APCN x TSN 2025
23rd Asian Pacific Congress of Nephrology
Gene, Immunology, Vast, MEtabolism at its Finest!
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TaiNEX 2, Taipei, Taiwan

Dept. of Nephrology
Juntendo University

Chairs：Prof. Seung Hyeok Han and Tai-Shuan Lai

Understanding the Pathophysiology in IgA Nephropathy

了解IgA腎病變的病理生理機制

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COI Disclosure

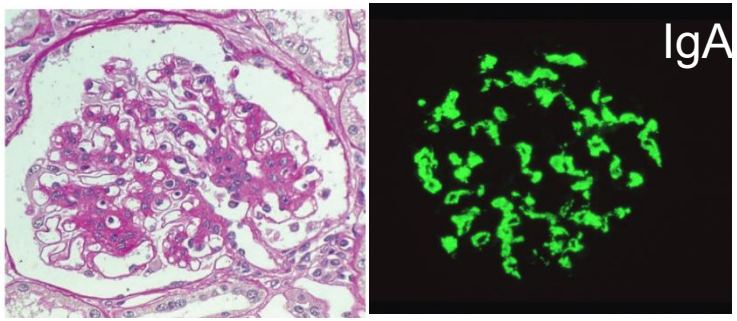
I have the following relationships to disclose any COI for this research presentation within the period of 36 months

* **Employment/Leadership position/Advisory role:** Otsuka Pharmaceutical, Vera therapeutics, Viatris
* **Stock ownership or options: none**
* **Patent royalties/licensing fees: none**
* **Honoraria:** Novartis, Alexion Pharma, Chugai, Viatris
* **Research funding:** Chugai Pharmaceutical, Otsuka Pharmaceutical
* **Subsidies or Donations: none**
* **Endowed departments by commercial entities: none**
* **Travel fees, gifts, and others: none**

Outline

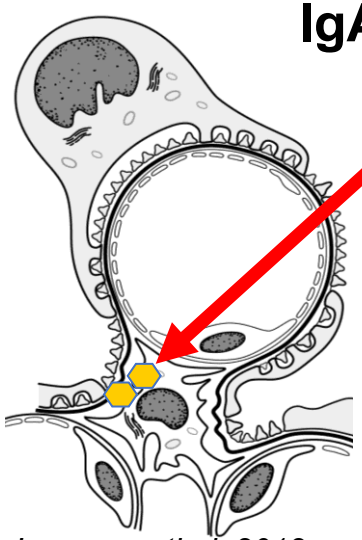
- Mucosal immunity of IgA nephropathy
- Mechanisms of glomerular deposition of IgA
- Role of BAFF and APRIL

IgA Nephropathy



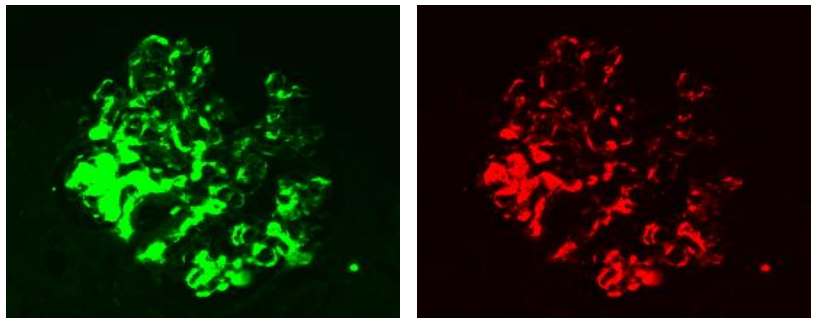
- **Described by Berger, 1968 based on**
  "intercapillary deposits of IgA-IgG" (IgA1, not IgA2)
- **Renal biopsy: IgA1 deposits, activation of mesangial cells: proliferation, ECM expansion**
- **Outcomes in this large IgA nephropathy cohort are generally poor with few patients expected to avoid kidney failure in their lifetime** *(Pitcher D, et al CJASN 2023).*
- **Recurrent after transplantation in >50% patients -> Key molecule is extra-renal origin = circulating immune complexes**

IgA1 deposition



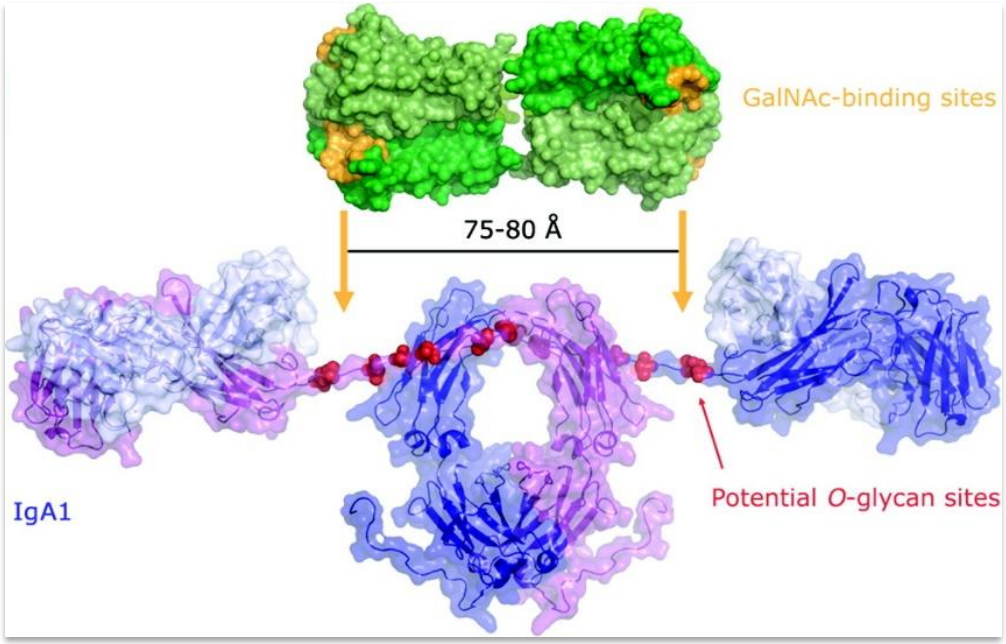
Modified from Novak J, et al. Semin Immunopathol, 2012

IgA **Gd-IgA1 (KM55 mAb)**



Suzuki H, et al. Kidney Int, 2018

Aberrantly glycosylated IgA1

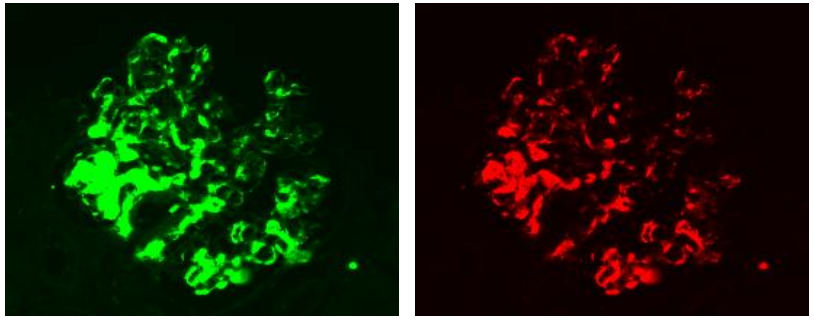


Gomes MM, Suzuki H, Biochemistry 49: 5671-82, 2010

Galactose-deficient IgA1: Gd-IgA1

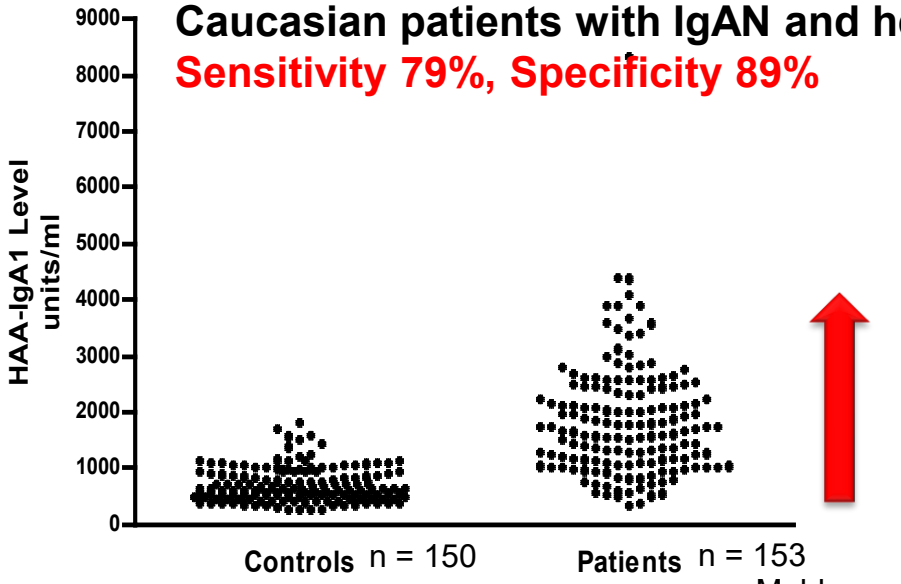
IgA1 in the circulation and glomerular deposits of IgAN patients is aberrantly glycosylated

