GEM idiopathiques et secondaires: des mystères élucidés

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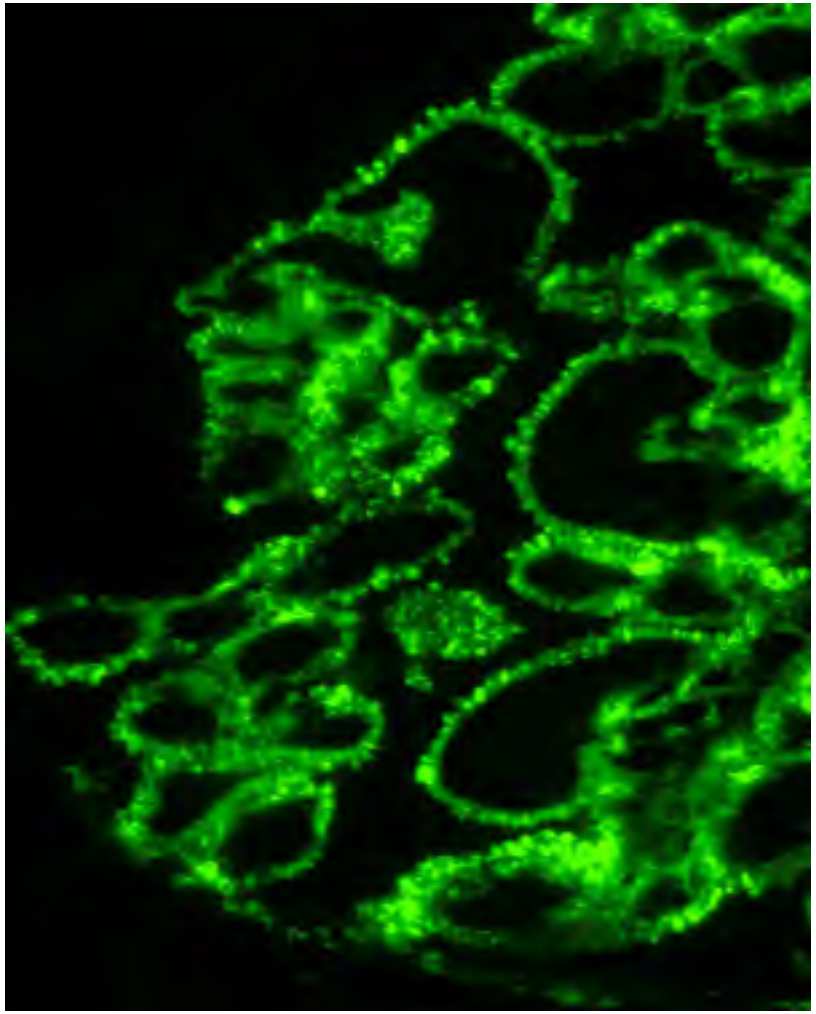
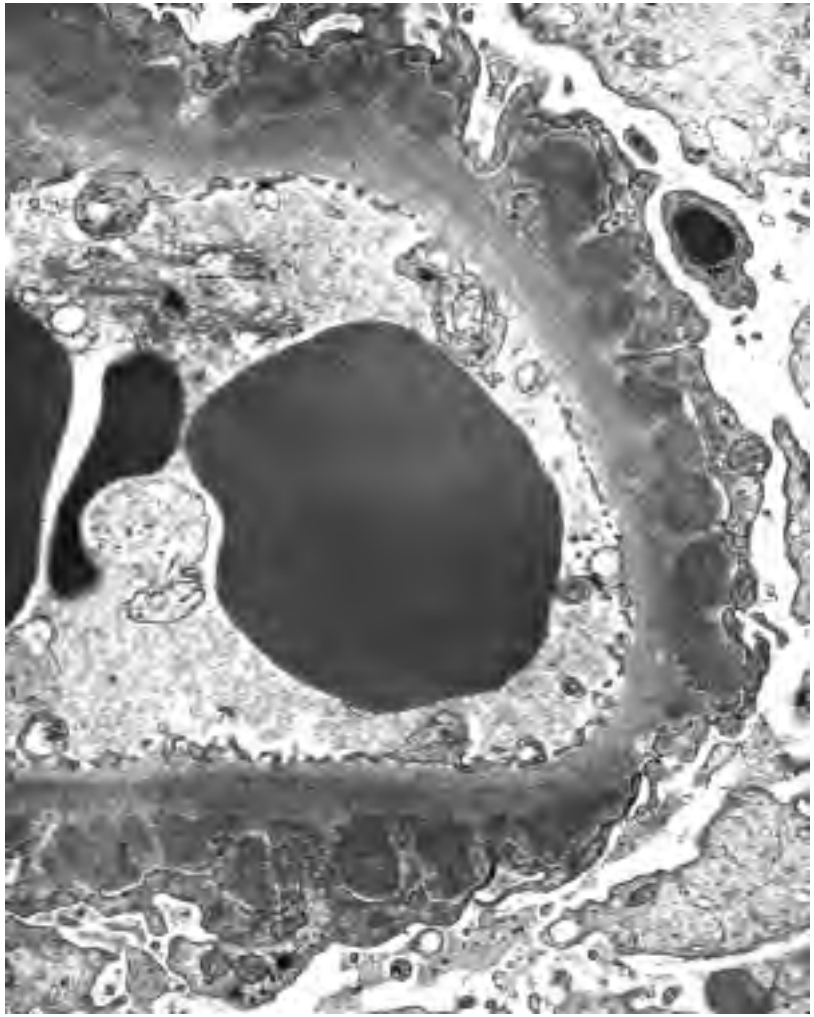
16 mars 2012

Membranous Nephropathy





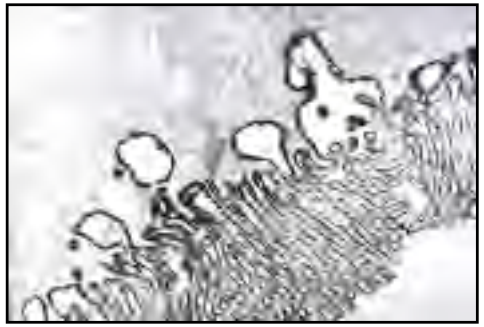
Major cause of nephrotic syndrome and chronic renal failure

Aetiologies of membranous nephropathy

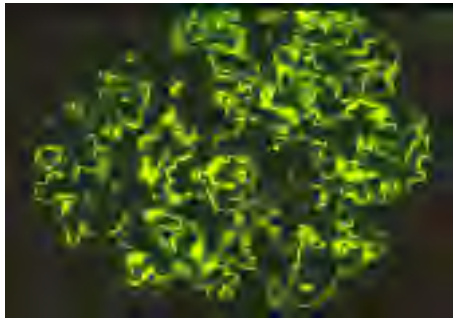
- 30% associated with
  - infections
  - cancers
  - autoimmune diseases
  - drugs
- 70% « idiopathic forms »
- Proteinuria is complement-dependent, and may involve production of oxygen free radicals and metalloproteases

