

Maladies Auto-Immunes et Environnement:

Etude de la Glomérulonéphrite Extra- Membraneuse

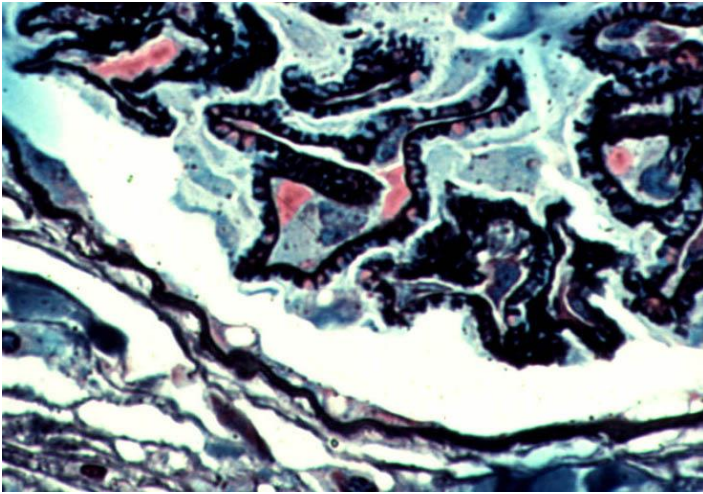
Dr Barbara Seitz-Polski

Laboratoire de Néphrologie

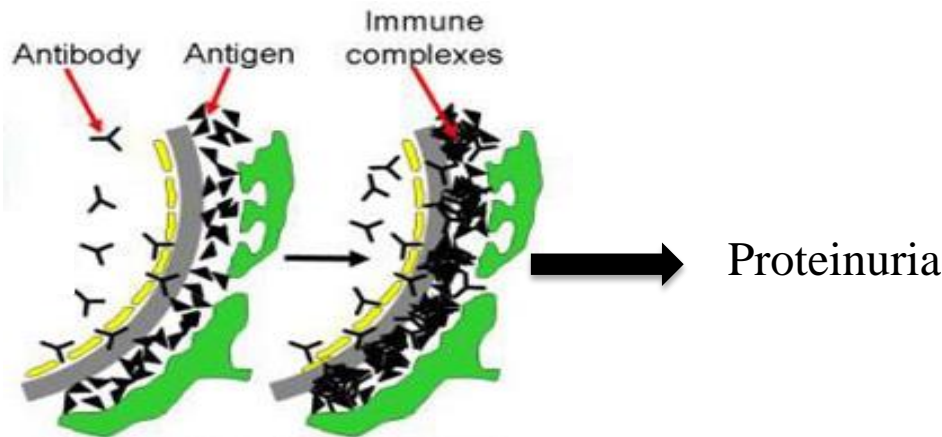
Centre de Référence Syndromes Néphrotiques

CHU de Nice

Glomérulonéphrite Extra-Membraneuse



- Maladie auto-immune rare :
1,3 cas pour 100 000
- H>F après 50 ans
- 1^{ère} cause de syndrome néphrotique
- Dépôts de complexes immuns (IgG4)
- 15% des cas secondaire LED, cancer, VHB, VHC
- 20% Thromboses

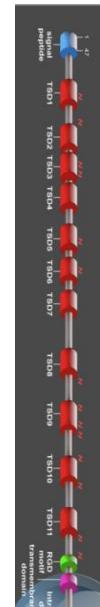


- 1/3 Rémission spontanée
- 1/3 Syndrome Néphrotique persistant
- 1/3 IRCT

PLA2R1

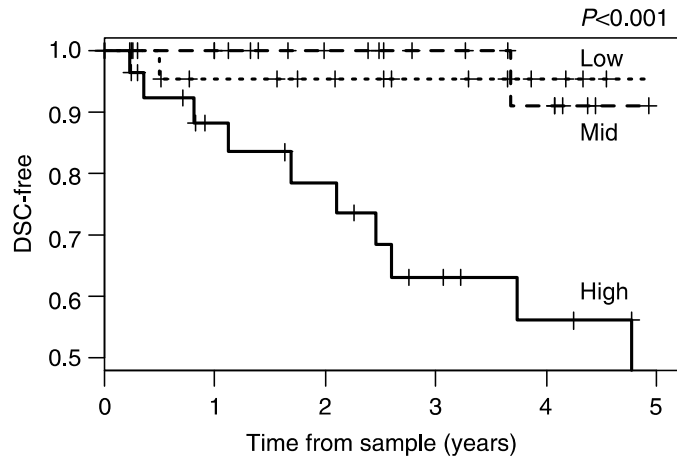


THSD7A



Titre d'Anticorps corrèle avec l'activité et prédit l'évolution

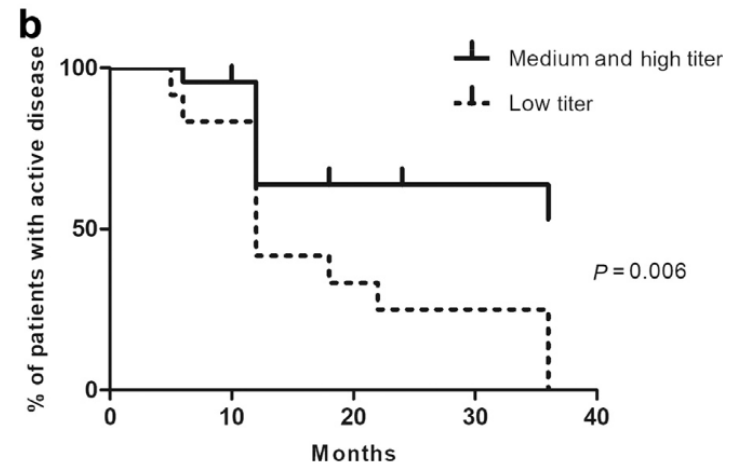
Anti-PLA2R1 Ab



Cohorte n=82

Kanigicherla et al., KI 2013

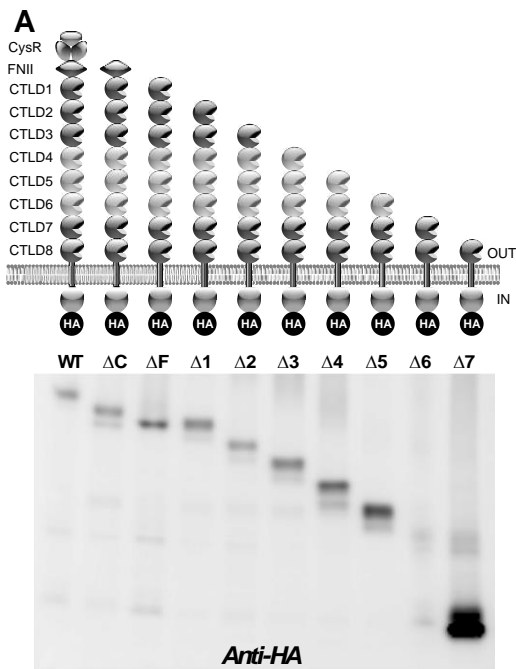
Anti-THSD7A Ab



Cohorte n=36

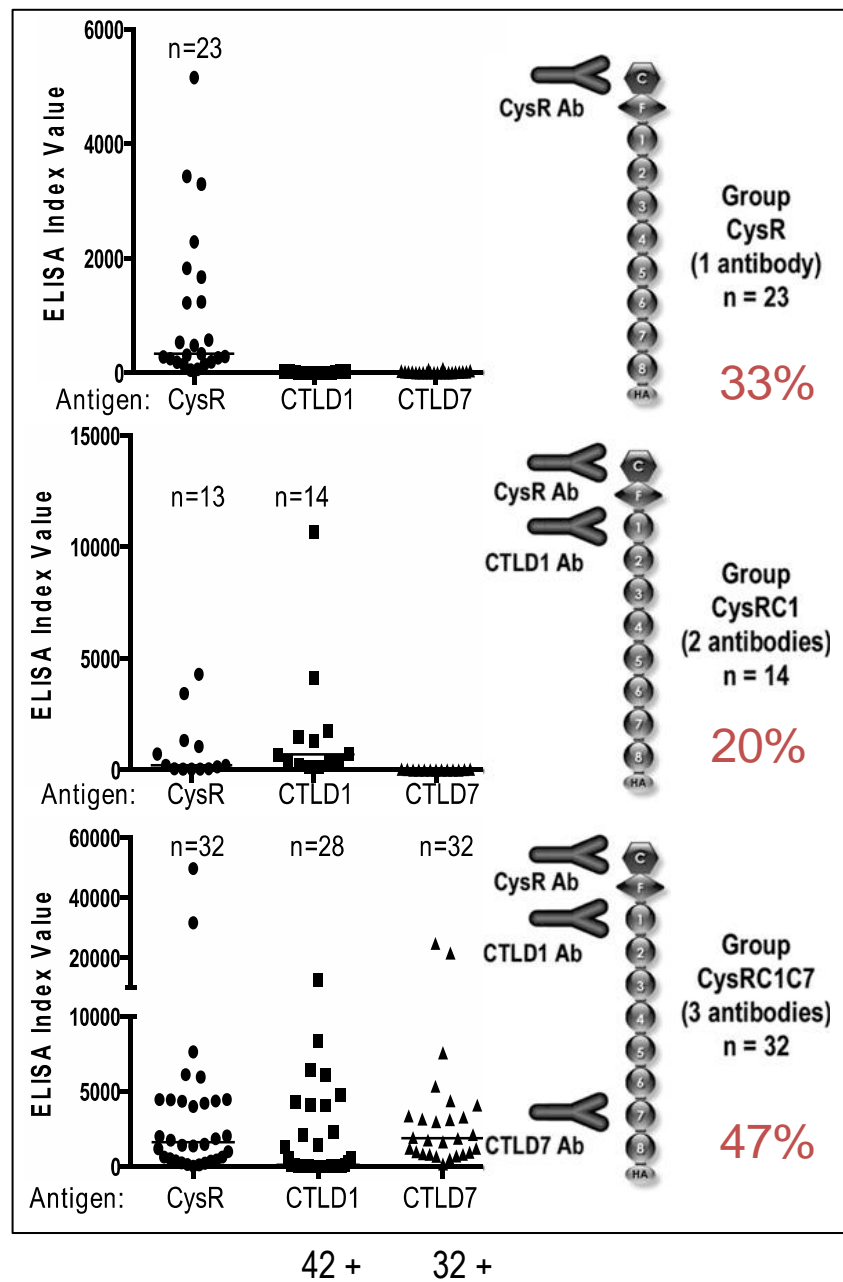
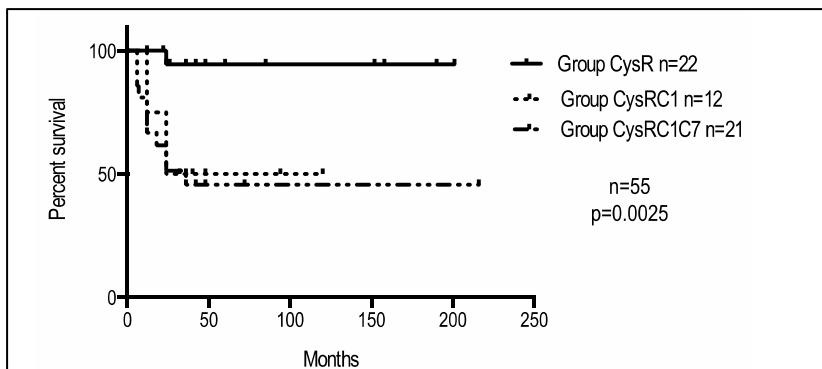
Zaghrini et al., KI 2019