IgA **Gd-IgA1 (KM55 mAb)**

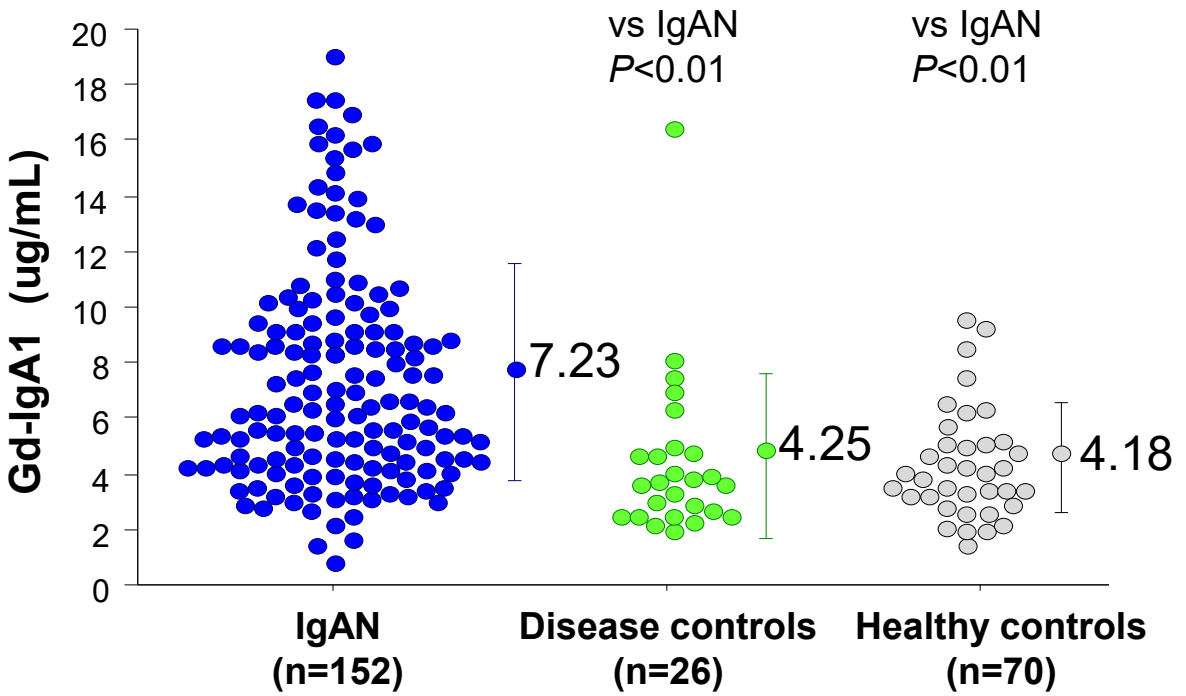


Suzuki H, et al. Kidney Int, 2018

Elevated levels of serum galactose-deficient IgA1 (Gd-IgA1) in IgAN

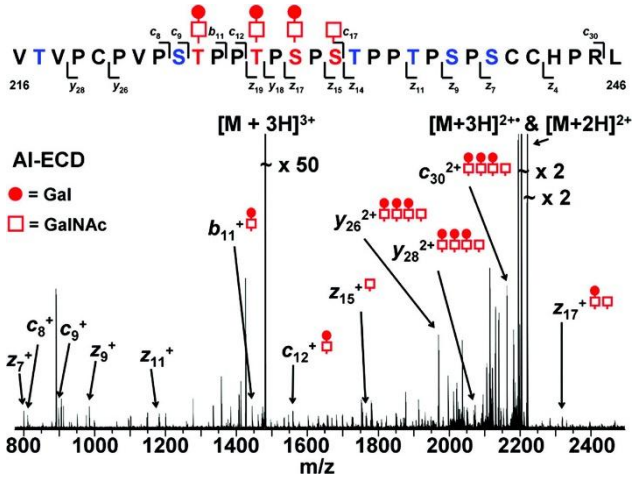


Moldoveanu Z. *Kidney Int* 2007



Yasutake J, et al. Nephrol Dial Transplant 2015

Aberrant *O*-Glycosylation in the IgA1 hinge region by electron capture dissociation FT-ICR mass spectrometry

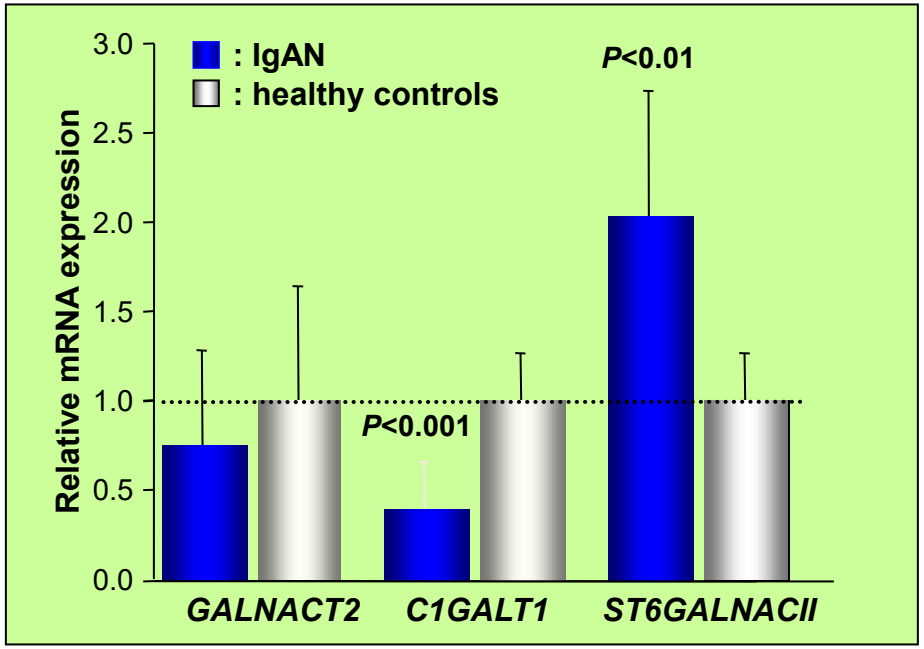


Matthew BR, et al, J Bio Chem, 2005

Gd-IgA1:

- ✓ **mostly polymeric**
- ✓ **form immune complexes**

Complex Changes in Biosynthetic Pathways of *O*-linked Glycans in IgA1-producing Cells from IgAN Patients