Walter Heymann, Cleveland, 1959

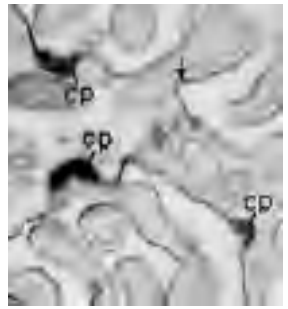
Heymann nephritis



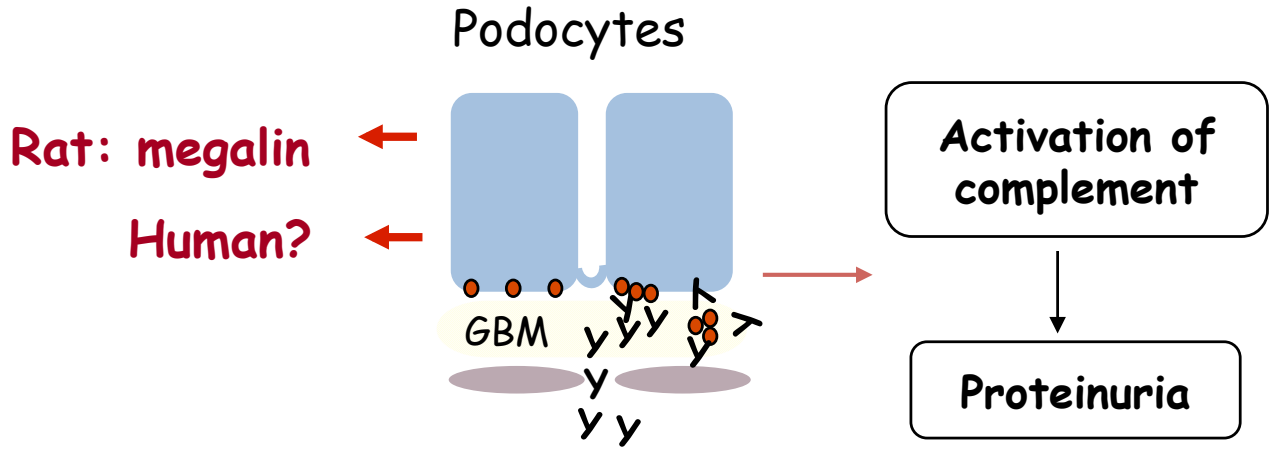
Renal BB



IgG deposits



Megalin, the target antigen of HN



In situ formation of immune deposits

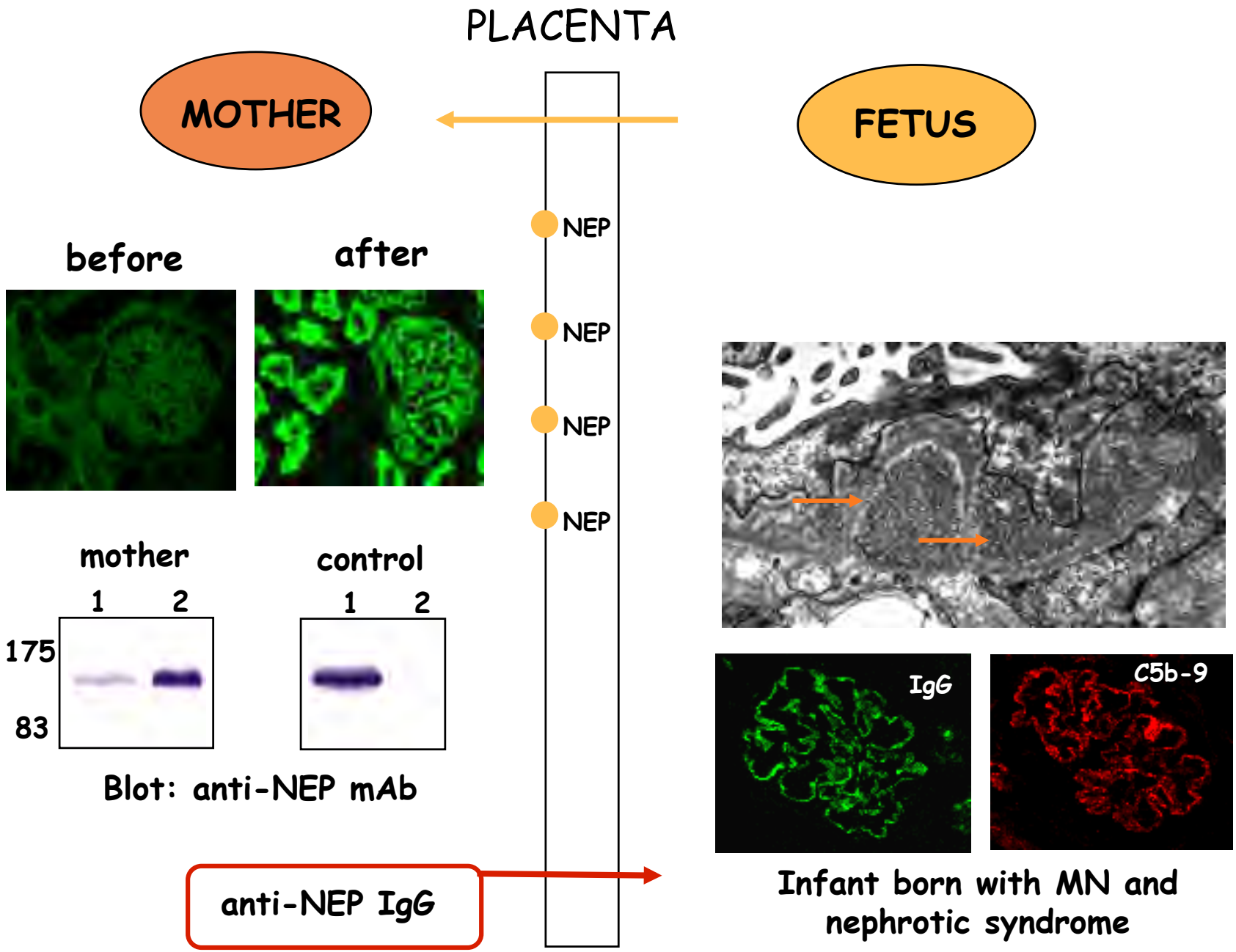
Kerjaschki and Farquhar PNAS 1982, 79:5557 ; Ronco et al J Immunol 1986, 136:125

From rats to men :
Allo-immune neonatal MN

1982-2002

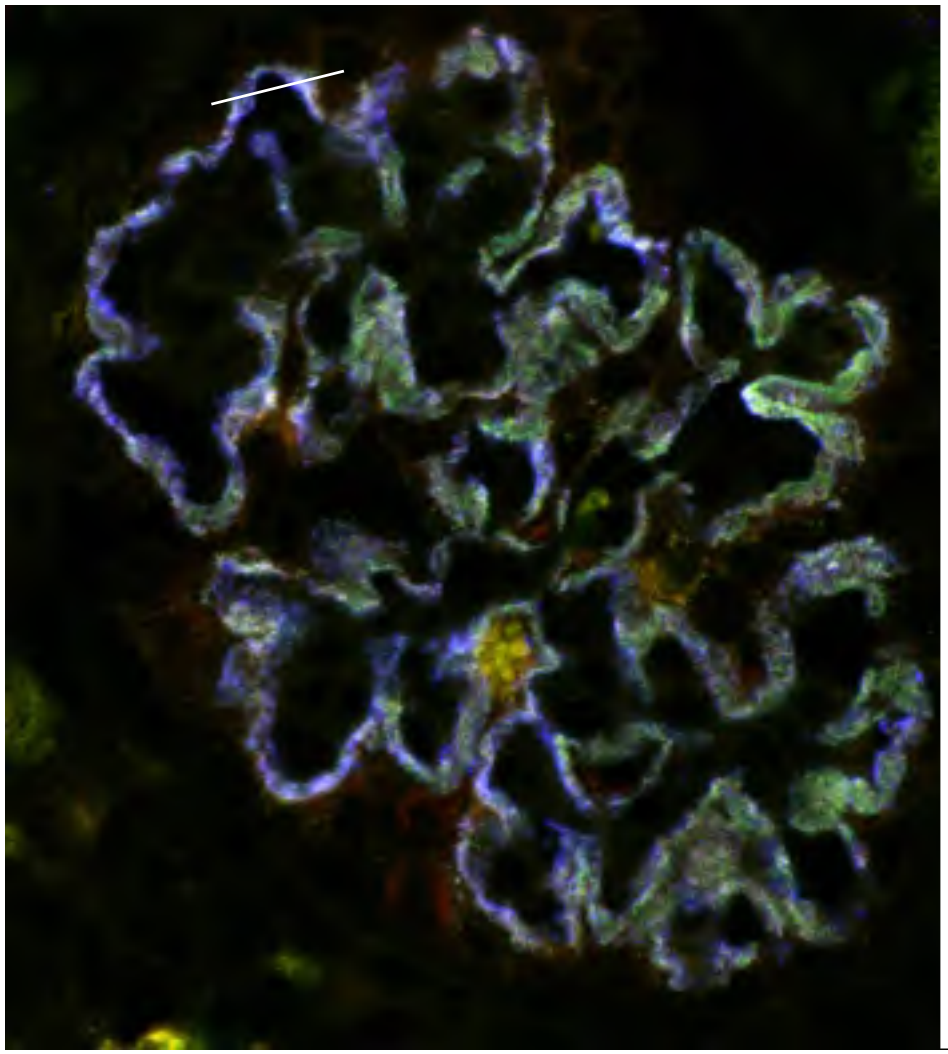
The case : Hugo D. (male gender)

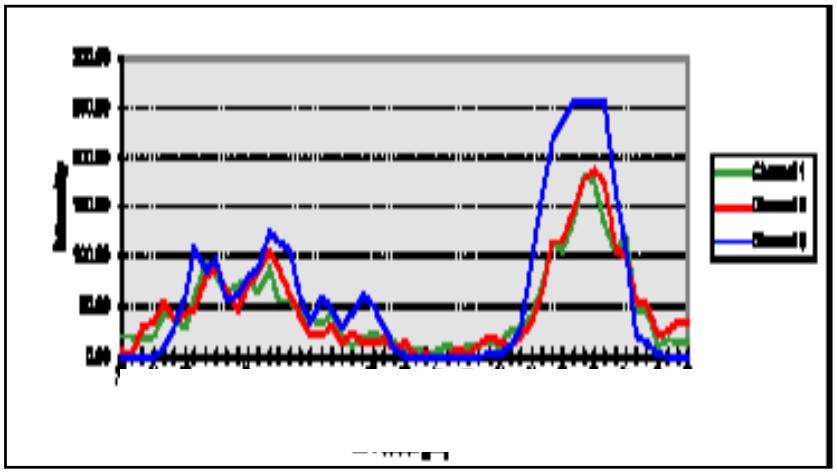
- 34 Wks of gestation : oligohydramnios and enlarged kidneys
- 38 Wks : birth
- 1st Days of life : respiratory distress and oligoanuria, followed by nephrotic range proteinuria and increased blood pressure
- 4 Wks : CT-guided kidney biopsy
- Negative tests for syphilis, toxoplasmosis, cytomegalovirus and hepatitis -B virus infections
- Negative Coombs' test. Normal levels of complement components at day 35



Debiec et al. N Engl J Med 2002, 346:2053

Potential mechanisms of albuminuria



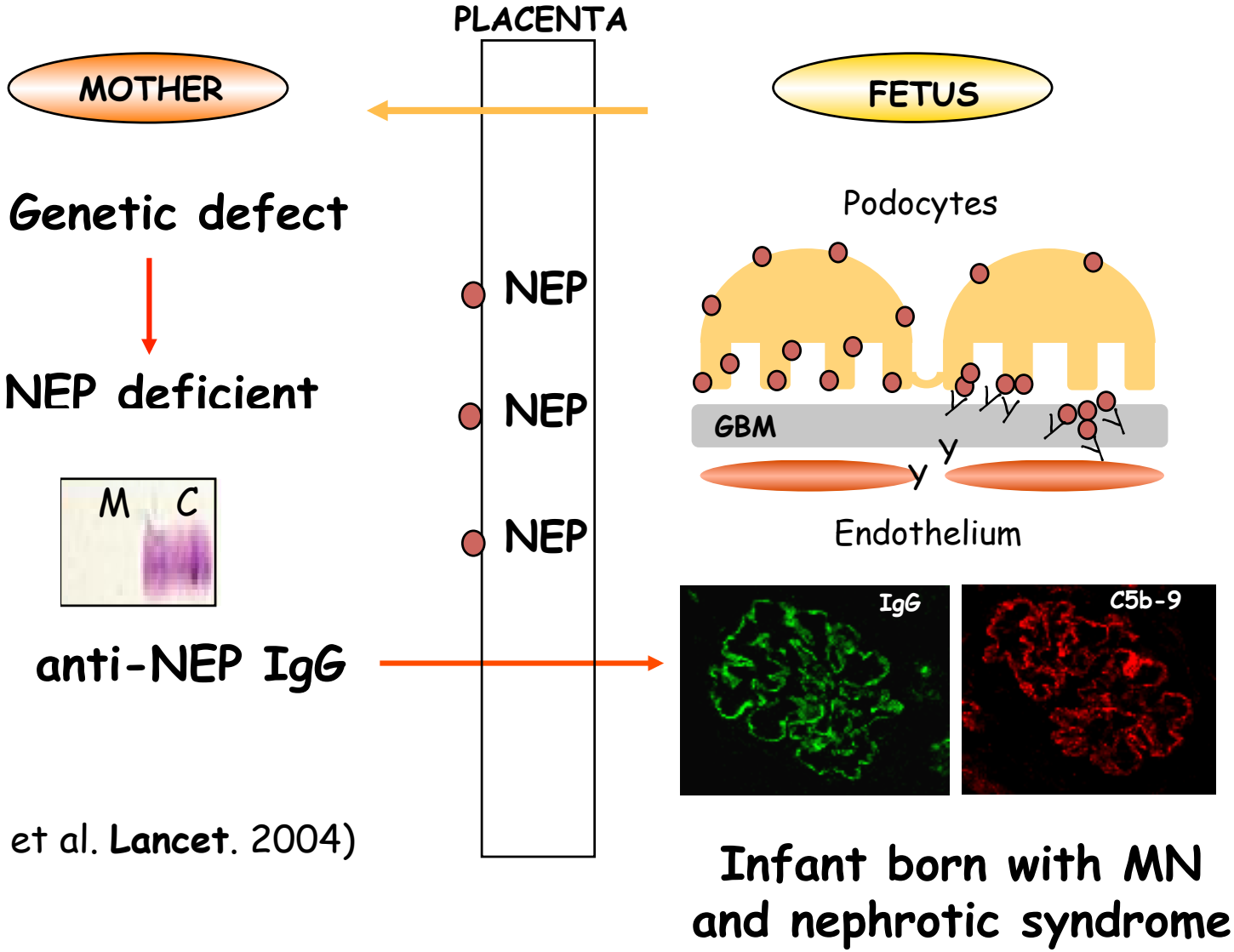


Green IgG

Red NEP

Blue C5b-9

Why did the mother become immunized without developing the renal disease ?



