La belle histoire des glomérulopathies extramembraneuses : du nouveau-né à l'adulte et aux maladies auto-immunes

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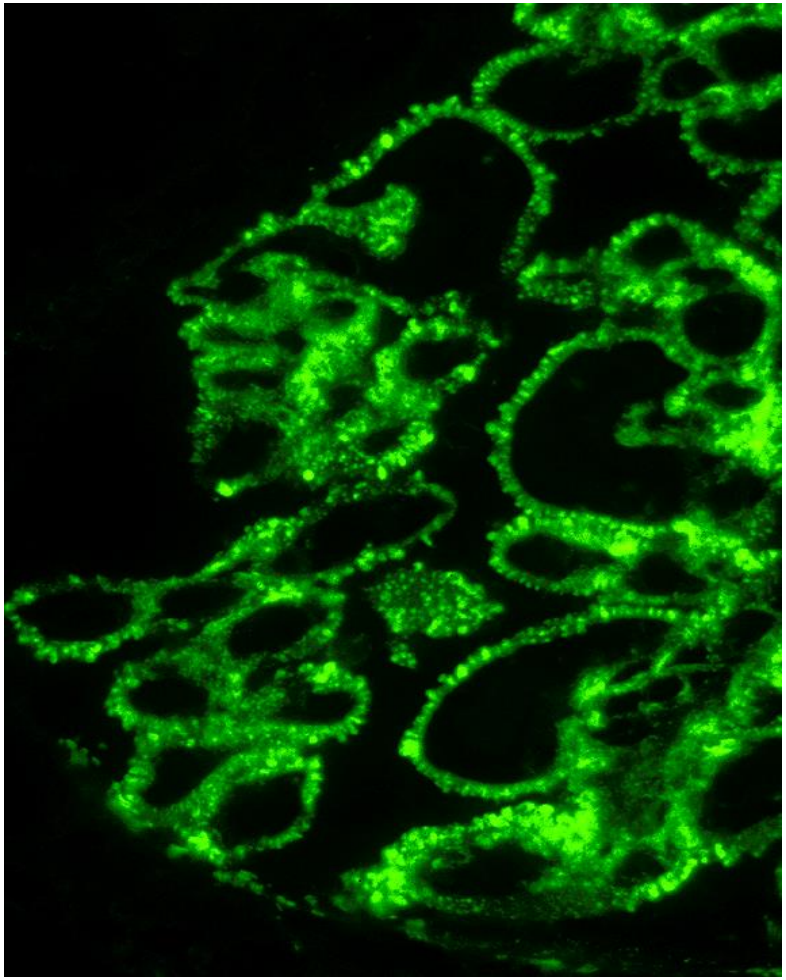
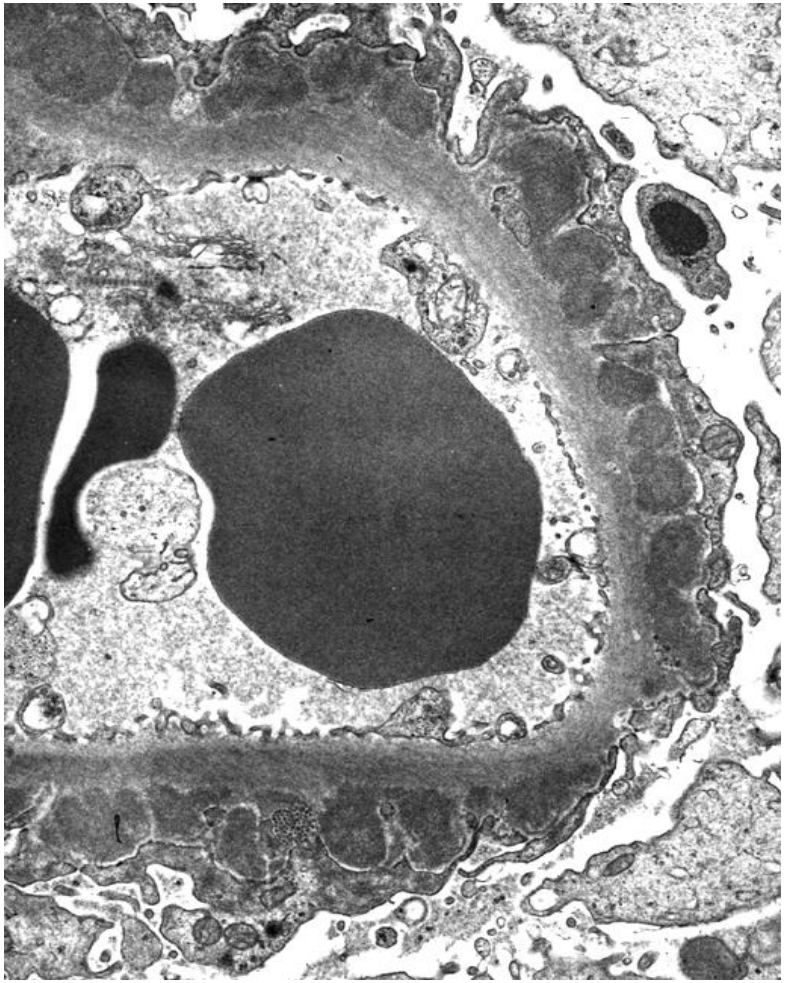
Hôpital Tenon, Paris, France

Journée annuelle de la filière ORKID
19 Novembre 2015

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 »
- Treatment is controversial because of unpredictable outcome vs side-effects and lack of pathophysiology-driven therapy
- Proteinuria as the only biomarker for disease follow-up!

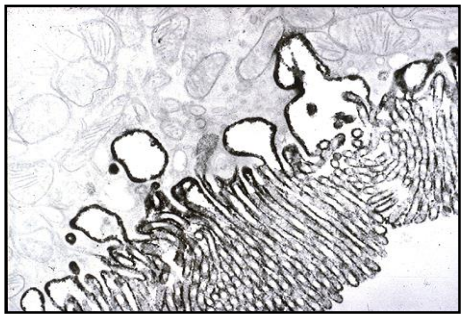
IgG subclass distribution according to underlying disease

	IgG_1	IgG_2	IgG_3	IgG_4
Idiopathic	+ to +++	+	+	+++
Lupus	+++	+++	++	±
Neoplasia	+++	+++	+	0 to ++
Recurrent MN in the allograft	++	++	+	+++
De novo MN in the allograft	+++	++	-	+

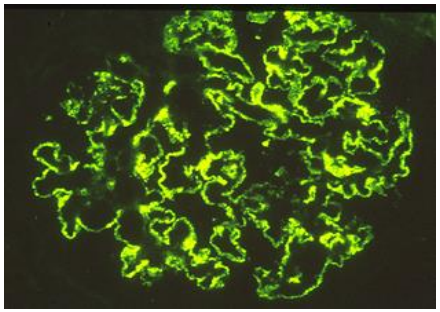
Noël LH et al, Clin Immunol Immunopathol 1988, 46:186 ; Ohtani et al, NDT, 2004, 19:574 ; Qu et al, NDT 2012, 27:1931 ; Debiec, personal data ; Markowitz, personal data