Gal
β1,3
GalNAc
Ser/Thr

Core 1 β1,3galactosyl-transferase

C1GALT1

ST6GALNACII

α2,6 GalNAc-sialyltransferase II

SA
α2,6
GalNAc
Ser/Thr

GalNAc
-Ser/Thr-

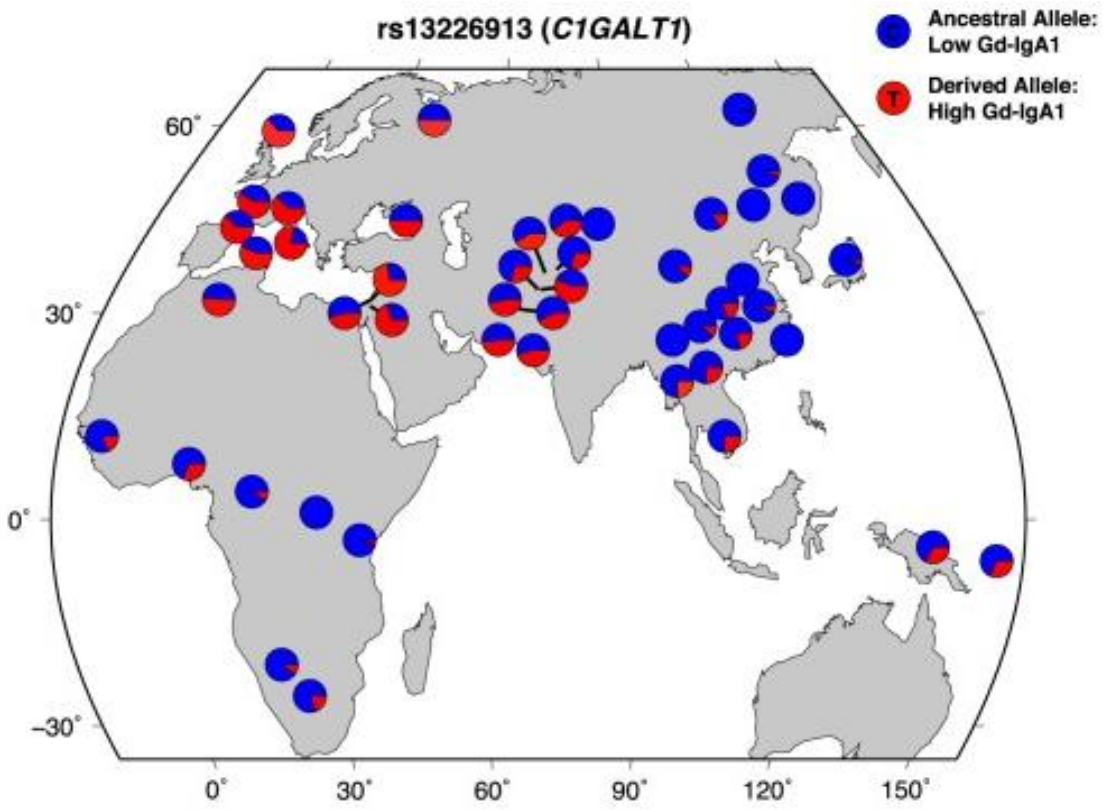
-Ser/Thr-

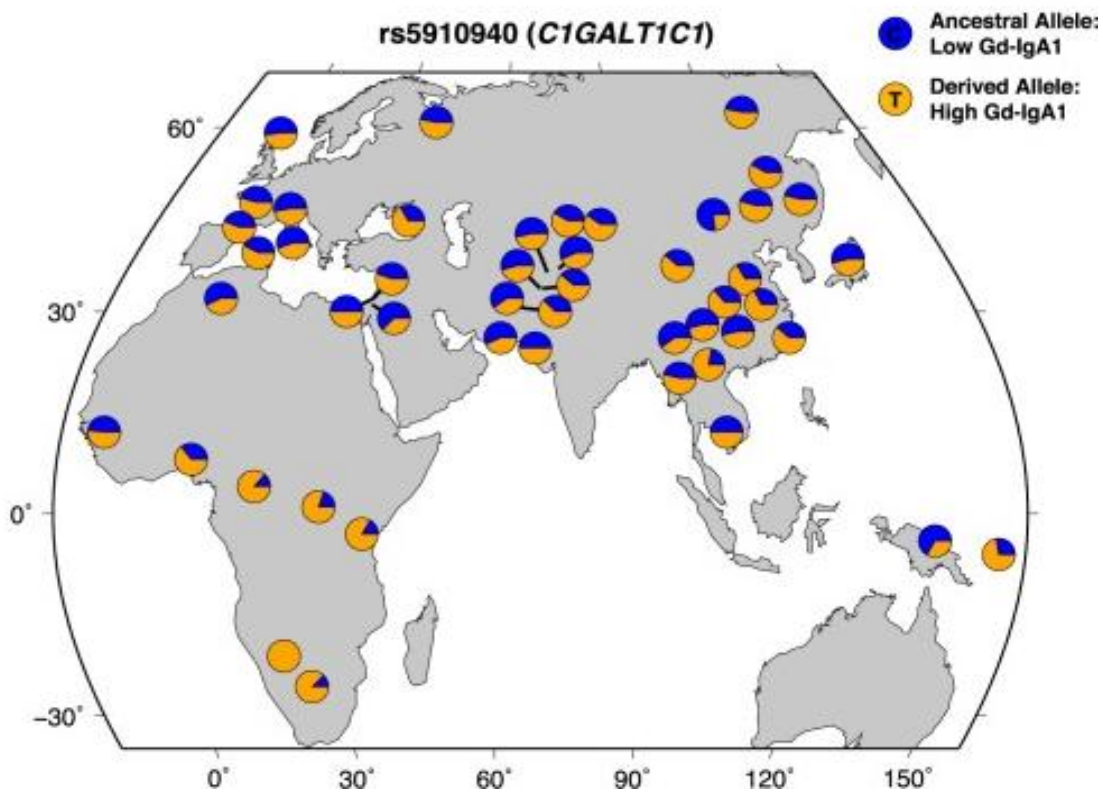
GalNAc-transferases

Elevated forms in serum IgA1 from IgAN patients

Suzuki H. *et al*, *J Clin Invest*, 2008

Genotypic effects and worldwide allelic frequency of glycosytransferases differ between ethnicities

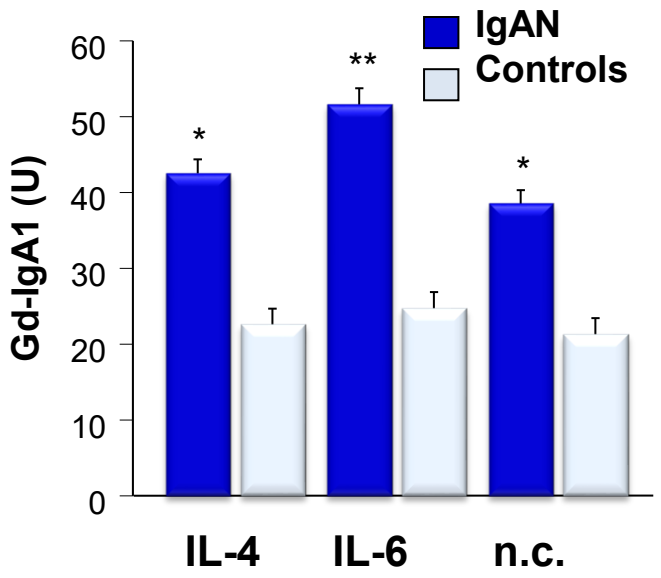




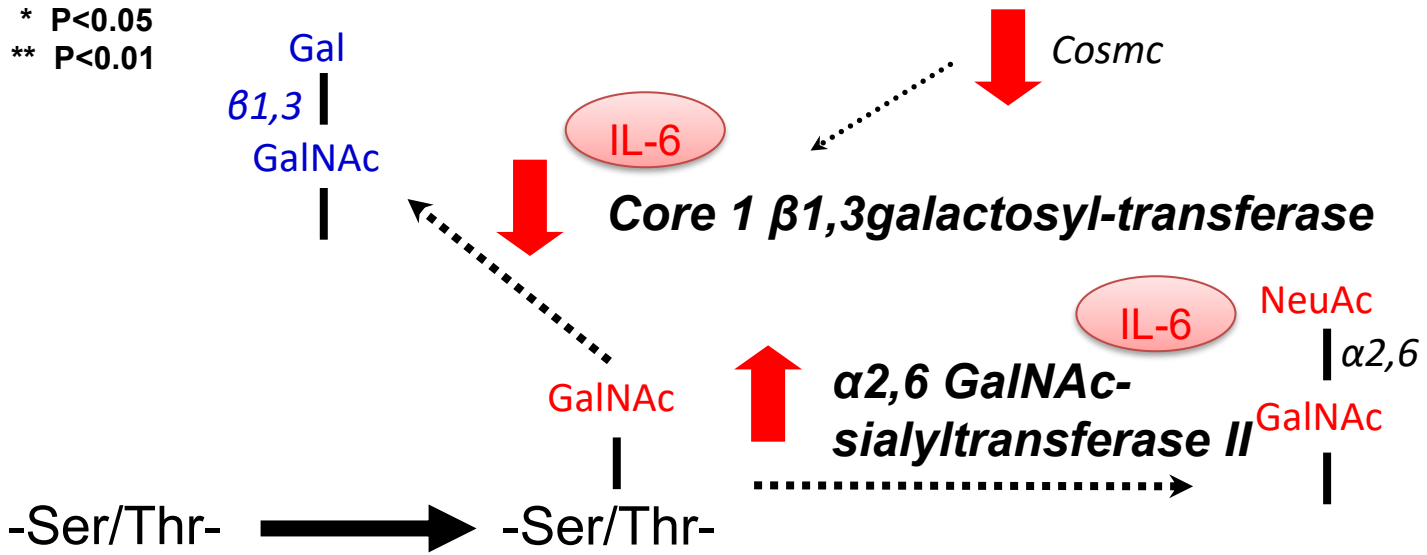
Kiryluk K, et al. Plos Genet 2017

IL-6 accentuated galactose deficiency of IgA1 via coordinated modulation of key glycosyltransferases

