

## The gut-kidney axis in IgA nephropathy

Rosanna Coppo

Turin, Italy

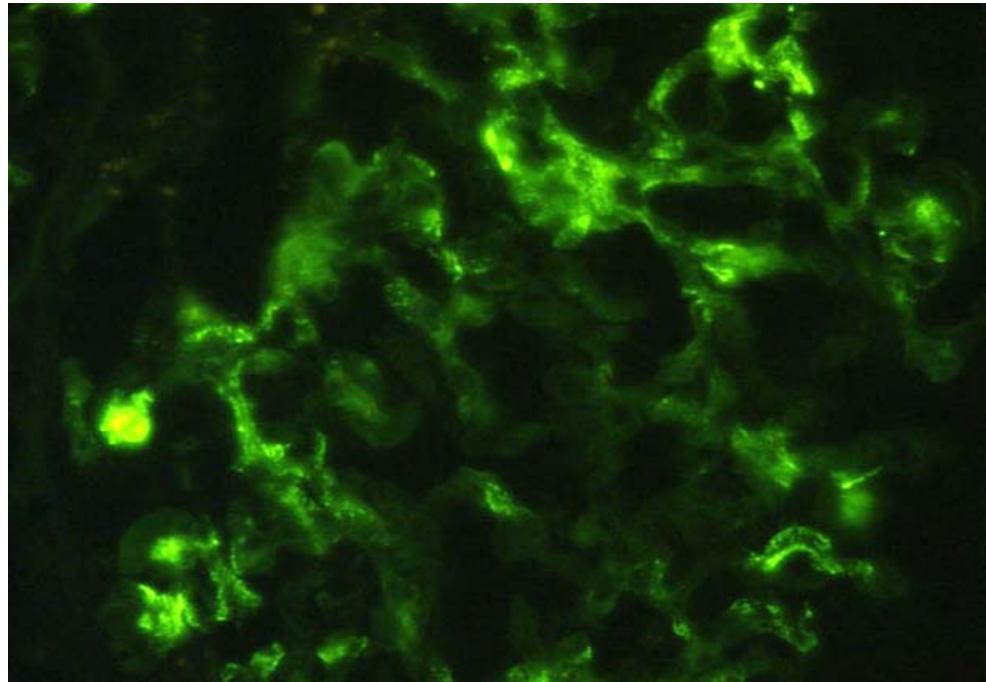
Fondazione Ricerca Molinette  
Torino



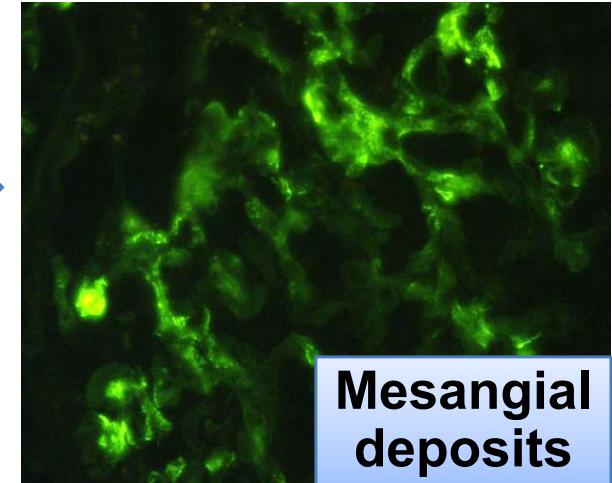
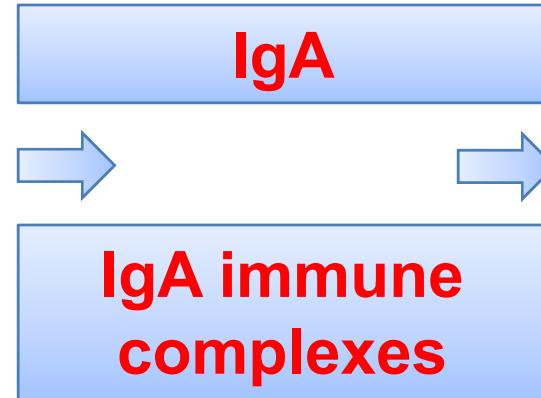
**Azienda Ospedaliera  
Città della Salute e  
della Scienza di Torino**

**IgA nephropathy (IgAN):  
a disease originated from mucosal immunity dysregulation**

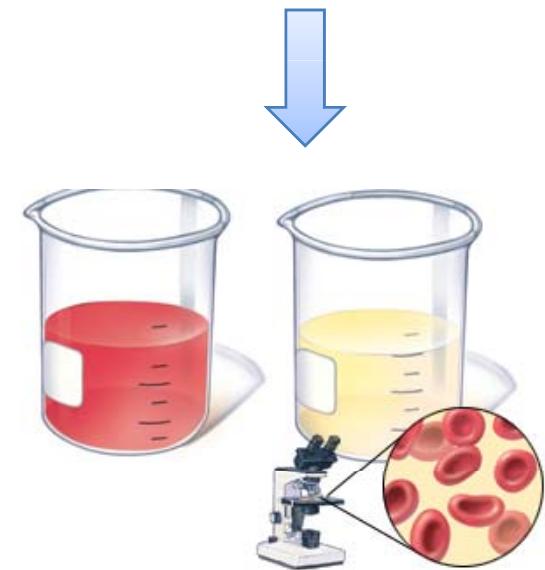
**IgA: most prevalent Ig in mucosal secretions.  
Deposited IgA are polymeric (of mucosal origins)**



# The tonsil-renal axis in IgAN



Mesangial deposits





## A potential treatment of IgAN: **TONSILLECTOMY**

Aimed at

removing a **source of pathogens**

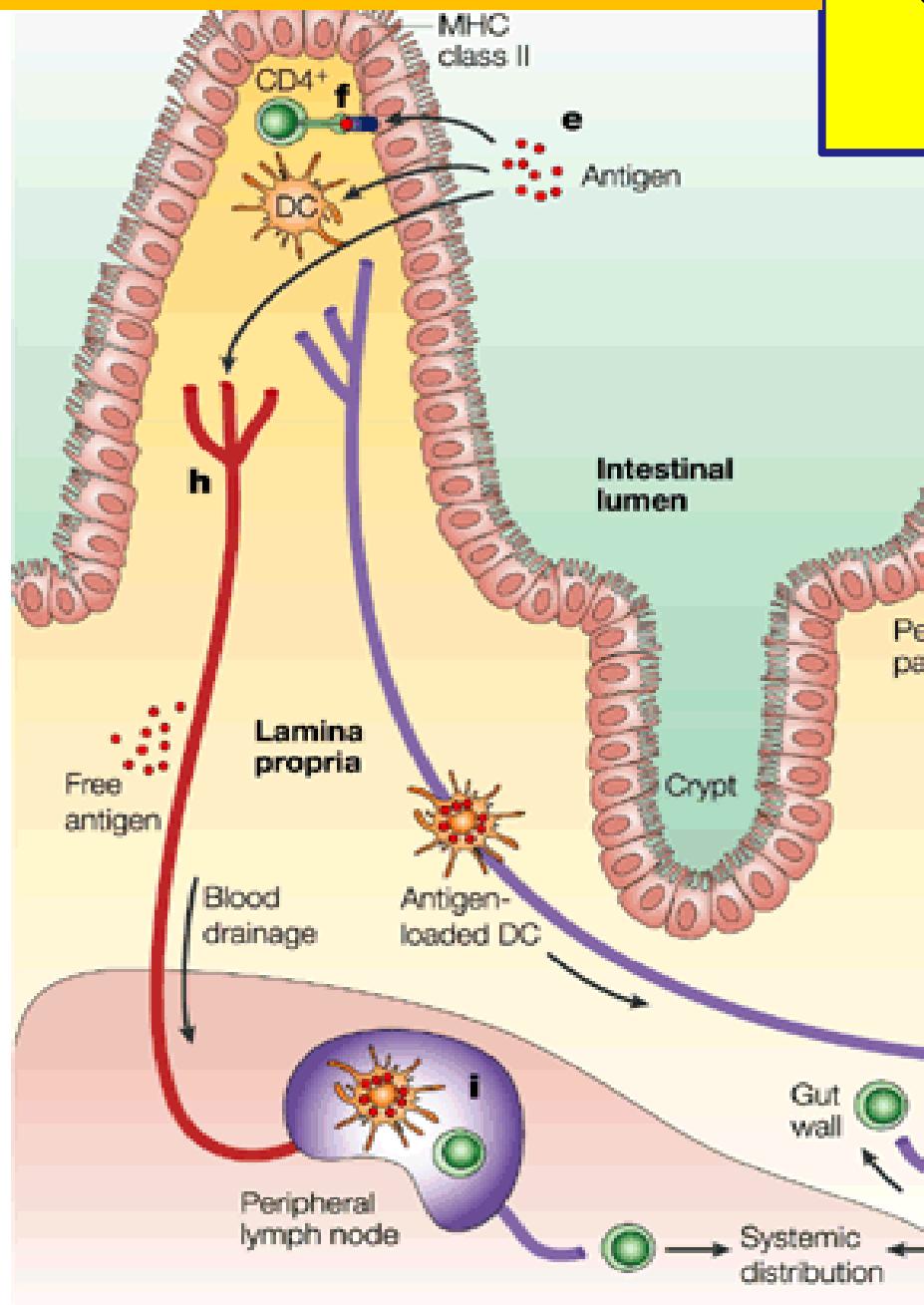
reducing Mucosal Associated Lymphoid Tissue (**MALT**)

decreasing polimeric mucosal **IgA synthesis**.

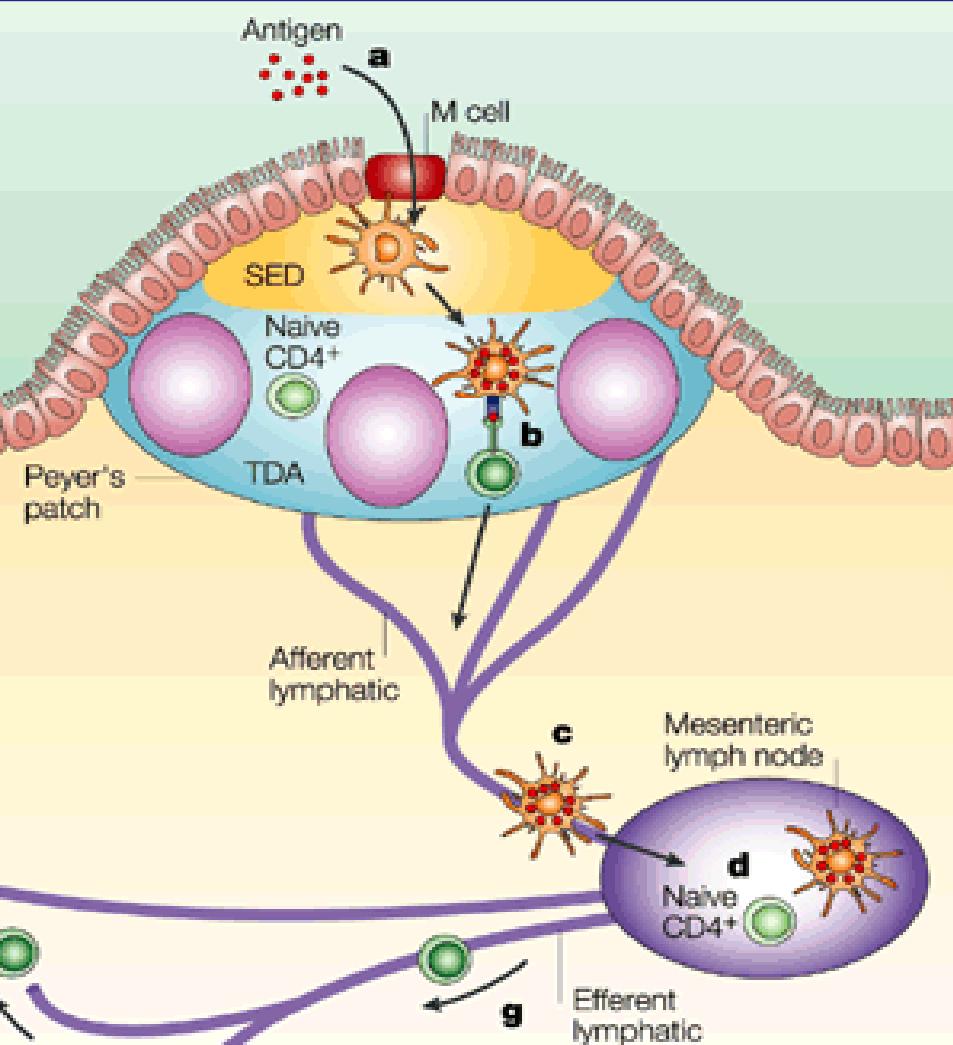
In Asia, benefits of tonsillectomy have been reported  
mostly in association with steroids

In **Western Countries** no benefits of tonsillectomy in IgAN has been proven

## GALT (gut associated lymphoid tissue)



## GALT intestinal immunity in IgAN: pathogenetical role and target for treatment



Pediatr Nephrol 2018 Jan;33(1):53-61.