Walter Heymann, Cleveland, 1959

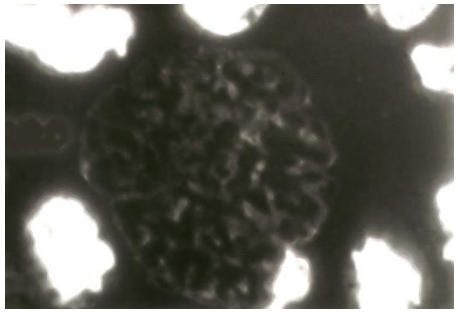
Heymann nephritis

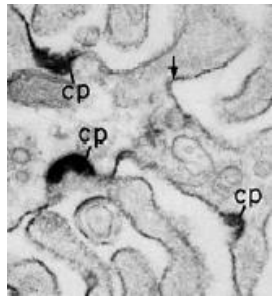


Renal BB

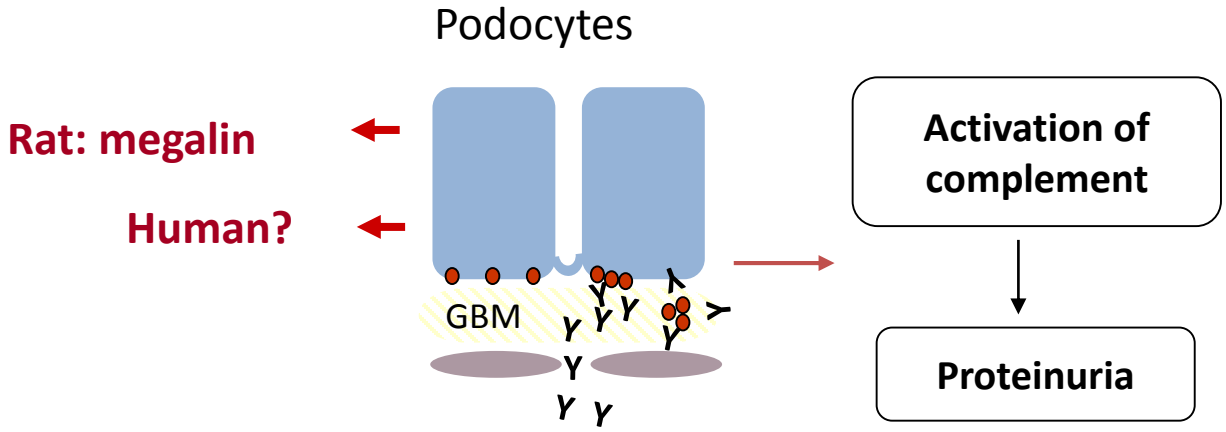


IgG deposits





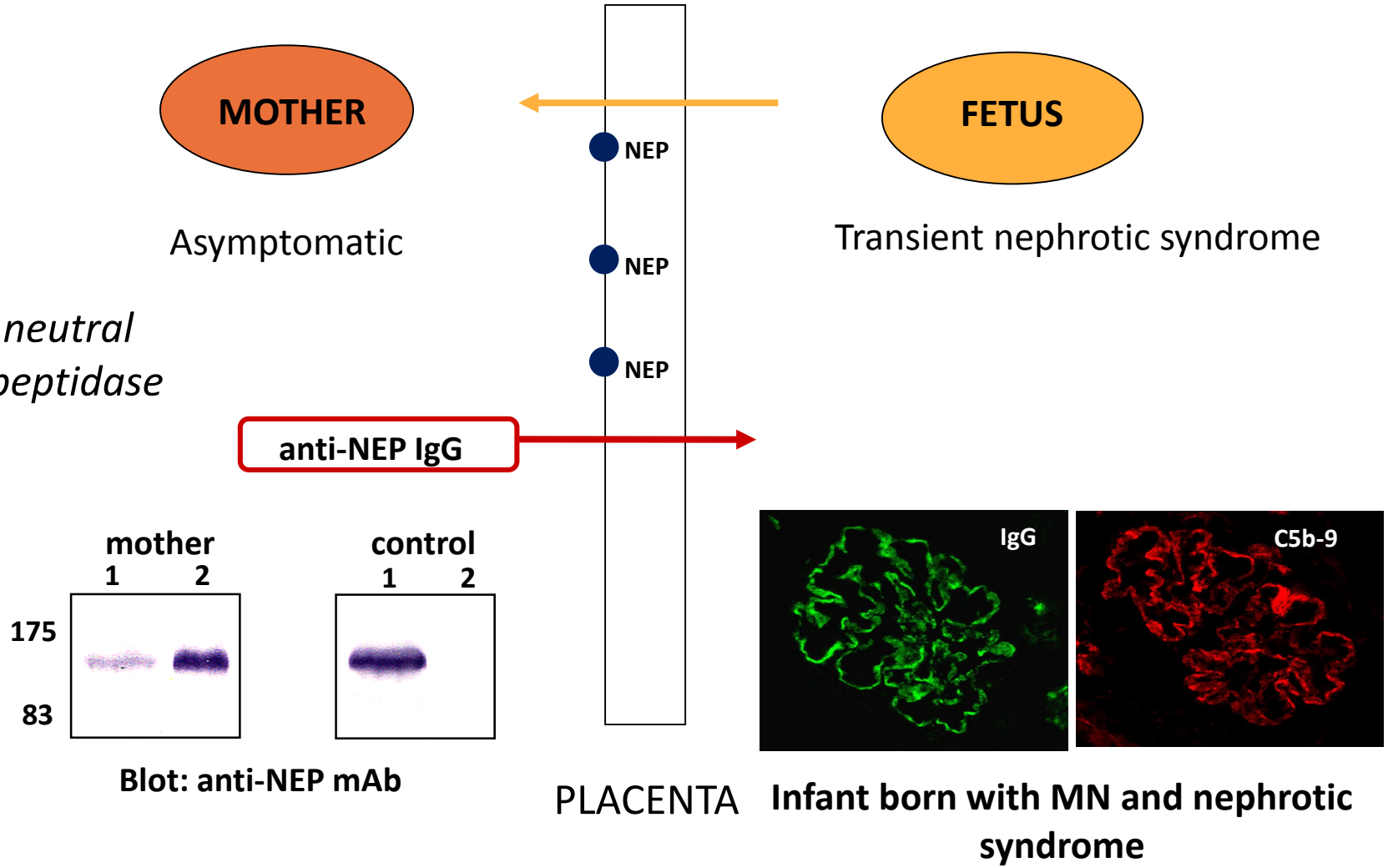
Megalin, the target antigen of HN



In situ formation of immune deposits

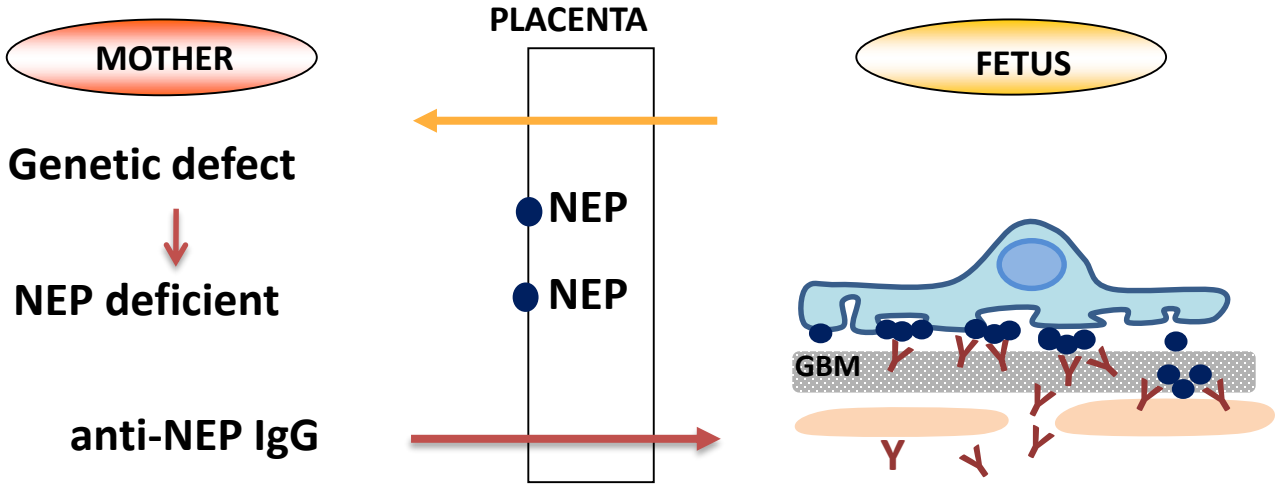
Kerjaschki and Farquhar PNAS 1982, 79:5557 ; Ronco et al J Immunol 1986, 136:125

Antigen identification from an extreme phenotype : Neonatal membranous nephropathy