~Infection or inflammation may trigger overproduction of Gd-IgA1~

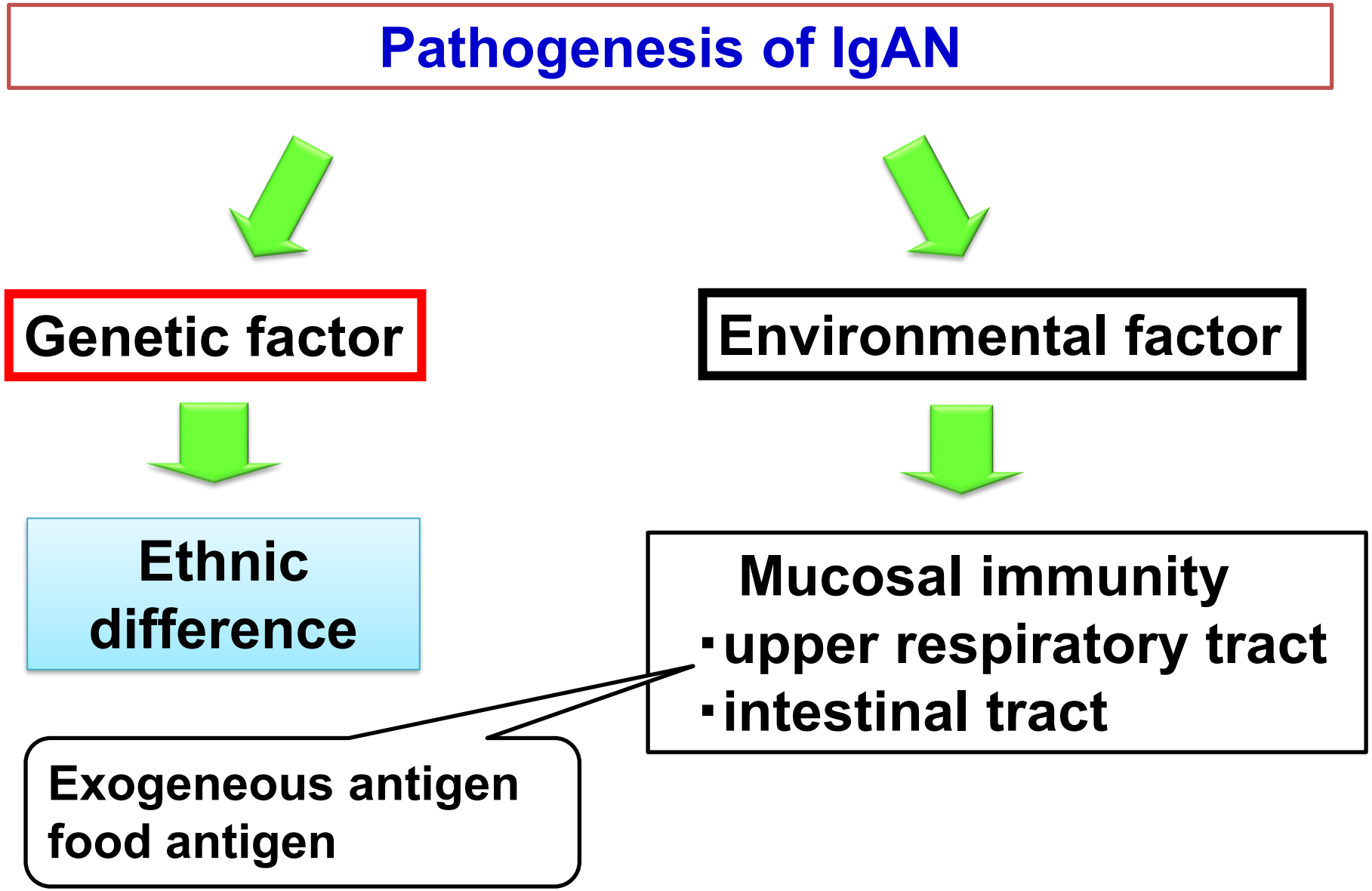


* P<0.05
** P<0.01

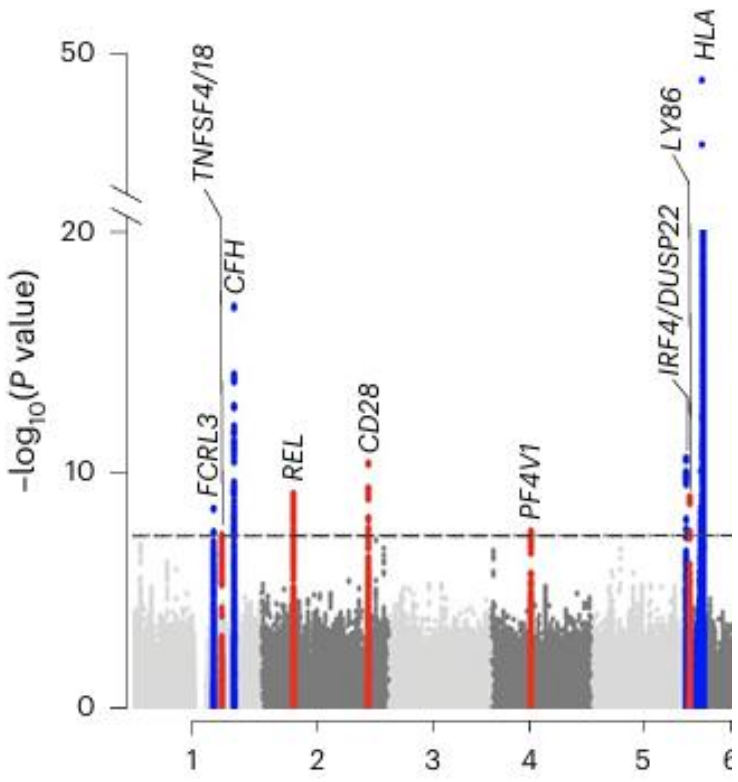


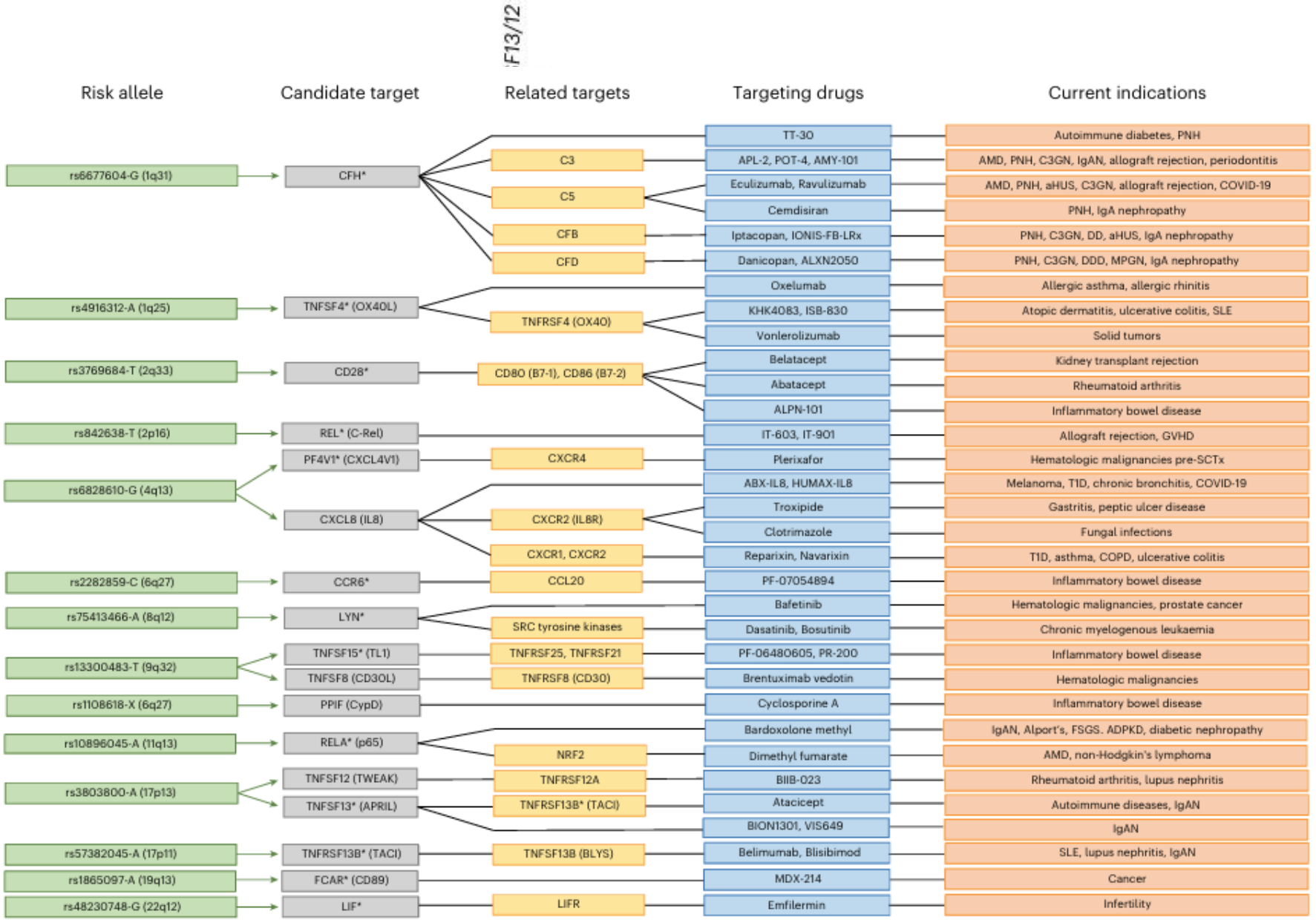
***GalNAc-transferases* (20 enzymes)**

Suzuki H, et al. J Biol Chem, 2014

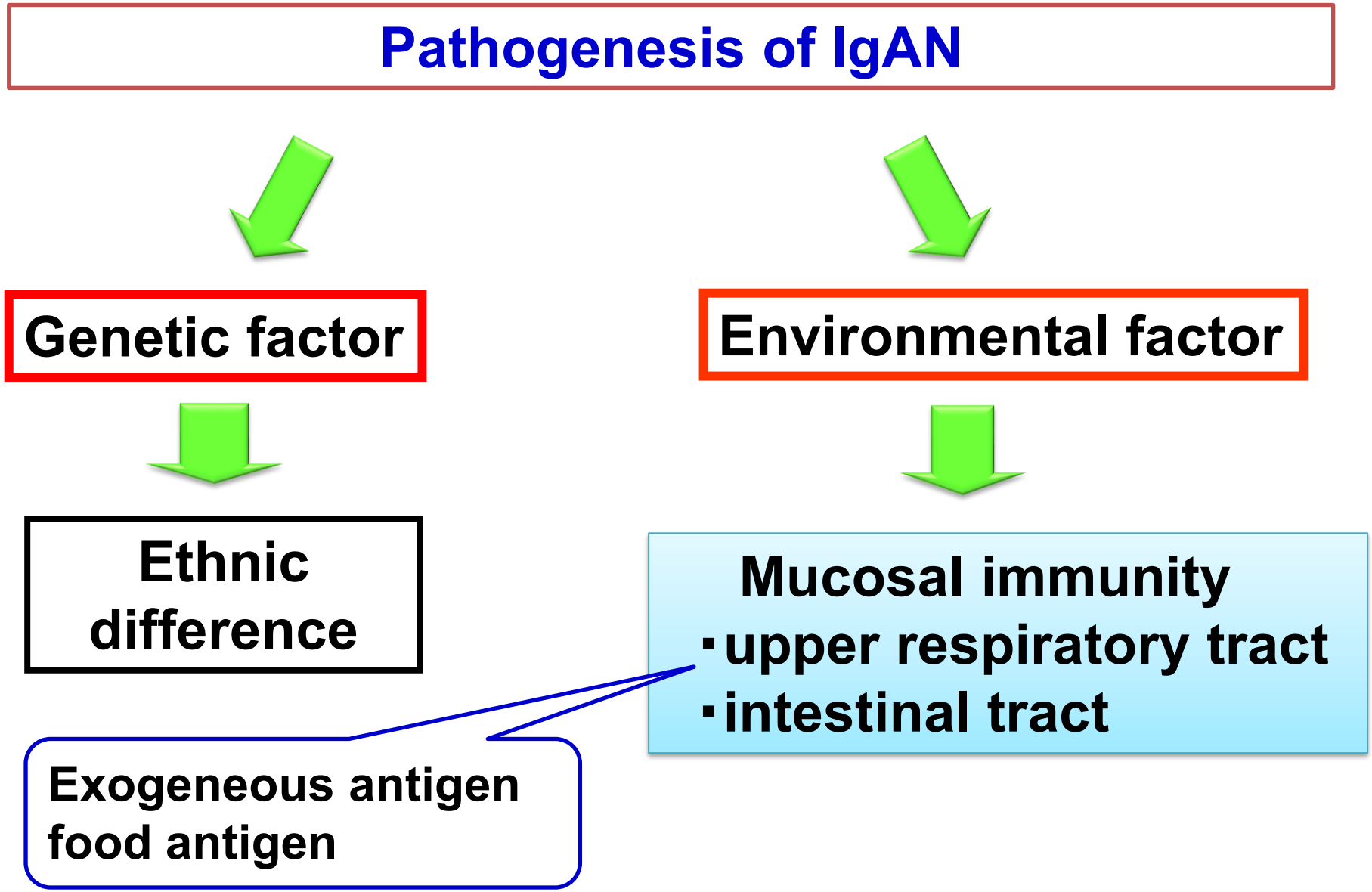

Pathogenesis of IgAN
Genetic factor
Environmental factor
Ethnic difference
Mucosal immunity
・upper respiratory tract
・intestinal tract
Exogeneous antigen
food antigen

GWAS reveals signaling pathways related to pathogenesis, enabling the identification of drug targets





Kiryluk K, Nat Genet 55, 7, 2023