Epitope Spreading et Pronostic

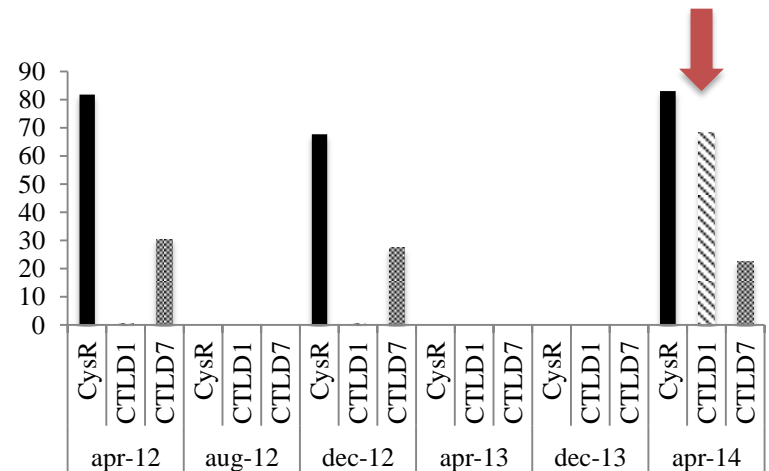
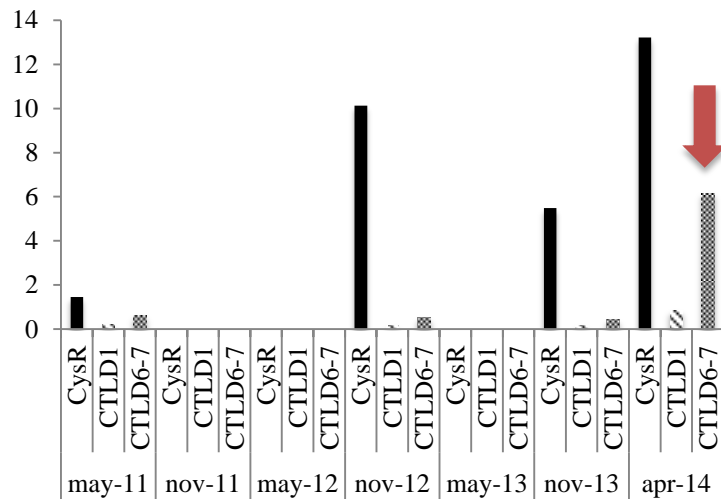
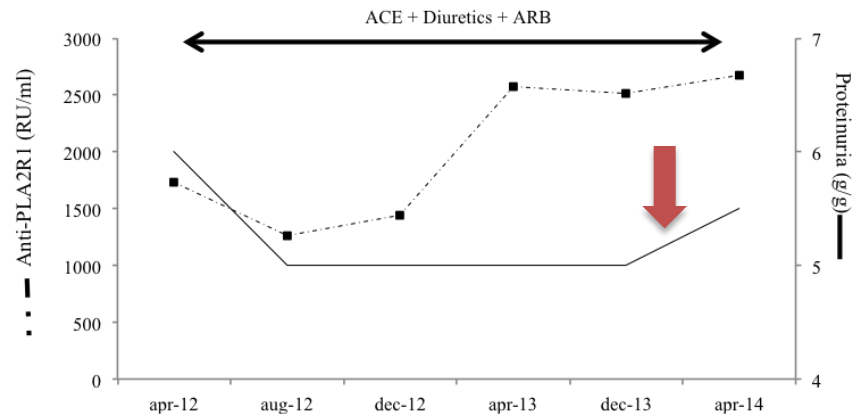
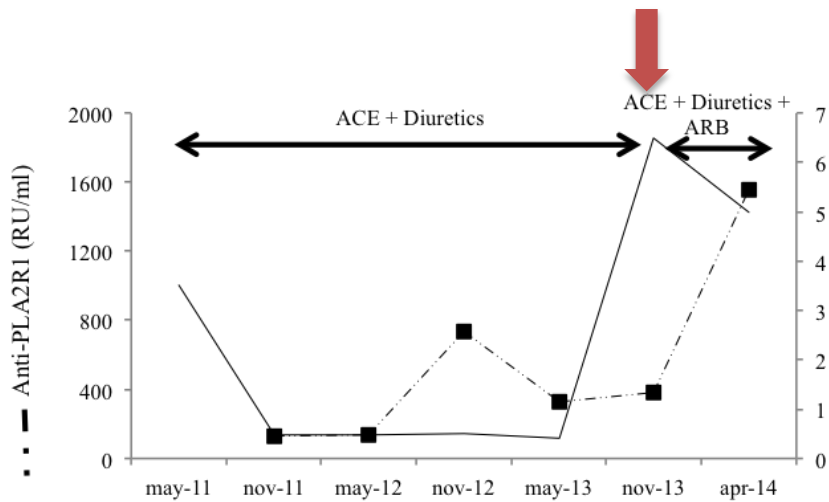


Expression of mutants

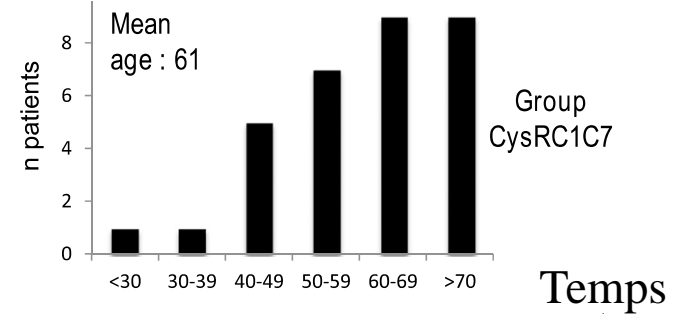
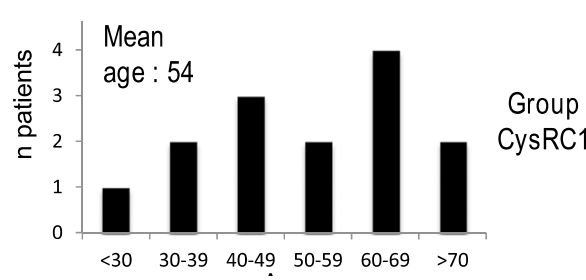
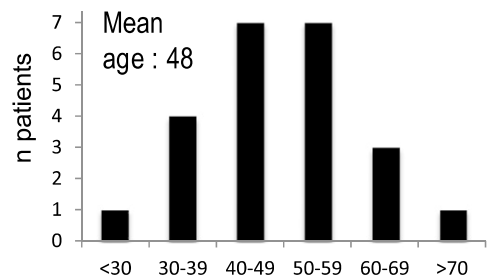
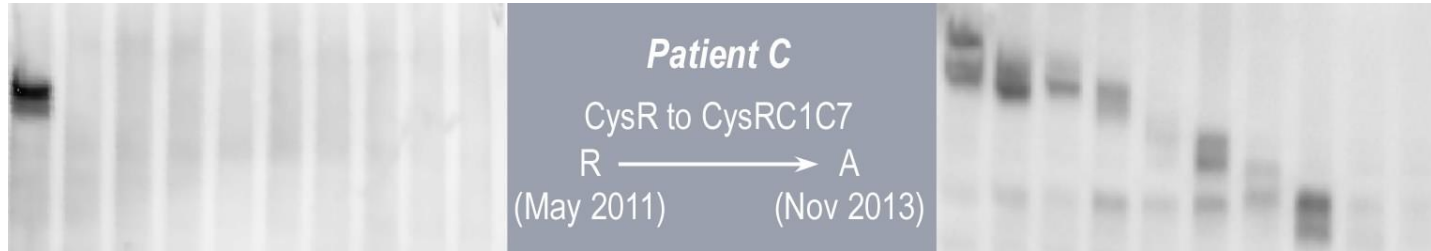
3 Profiles



Evolution au cours du suivi



Epitope Spreading : Histoire Naturelle



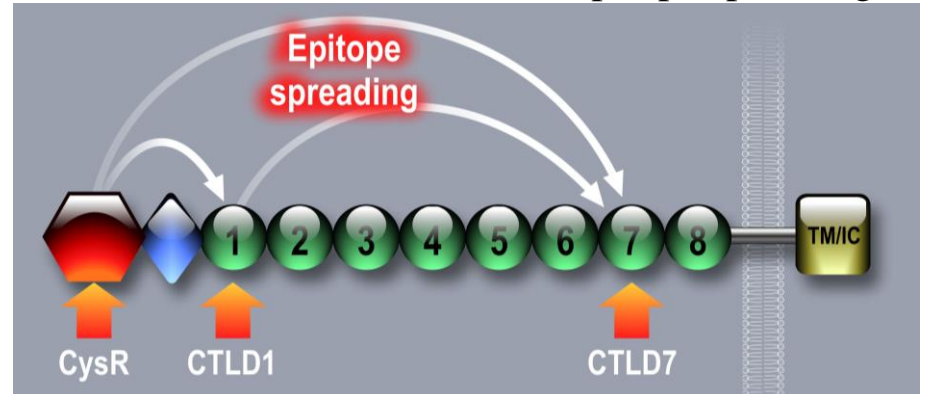
1^{er} évènement: anti-CysR activité

2^{ème} évènement: Intramolecular epitope spreading



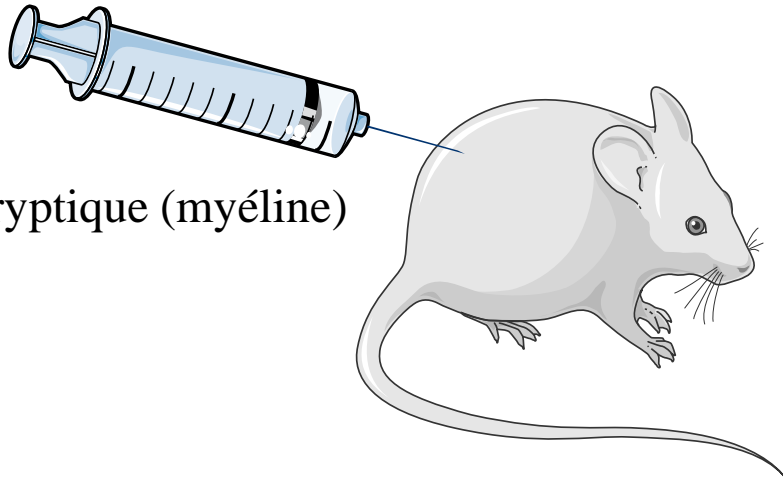
Mild disease

Spontaneous remission



Severe disease

Comment expliquer l'immunisation contre une protéine du Soi?