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

From antigen identification to genetic defect



Five families

Morocco **Netherlands** **Portugal** **Germany** **Italy**

Debiec et al. N Engl J Med 2002 and Lancet 2004

Auto-immune « idiopathic » MN in adults

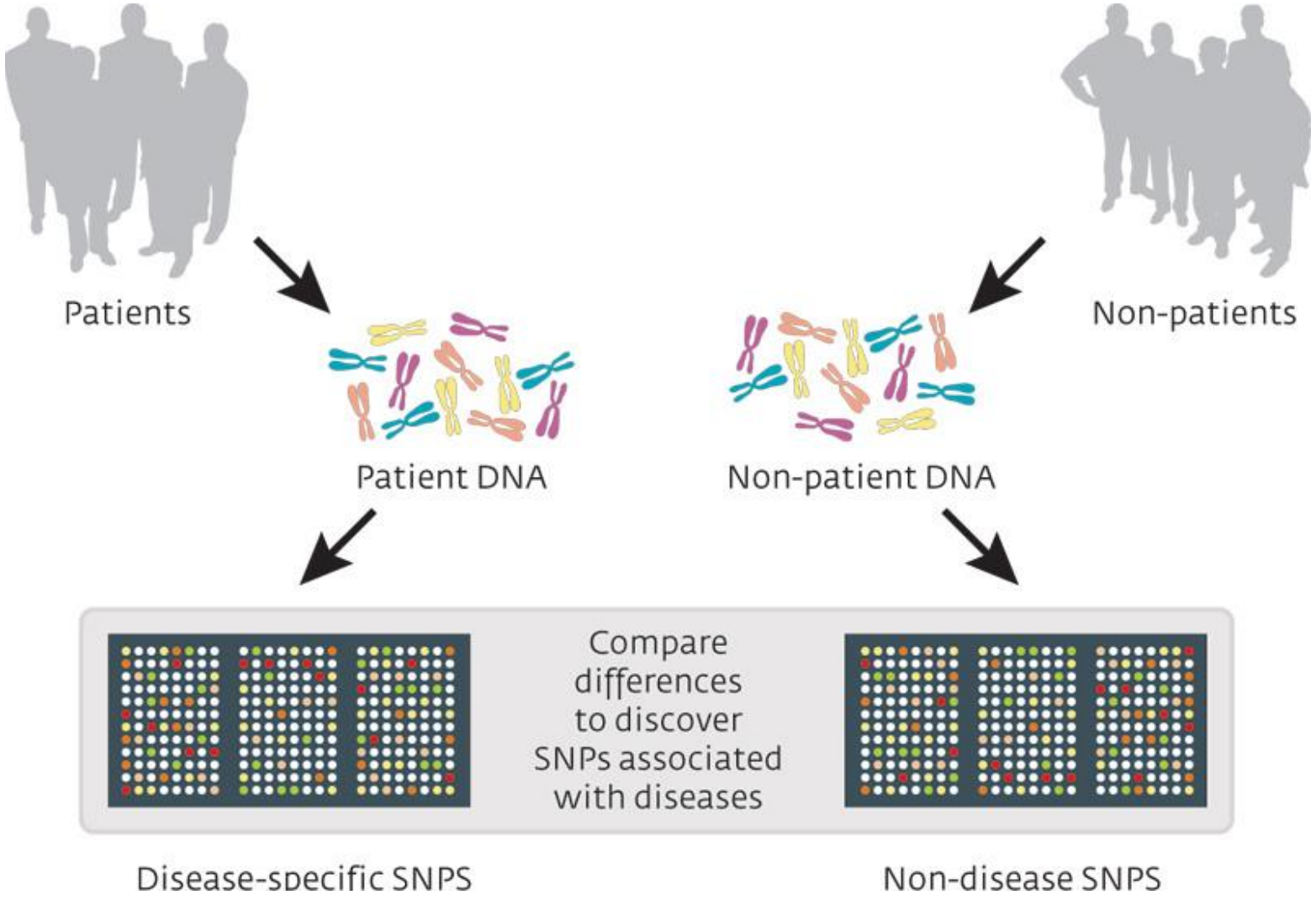
The NEW ENGLAND JOURNAL of MEDICINE

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

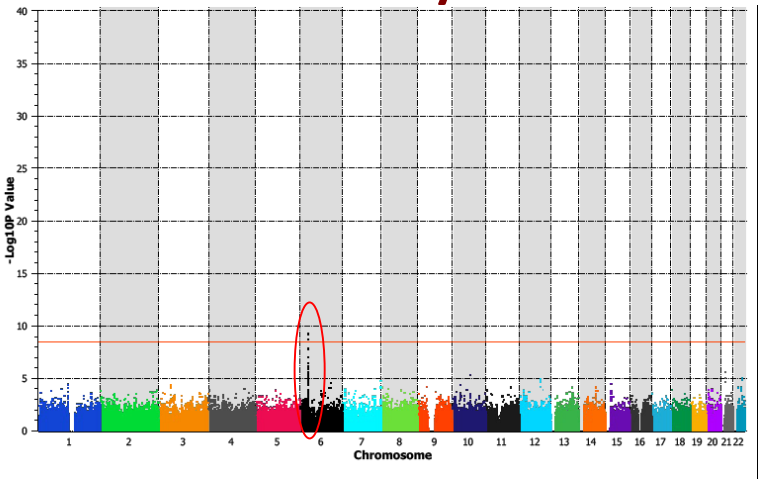
M-Type Phospholipase A_2 Receptor as Target Antigen in Idiopathic Membranous Nephropathy

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.

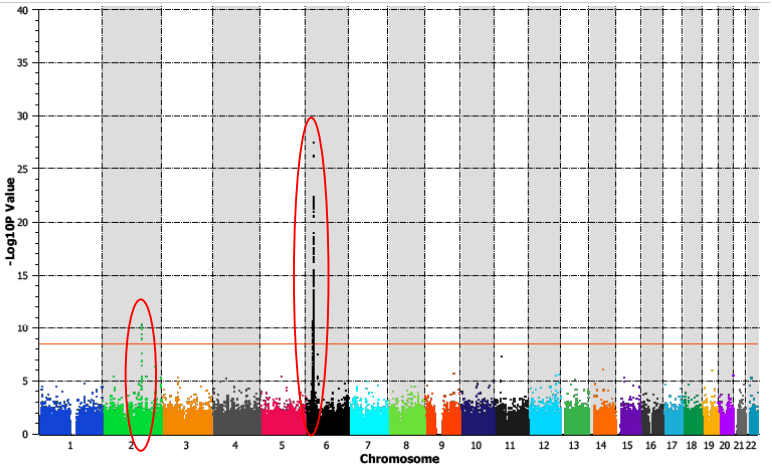
Principle of pangenomic (GWAS) studies



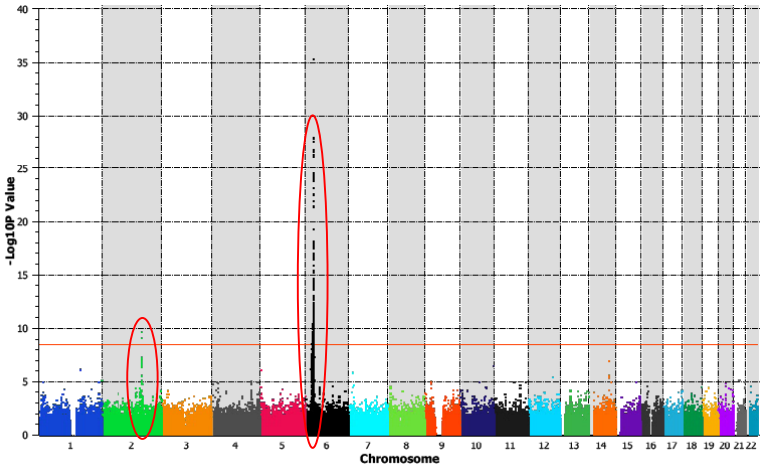
A risk HLA-DQA1 allele is associated with iMN and may interact with PLA2R alleles



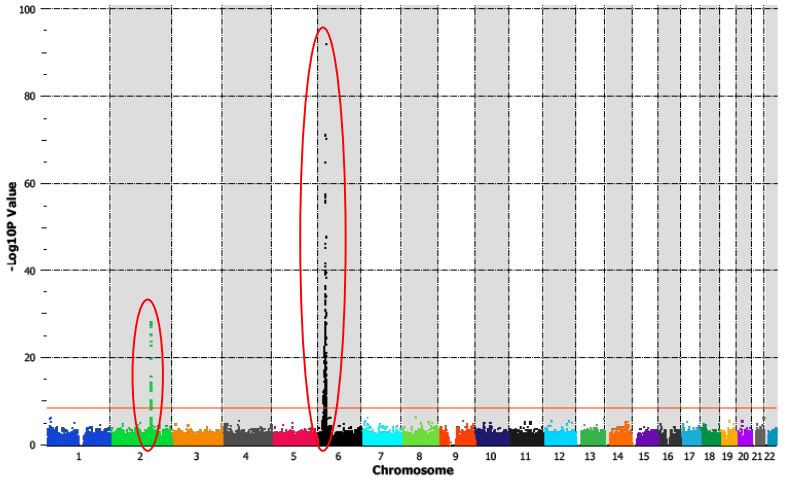
French (n=75 ; c=157)



Dutch (n=146 ; c=1832)



British (n=335 ; c=349)

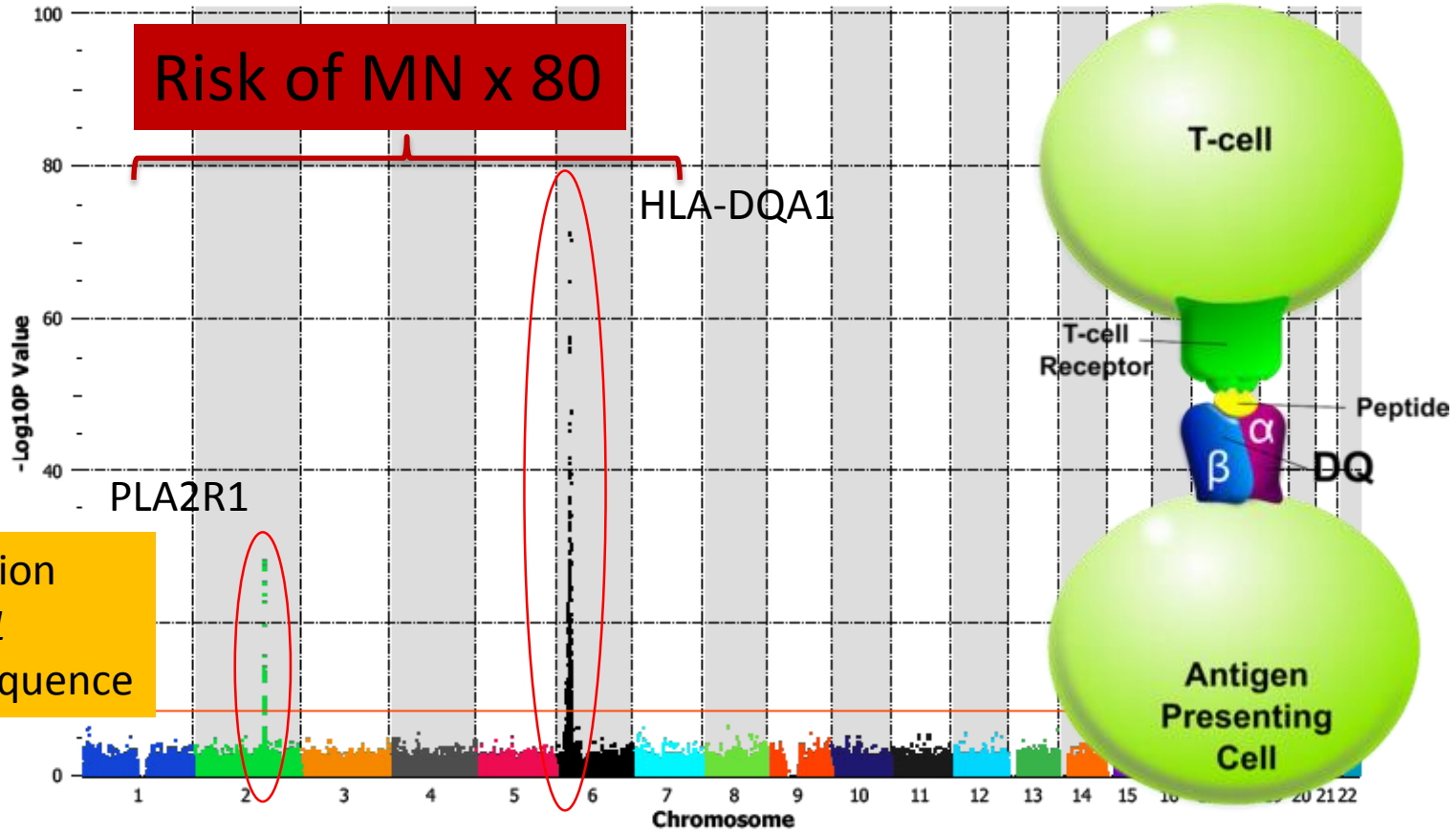


All patients (n=556; c=2338)