(Debiec et al. **Lancet**. 2004)

☞ Feto-Maternal Allo-Immunization with antenatal Glomerulopathies (FMAIG)

Auto-immune « idiopathic » MN in adults

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 2, 2009 VOL. 361 NO. 1

M-Type Phospholipase A_2 Receptor as Target Antigen in Idiopathic Membranous Nephropathy

Laurence H. Beck, Jr., M.D., Ph.D., Ramon G.B. Bonegio, M.D., Gérard Lambeau, Ph.D., David M. Beck, B.A., David W. Powell, Ph.D., Timothy D. Cummins, M.S., Jon B. Klein, M.D., Ph.D., and David J. Salant, M.D.

GWAS analysis of patients with idiopathic MN

- Three cohorts

	Patients	Controls
French	75	157
Dutch	146	1,832
British	335	349
Total	556	2,338

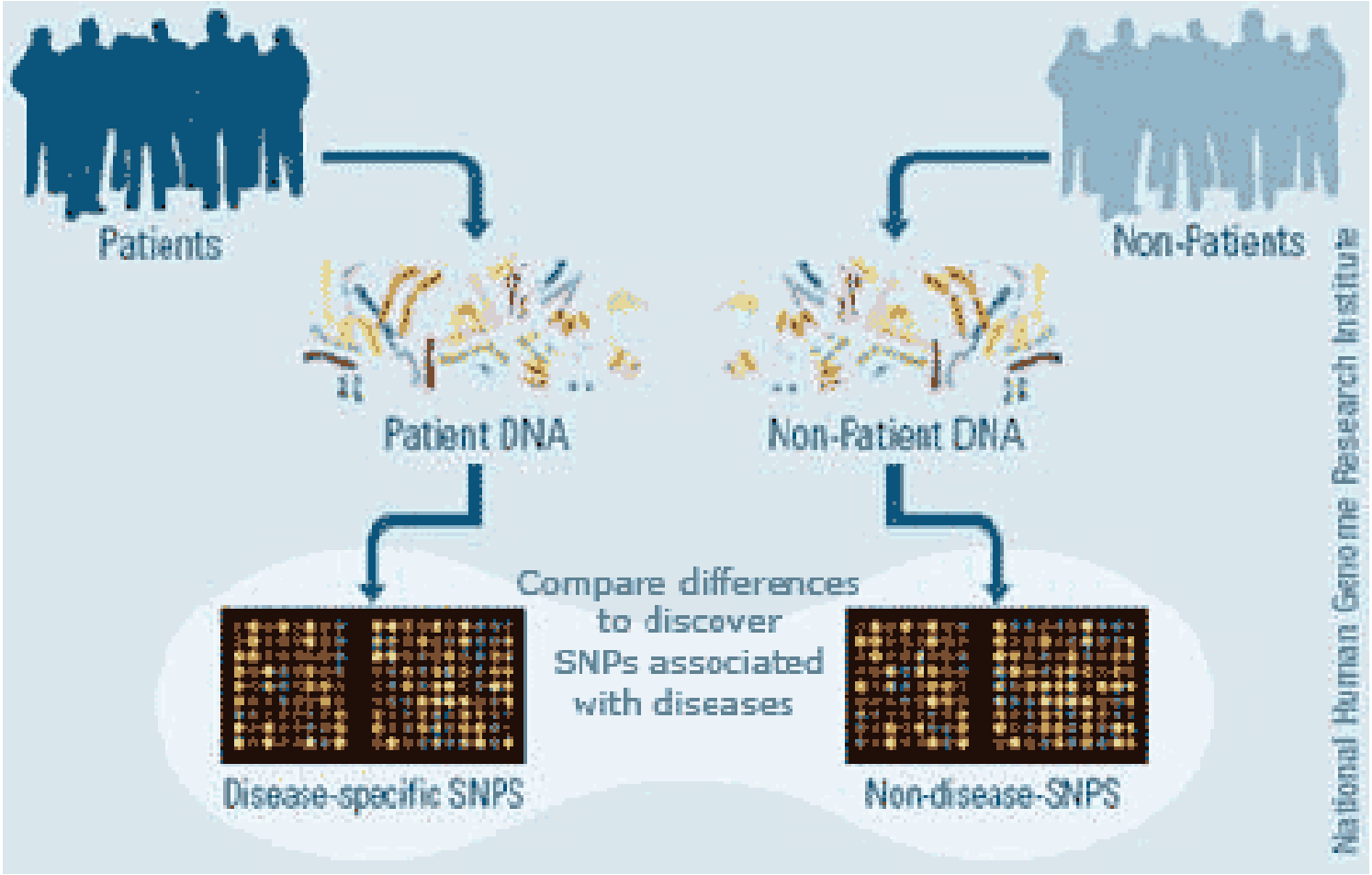
- Controls : ethnically matched
- Illumina platform : 300,000 SNPs
- Bioinformatics analysis

Stanescu et al, New Engl J Med, 2011, 364: 616

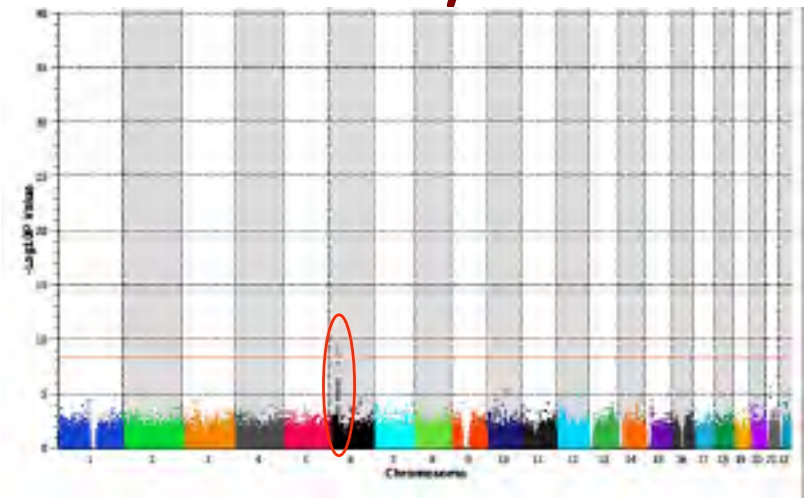
Single Nucleotide Polymorphisms (SNPs)

- Single base mutation in DNA
- Most simple form of genetic polymorphism
- 90% of all human DNA polymorphisms
- Occur 0.5-10 per every 1 000 base pairs
- Not uniformly distributed
- > 1, 000, 000 SNPs identified
- SNP in a coding region can be
  - Synonymous (silent mutation)
  - Non-synonymous (missense or nonsense mutation)

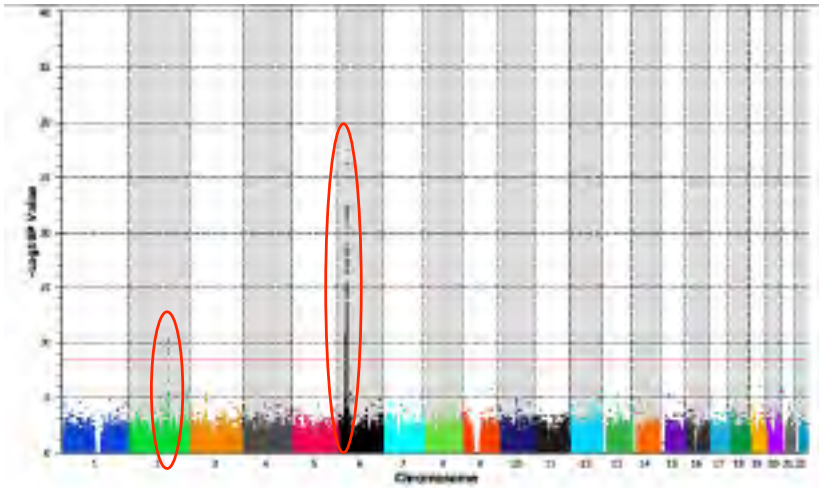
Principle of pangenomic (GWAS) studies



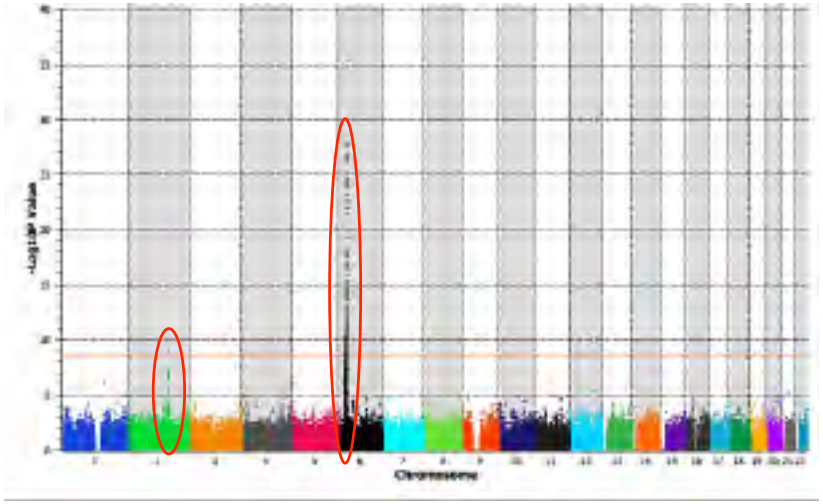
A risk HLA-DQA1 allele is associated with iMN and may interact with PLA2R alleles



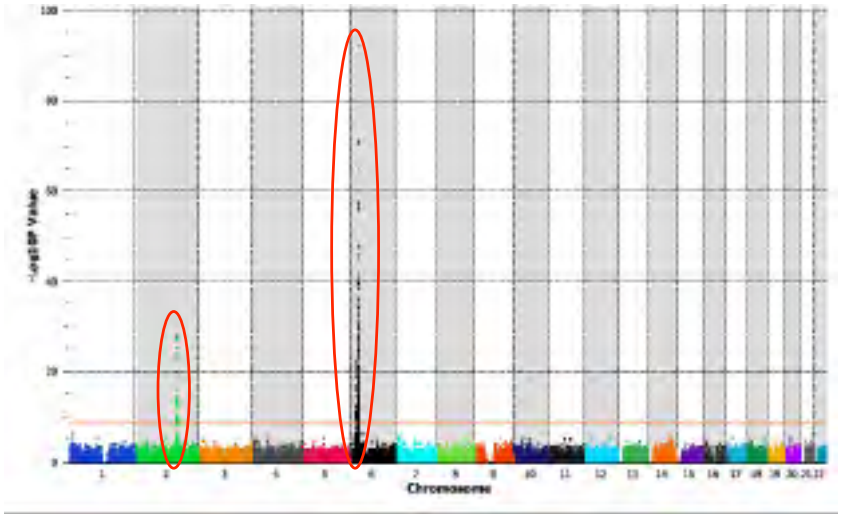
French (n=75 ; c=157)



Dutch (n=146 ; c=1832)



British (n=335 ; c=349)