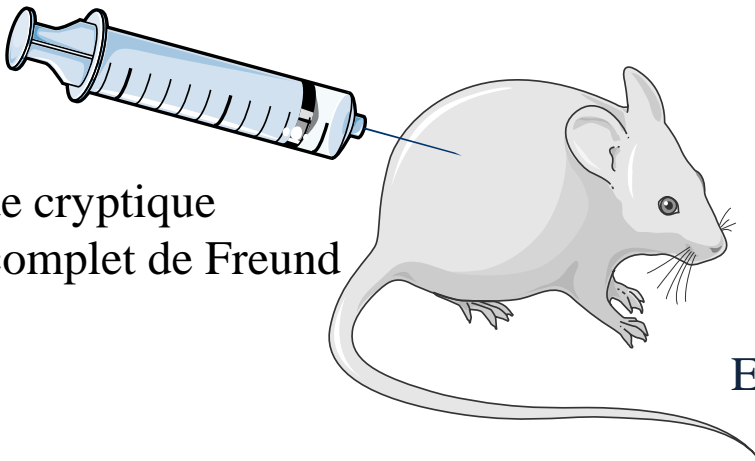


Peptide cryptique (myéline)

Pas d'encéphalite

*Importance des signaux de danger
pour l'activation des CPA
Expression du 2^{ème} signal de co-
stimulation*

Levée de l'anergie des LT

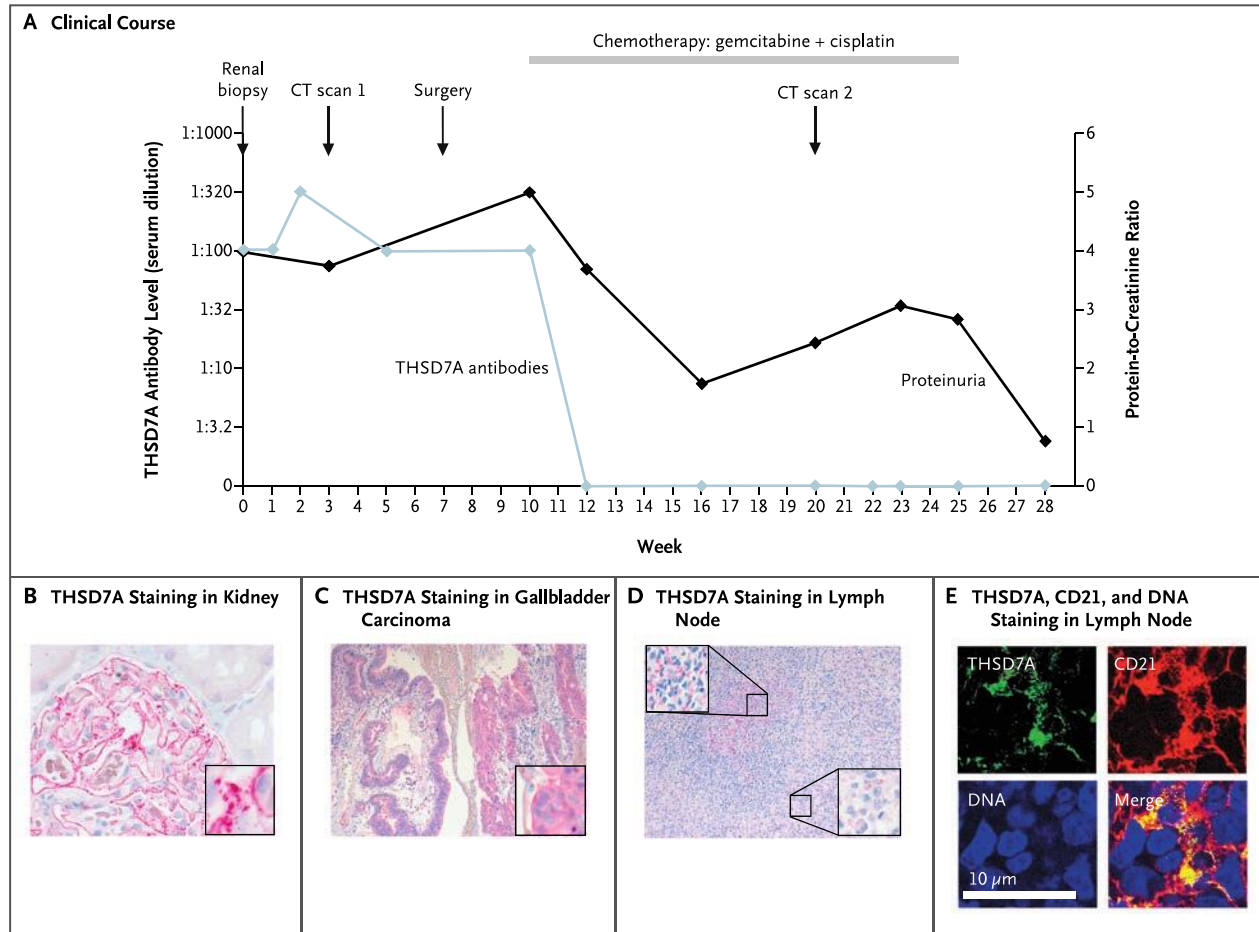


Peptide cryptique
+ adjuvant complet de Freund

Encéphalite

Encéphalomyélite auto-immune expérimentale

Ac Anti-THSD7A et Cancer

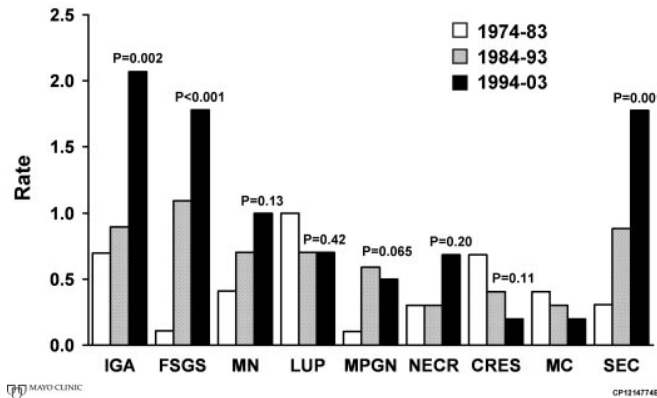


Hoxha NEJM 2016

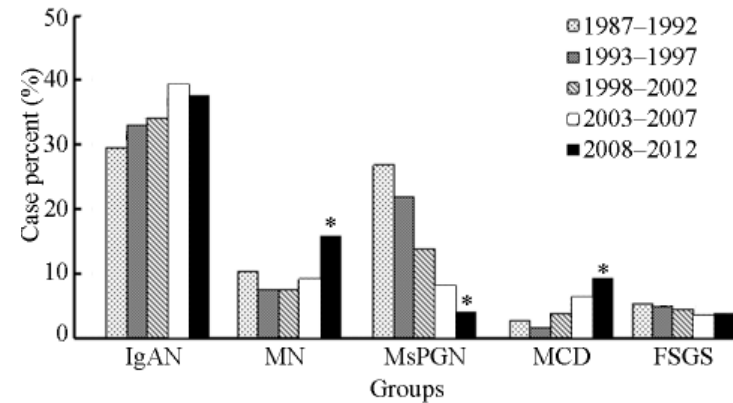
40 GEM THSD7A : 8 Cancers dans les 3 mois 20% *Hoxha JASN 2016*

Incidence des Glomérulopathies aux Etats-Unis et en Chine

Annual Olmsted County Age- Sex-Adjusted Rate per 100,000



Sundararaman CJASN 2006

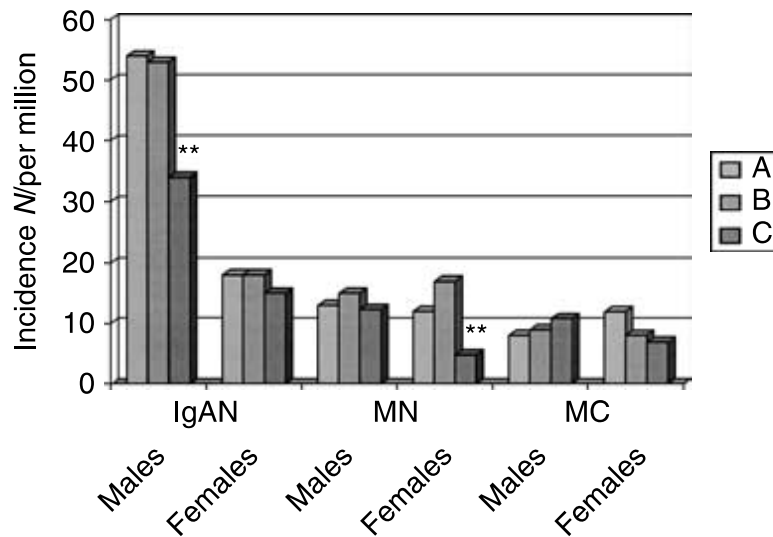


Zhang, Chin med 2014

Diminution des glomérulopathies post-infectieuses pour une augmentation des glomérulopathies « occidentales » secondaires au surpoids ou auto-immunes

Incidence des Glomérulopathies en France

Données issues des registres de biopsie du CHU de Rennes couvre Côtes d'Armor depuis 1976



variability of annual incidence of these two PGD during the study period suggests the possible role of some environmental factors such as infectious agents, drugs or solvents, which could be in contact with the aged population living in industrialized countries and which could create an alteration in immune balance of the T-helper subsets [4, 5].