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

From polygenic disease to rare association of common variants

556 Patients ; 2338 controls (Euro MN Consortium = F+UK+NL)



No mutation in *PLA2R1* coding sequence

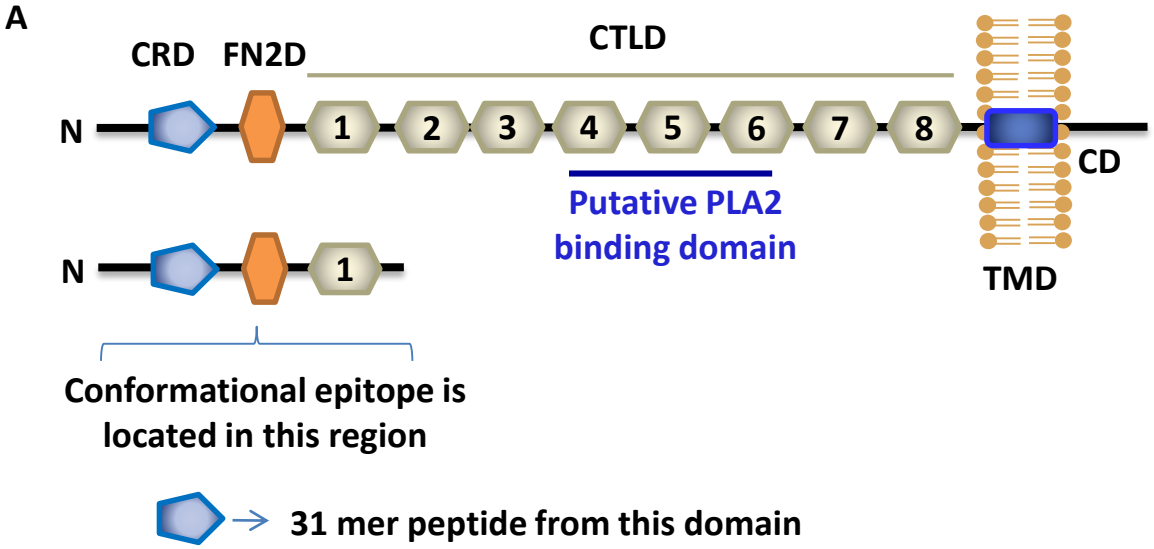
Stanescu et al, New Engl J Med, 2011, 364: 616 ; Coenen et al, J Am Soc Nephrol, 2013,24:677

Are anti-PLA2R antibodies pathogenic?

- Transfer experiments impossible because of lack of expression of PLA2R in mouse, rat and rabbit podocytes
- Lack of experimental model
- Strong predictive value of anti-PLA2R antibody
- Recurrence after transplantation : « The human model » of passive Heymann nephritis
- Exceptional case of recurrence related to PLA2R IgG3k mAb (Debiec et al, JASN 2012, 23:1949)

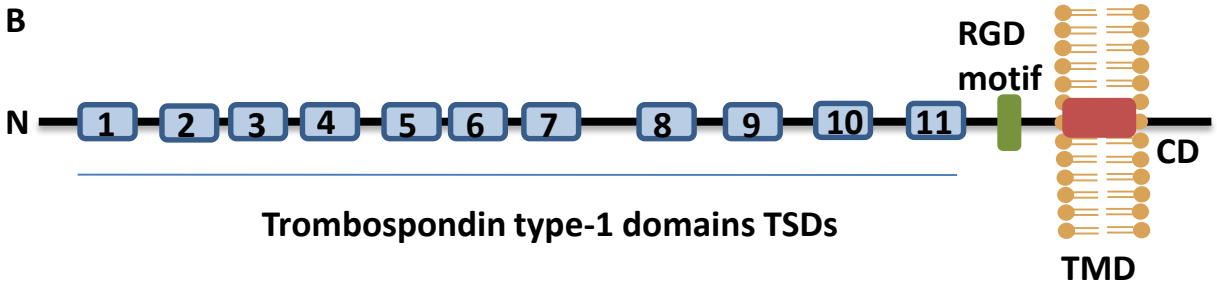
A new podocyte antigen in adult patients with MN : THSD7A

PLA2R



Kao et al, JASN 2014 , Sept 9 ;
Fresquet et al, JASN 2014, Oct 6

Thrombospondin type-1 domain containing 7A (THSD7A)



Tomas et al, NEJM 2014, 371: 2277

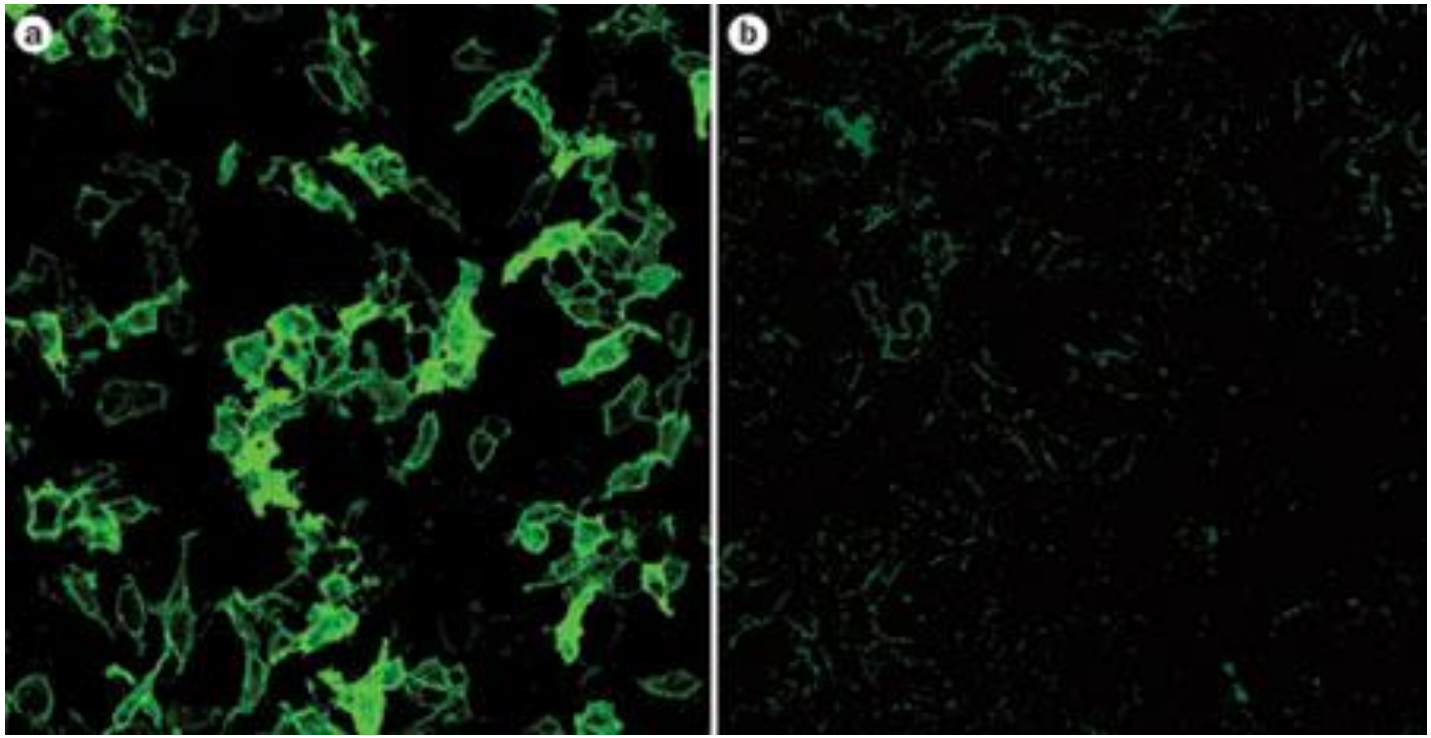
10 % of PLA2R-negative patients with MN

From the bench to the bedside : A success story of fast-speed translational research

