconess Medical Center, Boston, MA, United States; 2The Nephrology Group, Fresno, CA, United States; 3Ashland Bellefonte Cancer Center, Ashland, KY, United States

Treatment with rituximab early in the disease course appears to be effective and perhaps necessary given less likelihood of spontaneous remission

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