Fig. 3. Annual incidence of primary glomerular disease (PGD) according to period and gender (incidence number/per million). Abbreviations are: IsAN, IgA nephropathy (Bergers' disease); MN, membranous nephropathy; MC, minimal change; A, period A.

Baisse significative de l'incidence annuelle chez les femmes que les auteurs attribuent sans démonstration à une diminution de l'exposition à différents facteurs environnementaux: médicaments, agents infectieux, solvants organiques

Rôle des solvants organiques

Table 2. Solvent exposure by main job categories according to expert assessment

Jobs	n	% Exposed	
		Any Level	High Level
Professional technical workers	285	18	6
technicians: architects, engineers	45	31	9
life scientists and related technicians	13	77	61
sculptors, painters, creative artists	13	38	0
Administrative and managerial workers	50	6	4
Clerical workers	171	2	0
Sales workers	94	0	0
Service workers	142	3	0
Agricultural workers	20	0	0
Production and transport workers	355	32	22
production supervisors and general foremen	16	31	25
blacksmiths, toolmakers and machine tool operators	22	27	27
machinery fitters, machine assemblers	33	48	36
electrical and electronics workers	37	30	8
plumbers, welders	37	46	35
painters	7	100	86
construction workers	58	41	17
material-handling and transport workers	53	8	3
manual workers	24	26	17
Total	1117	17	9

Table 4. HR of ESRD associated with exposure before diagnosis for each histologic type^a

Parameter	n	No. of Events	Model 1 ^b (HR [95% CI])	Model 2 ^c (HR [95% CI])	Model 3 ^d (HR [95% CI])
Expert assessment					
IgAN					
no ^e	145	26	Reference	Reference	Reference
low ^f	24	6	1.6 (0.7 to 4.0)	1.6 (0.7 to 3.9)	2.0 (0.8 to 4.8)
high ^g	25	10	2.6 (1.3 to 5.5)	2.2 (1.0 to 4.8)	1.8 (0.8 to 3.9)
MN					
no	49	3	Reference	Reference	Reference
low	11	3	4.0 (0.8 to 21.4)	3.1 (0.5 to 18.2)	3.1 (0.5 to 20.0)
high	15	6	8.7 (2.1 to 35.1)	8.2 (1.9 to 34.7)	5.5 (1.3 to 23.9)
FSGS					
no	47	19	Reference	Reference	Reference
low	12	0	—	—	—
high	10	3	0.5 (0.2 to 1.8)	0.7 (0.2 to 2.4)	0.5 (0.1 to 2.1)
all					
no	241	48	Reference	Reference	Reference
low	47	9	1.0 (0.5 to 2.1)	1.0 (0.5 to 2.2)	1.0 (0.5 to 2.1)
high	50	19	2.2 (1.3 to 3.7)	2.2 (1.2 to 3.8)	1.6 (0.9 to 2.9)

Rôle de la vaccination

Campagne de vaccination universelle en 1984

TABLE 1 HBV Seropositivity and HBVMN in Children With NS

Group (Time Period of Hospitalization)	Total Patients With NS, <i>N</i>	Patients With HBsAg-Seropositive NS, <i>n</i> (%) ^a	Patients With HBsAg-Seropositive NS Via Horizontal Transmission, <i>n</i> (%) ^a	Total HBVMN, <i>N</i> (%) ^a	HBVMN Via Horizontal Infection, <i>n</i> (%) ^a	Focal Segmental Glomerulosclerosis, <i>n</i> (%)
A (July 1974– June 1984)	138	20 (14.5)	20 (14.5)	16 (11.6)	16 (11.6)	10 (7.2)
B (July 1984–June 1994)	133	9 (6.8)	9 (6.8)	6 (4.5)	6 (4.5)	10 (7.5)
C (July 1994–June 2004)	140	5 (3.6)	4 (2.8)	3 (2.1)	2 (1.4)	11 (7.9)
D (July 2004–June 2009)	60	1 (1.7)	1 (1.7)	0 (0.0)	0 (0.0)	6 (10.0)

Wilcoxon signed rank-sum test was used to test the trend in incidence change between 1974 and 2009. Horizontal transmission infection is HBV infection with negative maternal HBsAg status.

^a $P < .05$.

Données issues du registre d'hospitalisation pour SNI du Taoyan Armed Forces General Hospital, Taiwan

Rôle de la pollution industrielle

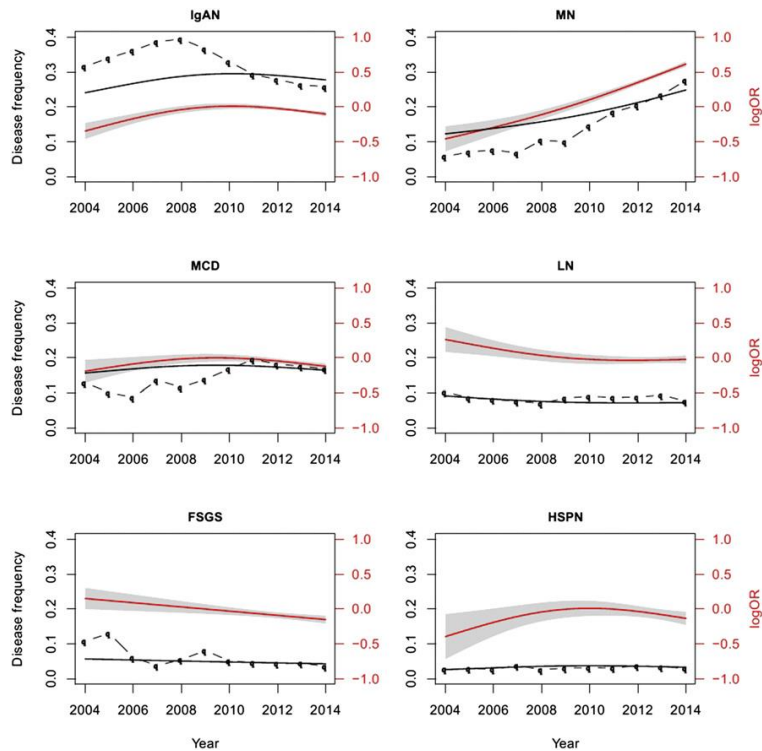
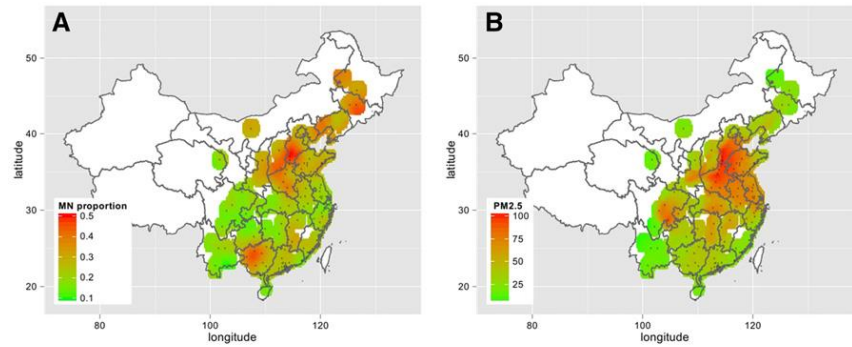


Figure 1. Trends in frequency of the most common glomerulopathies in China from 2004 to 2014. Open circles represent the unadjusted disease proportions among all glomerulopathies. Solid lines indicate the disease proportions estimated from generalized additive logistic models adjusted for age, gender, clinical syndromes, hospital type, pathologic laboratory, and region and weighted by regional population. Red lines and the corresponding gray zones, specify the ORs of the disease and their 95% CIs estimated from the generalized additive model with year 2009 as the reference.