NEPHROTIC SYNDROME

A new specific test for idiopathic membranous nephropathy

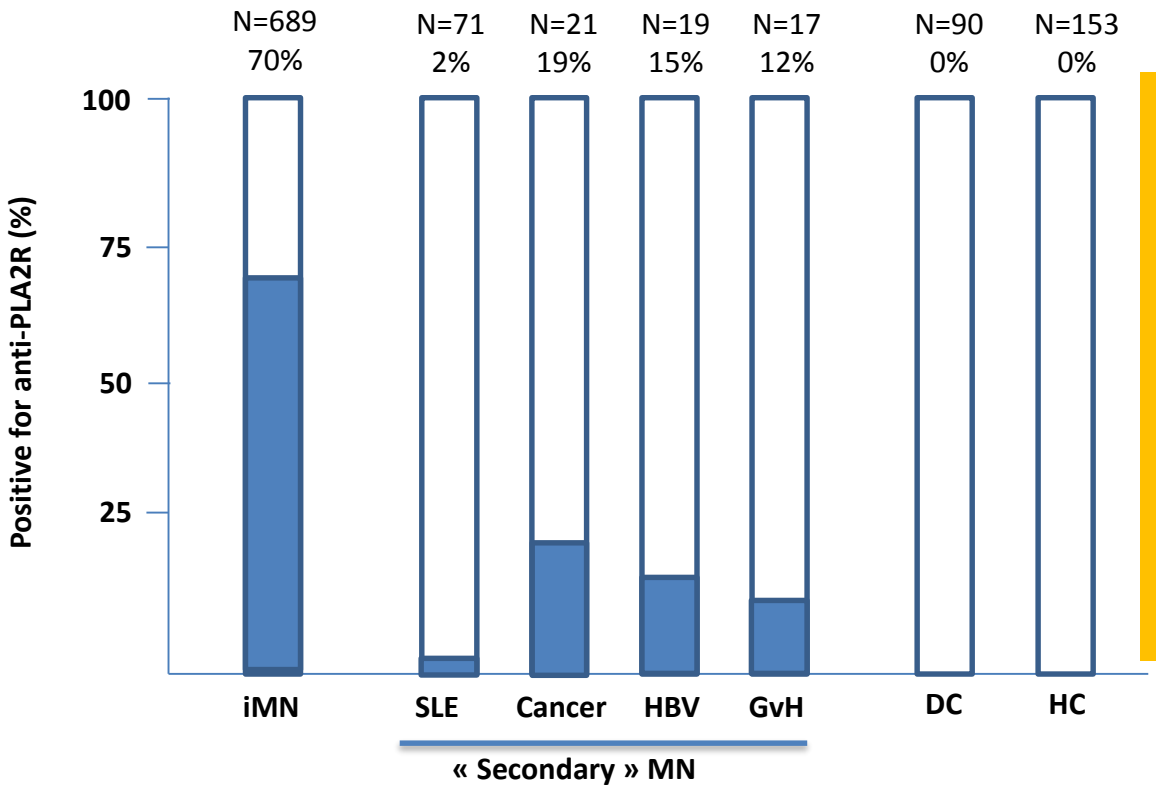
Hanna Debiec and Pierre Ronco



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

Hoxha E et al, NDT 2011, 26:2526

Specificity and sensitivity of PLA2R antibody



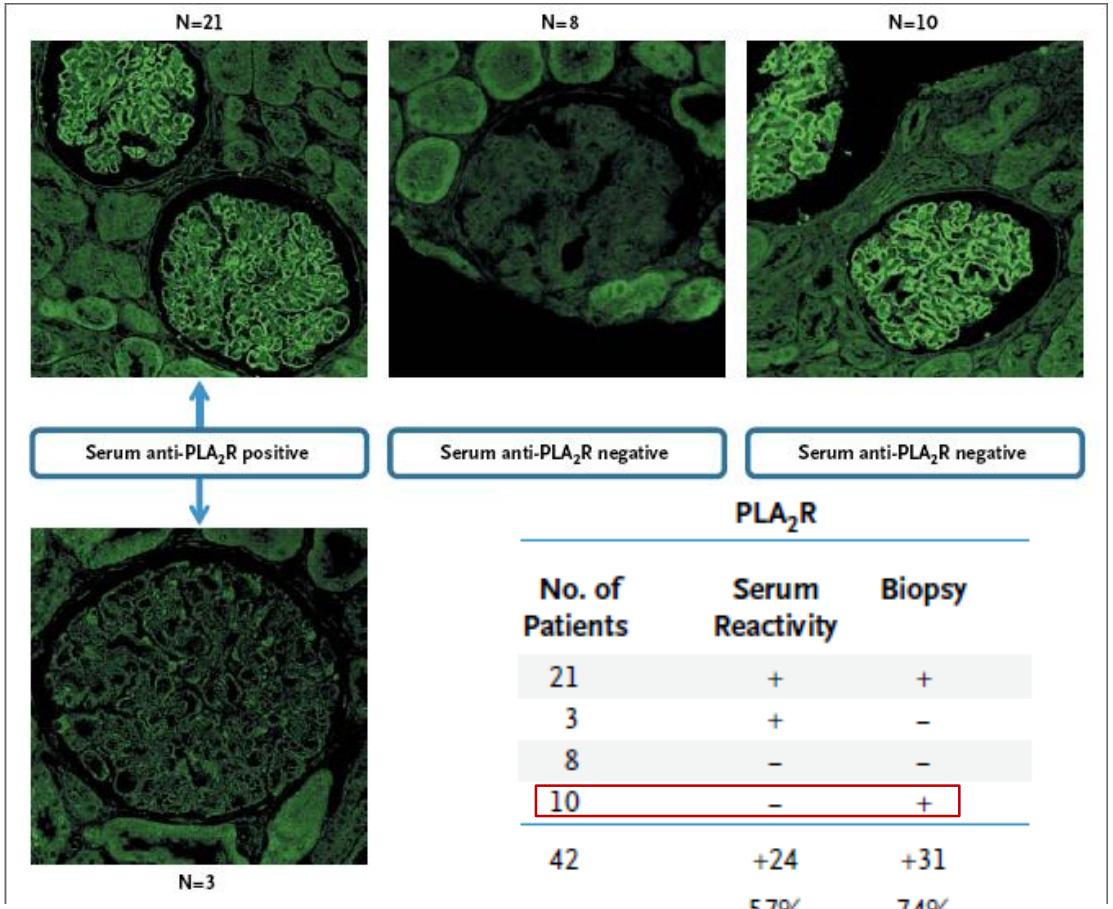
Meta-analysis (2014)

- 15 studies, 2212 patients
- **Specificity = 99%**
  (95% CI : 96-100%)
- **Sensitivity = 78%**
  (95% CI :66-87%)

Du et al, PLoSOne 2014, 9:e104936

Debiec ,Tesar and Ronco; Hofstra JASN 2012 ;
Hoxha et al, NDT 2011, KI 2012; Qin et al, JASN 2011

Antigen detection in biopsy is more sensitive than serology



	PLA$_2$R	
No. of Patients	Serum Reactivity	Biopsy
21	+	+
3	+	–
8	–	–
10	–	+
42	+24	+31
	57%	74%

Tenon cohort 2000-2014

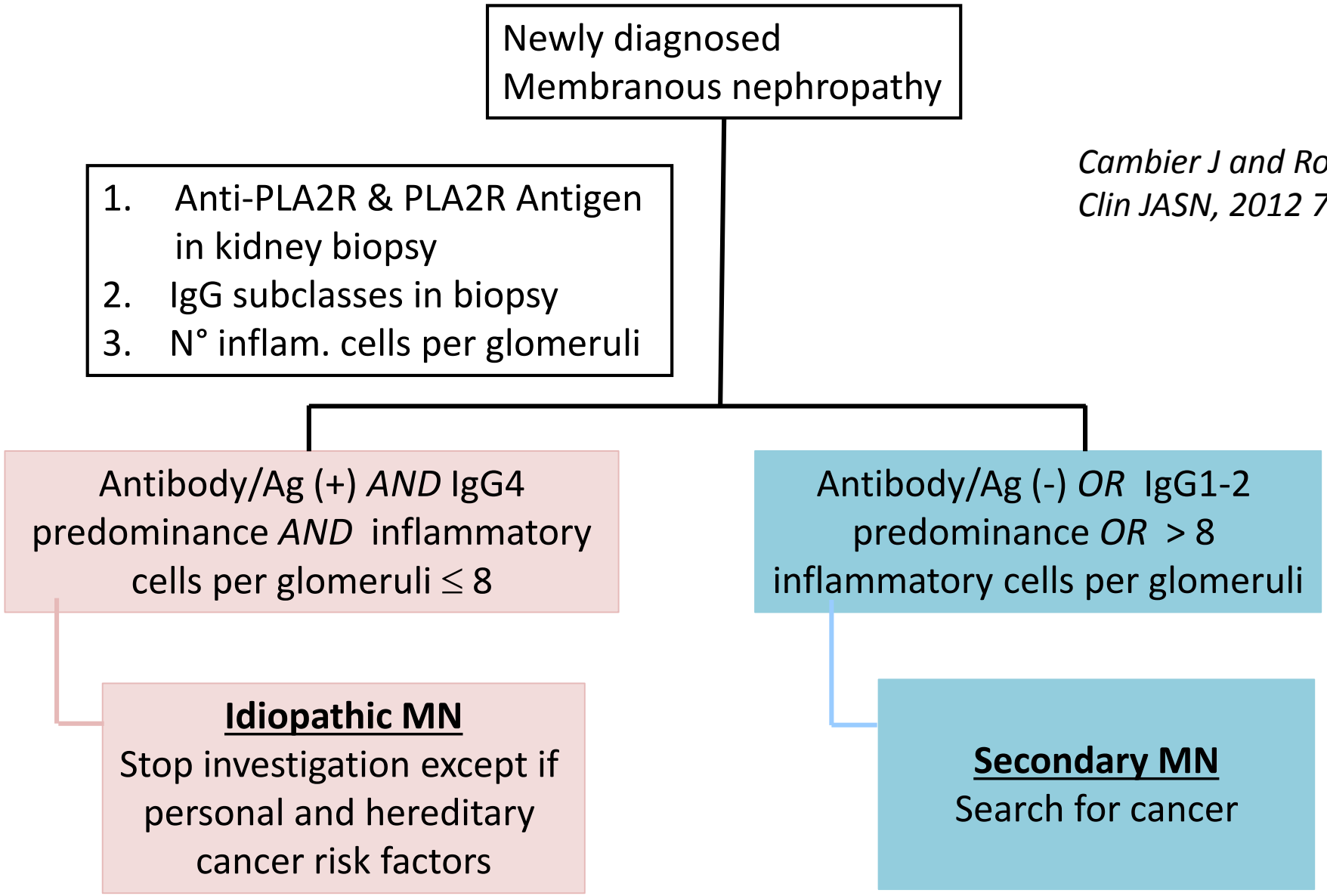
- n = 106 (84 iMN ; 22 sMN)
- sensitivity PLA2R - Ag : 86%
- " aPLA2R-Ab : 76%

Pourcine et al, unpublished

Retrospective diagnosis

Debiec and Ronco, New Engl J Med, 2011, 364 :689 ; Svobodova et al, NDT, 2013, 28:1839 ; Hofstra et al, J Am Soc Nephrol, 2012, 23:1735 ; Ruggenenti et al, J Am Soc Nephrol, 2015, March 24