Pathogenesis of IgAN
Genetic factor
Environmental factor
Ethnic difference
Mucosal immunity
・upper respiratory tract
・intestinal tract
Exogeneous antigen
food antigen

Postinfectious gross hematuria in patients with IgAN

Pharyngitis,
Tonsillitis,
Intestinal infections

1~3 days later

Gros

Dysregulation of mucosal immune system in IgAN

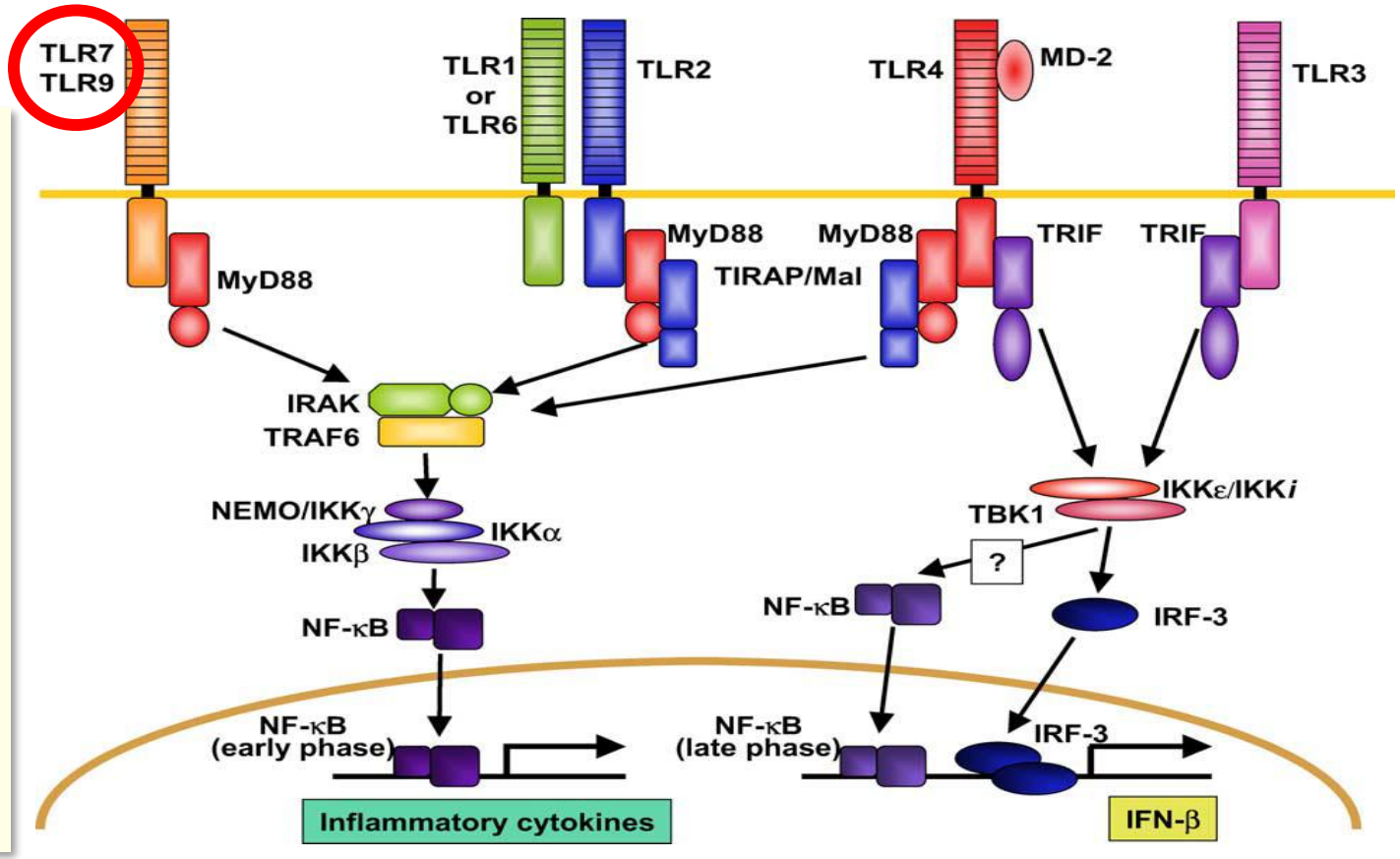
Clinical observation of episodes of gross hematuria with infections of upper respiratory tract or intestine associated with the mucosal immunity

Toll Like Receptors (TLRs)

Pattern-recognition receptors (PRR) are essential components of the innate immune response.