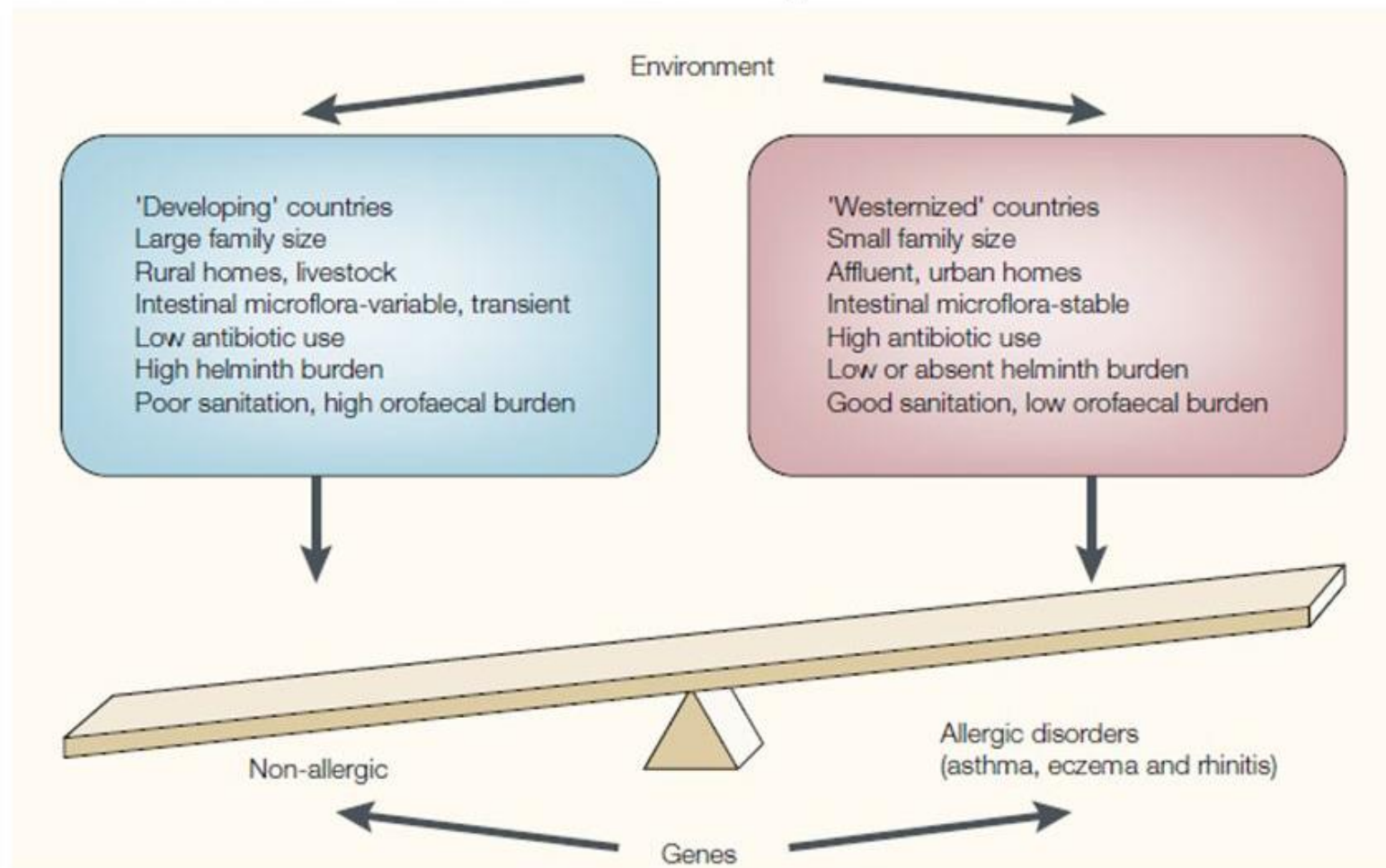
2014: 399 MN 332 PLA2R1+

Chaque augmentation de $10 \mu\text{g}/\text{m}^3$ du niveau de $\text{PM}_{2.5}$ est associée à une augmentation du risque de 14% de développer une GEM dans les régions $>70 \mu\text{g}/\text{m}^3$

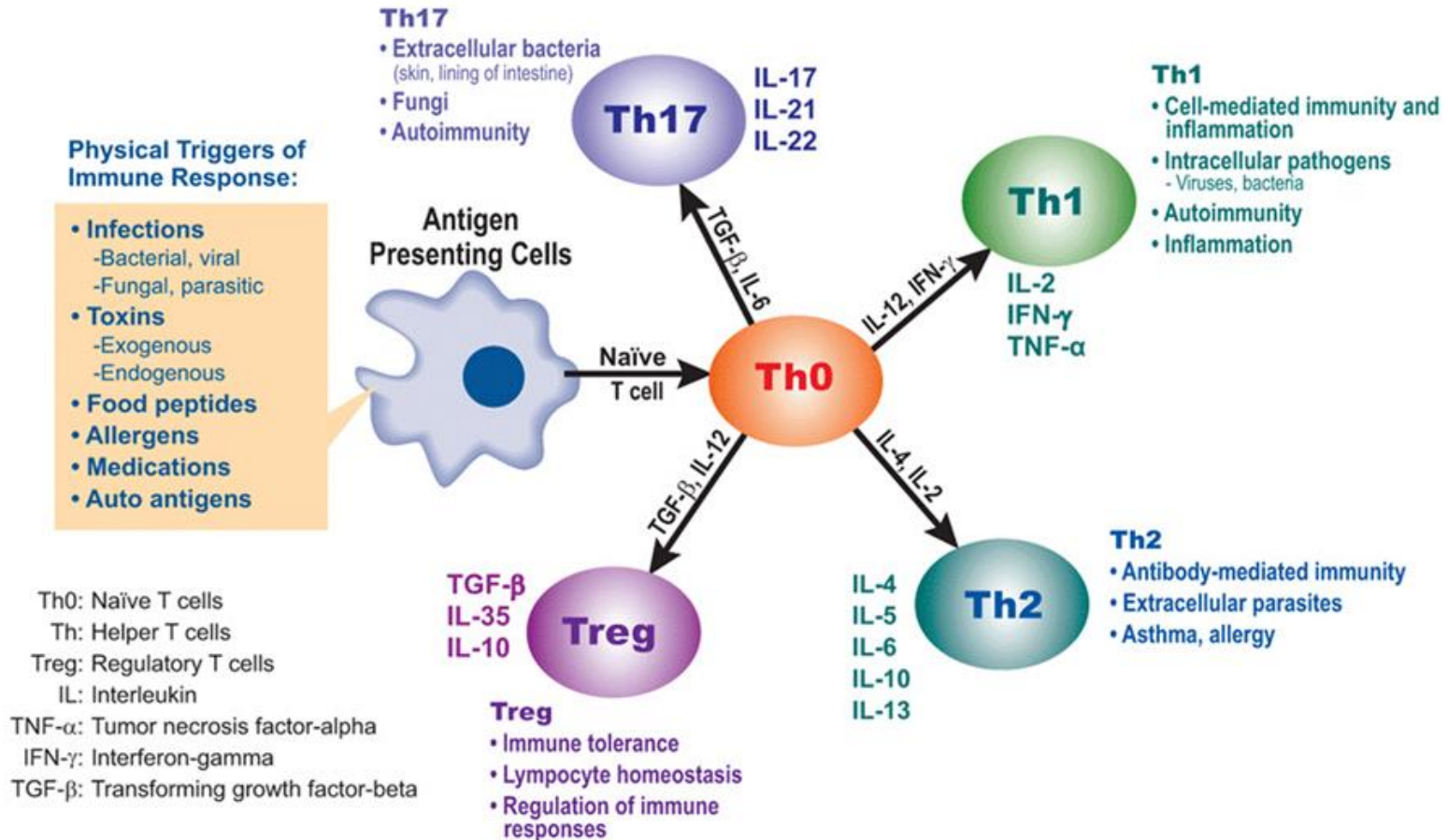
Théorie de l'hygiène

Augmentation de l'incidence des maladies auto-immunes et allergiques
3^{ème} cause de mortalité chez l'adulte

Un constat : \searrow des infections = \nearrow des Allergies



Profil cytokinique des GEM

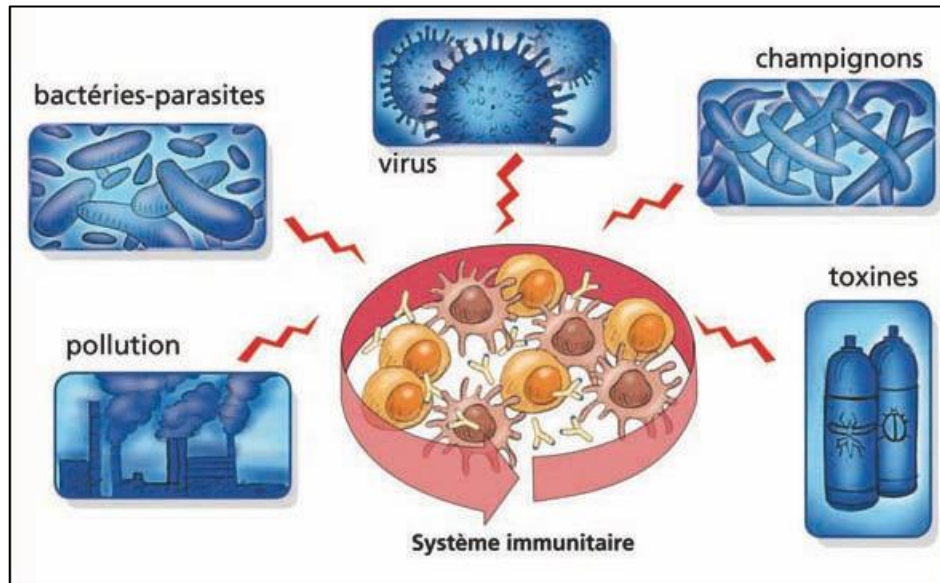


Projet GEM - environnement

Universal Hepatitis B Vaccination Reduces Childhood Hepatitis B Virus - Associated Membranous Nephropathy

Min-Tser Liao, Mei-Hwei Chang, Fu-Gong Lin, I-Jung Tsai, Yen-Wen Chang and Yong-Kwei Tsau

Pediatrics 2011;128:e600; originally published online August 22, 2011;



Profil cytokinique

Questionnaire
Environnemental

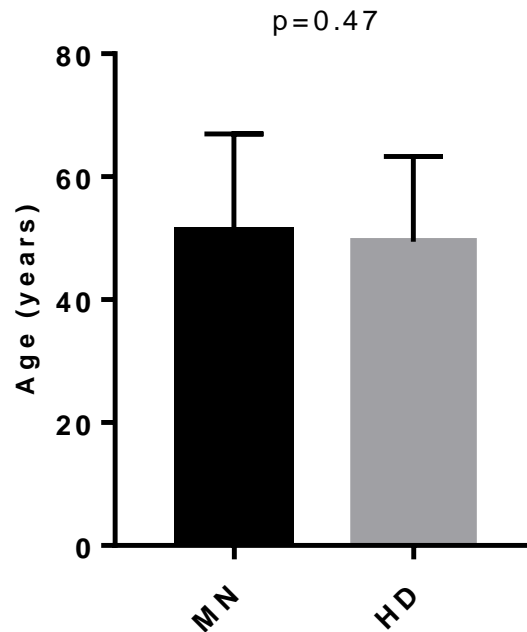
Long-Term Exposure to Air Pollution and Increased Risk of Membranous Nephropathy in China

Xin Xu,* Guobao Wang,* Nan Chen,[†] Tao Lu,* Sheng Nie,* Gang Xu,[‡] Ping Zhang,[§] Yang Luo,^{||} Yongping Wang,* Xiaobin Wang,^{||} Joel Schwartz,** Jian Geng,^{†††} and Fan Fan Hou*