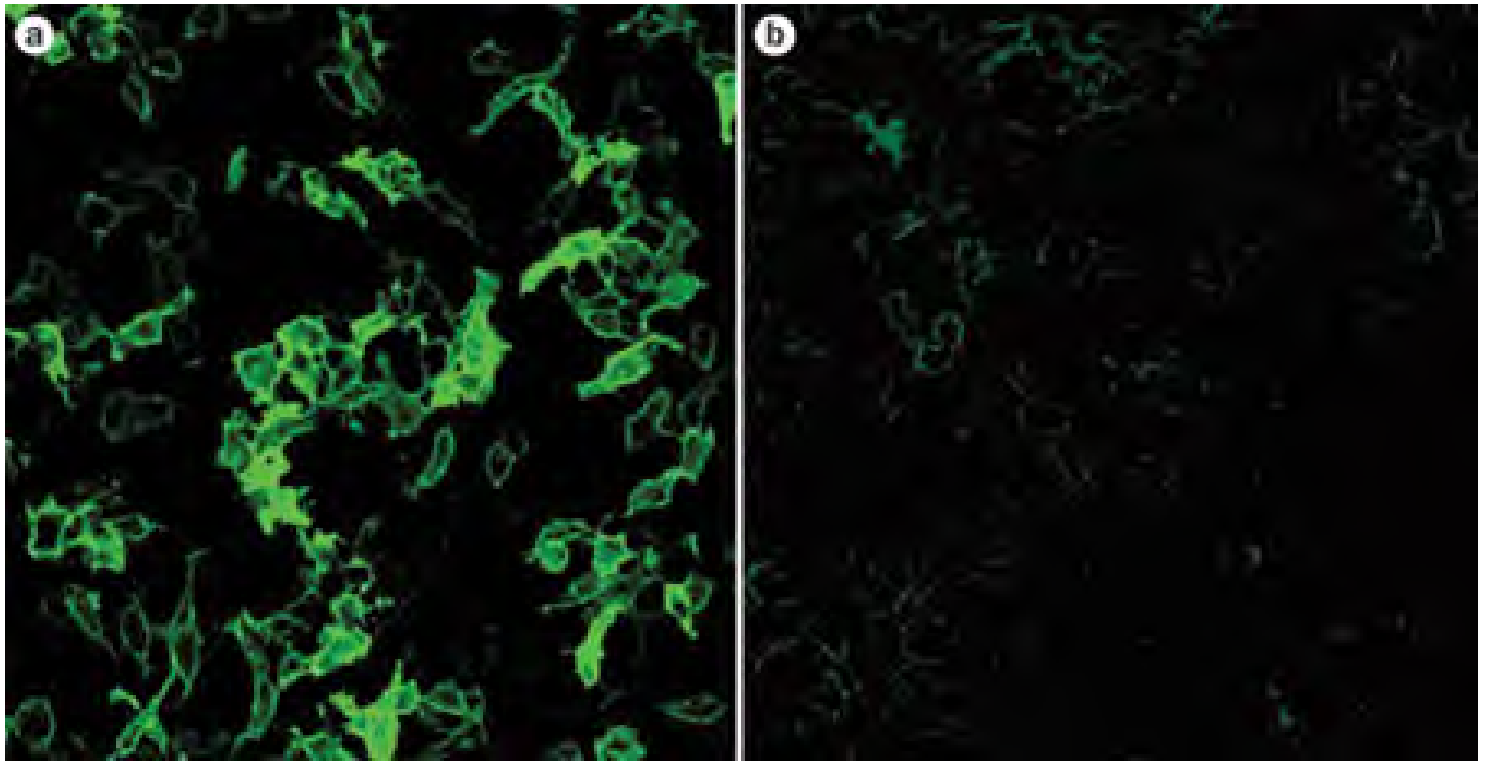
All patients (n=556; c=2338)

Stanescu et al, New Engl J Med, 2011, 364: 616

NEPHROTIC SYNDROME

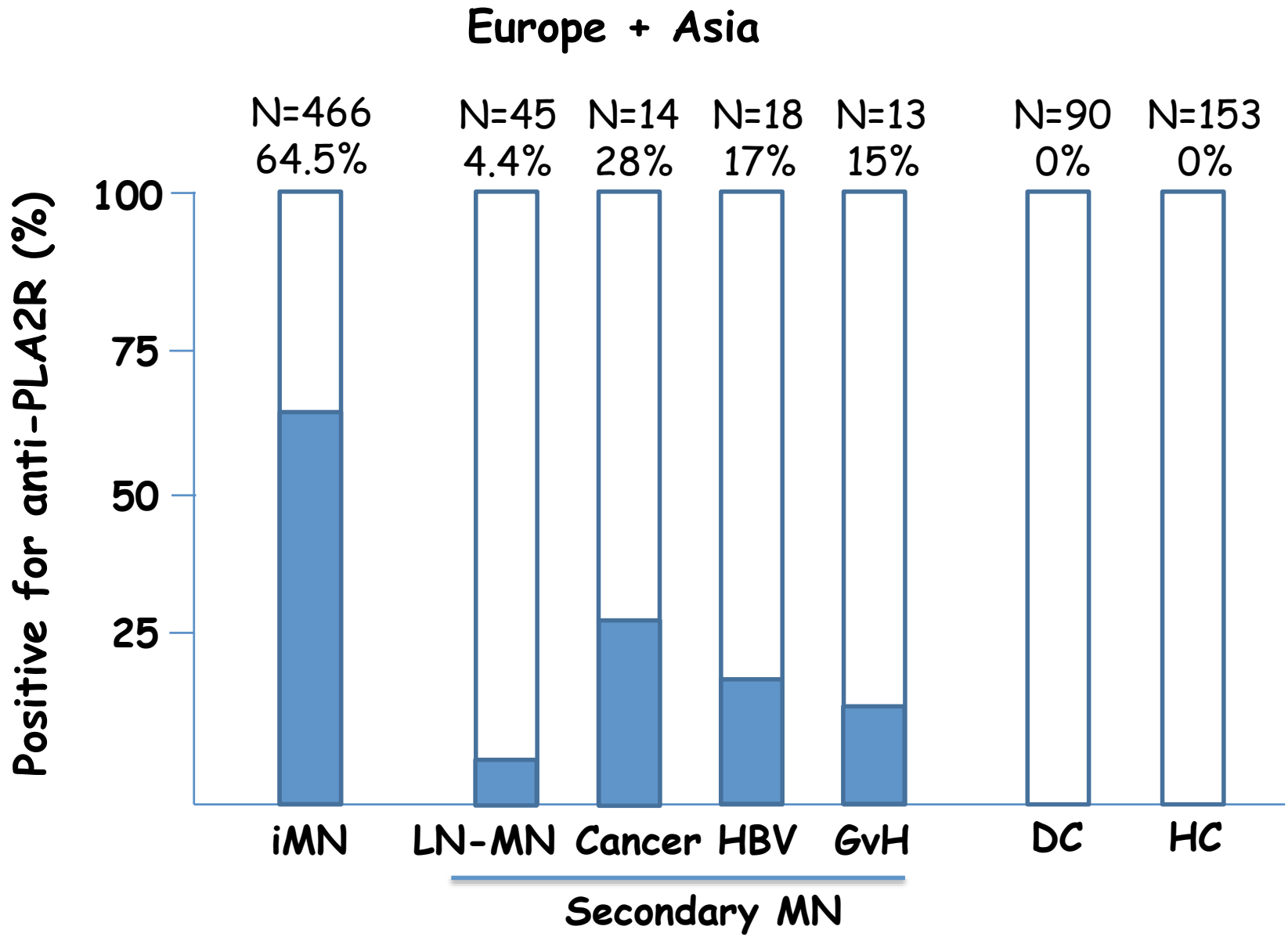
A new specific test for idiopathic membranous nephropathy

Hanna Debiec and Pierre Ronco



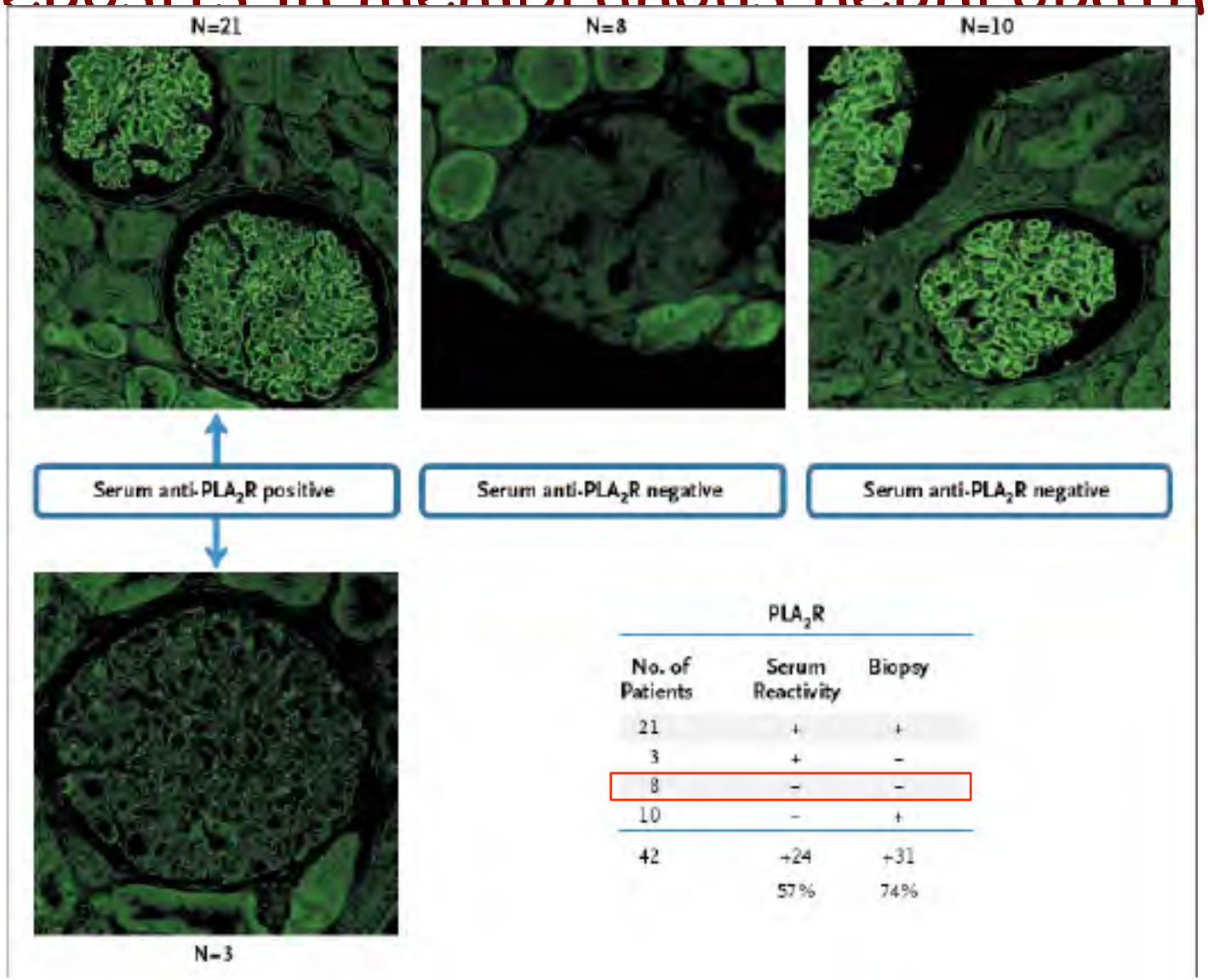
Debiec, H. & Ronco, P. *Nat. Rev. Nephrol.* **7**, 496–498 (2011)