---

EDUCATIONAL REVIEW

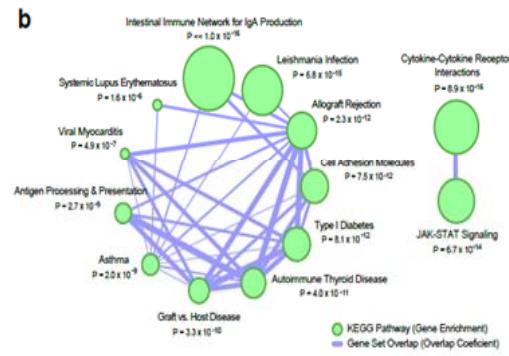
---

## The gut–kidney axis in IgA nephropathy: role of microbiota and diet on genetic predisposition

Rosanna Coppo<sup>1</sup>

# Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens

Krzysztof Kiryluk<sup>1</sup>, Yifu Li<sup>1</sup>, Francesco Scolari<sup>2,3</sup>, Simone Sanna-Cherchi<sup>1</sup>, Murim Choi<sup>4,5</sup>, Miguel Verbitsky<sup>1</sup>, Rakash<sup>1</sup>, Samantha Shapiro<sup>1</sup>, Clara Fischman<sup>1</sup>, Holly J Snyder<sup>1</sup>, sta Fabio Viola<sup>7</sup>, Nadia Dallera<sup>2,3</sup>, Lucia Del Vecchio<sup>8</sup>, Cristina Barlassina<sup>8</sup>, Martinetto<sup>9,10</sup>, Antonio Amoroso<sup>9,10</sup>, Silvana Savoldi<sup>11</sup>, Marcella Rocchietti<sup>11</sup>, Rosanna Coppo<sup>12</sup>, Maurizio Salvadori<sup>13</sup>, Pietro Ravani<sup>14,15</sup>, Ghiggeri<sup>17</sup>, Gianluca Caridi<sup>17</sup>, Monica Bodria<sup>17</sup>, Francesca Lugani<sup>17</sup>, e<sup>18,19</sup>, Mariarosa Maiorana<sup>18,19</sup>, Andrea Magnano<sup>18,19</sup>, Giovanni Frasca<sup>20</sup>, Claudio Ponticelli<sup>23</sup>, Renzo Mignani<sup>24</sup>, Carmelita Marcantoni<sup>25</sup>, Santoro<sup>26</sup>, Antonello Pani<sup>27</sup>, Rosaria Polci<sup>28</sup>, Sandro Feriozzi<sup>28</sup>, Maddalena Gigante<sup>30</sup>, Loreto Gesualdo<sup>31</sup>, Pasquale Zamboli<sup>32</sup>, Dario Garozzo<sup>33</sup>, Dita Maixnerová<sup>34</sup>, Vladimir Tesar<sup>34</sup>, Frank Eitner<sup>35,36</sup>, Ibor Kovacs<sup>37,38</sup>, Judit Nagy<sup>37,38</sup>, Krzysztof Mucha<sup>39</sup>, Leszek Pączek<sup>39</sup>, ska-Wasiak<sup>41</sup>, Maria Roszkowska-Blaim<sup>41</sup>, Krzysztof Pawlaczek<sup>42</sup>,

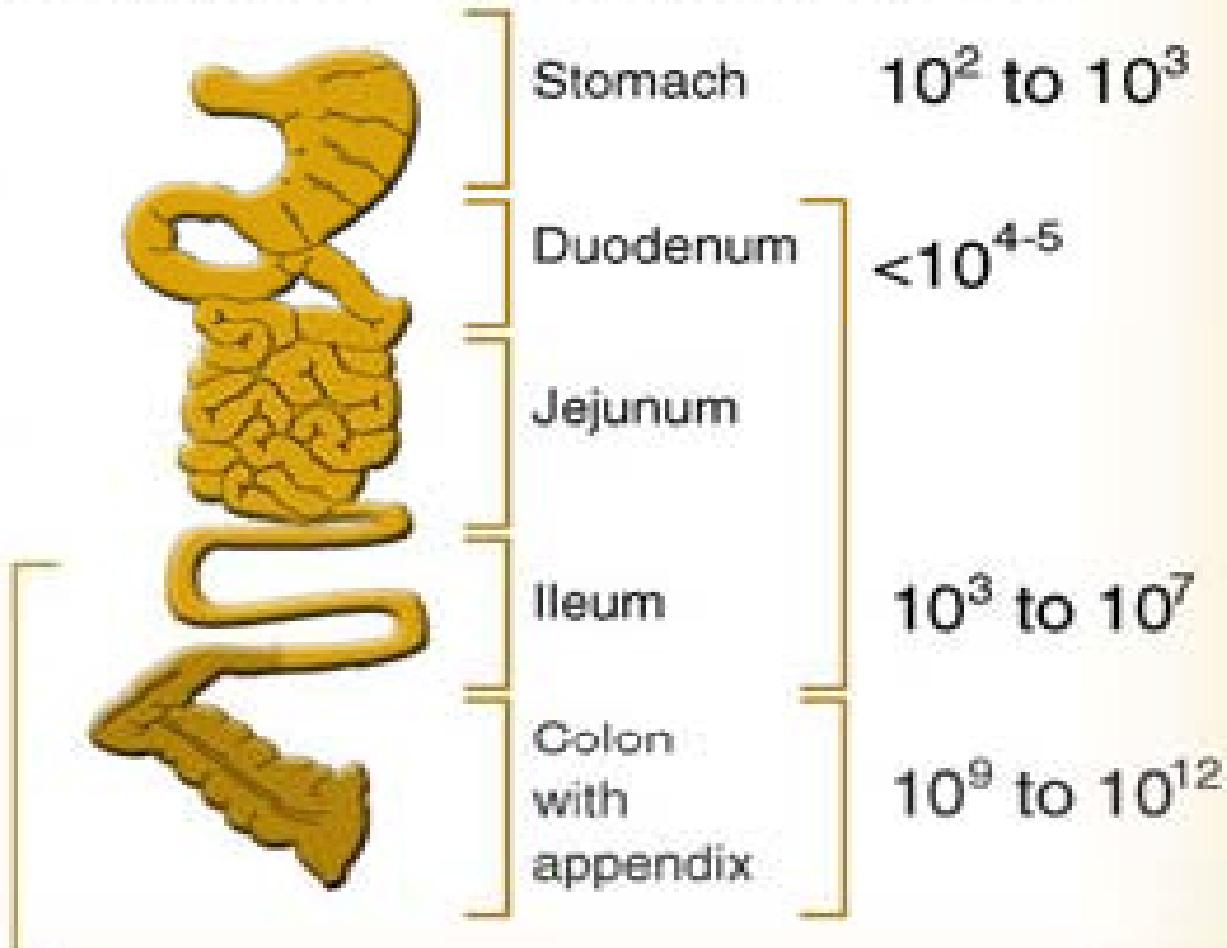


**most loci associated with IgAN  
are also associated with risk of inflammatory bowel diseases or  
maintenance of the intestinal barrier in response to intestinal pathogens**

## INTESTINAL MICROBIOTA

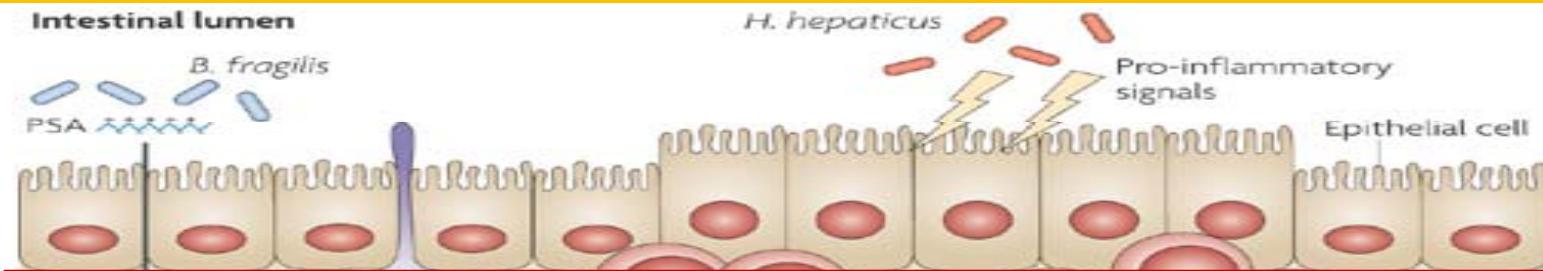
$10^{14}$  micro-organisms, >500 differentes species

Lactobacilli  
  
Streptococci  
Lactobacilli  
  
Enterobacteria  
Enterococcus  
Faecalis  
Bacteroides  
Bifidobacteria  
Peptococcus  
Peptostreptococcus  
Ruminococcus  
Clostridia  
Lactobacilli

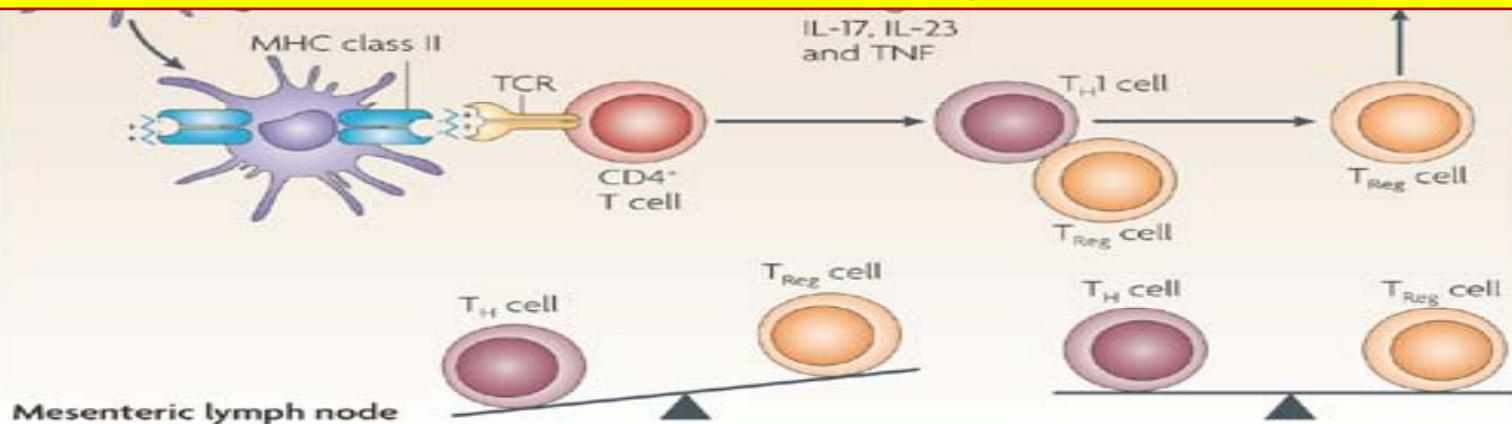


Modulated by diet, chemicals, host genes

## the gut microbiota shapes intestinal MALT in health and disease



### The gut-kidney axis in IgA nephropathy: the role intestinal dysbiosis

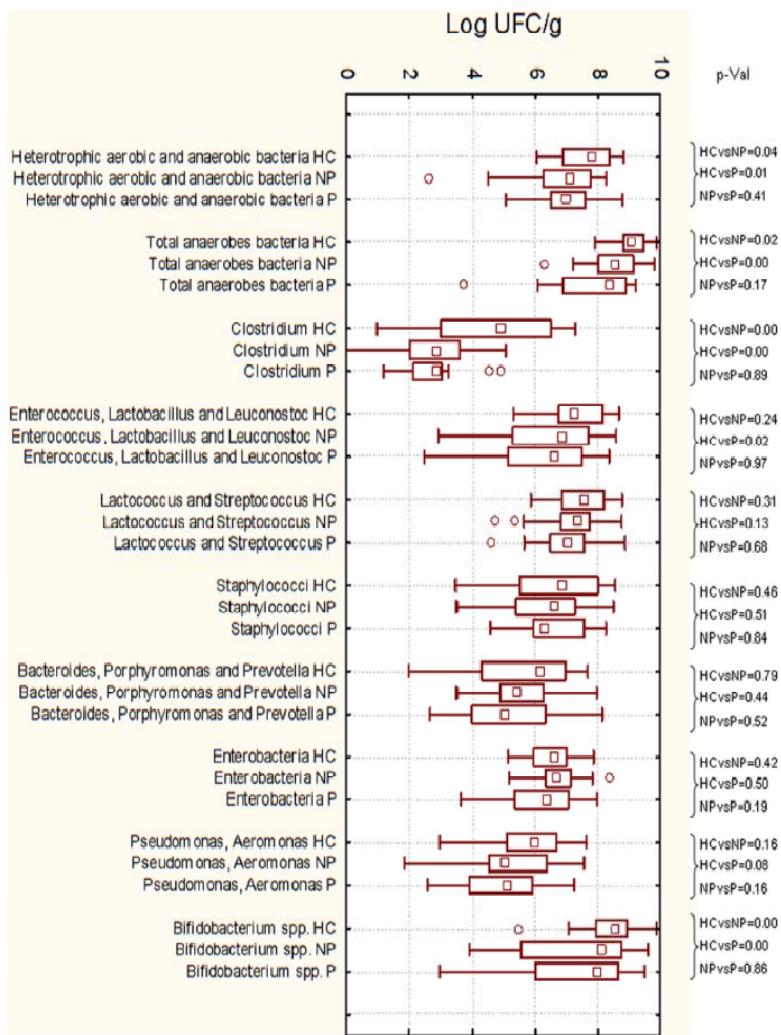


Effect on maturation of lymphoid tissue  
with  
local and systemic modulation  
of innate and adaptive immunity