Collaboration Dr S. Perez Géographe

Population

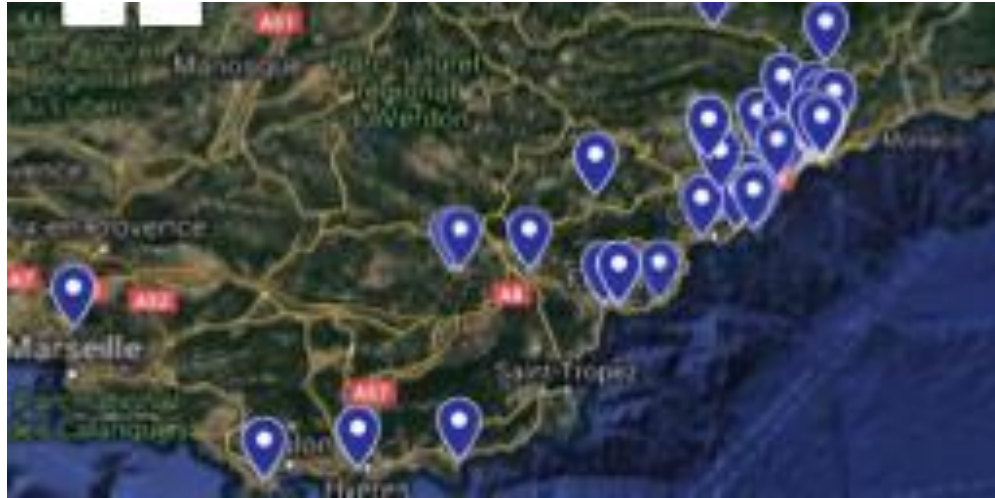
- 44 GEM actives, 1^{ère} poussée ou récursive, à plus de 6 mois d'un traitement immunosuppresseur
- 19 GEM en rémission (mêmes patients que précédemment après obtention de la rémission et à plus de 6 mois du rituximab)
- 29 sujets sains, appariés en âge et territoire géographique



Caractéristiques de la population

Age (years)	52 ± 15
Sex	
Male	30 (70%)
Female	13 (30%)
Etiology	
Anti-PLA2R-associated MN	29 (67%)
Anti-THSD7A-associated MN	1 (3%)
Antibody-negative patients	13 (30%)
Spreading patients	16 (59%)
Territory of habitation	
Urban	29 (67%)
Rural	14 (33%)
Pets	19 (63%)
Profession	
Manual	27 (67.5%)
Intellectual	13 (32.5%)
Comorbidities	
Autoimmune disease	8 (19%)
Cancer	6 (15%)
Atopy	19 (45%)
Asthma	8 (42%)
Allergic rhinitis	14 (74%)
Dermatitis	6 (32%)
Triggering factors	
Allergy	12 (28%)
Infection	9 (21%)
None	22 (51%)

Environnement



*84% vivent en zone péri-urbaine:
Route trafic « important » + végétation*

→ Analyser taux PM2.5, PM0.1, Pollens



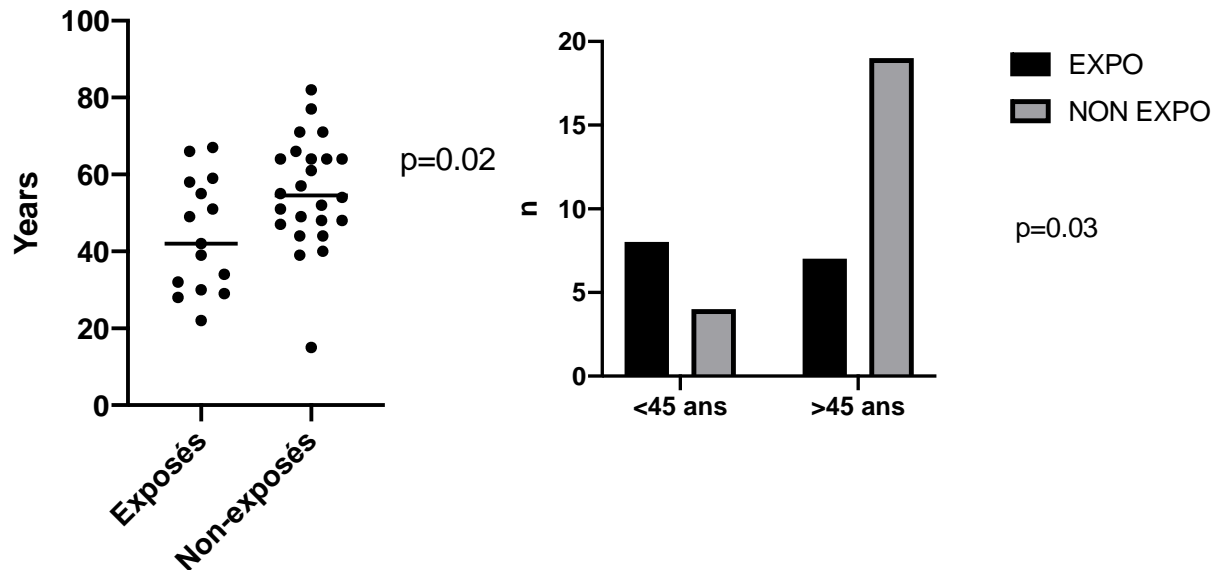
Profession

Table 2 Main solvent-exposed job categories

Patients with at least one job as:	ISCO code*	n	% Exposed at any level
Professional and technical workers	0-1	93	27%
Physician scientists and related technicians	01	3	33%
Architects, engineers and related technicians	02,03	34	44%
Life scientists	05	2	50%
Sculptors, painters, creative artists	16	11	40%
Administrative and managerial workers	2	16	12%
Clerical workers	3	63	1%
Sales workers	4	41	0%
Service workers	5	68	4%
Agricultural workers	6	16	0%
Production and transport workers	7-8-9	104	47%
Production supervisor and general foremen	70	10	30%
Blacksmiths, toolmakers and machine tool operators	83	10	40%
Machinery fitters, machine assemblers	84	15	47%
Electrical and electronics workers	85	14	36%
Plumbers, welders	87	17	53%
Printers	92	2	100%
Painters	93	6	100%
Construction workers	95	21	52%
Transport workers	98	17	12%
Manual workers	99	10	20%

*First digits (bold) or first two digits of the 1968 International Standard Classification of Occupations.¹⁶

*Professions Exposées aux solvants organiques
=> 20% exposés*



Méthodes

Sang total héparinisé



+

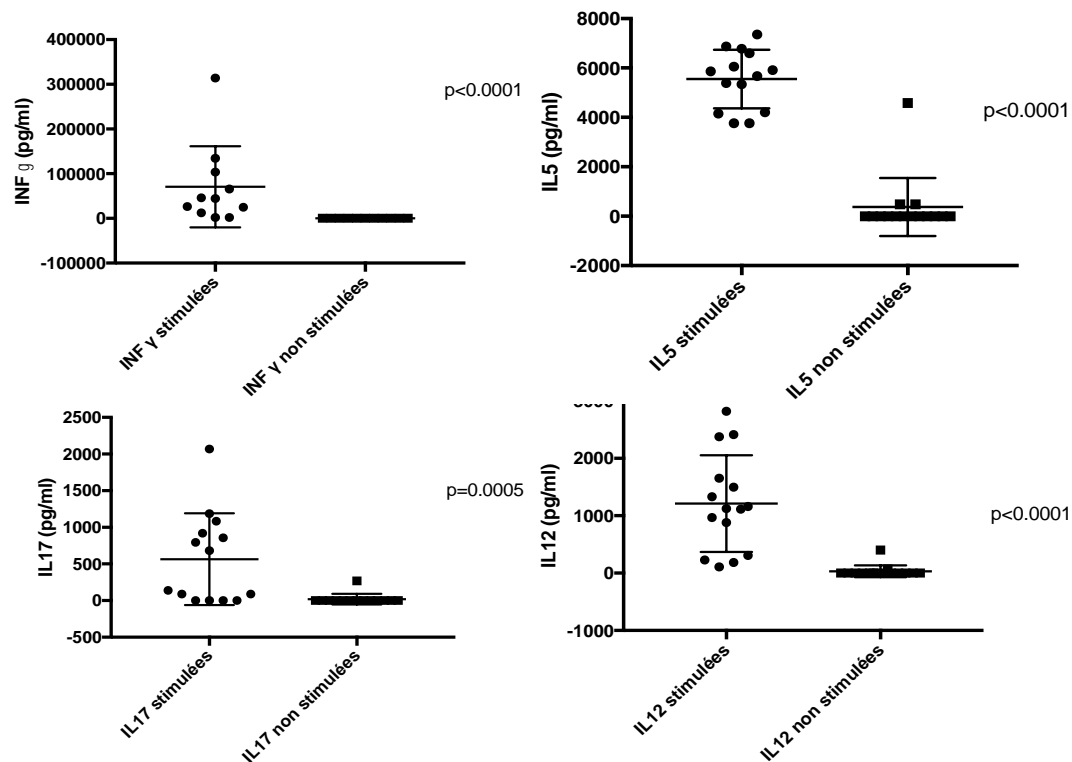
Stimulants de la réponse immunitaire
innée et adaptative



Incubation

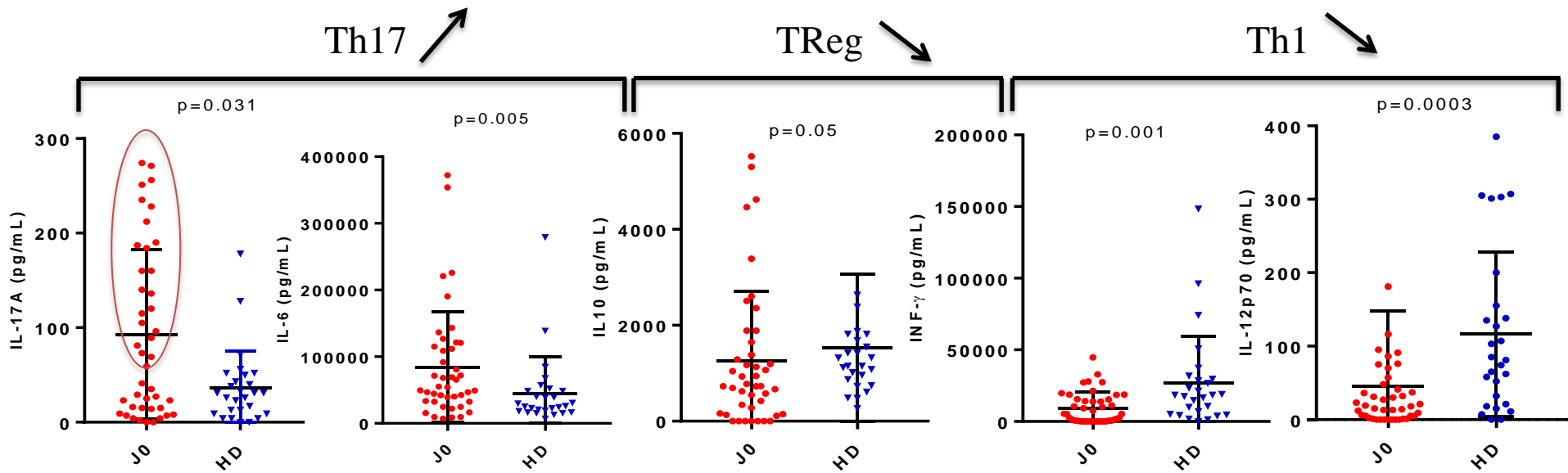
Centrifugation

Dosage profils cytokiniques après stimulation non spécifique des LT (CD3+) NK (TLR7 et 8) en luminex