Management of newly diagnosed MN



Cambier J and Ronco P, Clin JASN, 2012 7:1701

High levels of PLA2R-Ab are correlated with :

- A lower rate of remission, either spontaneous or induced by IS treatment
- A higher risk :

  - of occurrence of nephrotic syndrome in non-nephrotic patients

  - of renal function deterioration
- A longer time to remission under IS treatment

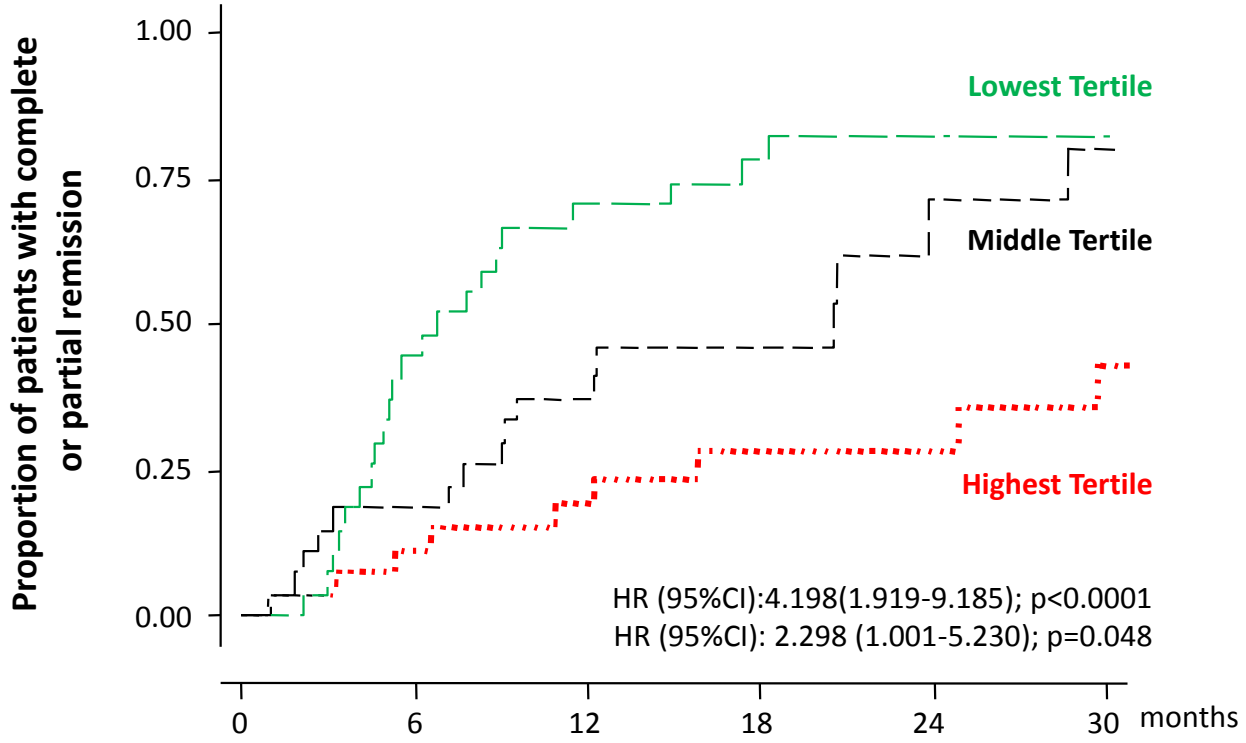
Kanigicherla D et al, Kidney Int 2013 83: 940 ;
Hofstra JM et al, JASN 2012 23: 1735 ; Hoxha E et al, JASN 2014 25:1357 ;
Ruggenenti P et al, JASN 2015, March 14; Hoxha E et al, PLoS One 2014 9:e110681

Predicting disease remission and relapse in patients treated with Rituximab

- Mario Negri cohort : 132 patients with idiopathic MN and long-lasting nephrotic syndrome
- Median follow-up of 31 months (6 to 145)
- 84/132 (63.6%) achieved complete or partial remission
- Antibodies measured by ELISA (EuroImmune)
- 81/101 (80%) with detectable antibodies (31 non available)

Ruggenenti, Debiec,…, Ronco, Remuzzi, J Am Soc Nephrol 2015 Mar 24.

Proportion of PLA2R-positive patients with remission is strongly dependent on antibody titer

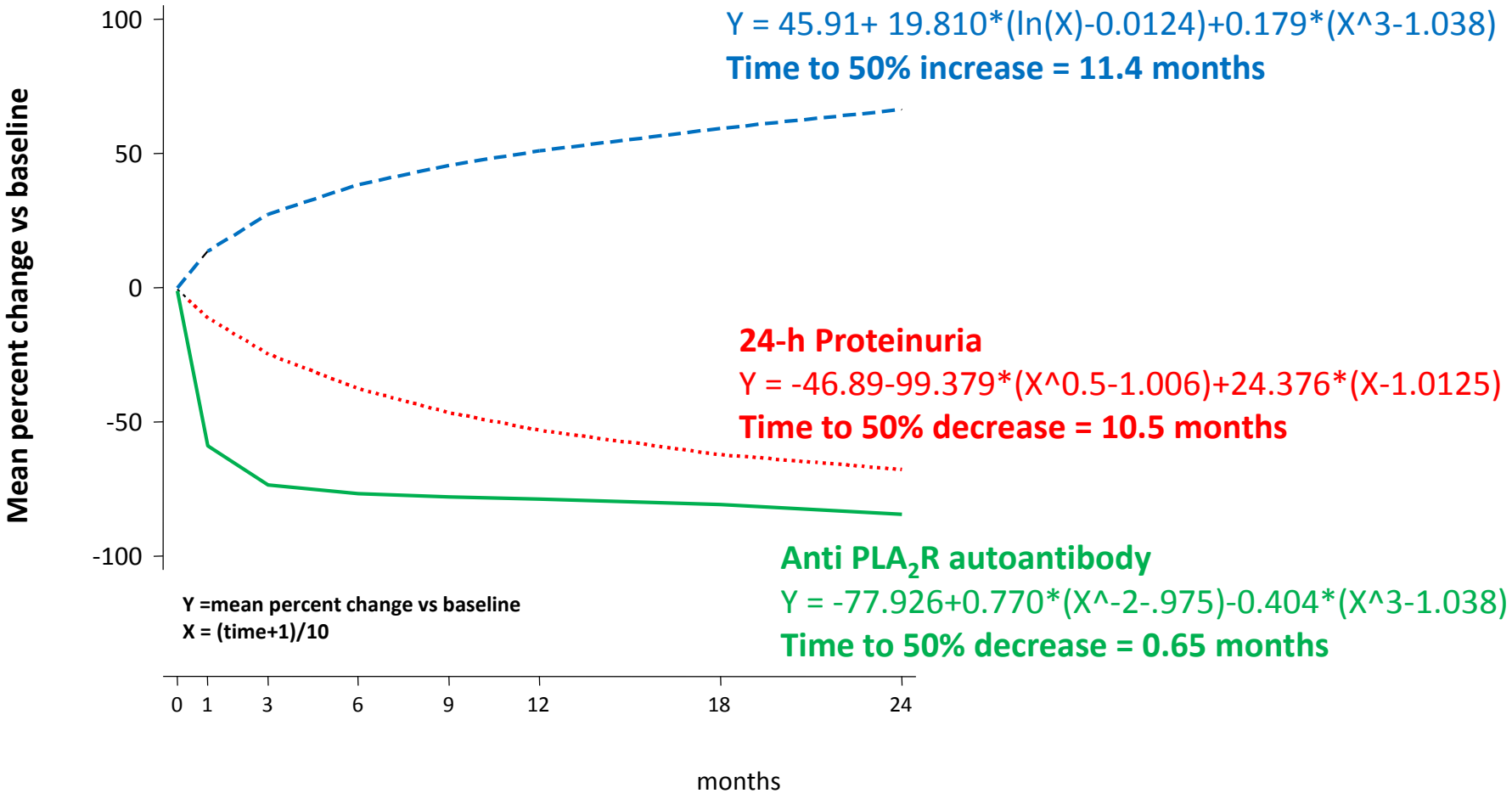


Patients at risk

Lowest Tertile	27	15	8	6	4	3
Middle Tertile	27	22	16	8	3	2
Highest Tertile	27	22	20	14	11	6

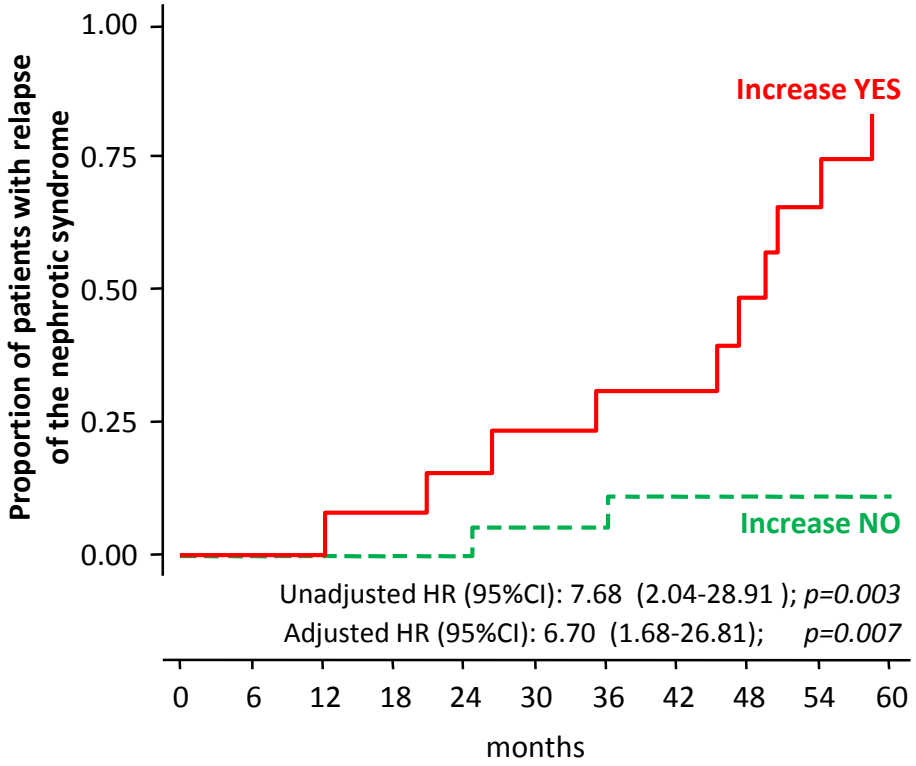
Ruggenenti, Debiec,…, Ronco, Remuzzi, J Am Soc Nephrol 2015 Mar 24.