TLRs play a critical role in the early innate and mucosal immune responses to the invading pathogens.

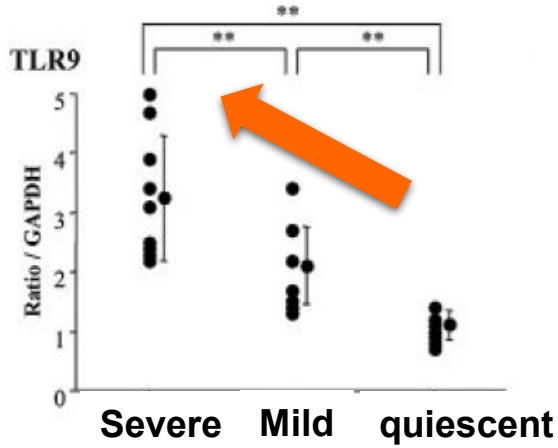
*different TLRs are located in different membranes

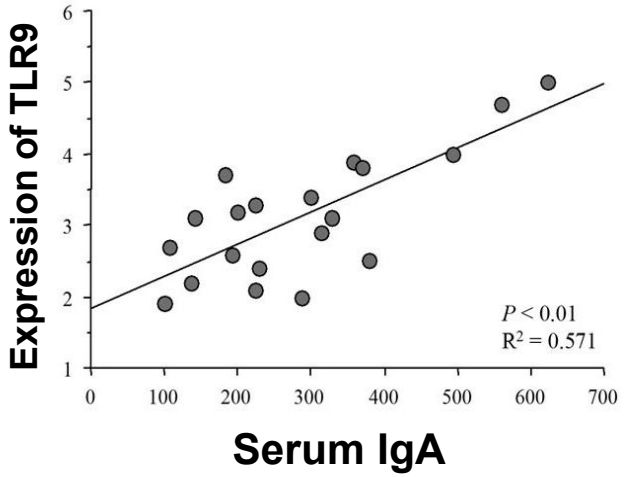


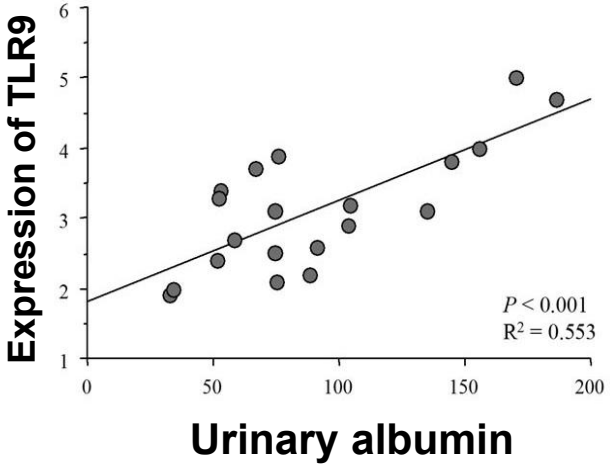
Brown J, et al. J Dent Res. 90: 417-427, 2011

TLR9 plays a critical role in the pathogenesis of IgAN

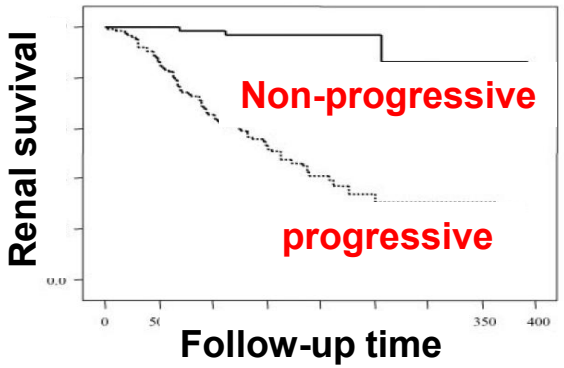
In IgAN onset model mice, transcript levels of TLR9 were associated with the severity of glomerulonephritis, levels of serum IgA, and urinary albumin







Polymorphisms of the TLR9 gene are associated with histological severity of patients with IgAN

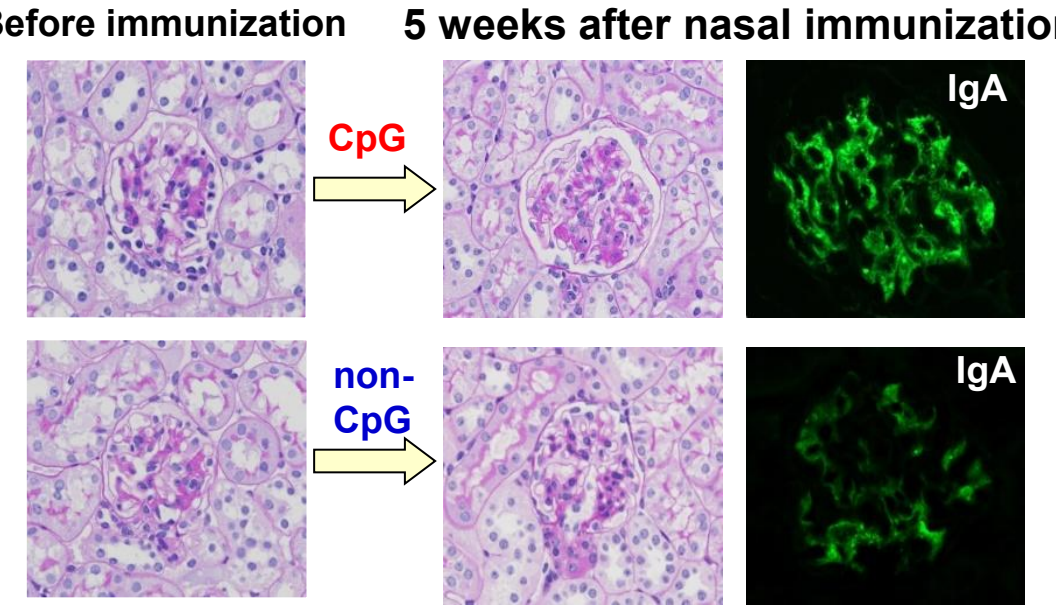


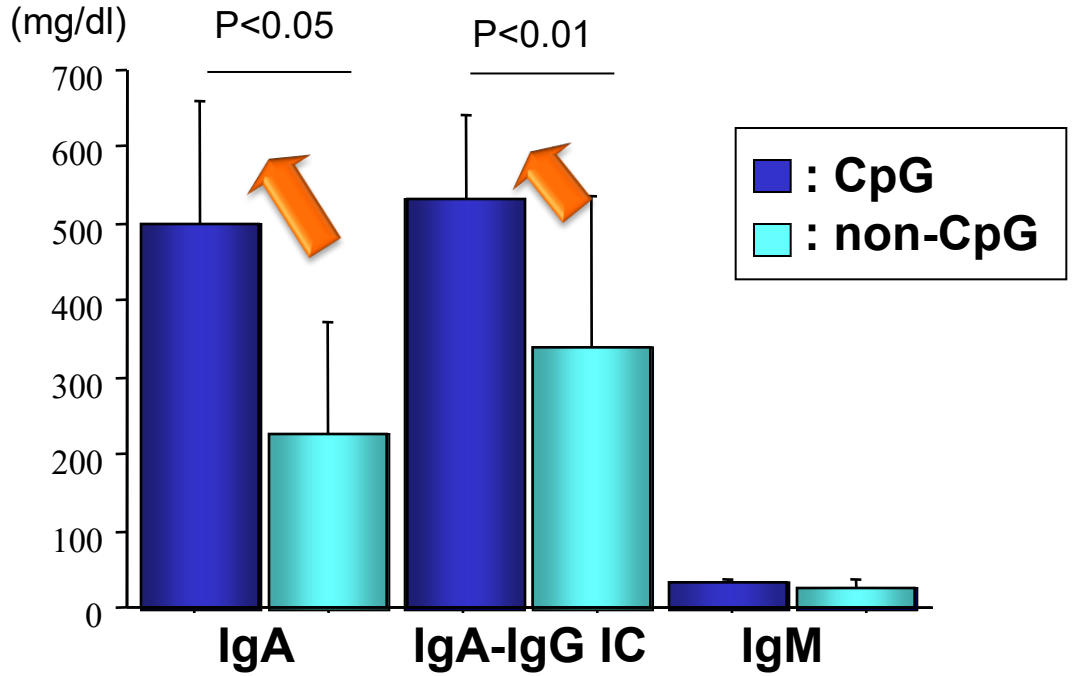
SNP analysis : TLR9 (rs352140)