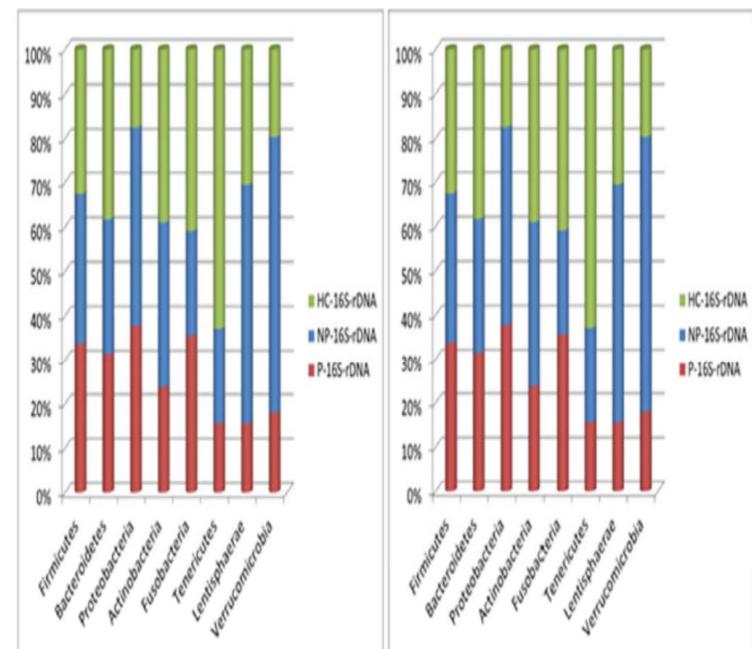
# Microbiota and Metabolome Associated with Immunoglobulin A Nephropathy (IgAN)

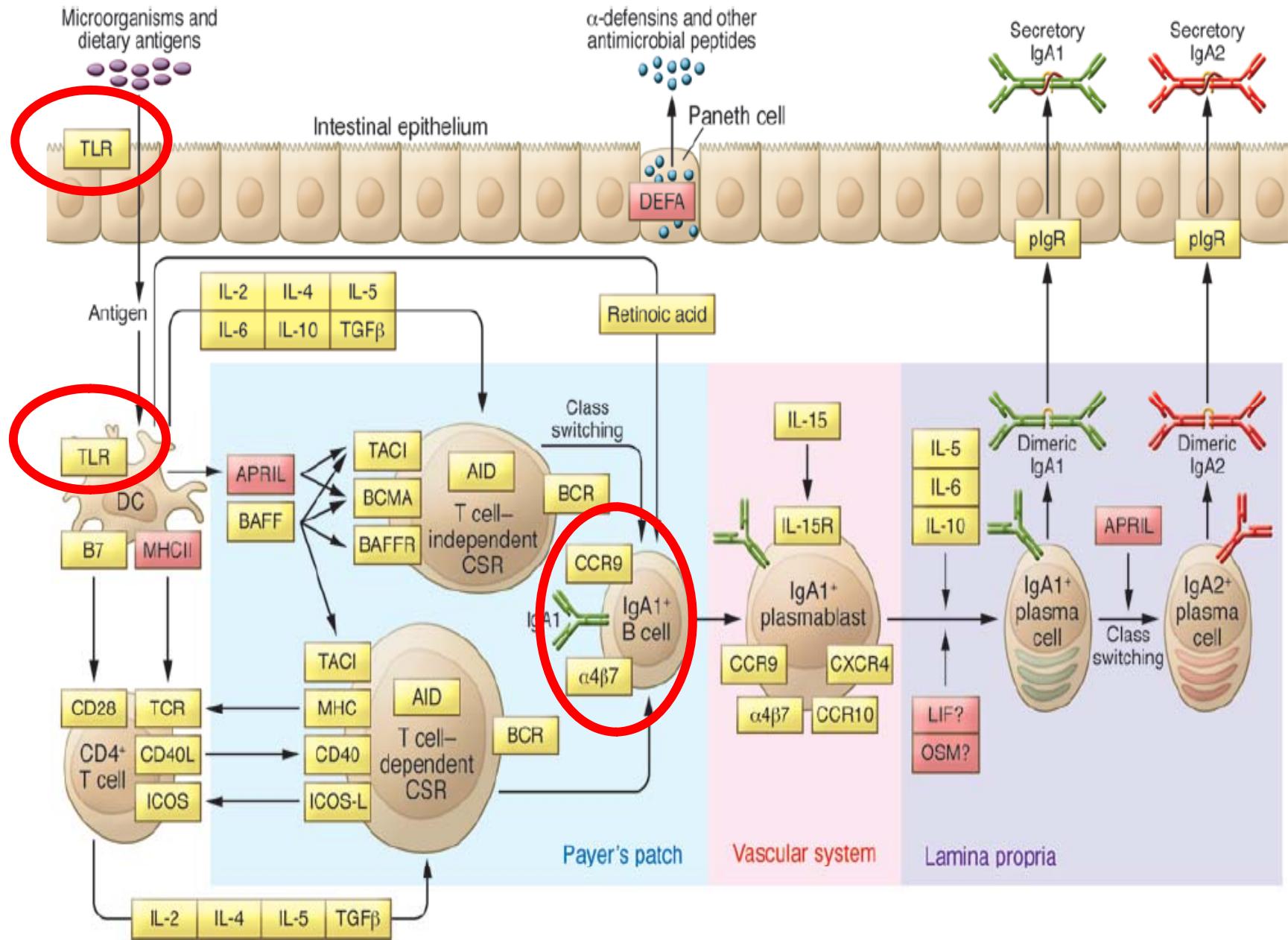
Maria De Angelis<sup>1\*</sup>, Eustacchio Montemurno<sup>2</sup>, Maria Piccolo<sup>1</sup>, Lucia Vannini<sup>3</sup>, Gabriella Lauriero<sup>2</sup>, Valentina Maranzano<sup>2</sup>, Giorgia Gozzi<sup>3</sup>, Diana Serrazanetti<sup>4</sup>, Giuseppe Dalfino<sup>2</sup>, Marco Gobbetti<sup>1</sup>, Loreto Gesualdo<sup>2</sup>

June 2014 | Volume 9 | Issue 6

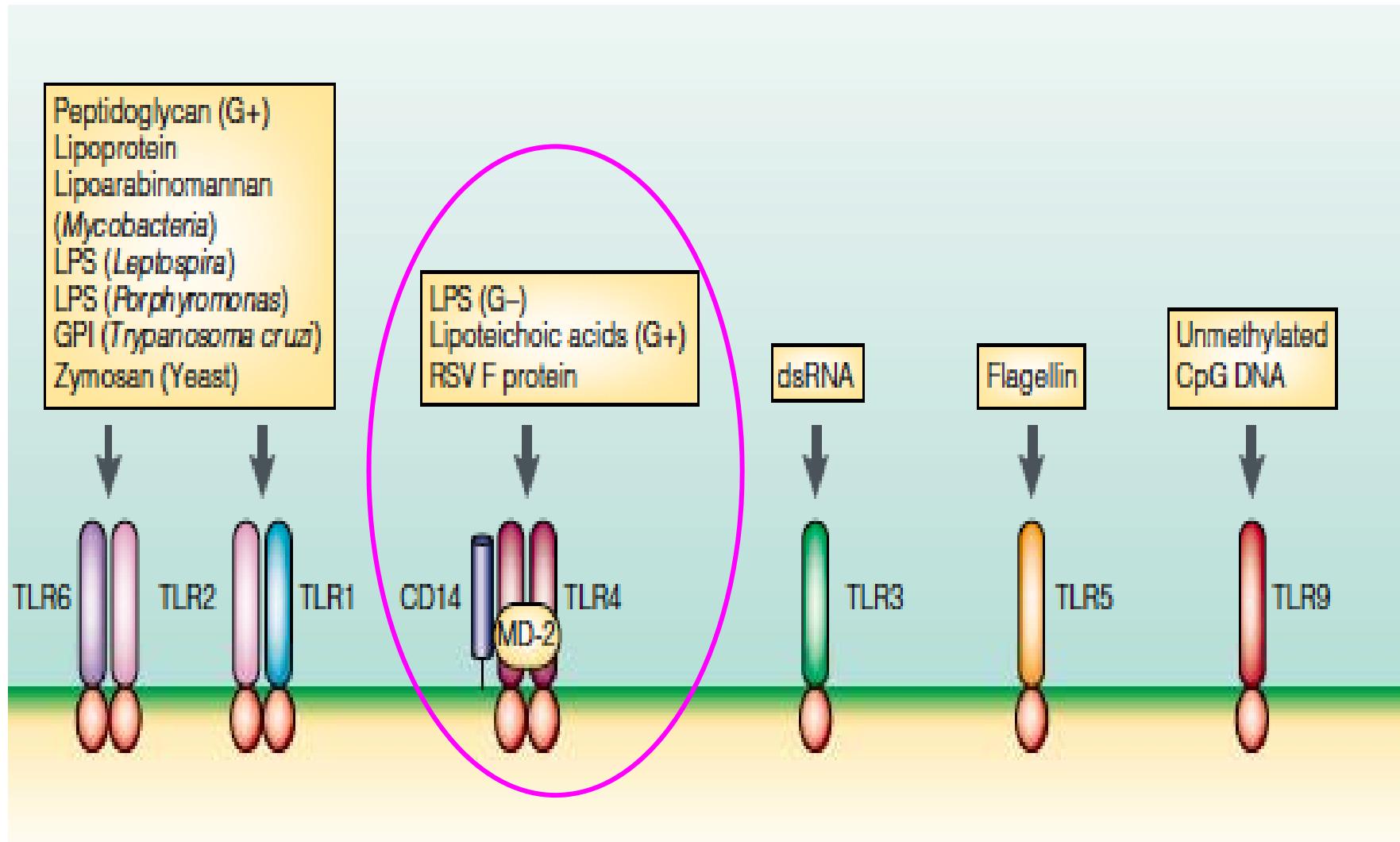


Pilot study in 34 IgAN patients:  
different microbiota in progressive IgAN





## Specific ligands for each TLR

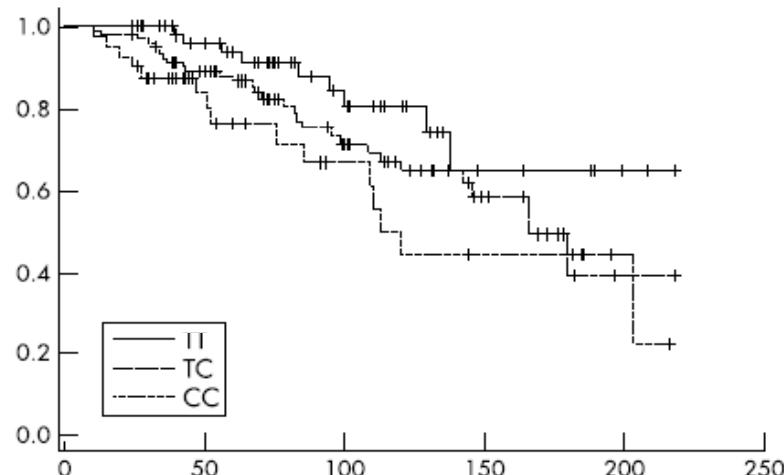


Medzhitov, Nat Rev Immunol

The LPS binding receptor CD14 and TLR4 initiate the response to microbes and influence various chronic inflammatory conditions

### Association of the CD14 gene -159C polymorphism with progression of IgA nephropathy

H-J Yoon, J H Shin, S H Yang, D-W Chae, H Kim, D-S Lee, H L Kim, S Kim, J S Lee, Y S Kim



**Figure 1** Probability of patients with IgAN not reaching doubling of baseline serum creatinine according to the genotypes of CD14 (Kaplan-Meier analysis,  $p=0.03$  by log rank test).