Percent changes in proteinuria, serum albumin and anti-PLA2R antibody levels



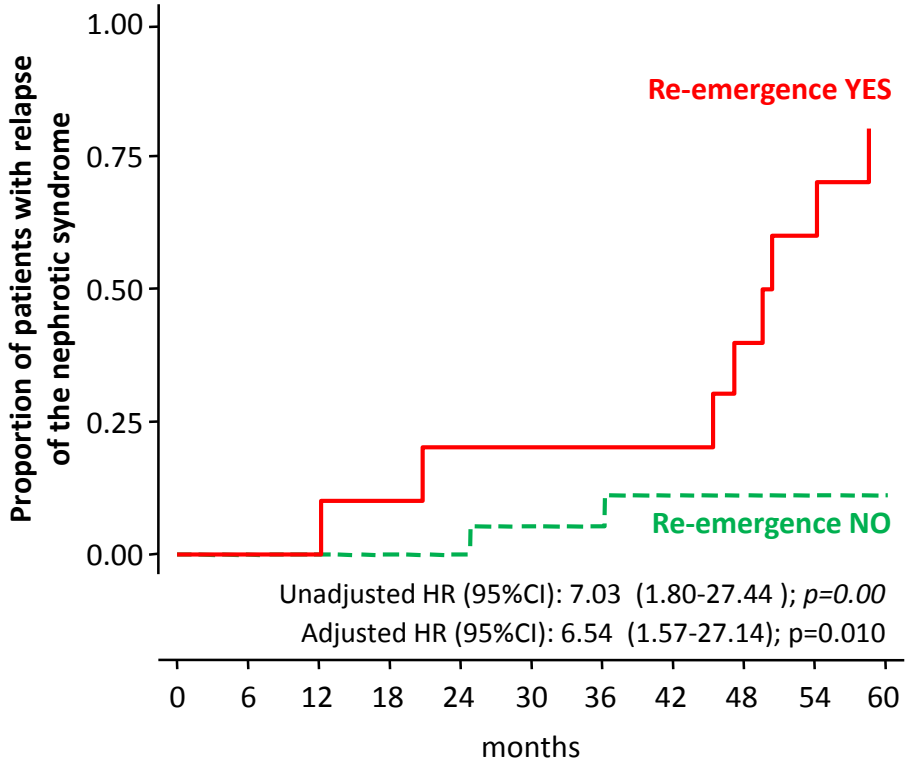
Ruggenenti, Debiec,…, Ronco, Remuzzi, J Am Soc Nephrol 2015 26:2545

PLA2R Ab titer increase or antibody re-emergence is associated with a high risk of relapse



Patients at risk

Increase NO	31	31	27	26	24	16	16	12	12	11	10
Increase YES	13	13	13	12	11	10	9	8	6	4	2



Patients at risk

Emergence NO	31	31	27	26	24	16	16	12	12	11	10
Emergence YES	10	10	10	9	8	8	8	8	6	4	2

Ruggenenti, Debiec,…, Ronco, Remuzzi, J Am Soc Nephrol 2015 26:2545

What should we do in 2015?

- Assess anti-PLA2R antibody in all adult patients with a suspected diagnosis of MN, starting with the IF test (specificity, 100% ; sensitivity, 70 to 80%), and anti-THSD7A antibody in PLA2R-negative patients

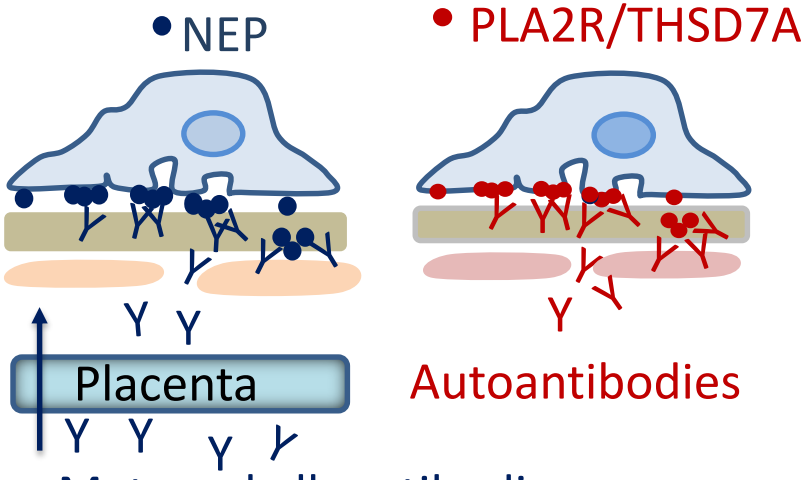
- Search for PLA2R antigen in kidney biopsies from all patients with MN, and for THSD7A in PLA2R-negative biopsies

- Determine Ig subclass in kidney biopsies from all patients with MN

- Monitor anti-PLA2R antibody titer during follow-up and in grafted patients with MN

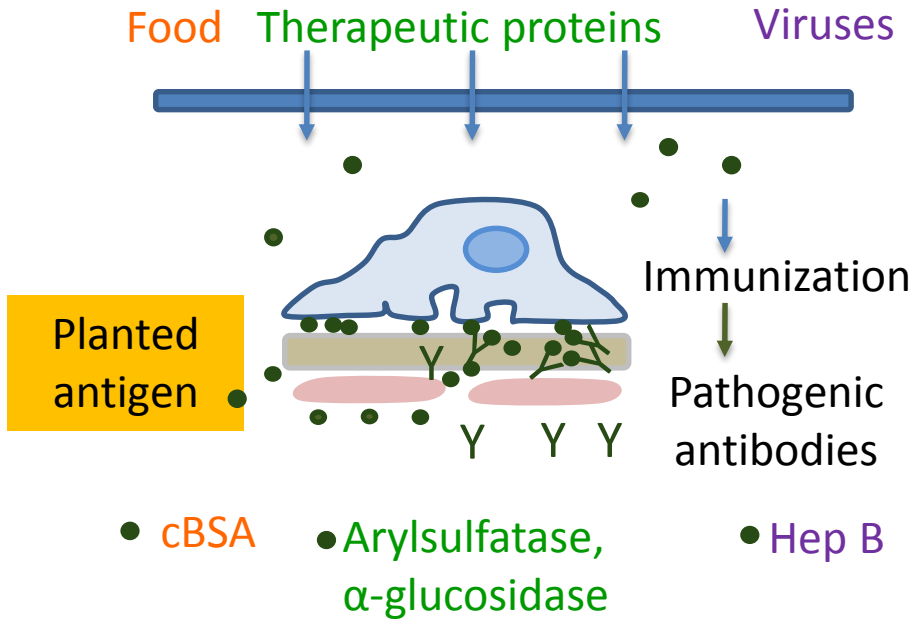
Antibodies and their targets

A **Endogenous antigen and allo- or autoantibodies**



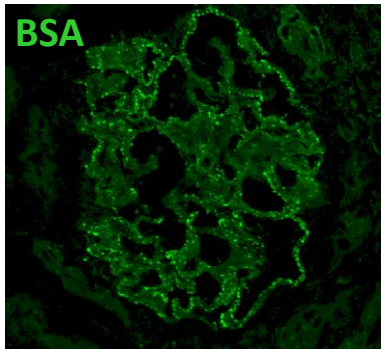
α-enolase
SOD2
Aldose reductase

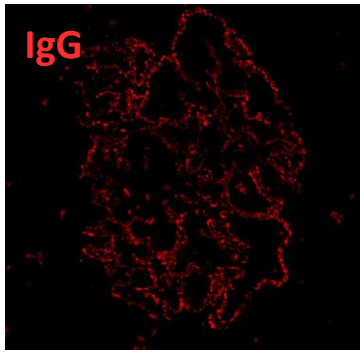
B **Exogenous antigen and allo- or xenoantibodies**