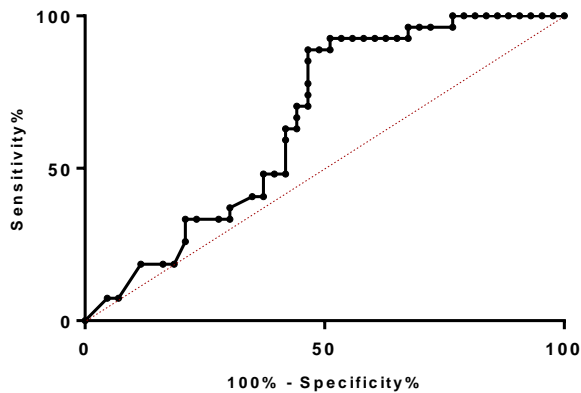


Pas de cytokines détectables en périphérie chez patients GEM sans stimulation des LT

Profil Th17

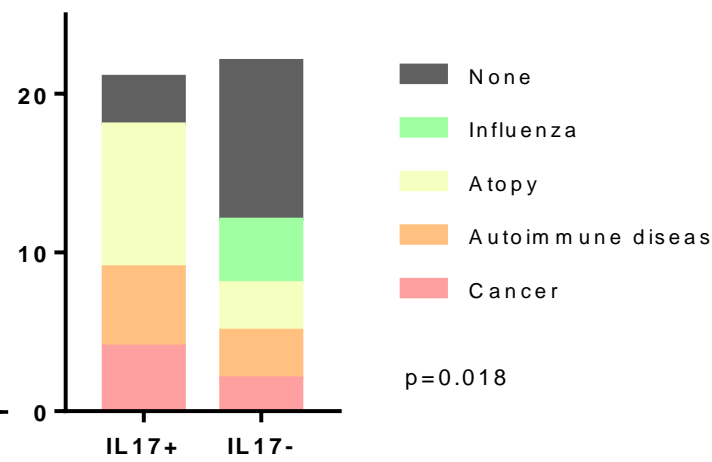
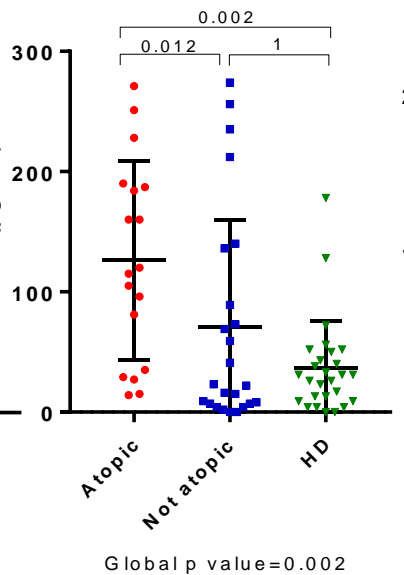
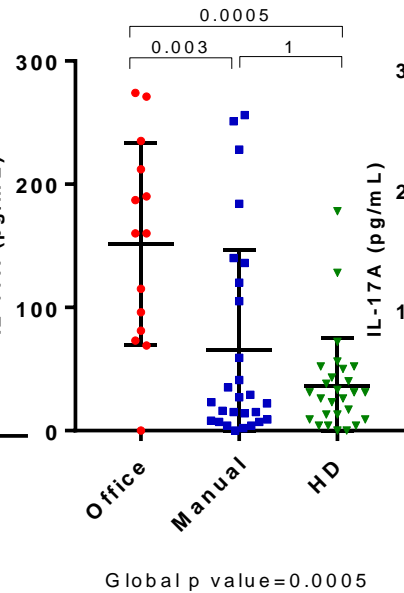
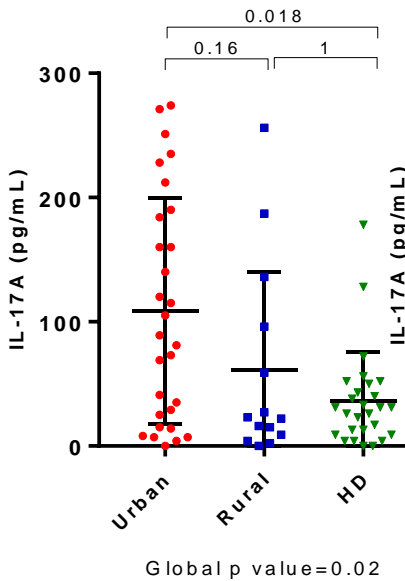
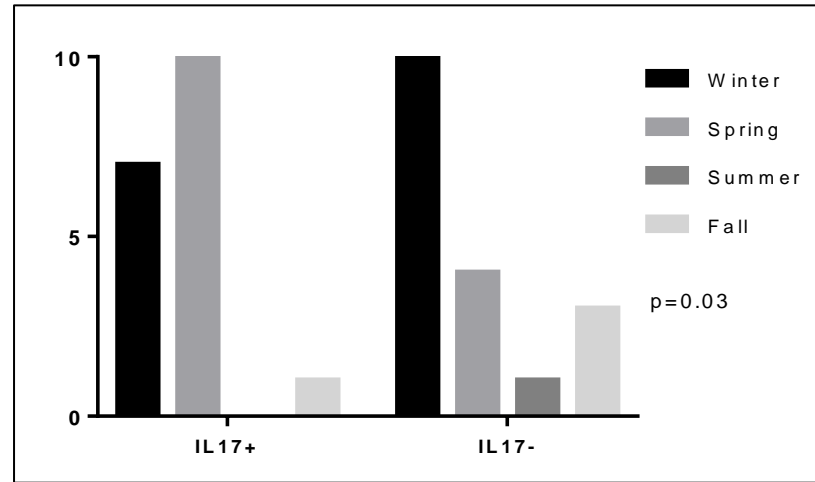


IL-17 : ROC of MN vs HD



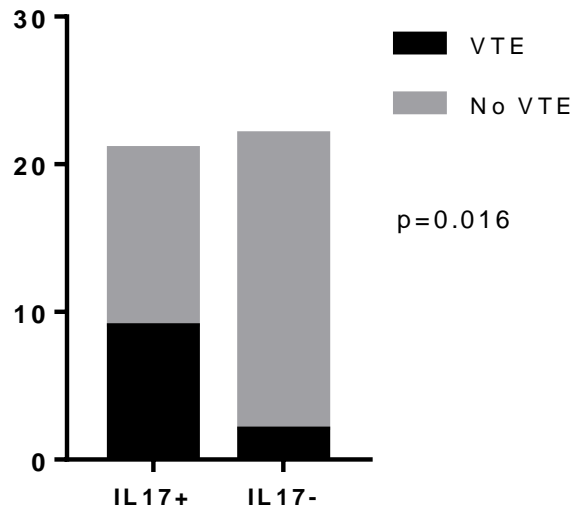
- Activation de la voie Th17
- Inhibition de la voie Treg, Th1
- Pas de modification de la voie Th2

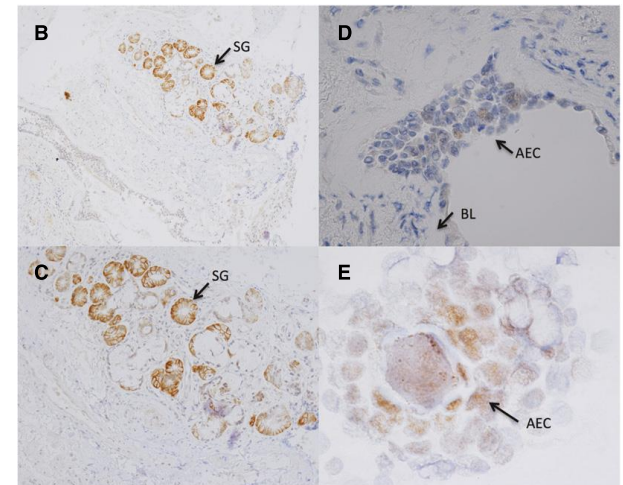
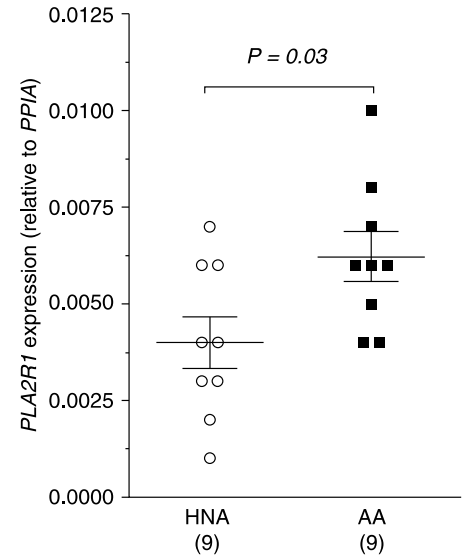
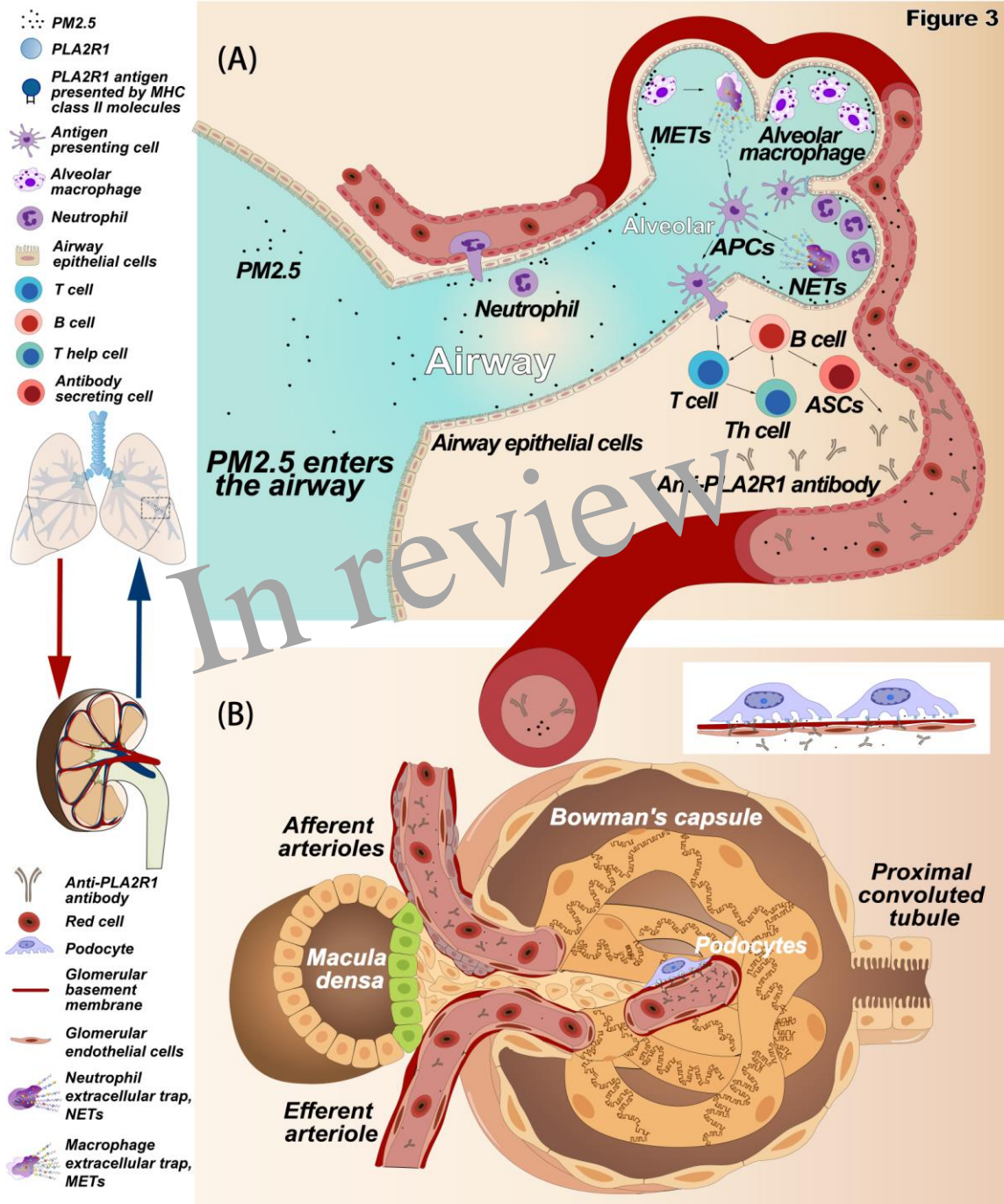
Mode de vie et Profil cytokinique