**Table 4** Predictors for the progression of renal disease by the Cox proportional hazards analysis

Variables	Hazard ratio	p value	95% confidence interval
Proteinuria*†			
>3000 mg/day	4.0	0.0004	1.8 to 8.5
1000–3000 mg/day	1.6	0.28	0.7 to 3.9
Genotype of CD14‡			
CC	3.2	0.025	1.2 to 8.8
TC	1.7	0.21	0.7 to 4.1
Creatinine*§			
>1.4 mg/dl	3.6	0.0015	1.9 to 5.8

\*At the time of histological diagnosis. †Compared with proteinuria <1000 mg/day. ‡Compared with TT genotype. §Compared with ≤1.4 mg/dl.

a genetic modification of the membrane receptor for LPS may modulate the inflammatory response and the progression of IgAN

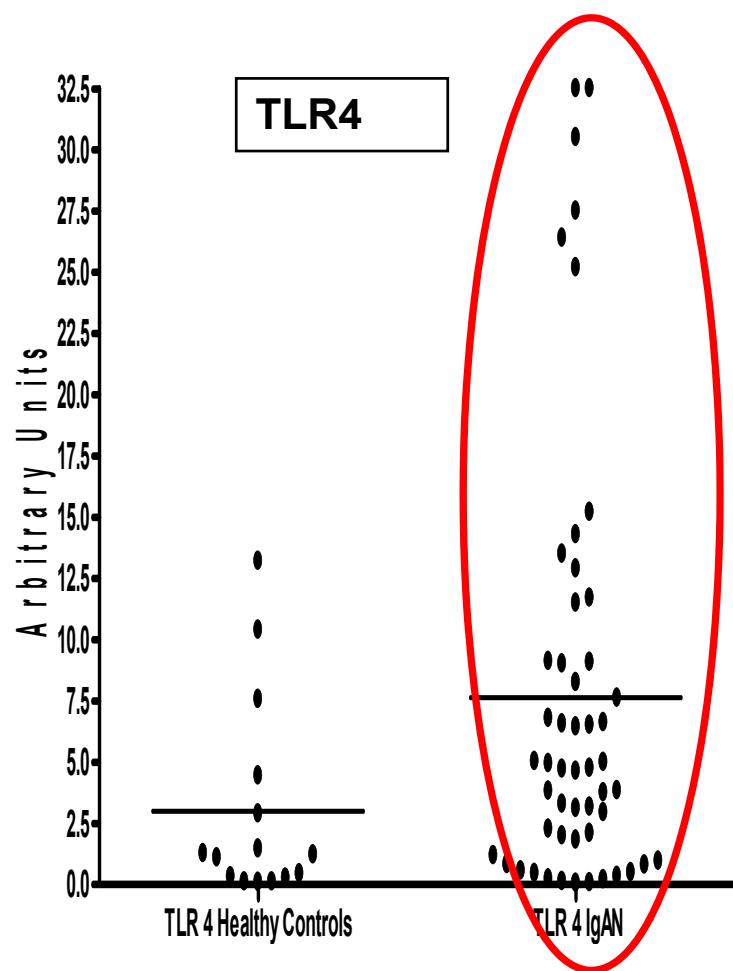
**Toll-like receptor 4 expression is increased in circulating mononuclear cells of patients with immunoglobulin A nephropathy**

**Coppo et al**

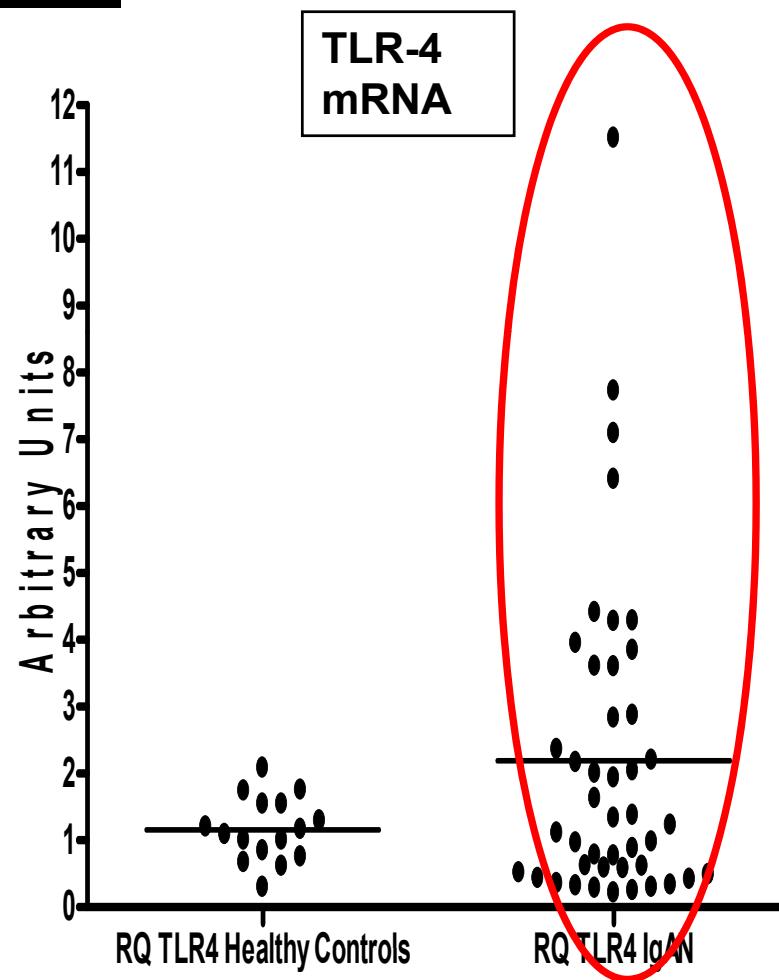
**Clinical & Experimental Immunology**

1365-2249.2009.

**The Journal of Translational Immunology**

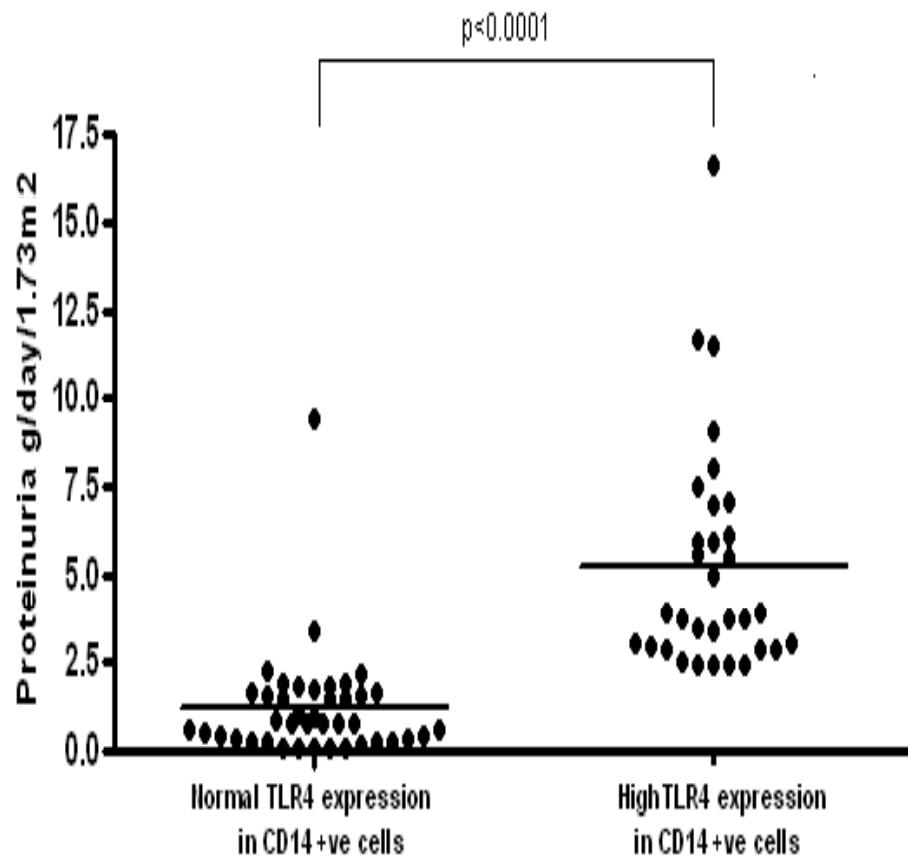
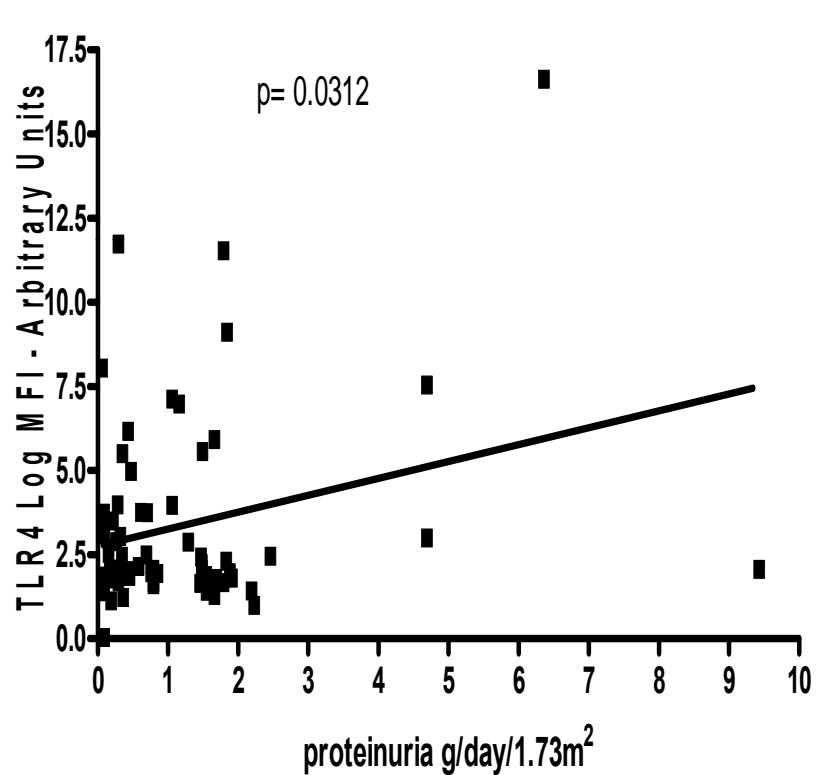


**FACS**



**Taqman**

# Significant correlation in IgAN between TLR4 expression in PBMC and proteinuria



Pediatr Nephrol  
DOI 10.1007/s00467-014-2807-6  
ORIGINAL ARTICLE

**Toll-like receptors, immunoproteasome and regulatory T cells in children with Henoch–Schönlein purpura and primary IgA nephropathy**

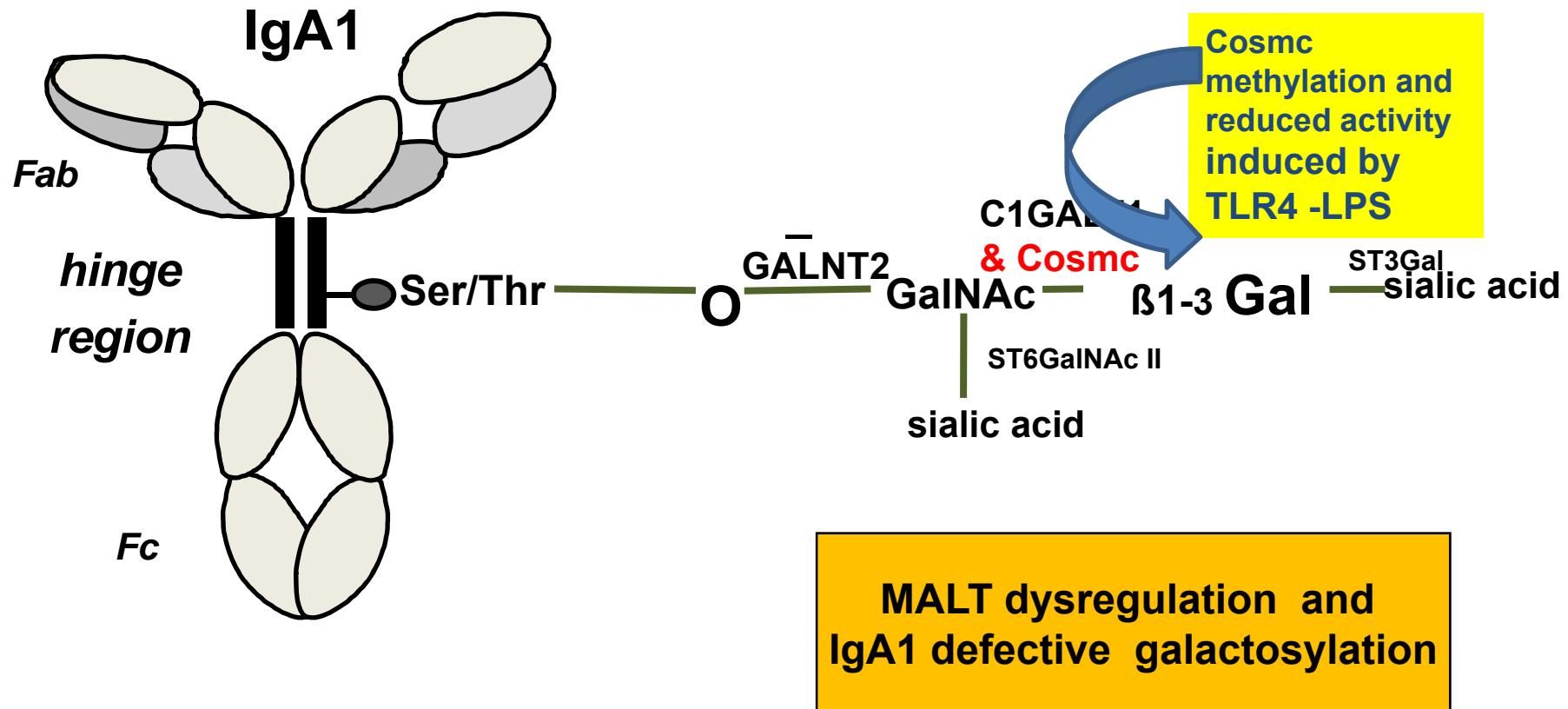
Maria Elena Donadio • Elisa Loiacono • Licia Peruzzi • Alessandro Amore • Roberta Camilla • Federica Chiarelli • Luca Vergano • Alberto Boido • Margherita Conrieri • Manuela Bianciotto • Francesca Maria Bosetti • Rosanna Coppo