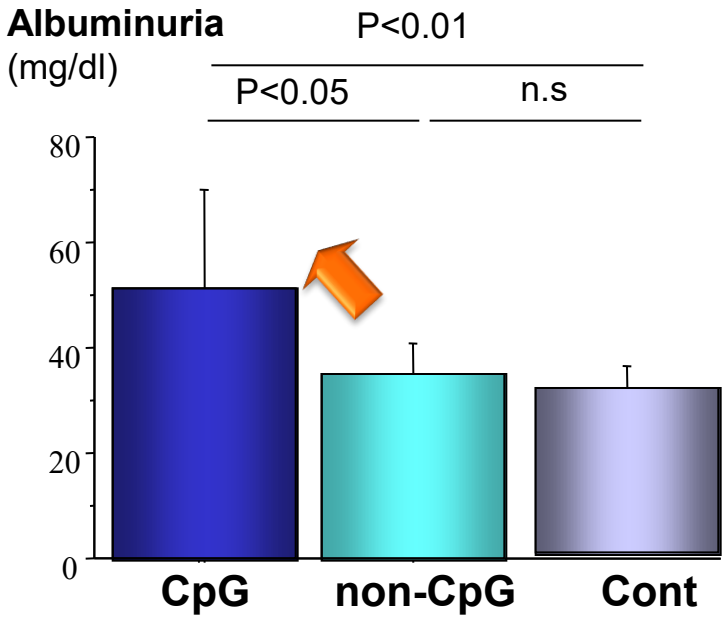
$\chi 2 = 52.014$, $P < 0.0001$

Suzuki H, et al: J Am Soc Nephrol, 2008

CpG Oligodeoxynucleotides (ligands for TLR9) aggravated renal injury with elevation of serum IgA and IgA-IgG IC



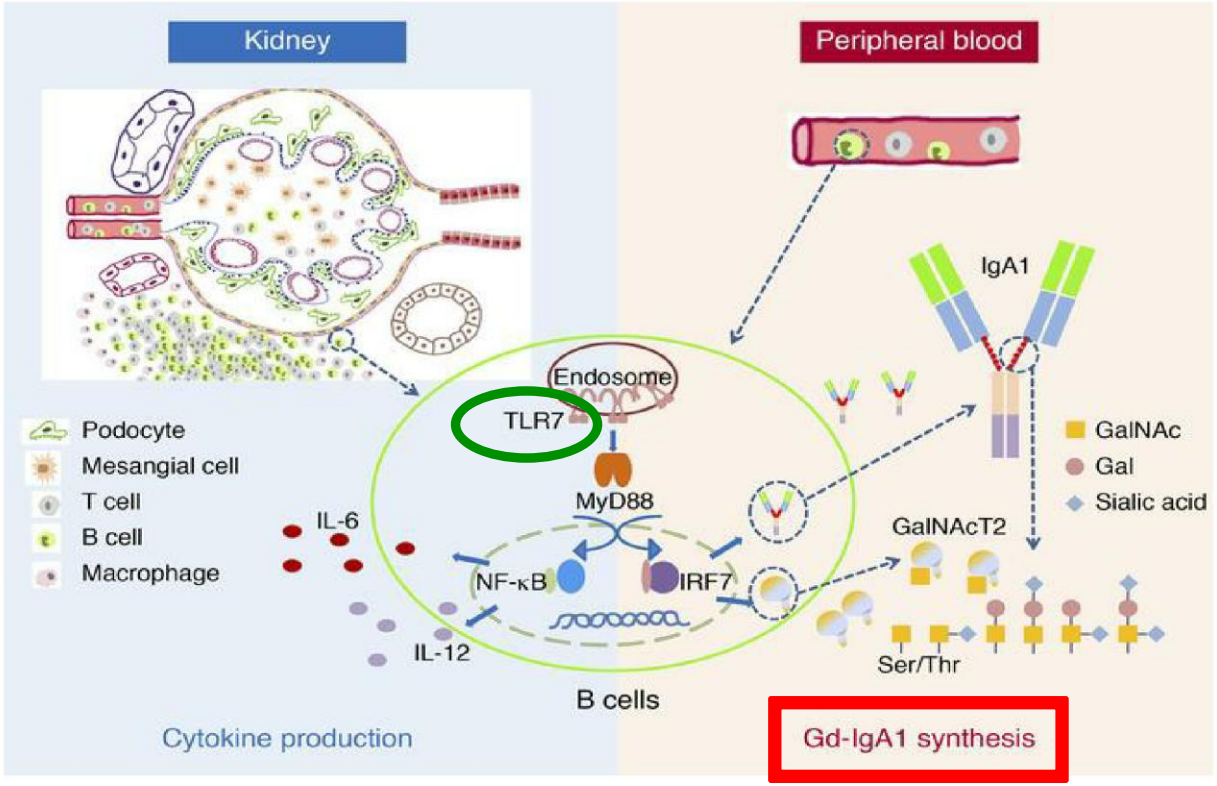


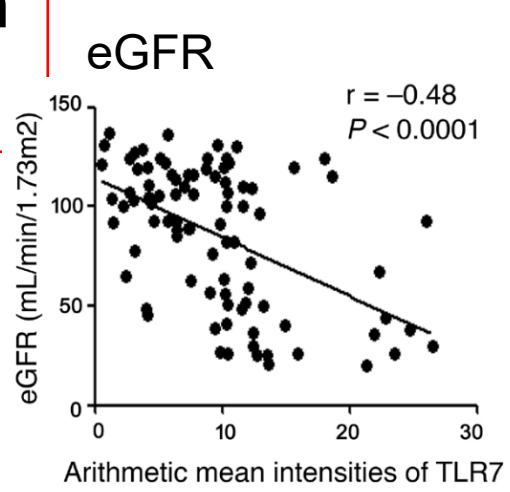


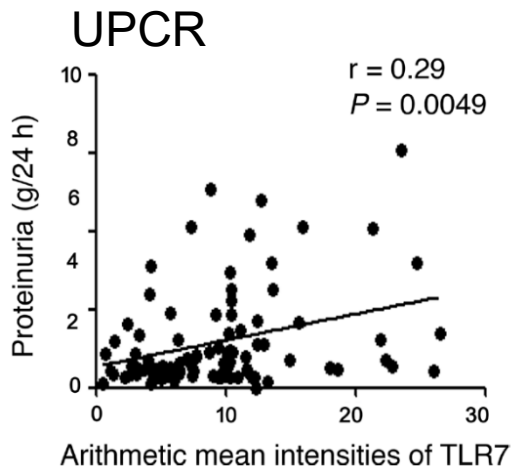
Suzuki H, et al, J Am Soc Nephrol, 2008

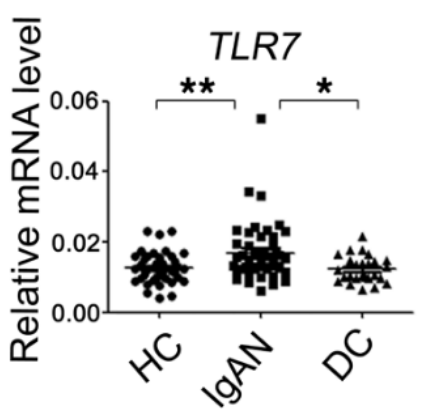
TLR7, recognizing RNA, is also involved in IgAN

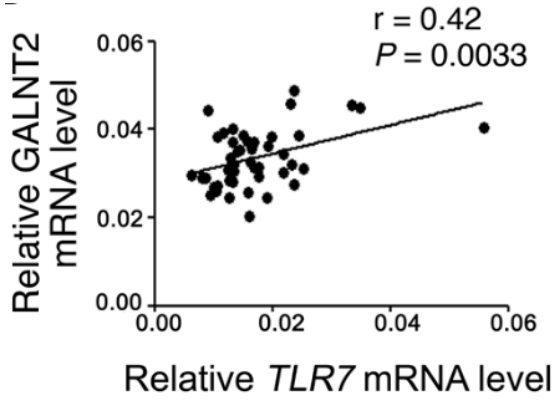
TLR7 in B cells promotes renal inflammation and Gd-IgA1 synthesis in IgAN