Anti-PLA2R antibody in membranous nephropathy



Debiec ,Tesar and Ronco; Hoxha et al, NDT 2011; Qin et al, JASN 2011

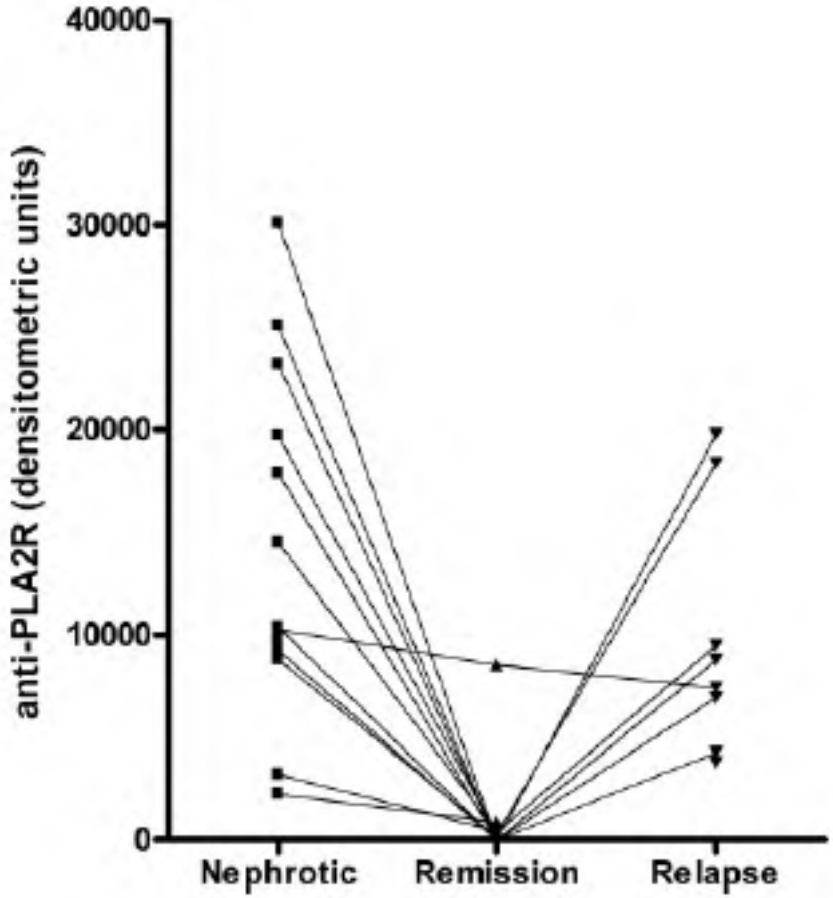
PLA2R autoantibodies and PLA2R glomerular deposits in membranous nephropathy

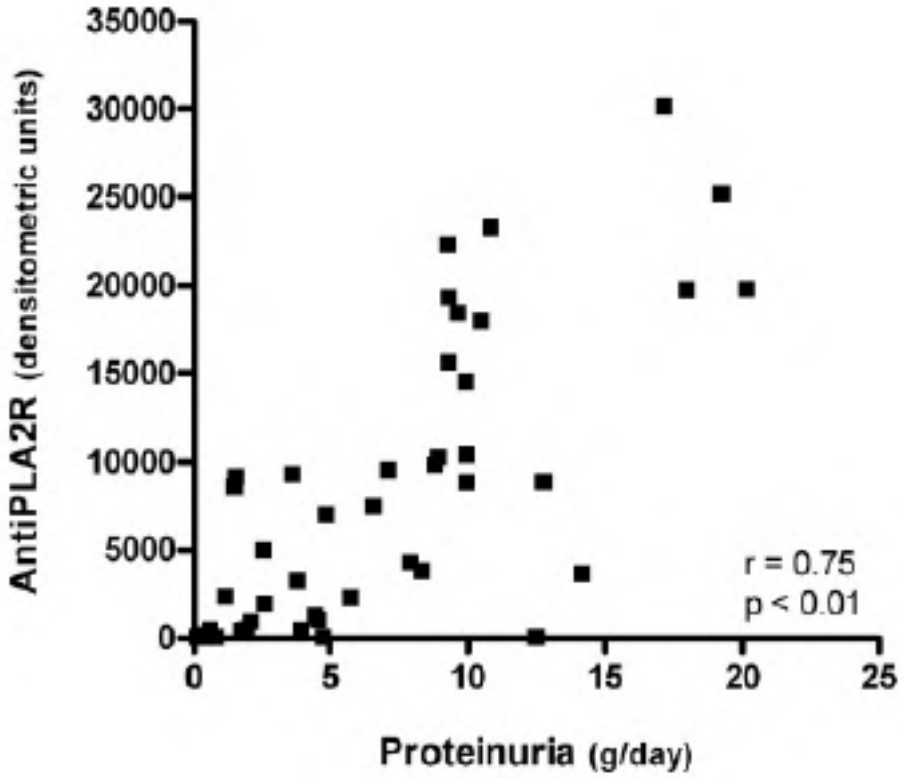


	PLA2R	
No. of Patients	Serum Reactivity	Biopsy
21	+	+
3	+	–
8	–	–
10	–	+
42	+24	+31
	57%	74%

Debiec and Ronco, New Engl J Med, 2011, 364 :689

Correlation of anti-PLA_2R with disease activity and proteinuria





Hofstra et al, Clin JASN 2011, 6:1286

Rituximab-Induced Depletion of Anti-PLA_2R Autoantibodies Predicts Response in Membranous Nephropathy

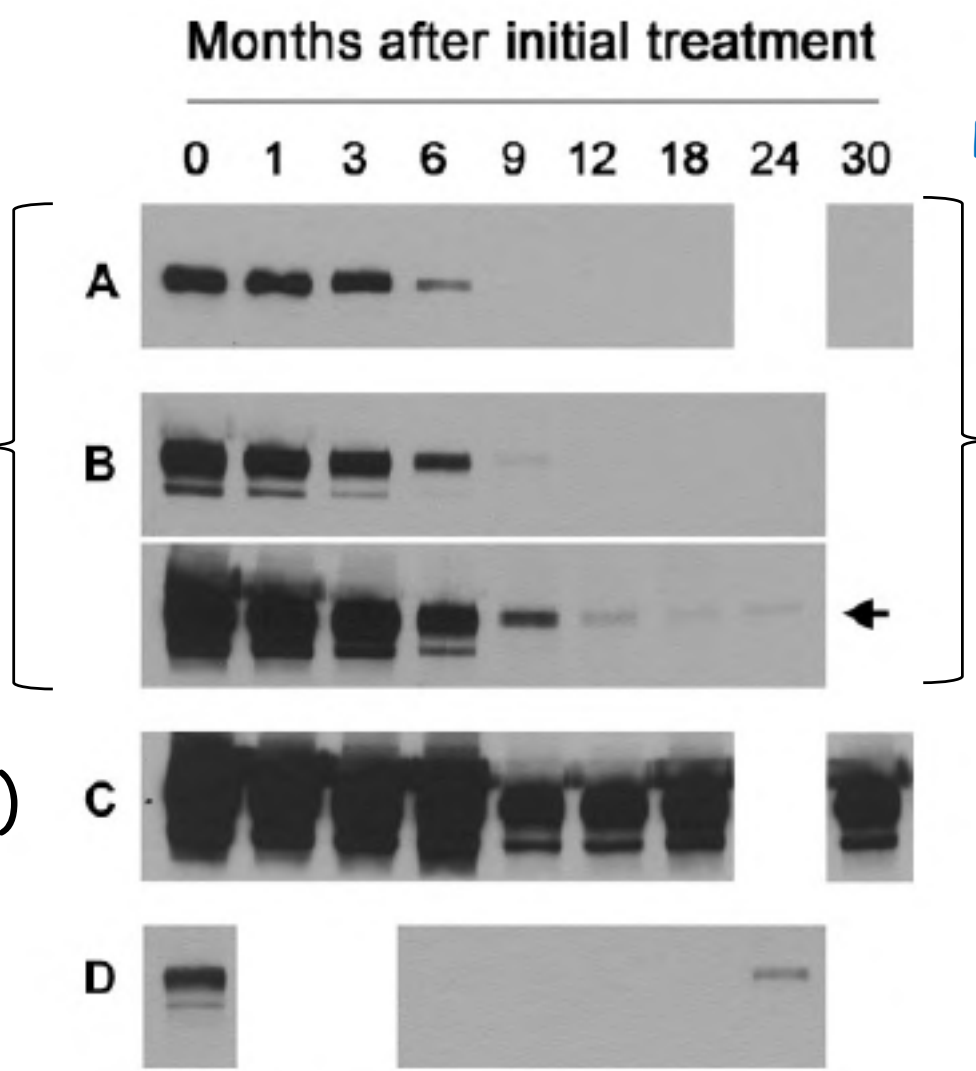
Laurence H. Beck, Jr.,* Fernando C. Fervenza,†
David M. Beck,* Ramon G.B. Bonegio,* Fahim A. Malik,* Stephen B. Erickson,†
Fernando G. Cosio,† Daniel C. Cattran,‡ and David J. Salant*

J Am Soc Nephrol 22: 1543–1550, 2011.

N= 35

25 (71%) PLA2R⊕

Patterns of response of IgG4 anti-PLA2R1 signal



Remission

Partial Complete

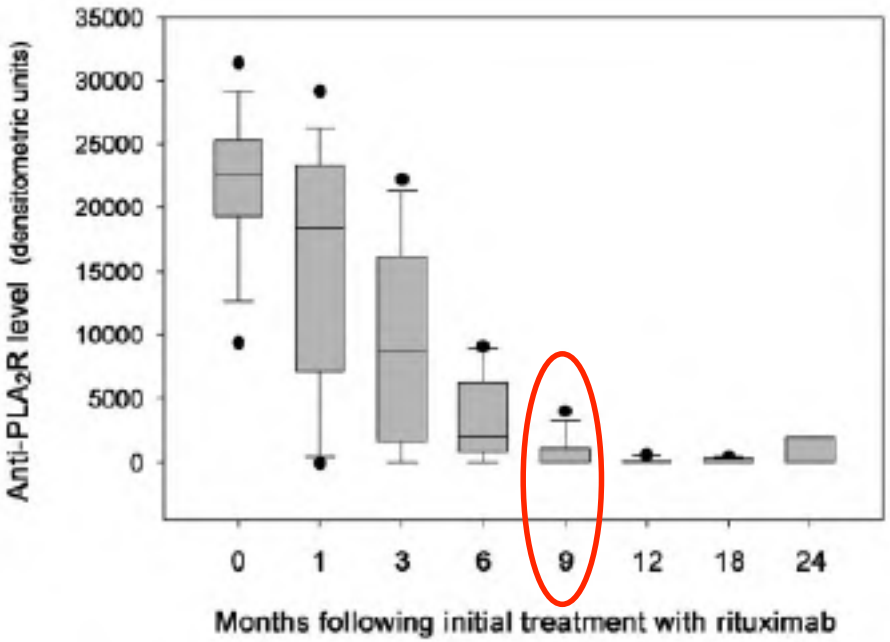
Disappearance (n = 17) — 88% 59%

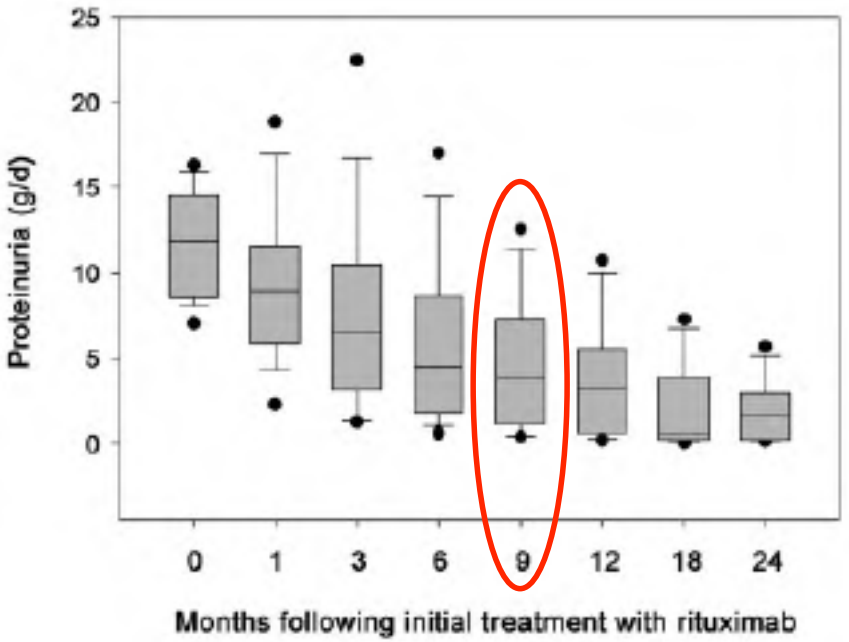
No decline (n = 6) — 33% 0%

Relapse (n = 1)