**Pediatr Nephrol.**  
2014 Sep;29(9):1545-51.

## External suppression causes the low expression of the *Cosmc* gene in IgA nephropathy

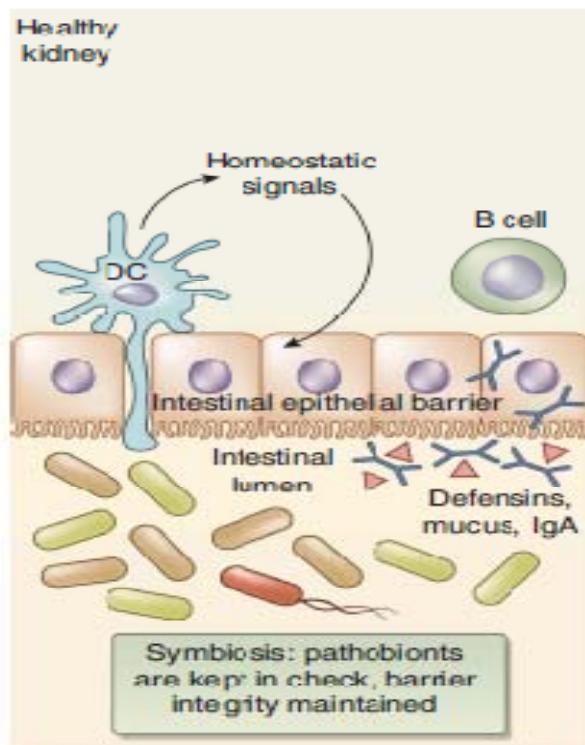
Wei Qin<sup>1</sup>, Xiang Zhong<sup>1</sup>, Jun Ming Fan, Ying Juan Zhang, Xian Rong Liu and Xing Yi Ma

Department of Medicine, Division of Nephrology, West China Hospital of Sichuan University, Chengdu, Sichuan, People's Republic of China

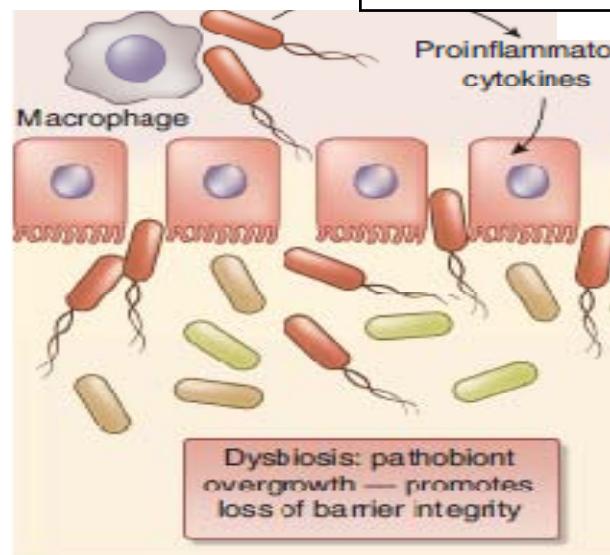


## The intestinal microbiota, a leaky gut, and abnormal immunity in kidney disease

Hans-Joachim Anders<sup>1</sup>, Kirstin Andersen<sup>1</sup> and Bärbel Stecher<sup>2</sup>



LPS Endotoxin  
from Gram –  
intestinal germ dysbiosis  
as a trigger for  
intestinal immunity  
response in IgAN



Pathobionts



Symbionts



## **The gut-kidney axis in IgA nephropathy**

**High intestinal permeability in children and adults with IgAN (Davin & Nagy 1985)**

**High levels of IgA anti alimentary antigens in IgAN**

**Case reports of association between celiac disease and IgAN**

## Gluten-induced experimental IgA glomerulopathy

Coppo R, et al Mazzucco G, Martina G, Roccatello D, Amore A, Novara R, Bargoni A, Piccoli G, Sena LM. Lab Invest. 1989;60:499-506.

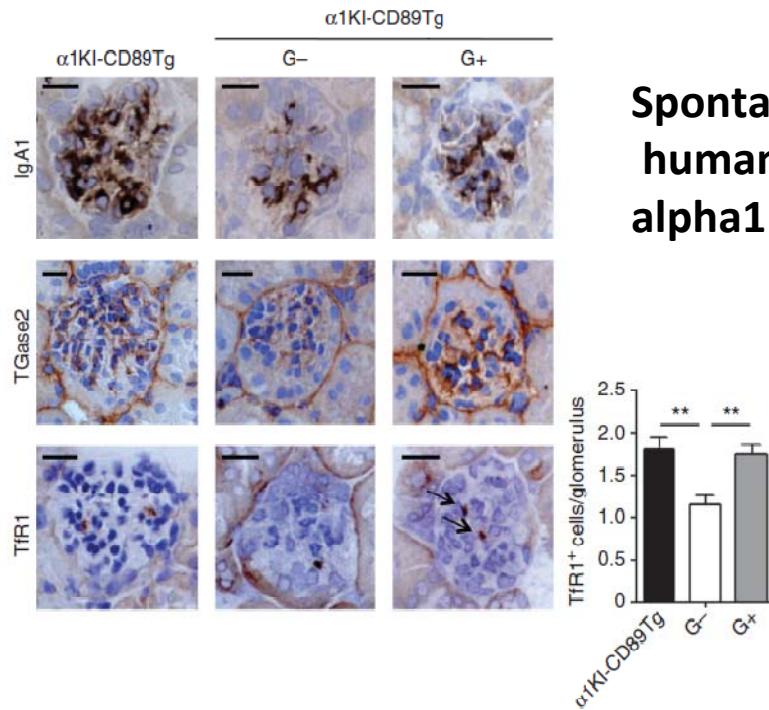


Figure 2. Semiquantitative analysis of IgA immune deposits in BALB/c mice after 14 wk of different diets.

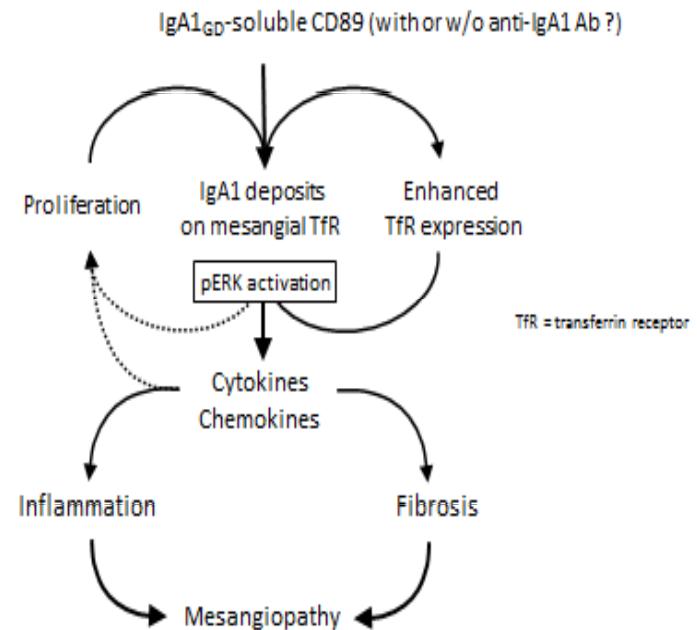
# Gluten exacerbates IgA nephropathy in humanized mice through gliadin–CD89 interaction

Kidney International (2015) 88, 276–285

Christina Papista<sup>1,2,3,4</sup>, Sebastian Lechner<sup>1,2,3,4</sup>, Sanae Ben Mkaddem<sup>1,2,3,4</sup>, Marie-Bénédicte LeStang<sup>1,2,3,4</sup>, Lilia Abbad<sup>1,2,3,4</sup>, Julie Bex-Coudrat<sup>1,2,3,4</sup>, Evangéline Pillebout<sup>5</sup>, Jonathan M. Chemouny<sup>1,2,3,4</sup>, Mathieu Jablonski<sup>6</sup>, Martin Flamant<sup>1,2,4,7</sup>, Eric Daugas<sup>1,2,3,4,6</sup>, François Vrtovsnik<sup>1,2,3,4,6</sup>, Minas Yiangu<sup>8</sup>, Laureline Berthelot<sup>1,2,3,4,10</sup> and Renato C. Monteiro<sup>1,2,3,4,9,10</sup>



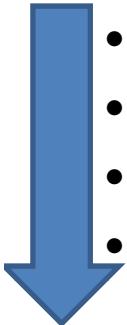
## Spontaneous IgAN mouse model expressing human IgA1 and CD89 (double transgenic alpha1KI-CD89Tg mice)



# Gluten free diet for 3 generations

reduction in

- IgA1 mesangial deposition
- glomerular inflammatory-cell infiltration
- IgA1–sCD89 complexes in serum and kidney eluates
- hematuria



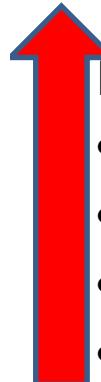
# Gluten diet for 30 days

Intestinal injury

(inflammation and villous atrophy)

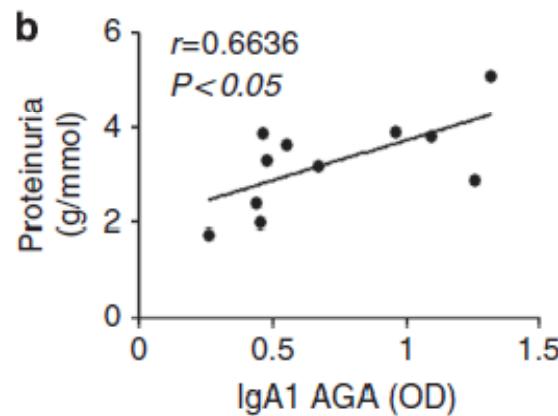
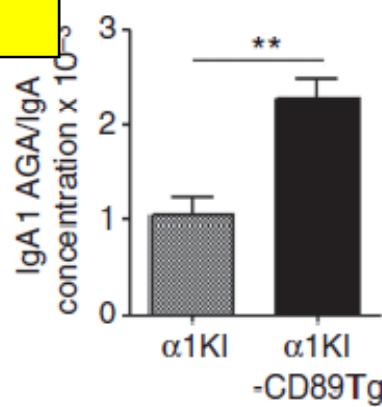
Increase in

- IgA1–sCD89 complexes
- IgA1 mesangial deposition
- IgA1 antigliadin Ab
- correlation with proteinuria