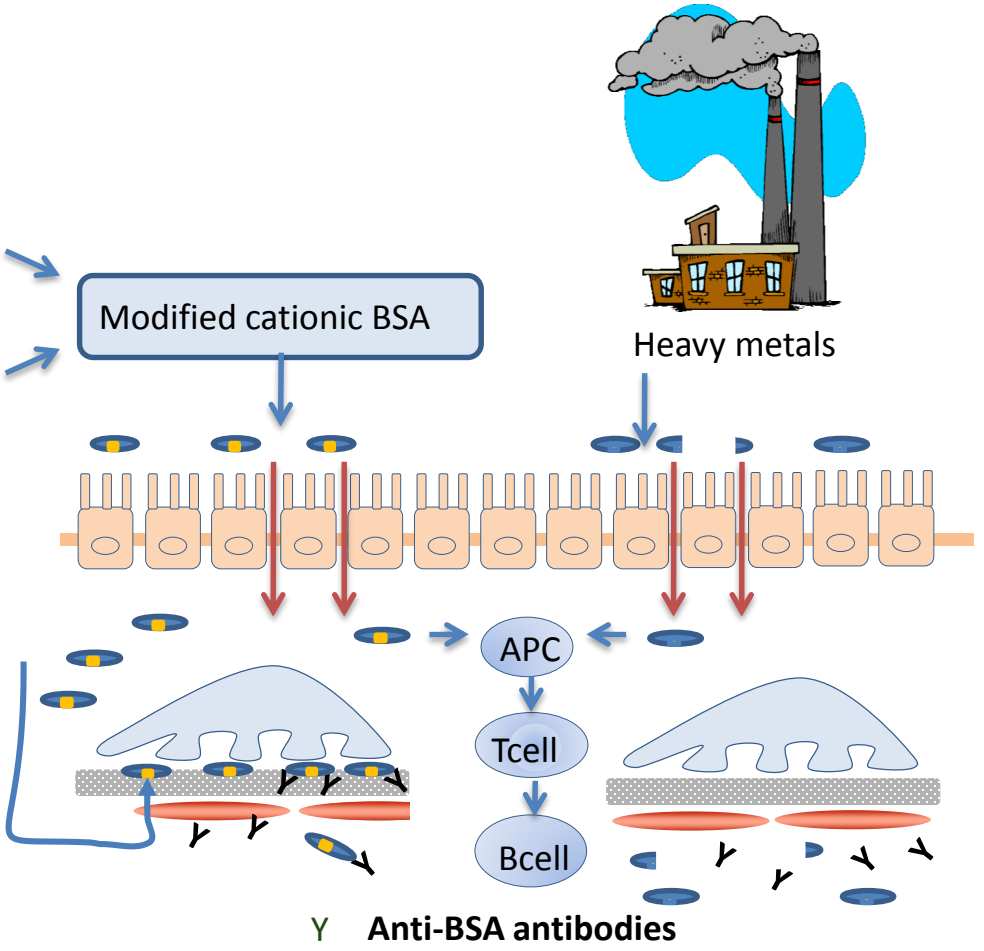


Debiec et al, Semin Immunopathol 2014, 36:381

Identification of new triggering factors : The example of bovine serum albumin (BSA)







Debiec et al, New Engl J Med, 2011, 364:2101

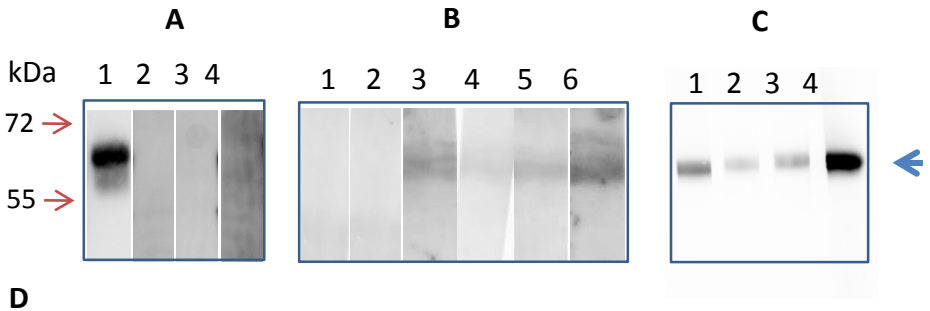
Why is it important to detect BSA antigen in immune deposits in children < 5 years ?

- Circulating anti-BSA antibodies are not rare in all ages, including adult patients with MN

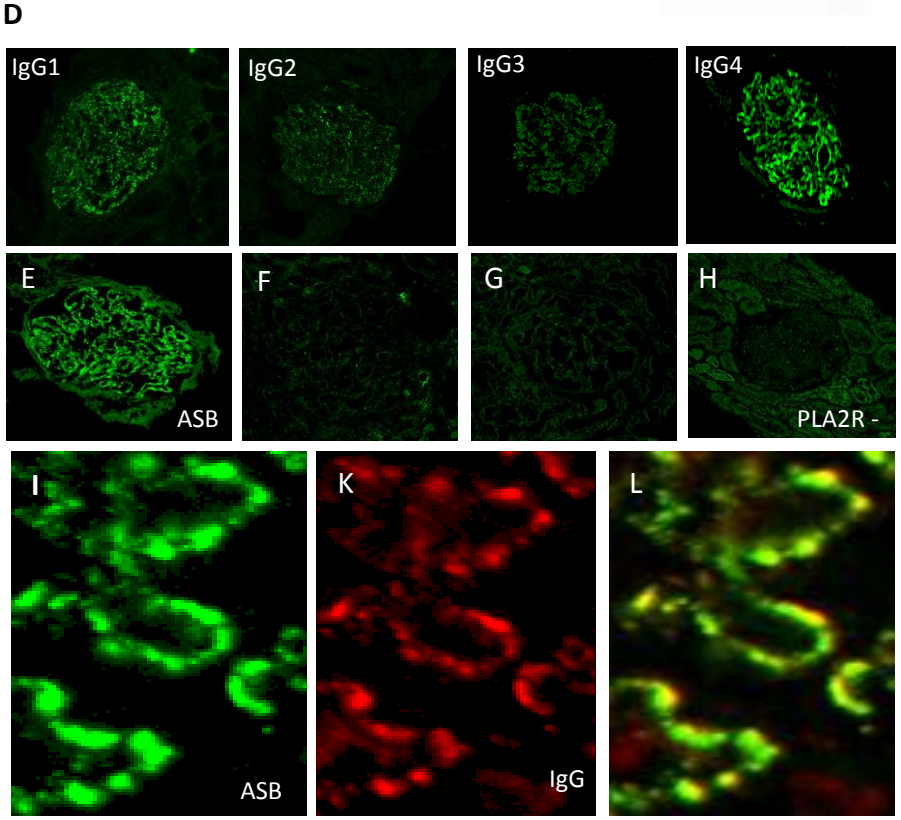
- Only children have circulating cationic BSA antigen together with circulating antibodies, and BSA antigen deposited in glomeruli

- Withdrawal of BSA from the food may cure the disease without steroids

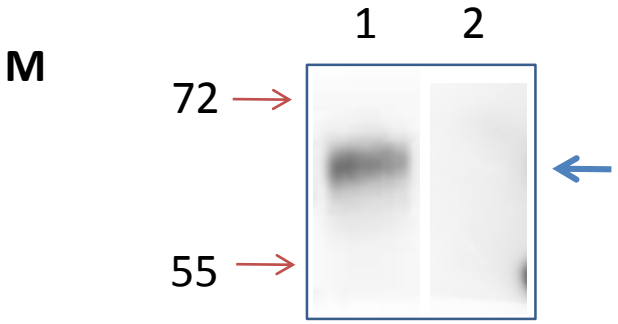
rhArylsulfatase B– induced allo-immune MN in a child treated with ERT



Circulating antibody

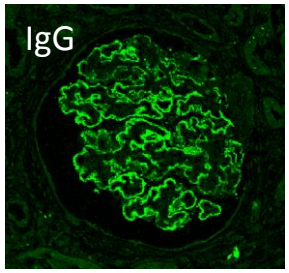


Eluted Ig



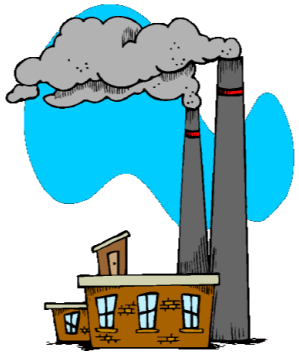
Debiec and Ronco, JASN, 2014, 25:475

From the podocyte to new therapeutic approaches of autoimmune diseases



Debiec et al, Lancet, 2015, 385:1983

Eliminating environmental factors: diet, toxin



Reducing autoantibodies

Depletion of B-cells (non specific)

Depletion of B-cells producing pathogenic antibodies

Development of antibody traps or decoys

ER stress

Ubiquitin proteasome system

Protecting the podocyte

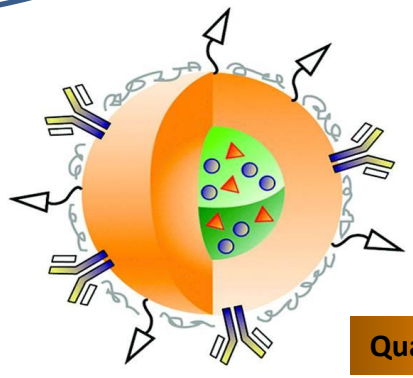
Inhibitors of ER stress

C5b-9 complex

Inhibiting complement activation

Drug design

B. Iorga, CNRS Gif



40-400 nm

Quantum Rattle

Humbury, PNAS 2015

D. Bazin & C. Sanchez, Collège de France

The expanding spectrum of human membranous nephropathies

- Neonatal, alloimmune : NEP
- Early childhood MN : cationic BSA
- Enzymotherapy-induced MN in patients treated with ERT
  - a-glucosidase
  - arylsulfatase
- « Idiopathic » MN
  - 75-85%: PLA_2R (+ other specificities : AR, SOD2, enolase…?)
  - <10 %: THSD7A (10% of PLA2R negative MN), associated with cancer?
- Secondary MN : Hep B antigens, other antigens to be identified
- Graft MN :
  - Recurrent : PLA2R (> 50%)
  - De novo : allo-immune

What's next ?

- Understand the genetic bases of disease triggering, spontaneous remission and progression by next generation sequencing

- Identify additional antigens and T cell populations involved in triggering and progression

- Design new therapeutic strategies based on specific immunointervention and complement inhibition

- Substitute molecular signatures for uniform histological definition : Towards new ontology…

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

EUReniOmics

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TENON CENTER OF NEPHROLOGY

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