Beck et al, JASN 2011, 22:1543

Disappearance of anti-PLA2R1 precedes that of proteinuria





Beck et al, JASN 2011, 22:1543

Autoantibodies Specific for the Phospholipase A_2 Receptor in Recurrent and *De Novo* Membranous Nephropathy

H. Debiec[a,b,c,*], L. Martin[d,e], C. Jouanneau[a,b], G. Dautin[f], L. Mesnard[a,b,c], E. Rondeau[a,b,e], C. Mousson[e,g,†] and P. Ronco[a,b,c,†]

American Journal of Transplantation 2011; 11: 2144–2152
Wiley Periodicals Inc.

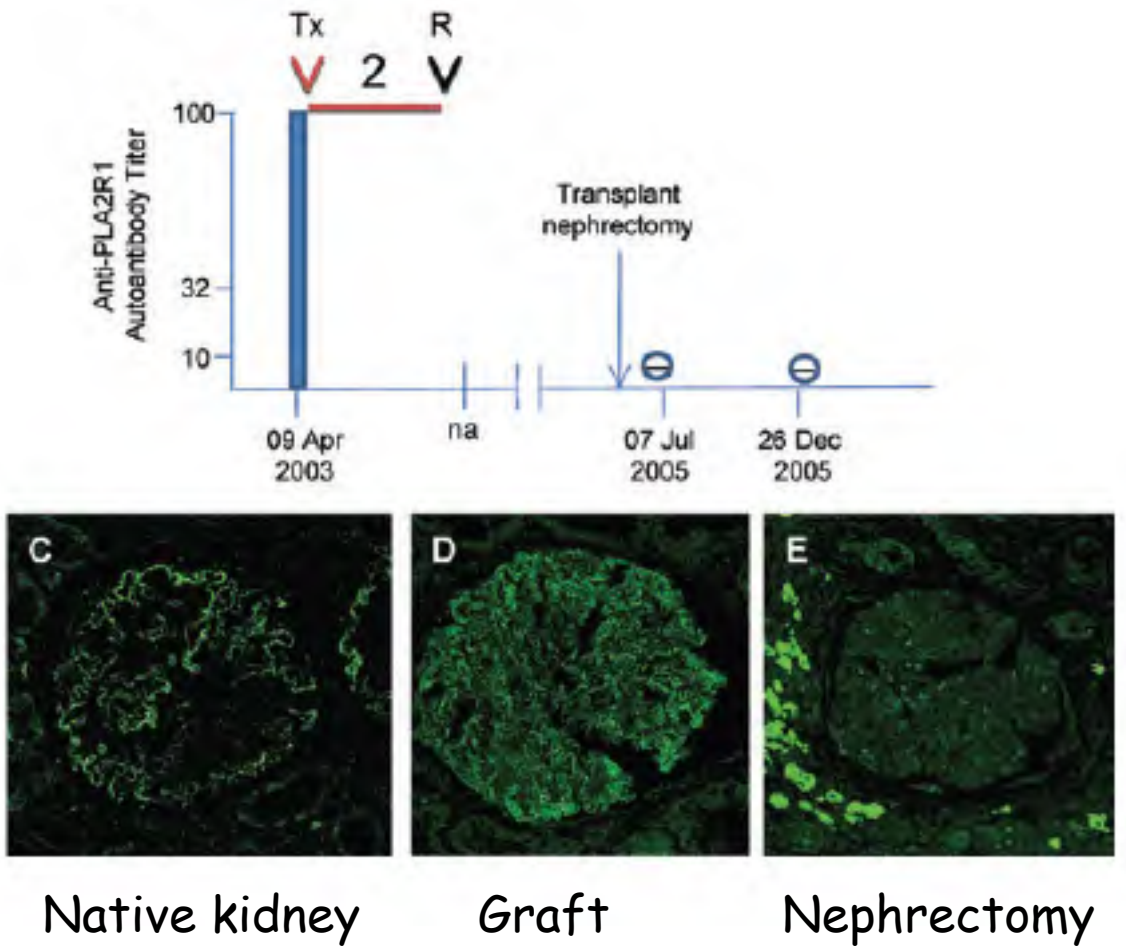
10 recurrent MN ; 9 **de novo** MN

Prevalence of anti-PLA2R1 antibodies in recurrent and **de novo** MN

- Recurrent : about 50%
- De novo : 0

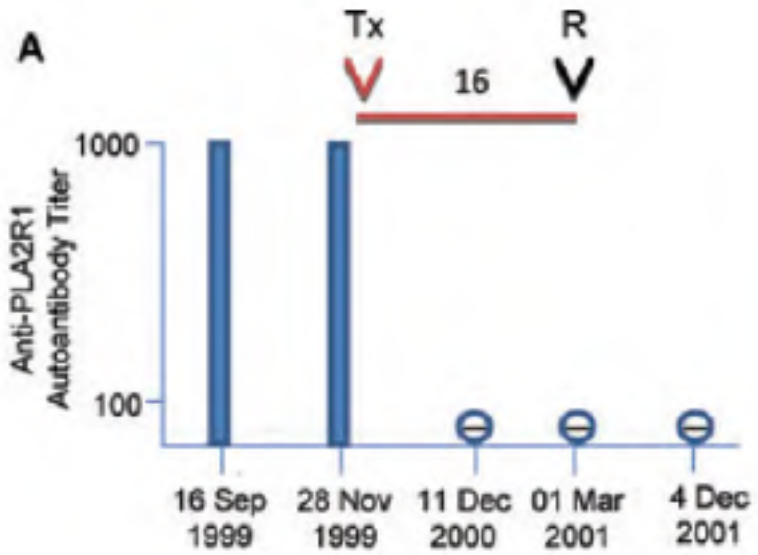
Debiec et al, Am J Transplant 2011, 11:2144 ; Salant, ASN 2011, Philadelphia

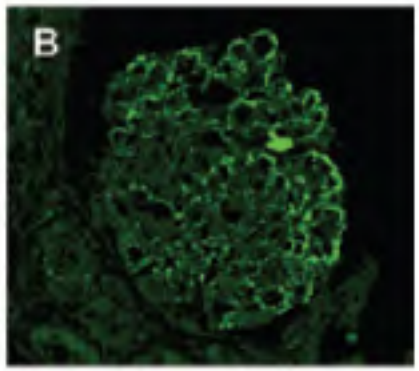
A typical case of PLA2R1-related recurrent MN