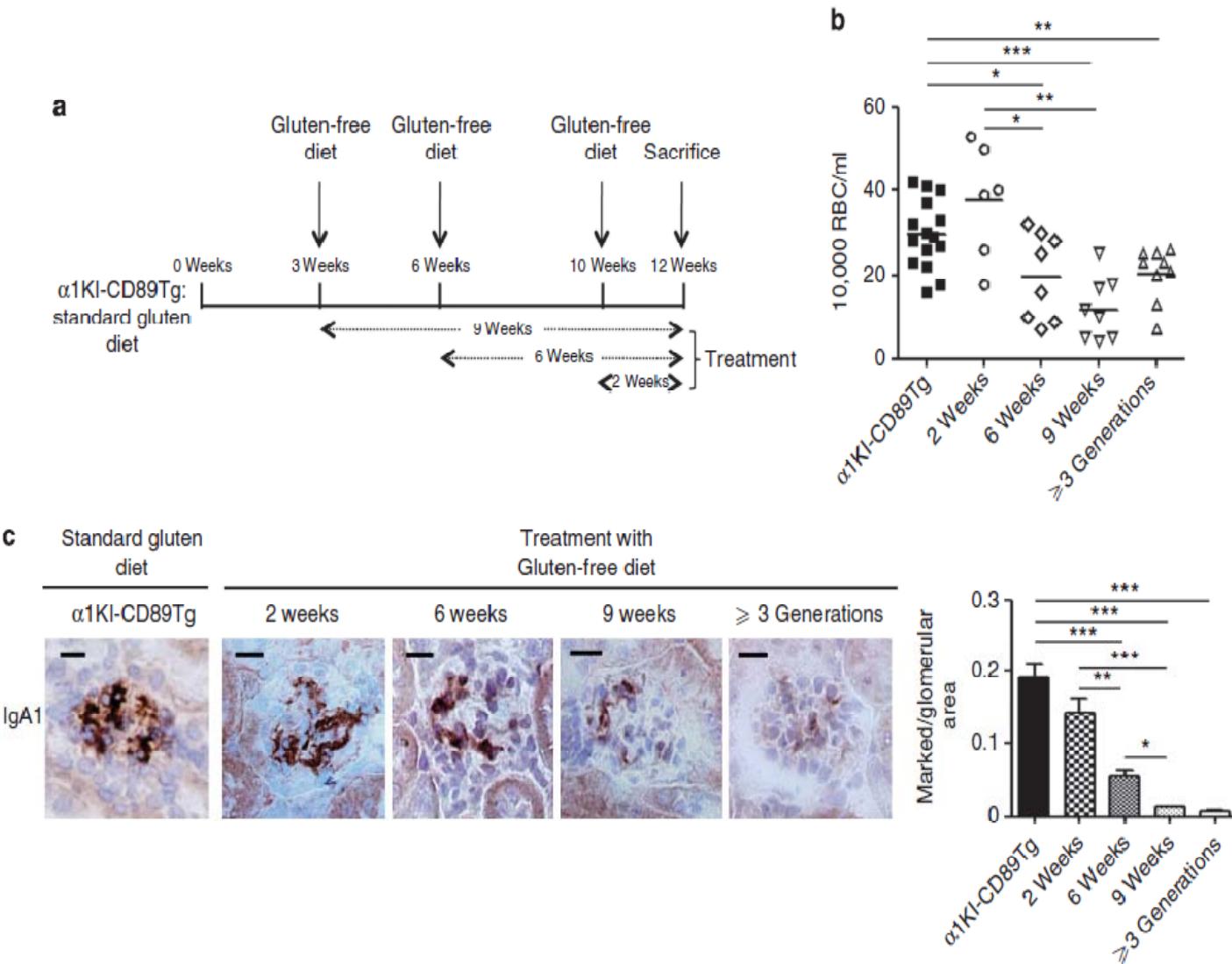


## Correlation between anti-gliadin antibodies and proteinuria

in experimental  
alpha1KI-CD89 mice  
on gluten diet



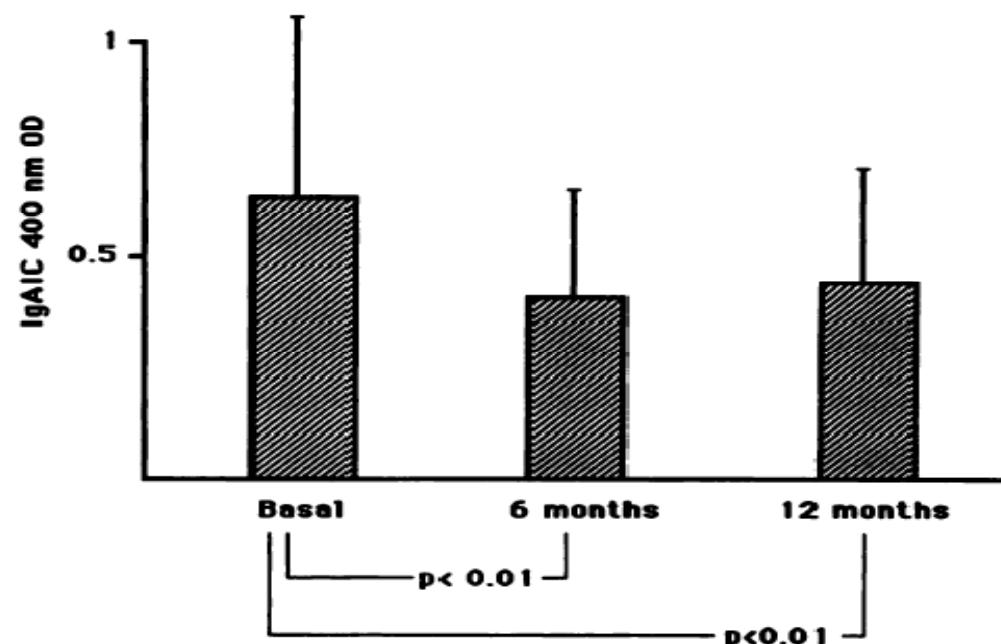
# Early gluten-free diet abolishes IgAN development, hematuria and proteinuria in alpha1KI-CD89Tg mice



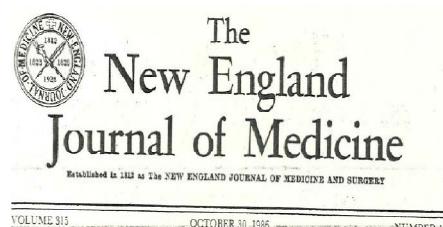
**MAY GLUTEN-FREE DIET REDUCE THE LEVELS OF IgA IMMUNE COMPLEXES IN PRIMARY IgA NEPHROPATHY?**

R. Coppo, B. Basolo, C. Rollino, D. Roccatello, G. Martina, A. Amore,  
\*G. Bongiorno, G. Piccoli

*University of Turin Nephrology and Dialysis Unit, \*Dietetic Service,  
S Giovanni Hospital, Turin, Italy*



**Figure 4. Effects of a gluten-free diet on the levels of IgAIC in IgAGN patients.**



**NEJM correspondence**  
**Coppo R et al**  
**October 30, 1986**

**Dietary Antigens and Primary Immunoglobulin A Nephropathy**

(J. Am. Soc. Nephrol. 1992; 2:S173-S180)

## Mediterranean diet and primary IgA nephropathy

R. COPPO<sup>1</sup>, B. BASOLO<sup>1</sup>, C. ROLLINO<sup>1</sup>, D. ROCCATELLO<sup>1</sup>, G. MARTINA<sup>1</sup>, A. AMORE<sup>1</sup>,  
G. BONGIORNO<sup>2</sup> and G. PICCOLI<sup>1</sup>

<sup>1</sup>Medical Nephrology Institute, University of Turin, Division of Nephrology and Dialysis,

Nuova Astanteria Martini Hospital, Turin, Italy

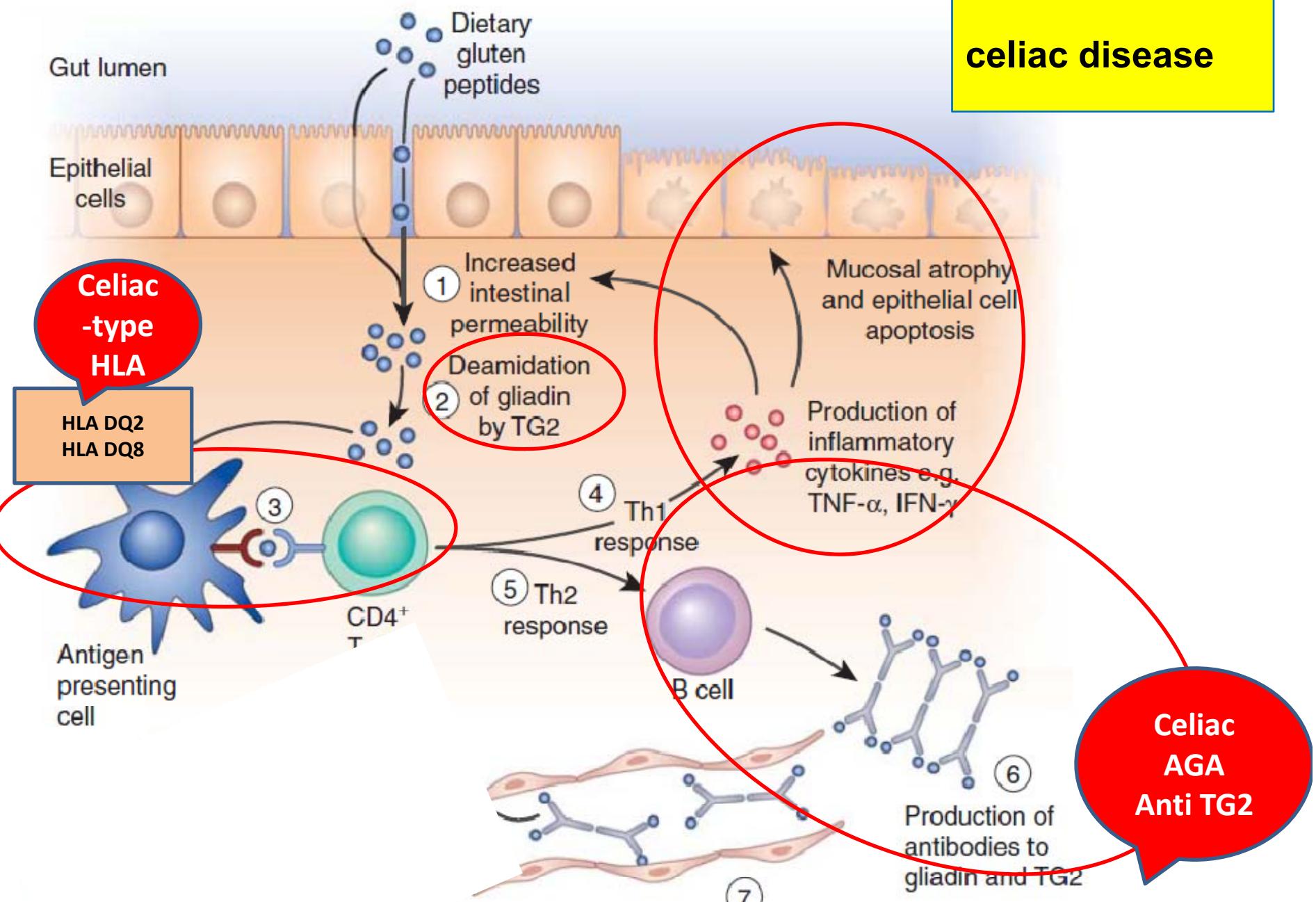
<sup>2</sup>Dietetic Division, S. Giovanni Hospital, Turin, Italy

### Conclusion of early studies (30 years ago) to target gluten for treating patients with IgAN

- **Gluten-free diet was of some benefit in our exploratory study (29 patients without evidence of celiac disease) with reduction of proteinuria, but without effect on renal function decline after 4 years.**
- The gluten-free diet is difficult to be followed by patients without GI symptoms

A next RCT testing gluten-free diet in IgAN ?

## celiac disease



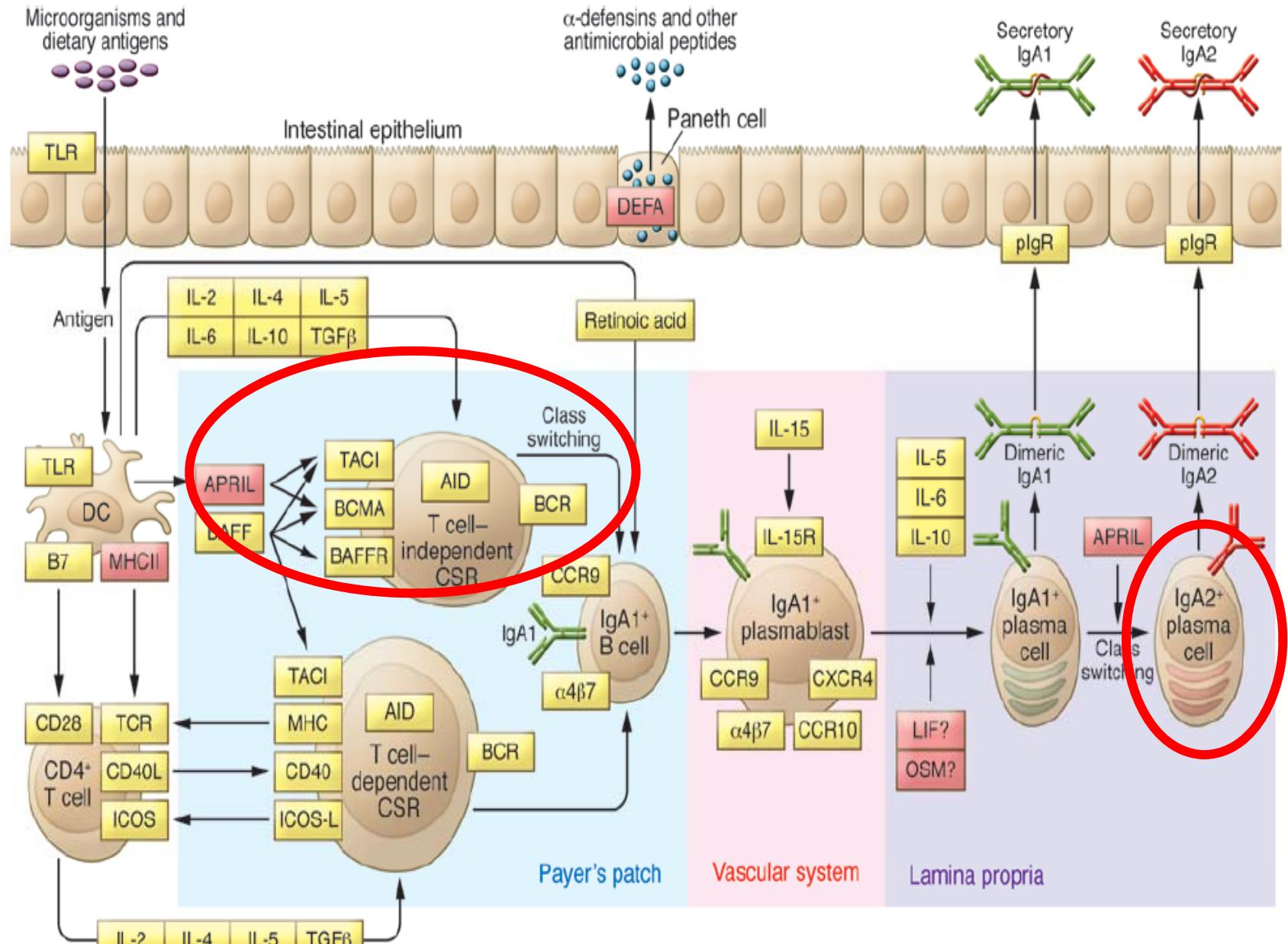
- In IgAN : **increased risk of celiac disease (4% vs 0.5-1%)**
  - In celiac disease **increased risk of IgAN (0.26%° versus 0.08%°)**
- 
- **Anti-gliadin AGA in 3-70% IgAN**  
Negative anti-endomisium /tissue transglutaminase antibodies in IgAN
  - No association with HLA DQ2-DQ8

In inflammatory bowel diseases IgAN is more frequent than other glomerular diseases (24% vs 8%)