Profil cytokinique et complications thrombo-emboliques

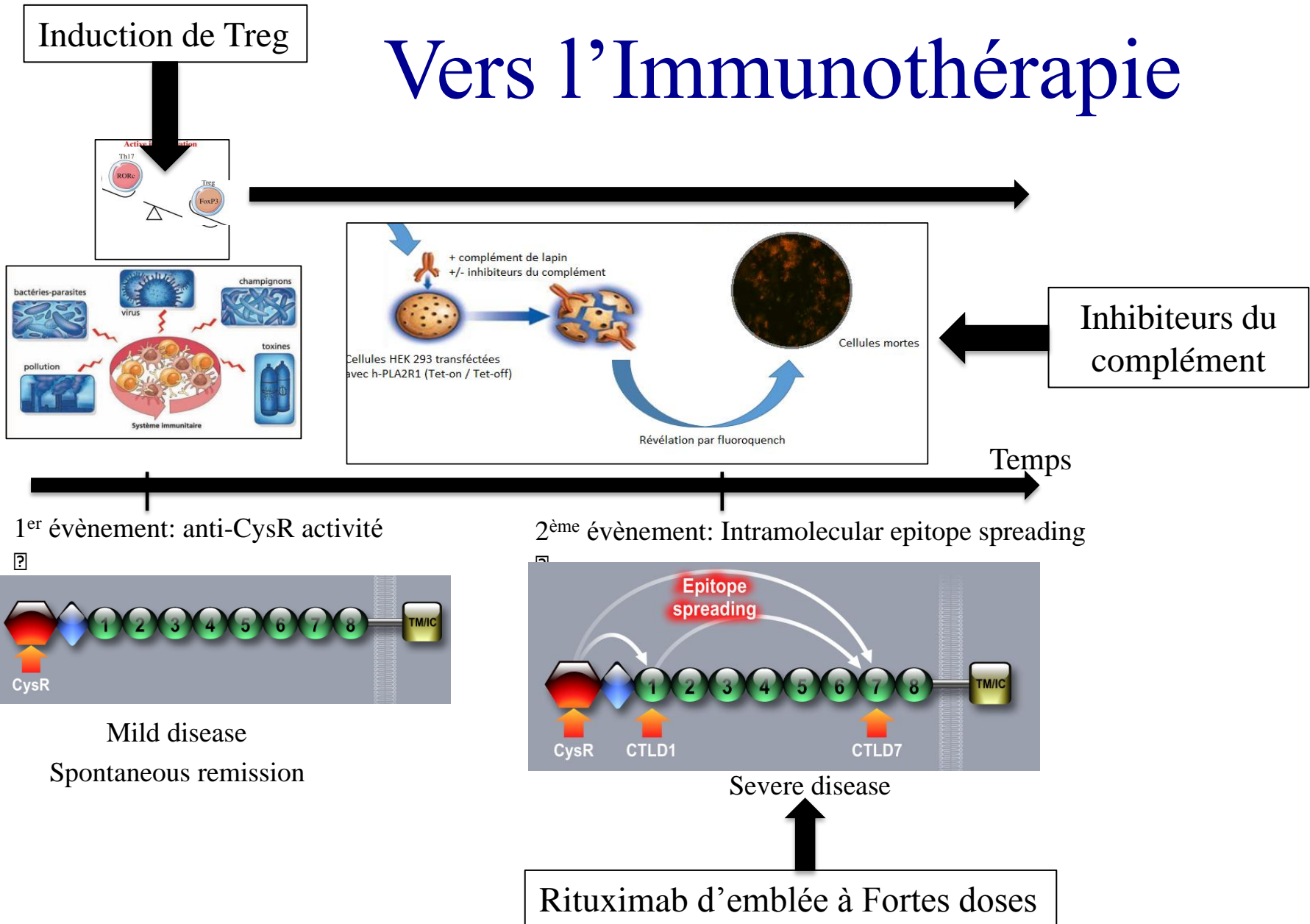
Venous Thromboembolic Event (VTE)



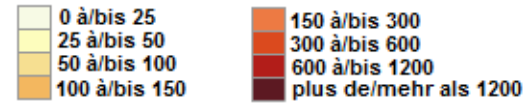
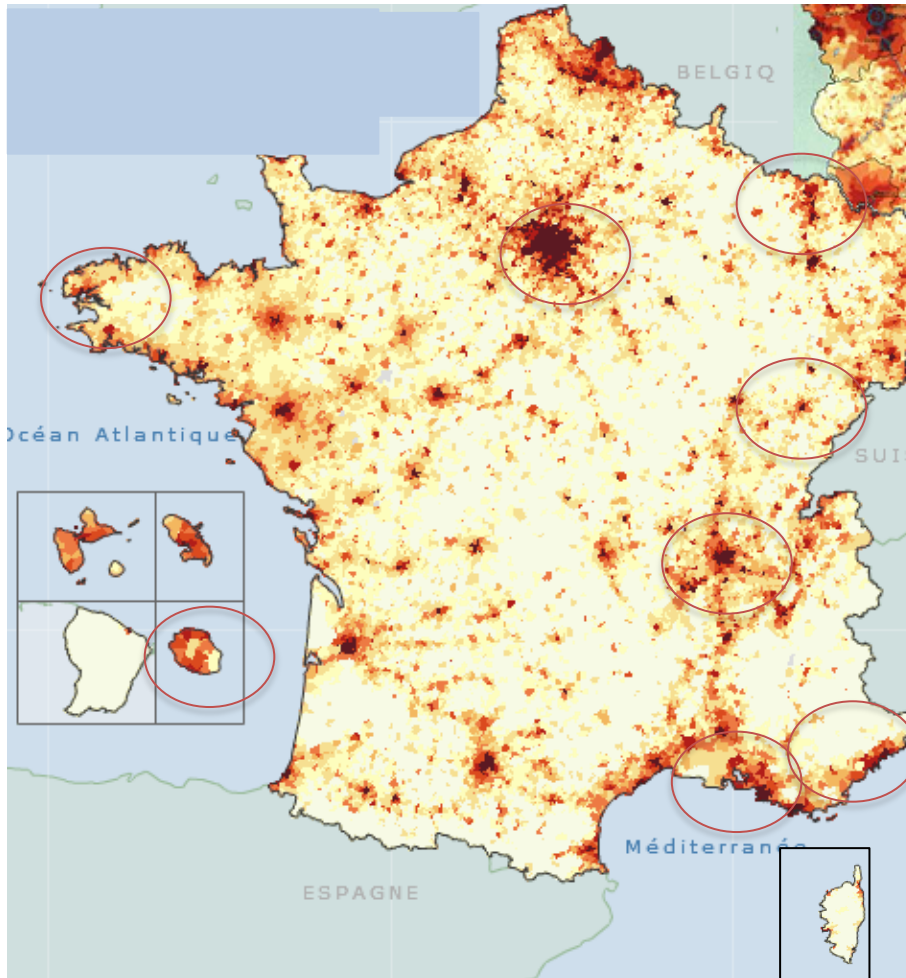


Physiopathologie des GEM

Vers l'Immunothérapie



Enquête Nationale *GIRCI 2018 CD 2017*



Sur 20 centres:

- Questionnaire environnemental
- Biopsie rénale
- Ac anti-PLA2R1, THSD7A
- ADN

Sur 8 centres:

- Profil cytokinique
- Questionnaire environnemental
- Données PM
- Ac anti-PLA2R1, THSD7A
- ADN
- Microbiote

Merci

Allergie et Théorie de l'Hygiène

L'hypothèse du déséquilibre de la balance Th1/Th2