Debiec et al, Am J Transplant 2011, 11:2144

Late recurrence of PLA2R1-related MN : early disappearance of antibodies

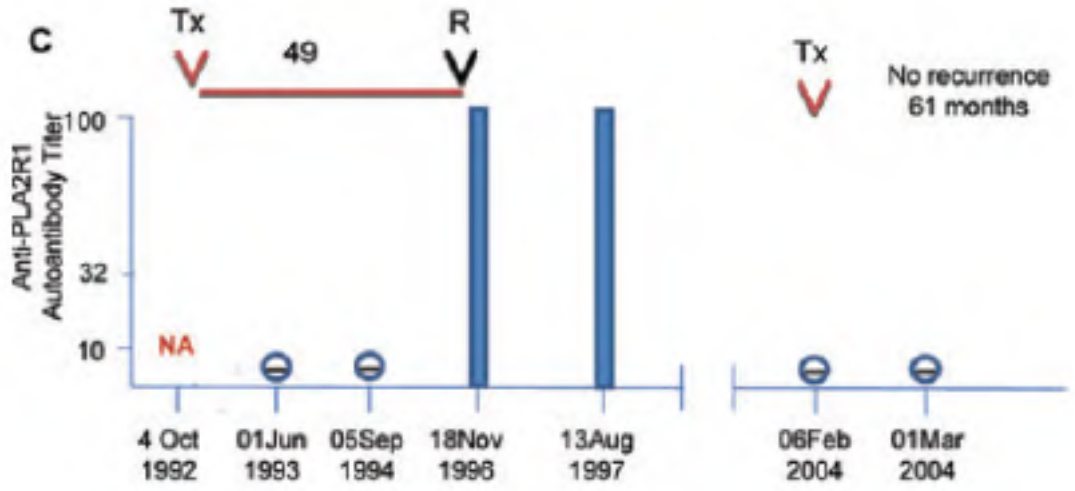


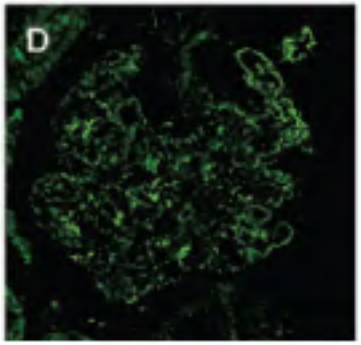


Graft

Debiec et al, Am J Transplant 2011, 11:2144

Late recurrence of PLA2R1-related MN : delayed appearance of antibodies





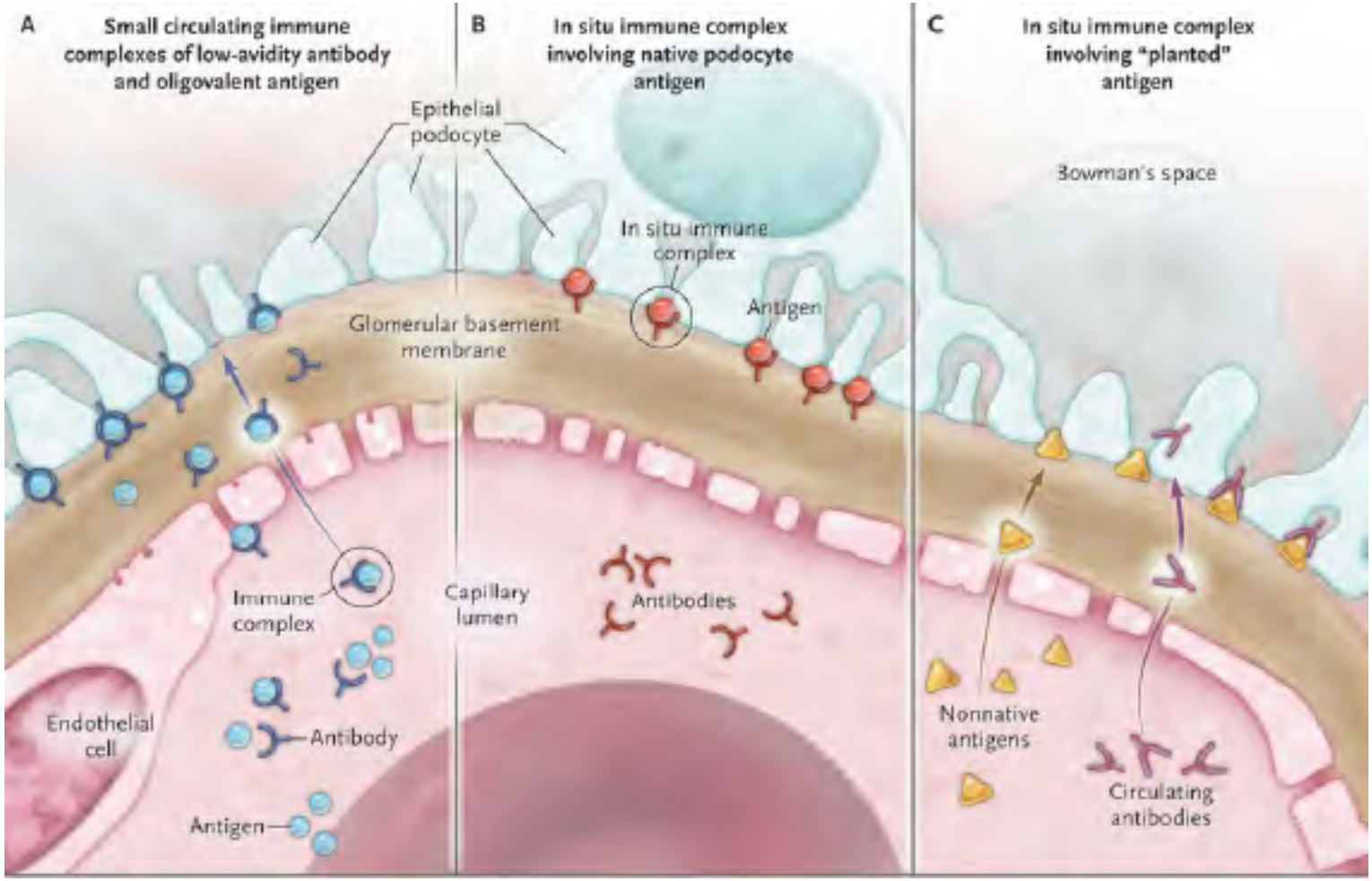
Graft

Debiec et al, Am J Transplant 2011, 11:2144

Conclusion

- Anti-PLA2R1 antibody is a specific biomarker of MN
- Prevalence is about 65% in « idiopathic » MN and very low in secondary MN
- There is no correlation between presence of anti-PLA2R1 at diagnosis and response to treatment
- However, a marked reduction of anti-PLA2R1 antibody predicts renal response
- About 50% of recurrent MN are associated with PLA2R antibody but with marked heterogeneity in the kinetics and titers
- The presence of anti-PLA2R1 antibody at the time of transplantation is not always associated with recurrence

A role for nonnative antigens?