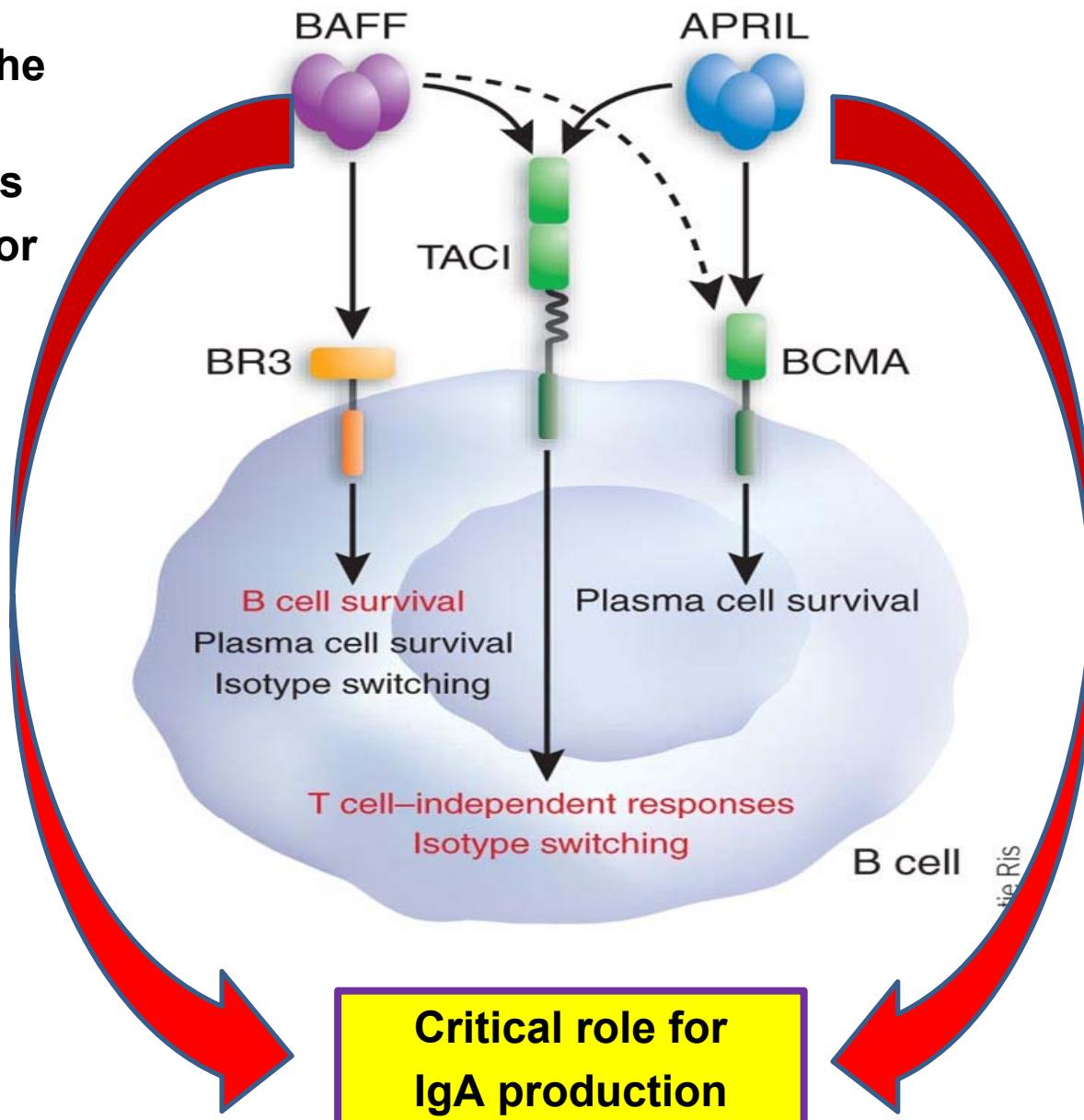
#### In IgAN

- Duodenal inflammation of varying degree
- Ongoing small bowel inflammation with signs of stress, despite normal morphology.
- Increase in intestinal permeability

Can we target the GALT to treat IgAN?



**Factors controlling the switch to IgA:**  
TNF family members  
B cell activator factor  
**BAFF (BlyS)**  
**APRIL**

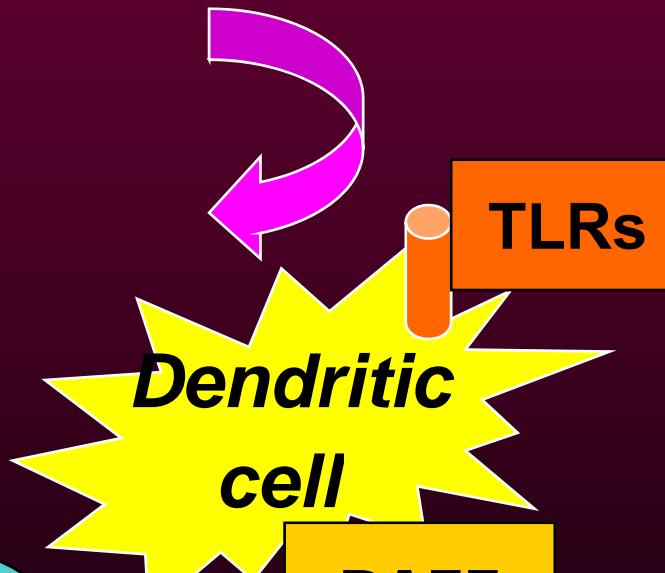
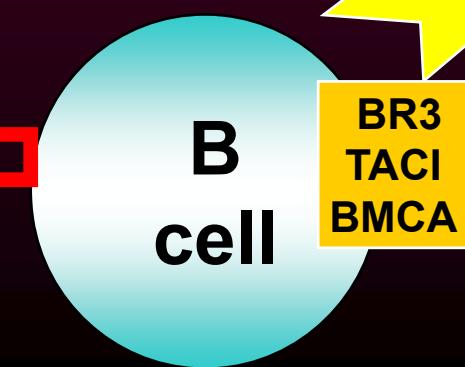
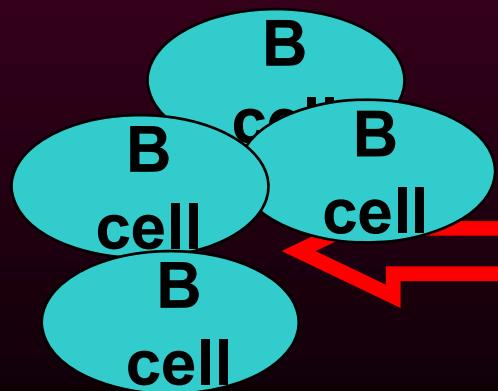


## MICROBICAL AGENTS

IgAN in transgenic mice  
hyperexpressing  
BAFF

IFN  $\gamma$  and  $\alpha$

IgA

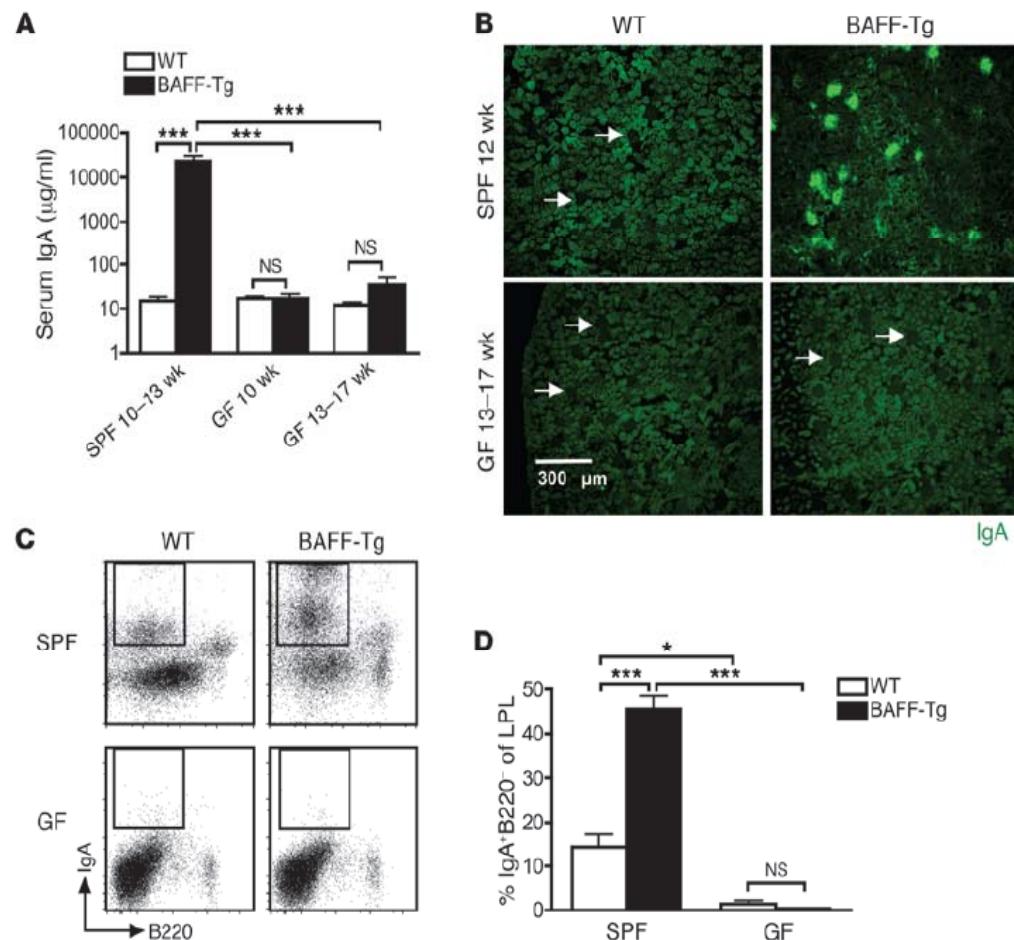


BR3  
TACI  
BMCA

BAFF  
Blys

# Mice overexpressing BAFF develop a commensal flora-dependent, IgA-associated nephropathy

Douglas D. McCarthy,<sup>1</sup> Julie Kujawa,<sup>2</sup> Cheryl Wilson,<sup>2</sup> Adrian Papandile,<sup>2</sup> Urjana Poreci,<sup>2</sup>



**PATHOGENESIS  
of IgAN**

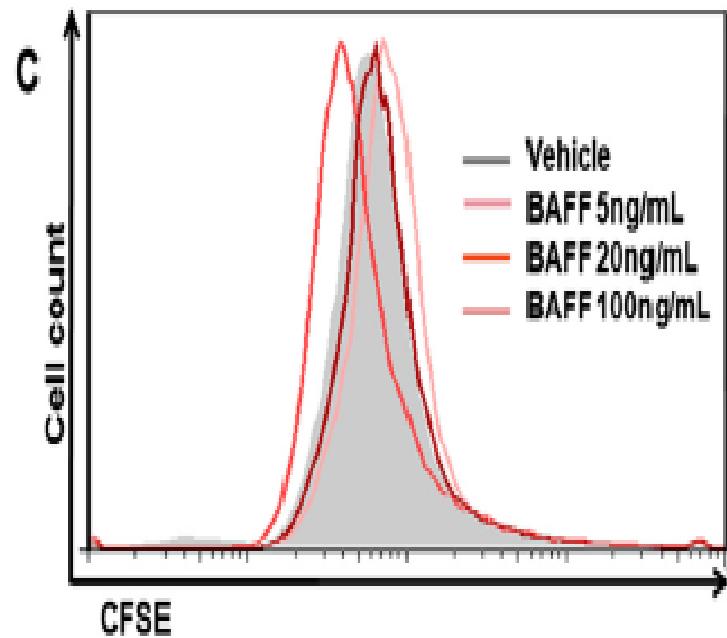
**Genes**

**B cell activity and  
IgA synthesis**

**Intestinal immunity  
(GALT)**

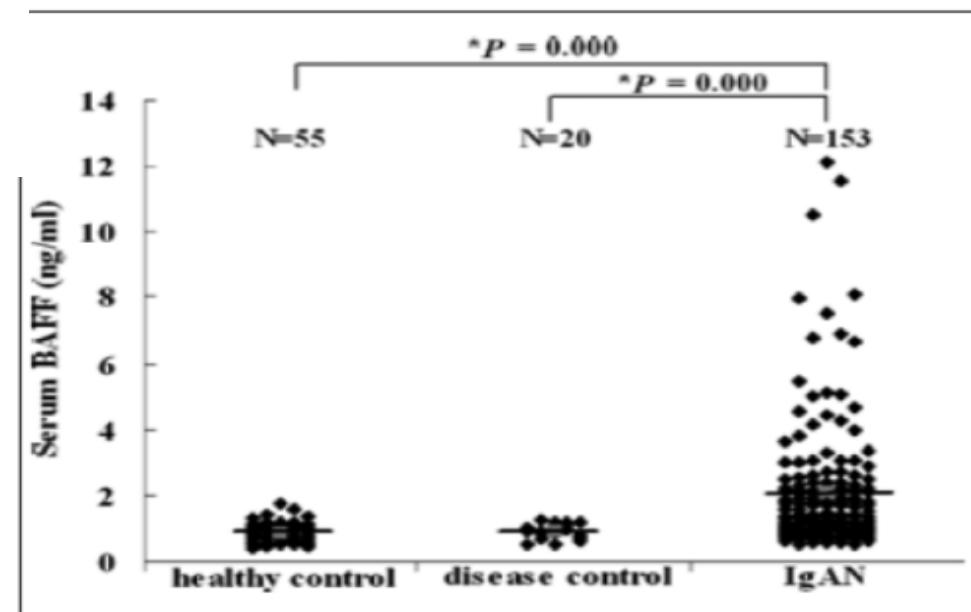
**Diet**

## Clinical data Experimental evidence



Serum BAFF is increased  
in IgAN patients

BAFF promotes proliferation  
of mesangial cells



## *Clinical Trials. Gov*

NCT02062684

Recruiting

BRIGHT-SC: Blisibimod Response in IgA Nephropathy Following At-Home Treatment by Subcutaneous Administration

Target: BAFF

Interventions

drug: Blisibimod;  
drug: Placebo

NCT02808429

Recruiting

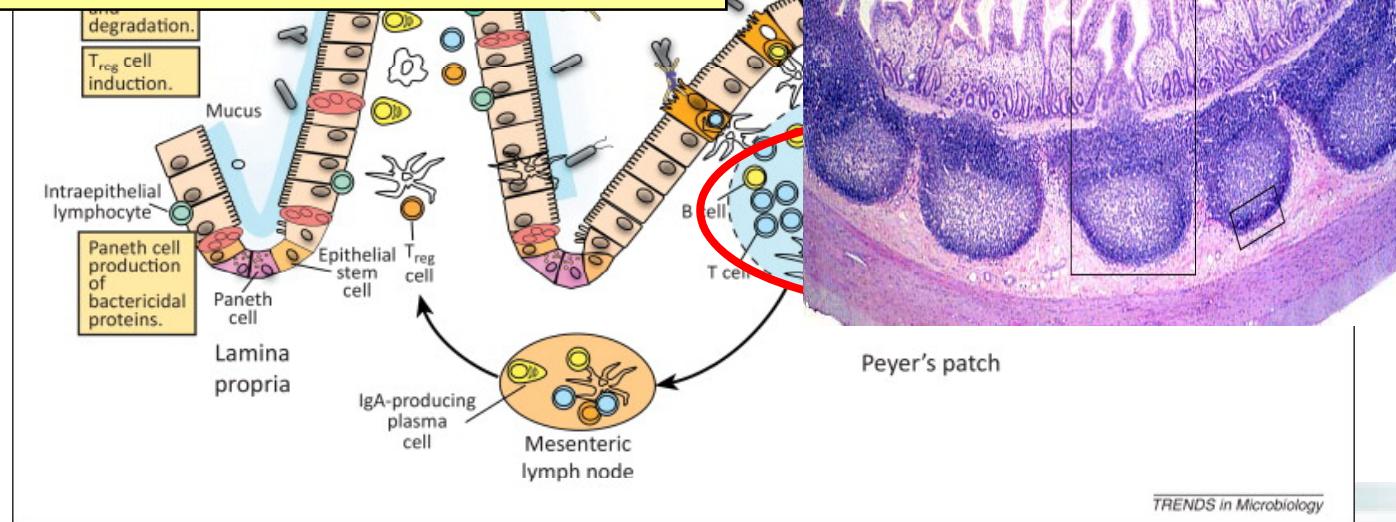
Safety and Efficacy Study of Atacicept 25 mg to treat IgAN

Interventions

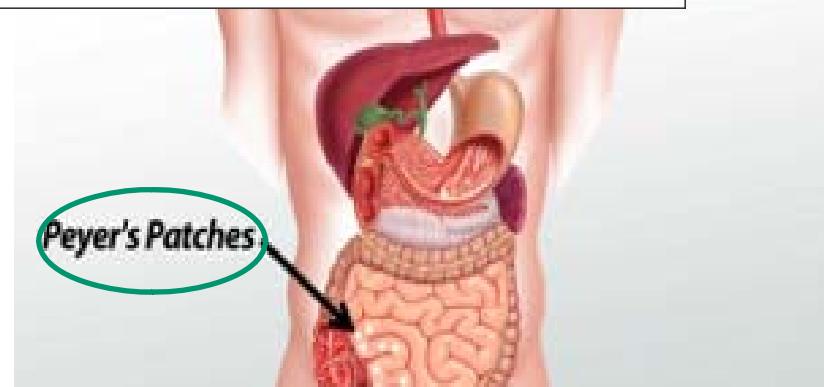
drug: Atacicept 25 mg  
drug: Placebo

Target:TACI

## Activation of intestinal immunity in IgAN: subclinical intestinal mucosa inflammation leading to IgA dysregulated synthesis



Sites of mucosal B cell induction:  
lower ileum and ascending colon  
with high density of Peyer's patches.

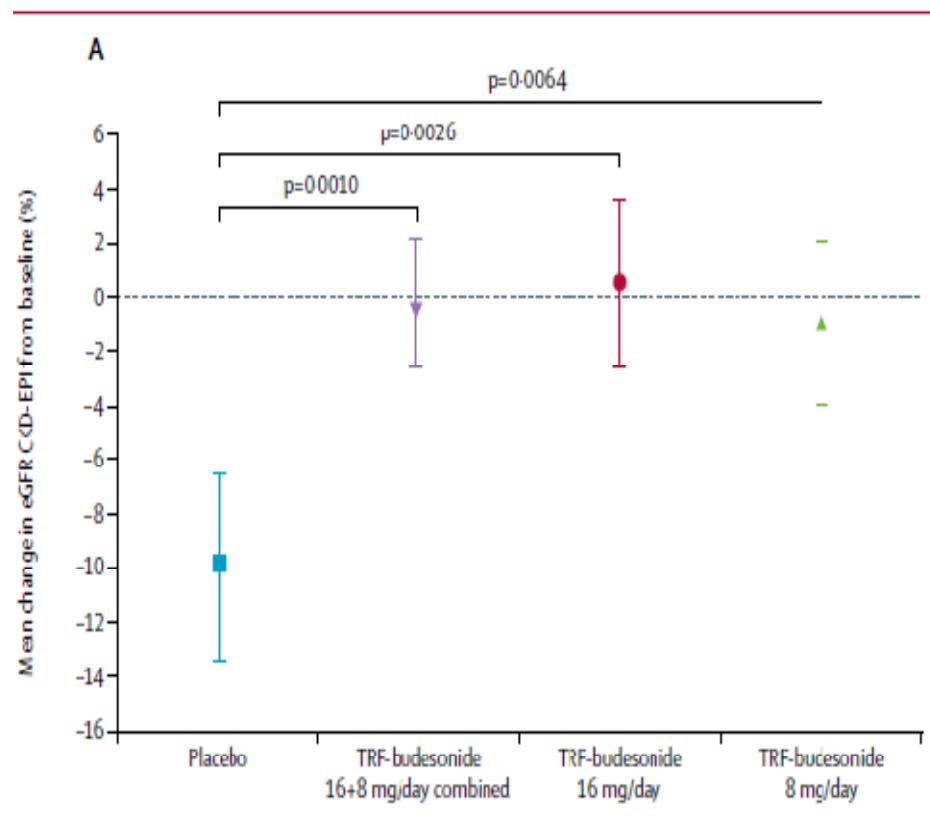
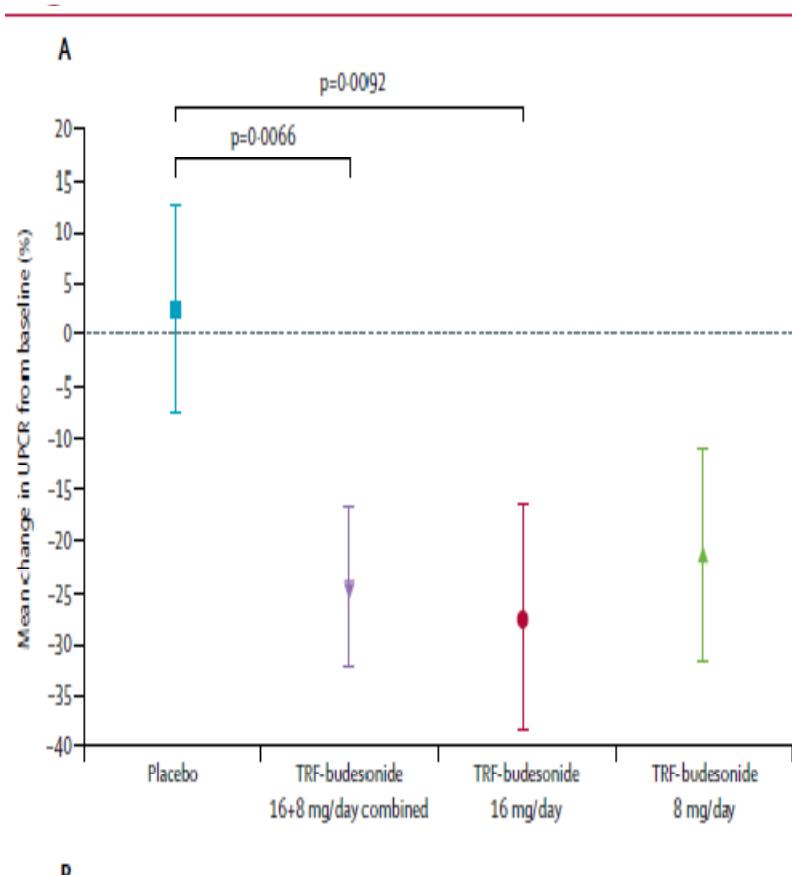


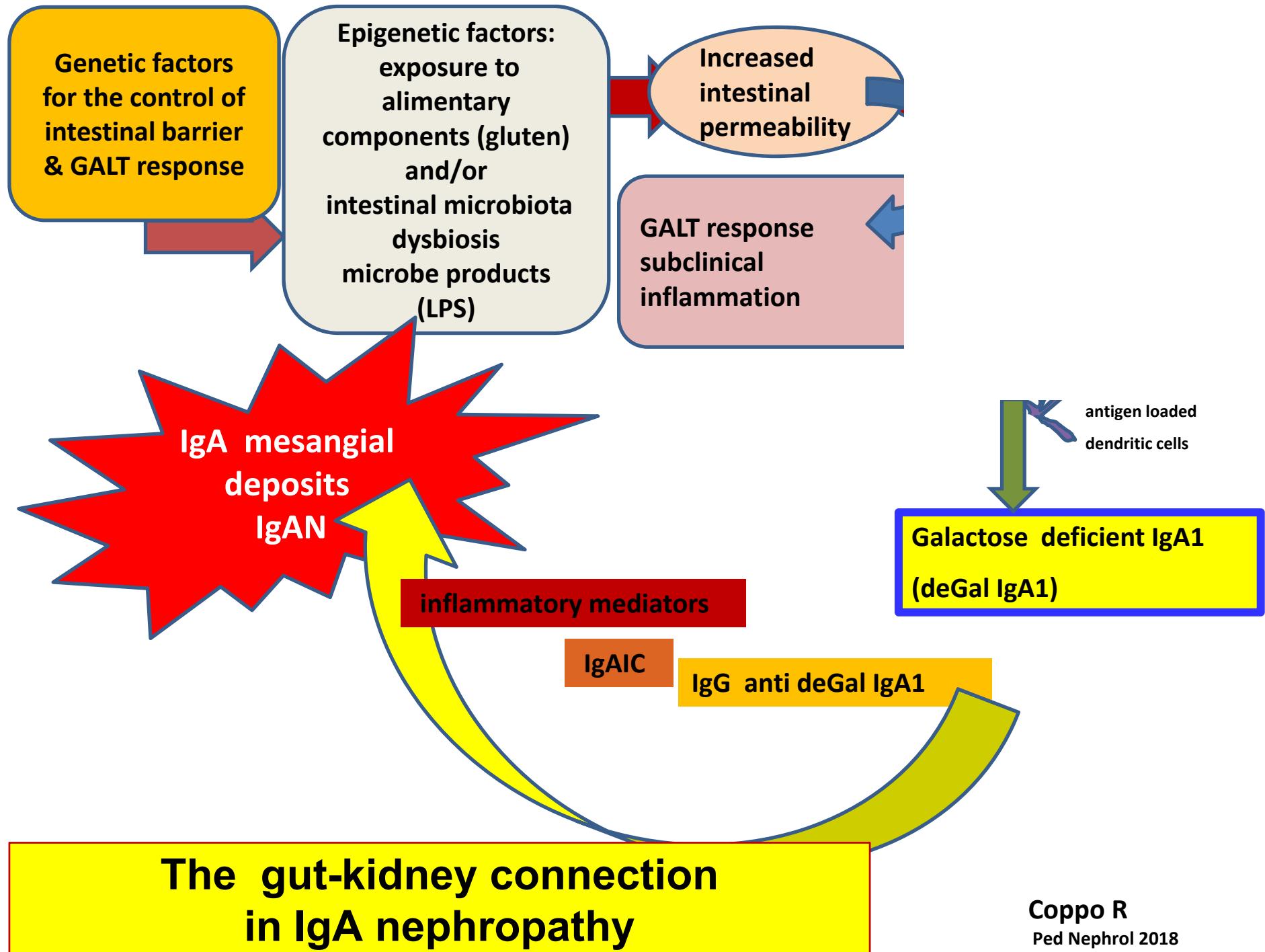
**target release formulation of the glucocorticoid budesonide:  
coated starch capsules for site-specific drug delivery at the ileo-cecal junction**

# Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial

Bengt C Fellström, Jonathan Barratt, Heather Cook, Rosanna Coppo, John Feehally, Johan W de Fijter, Jürgen Floege, Gerd Hetzel, Alan G Jardine, Francesco Locatelli, Bart D Maes, Alex Mercer, Fernanda Ortiz, Manuel Praga, Søren S Sørensen, Vladimir Tesar, Lucia Del Vecchio, for the NEFIGAN Trial Investigators

[www.thelancet.com](http://www.thelancet.com) Published online March 28, 2017 <http://dx.doi.org/10.1016/j.laneuro.2017.03.001>





Muchas gracias

Thank you for your attention



50 years  
later

15th International Symposium on IgANephropathy

# IIGAN 2018

September 27th-29th, 2018 - The Brick Hotel, Buenos Aires, Argentina

<https://www.iigann2018.com>

50th Anniversary of IgA Nephropathy  
 The International  
IgA Nephropathy Network