rhASB
BSA

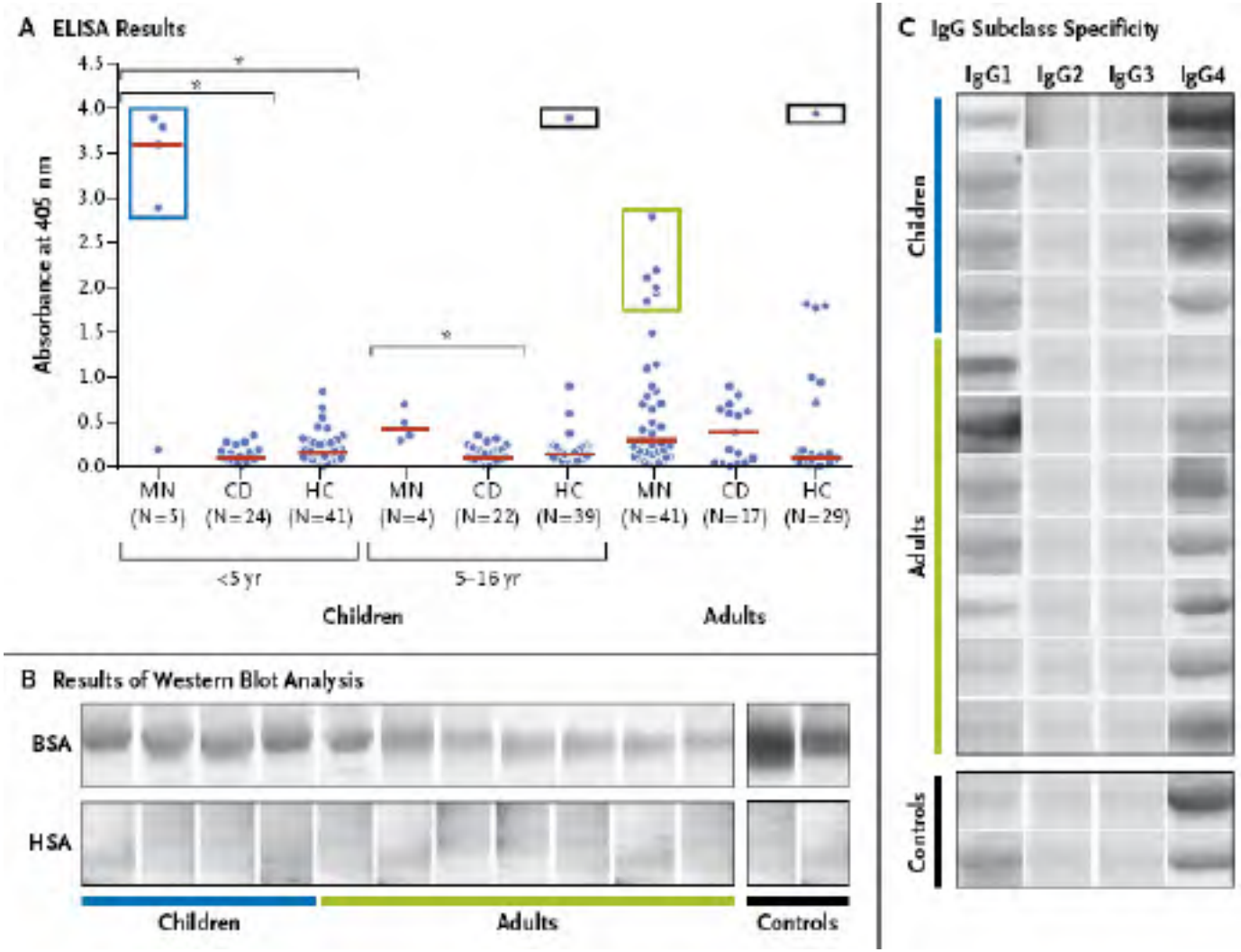
Serum Sickness

Megalin, NEP, PLA2R

« Planted » antigen

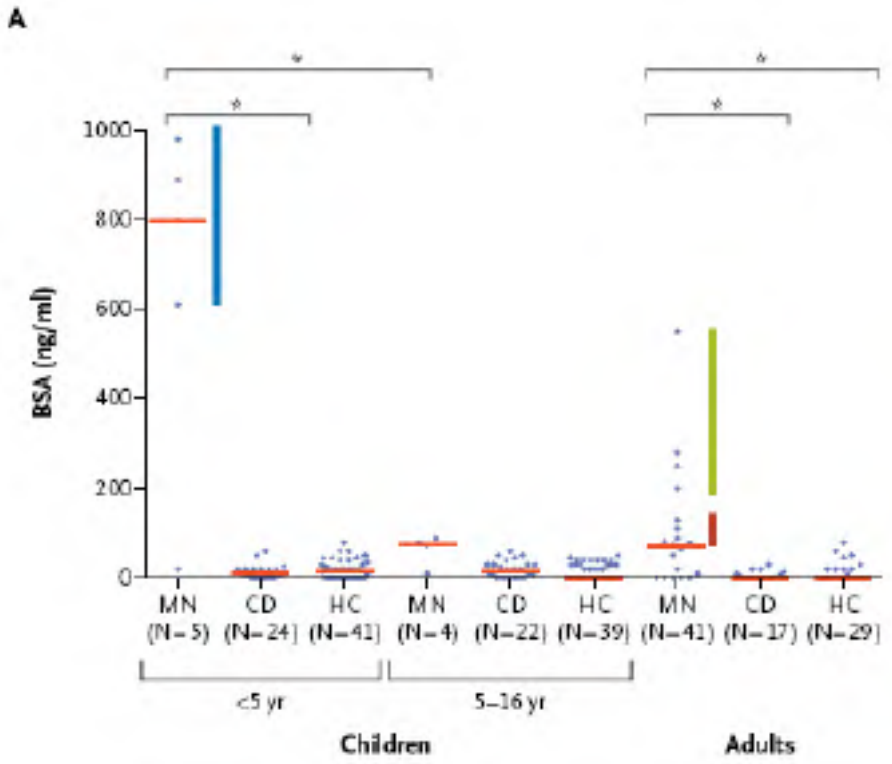
Glassock , New Engl J Med 2009, 361:81

Anti-BSA antibodies in patients with MN

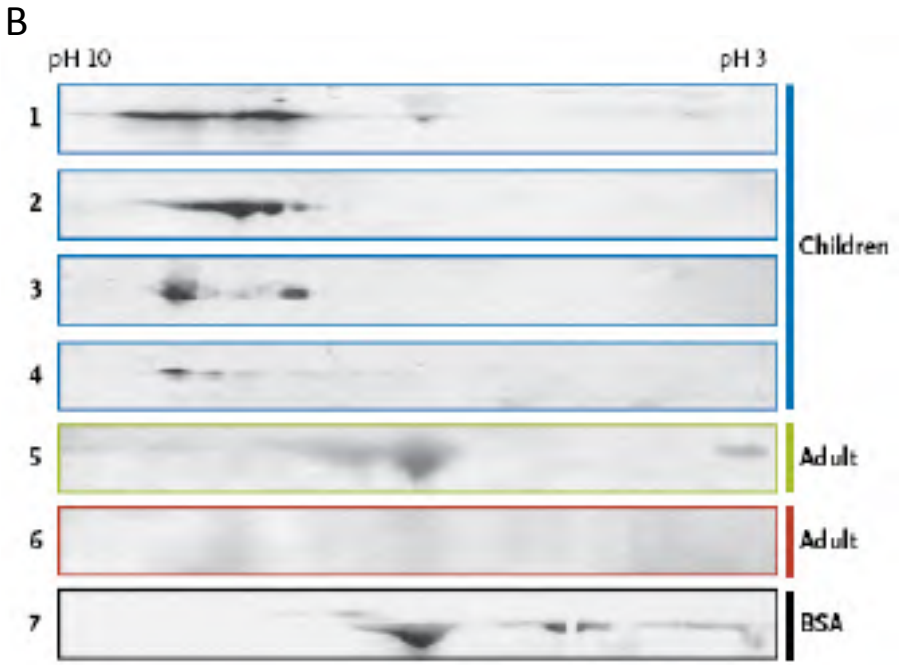


Debiec et al, NEJM 2011, 364 : 2101

Circulating BSA in patients with MN



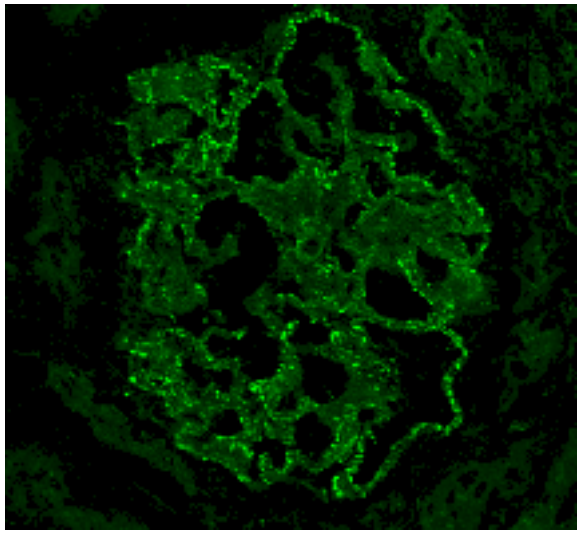
ELISA BSA

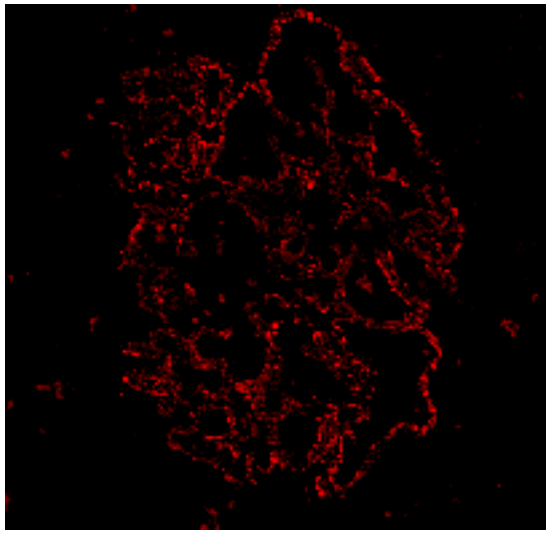


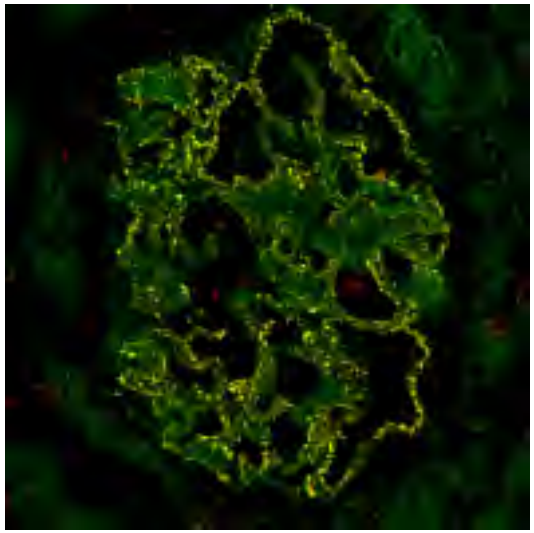
2D electrophoresis and immunoblot

Debiec et al, NEJM 2011, 364 : 2101

Colocalization of BSA and IgG in immune deposits

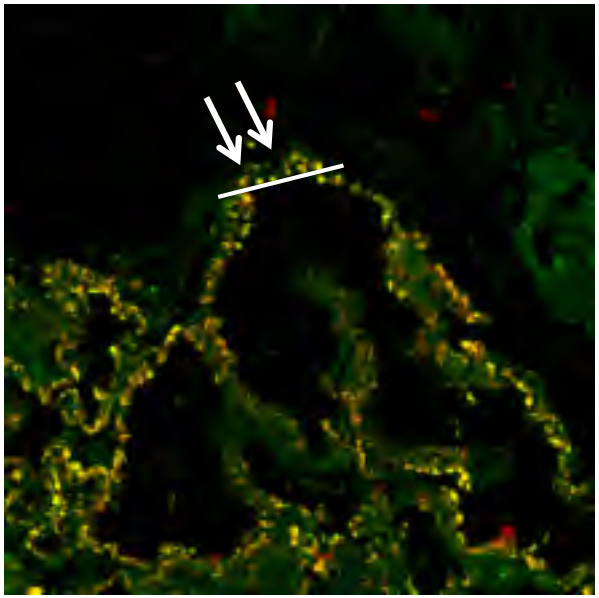


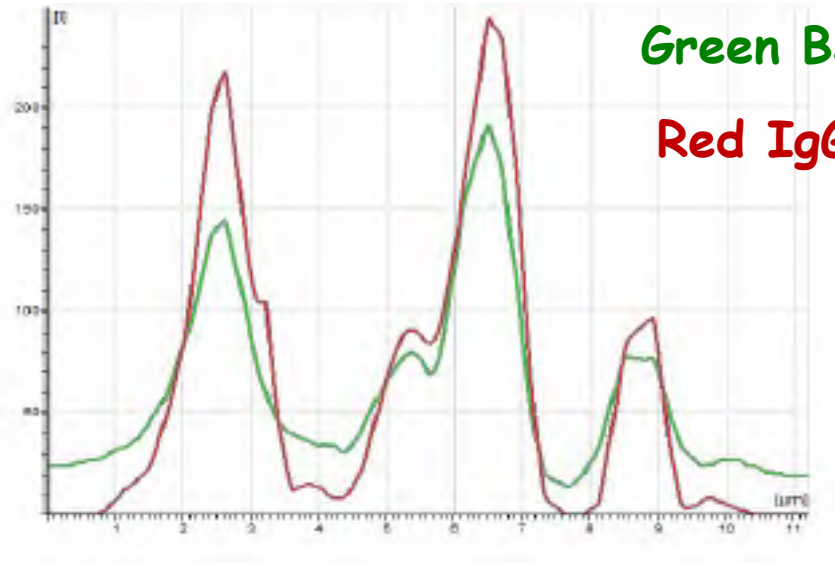




BSA

IgG

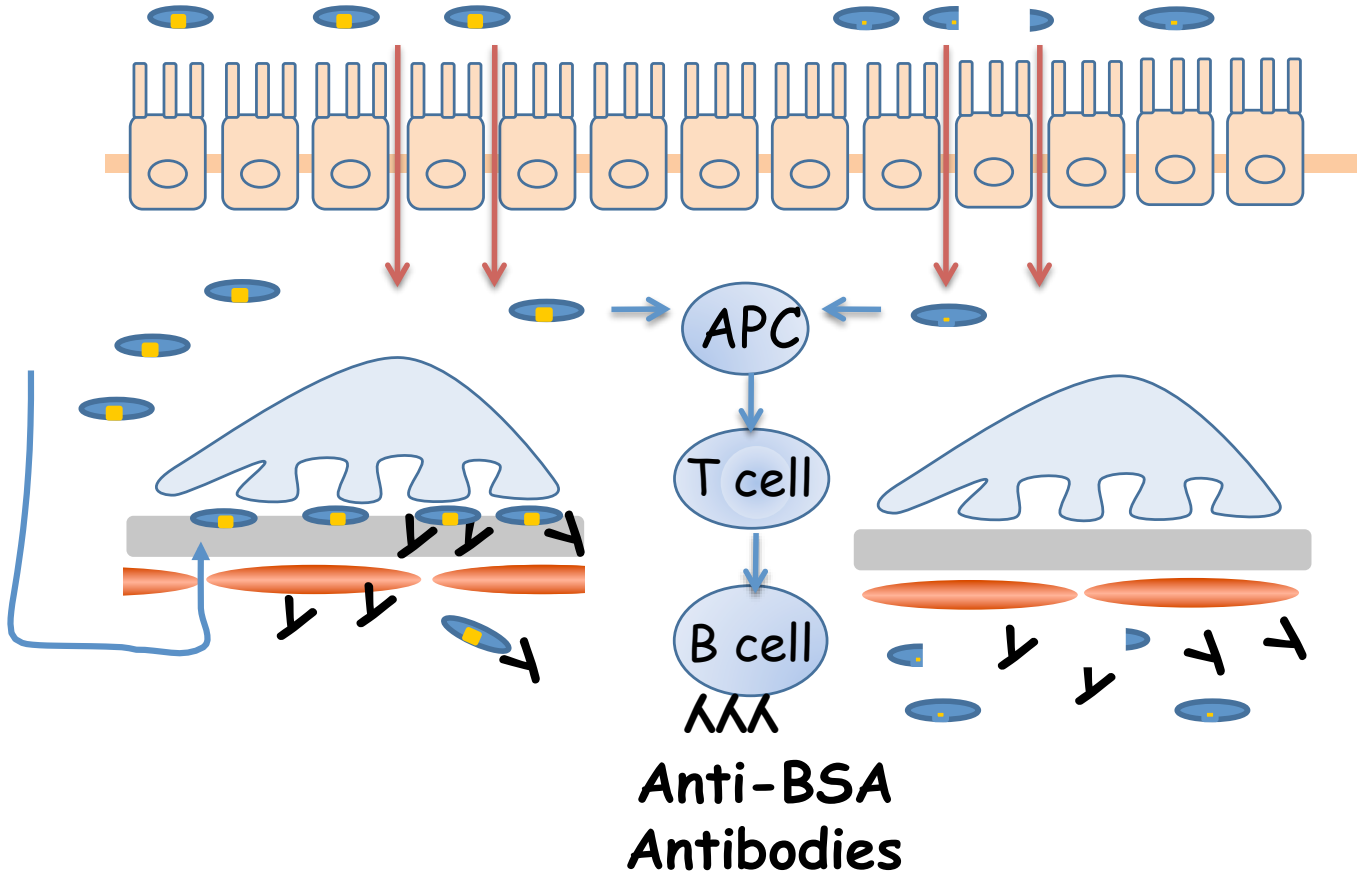




Role of BSA in the pathophysiology of MN

BSA → Processing → Digestion

Absorption of antigen from the intestinal tract



Conclusion

- BSA should be searched in glomeruli of children with MN under the age of 5 years

- Dietary modifications may improve the disease

The spectrum of human membranous nephropathies

- Neonatal, alloimmune : NEP
- Early childhood MN : BSA

- « Idiopathic » MN
  - 70-80% : PLA_2R
  - 20-30% : other Ags including food/environmental Ag (BSA)

- « Secondary » MN
  Ags to be identified

- Graft MN
  - Recurrent : PLA_2R (and other antigens)
  - de novo : allo-immune

- Substitute molecular signatures for uniform histological definition

- Toward personalized medicine, diagnostic and therapy (specific immunoadsorption)


EUNEFRON
ANR
TENON CENTER OF NEPHROLOGY
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