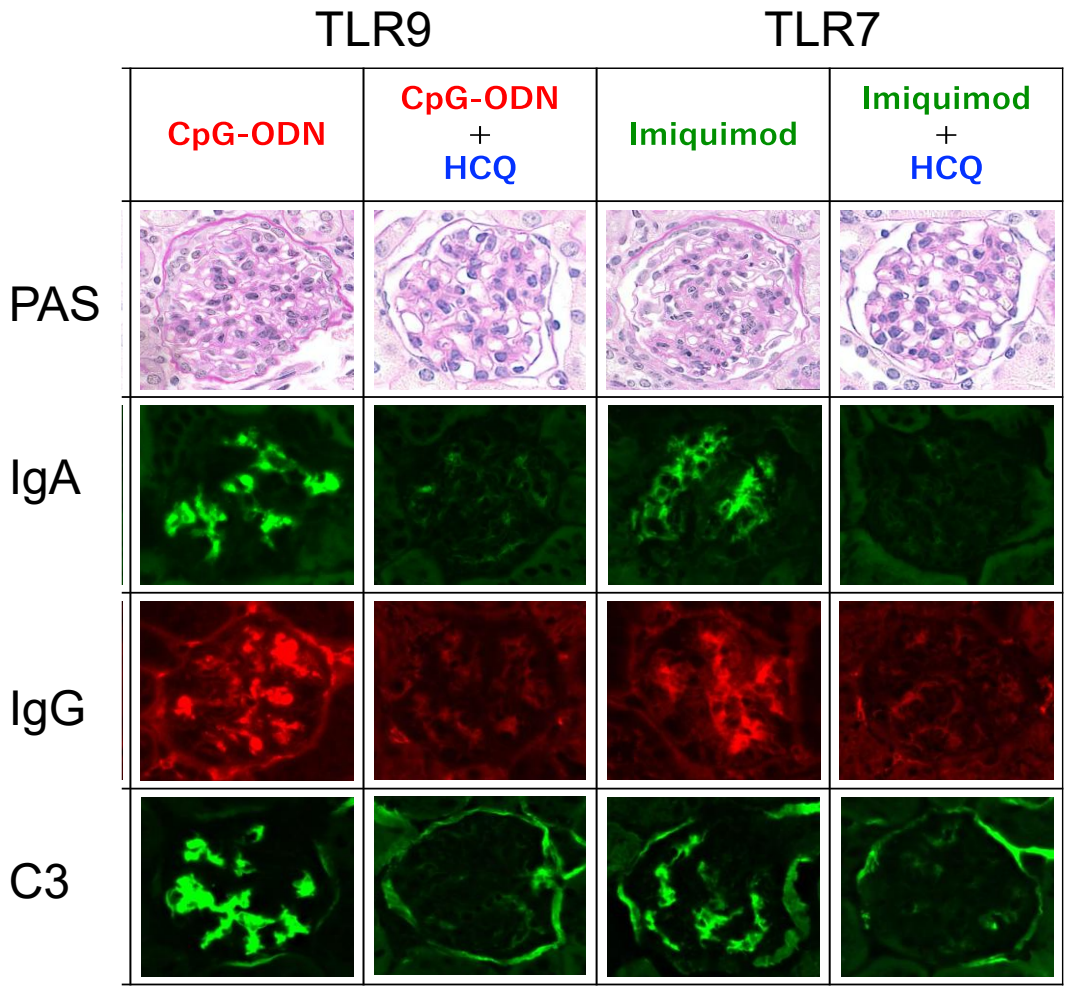


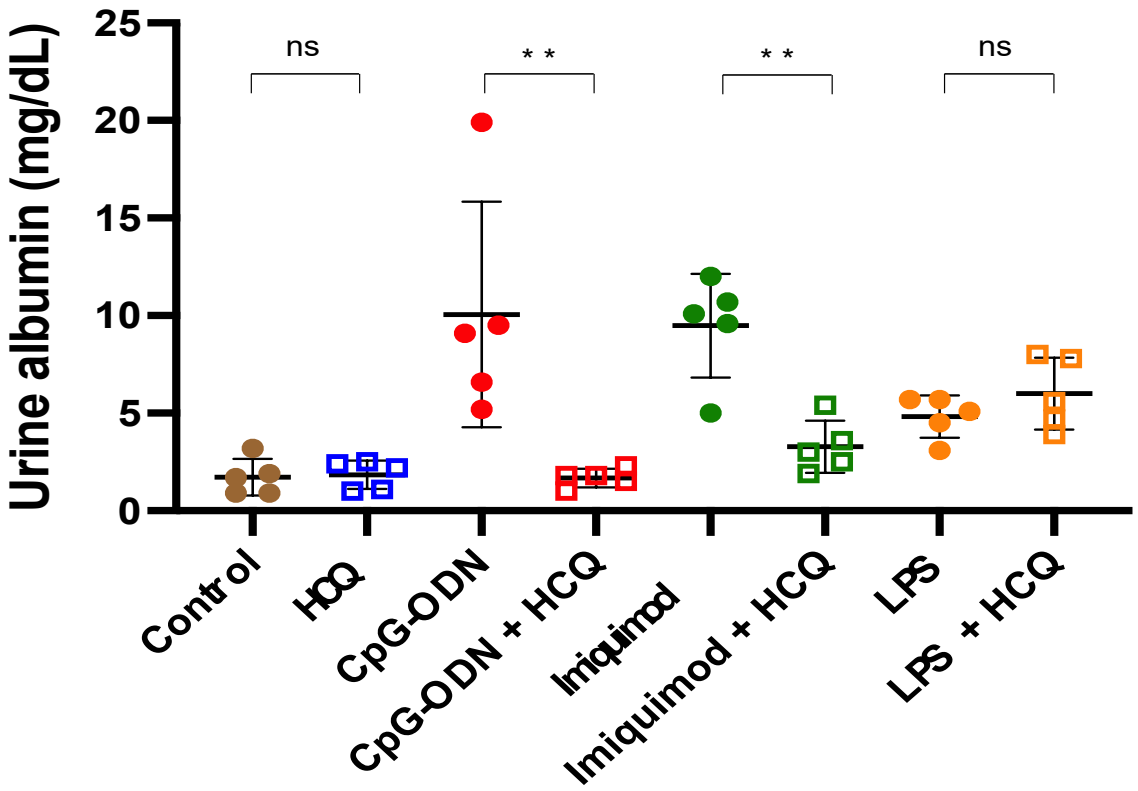




Zheng N, et al. JCI Insight, 2020

- **Nasal administration of CpG-ODN and imiquimod developed IgAN**
- **Co-administration of Hydroxychloroquine (HCQ) improved glomerular deposition of IgA and C3**





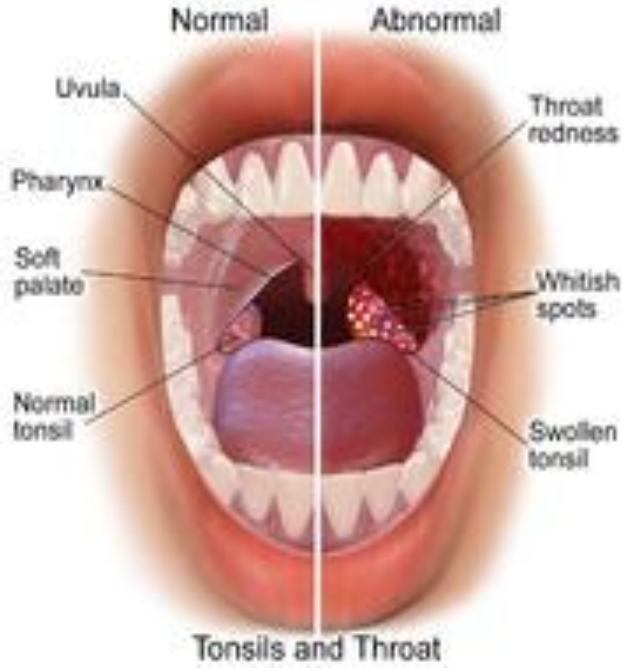
HCQ is treatment option for IgAN

Lee M, Kidney Int 2023

Responsible mucosal site for the pathogenesis of IgA nephropathy

Which is responsible for the pathogenesis of IgA nephropathy?

NALT: Nasal-associated lymphoid tissue



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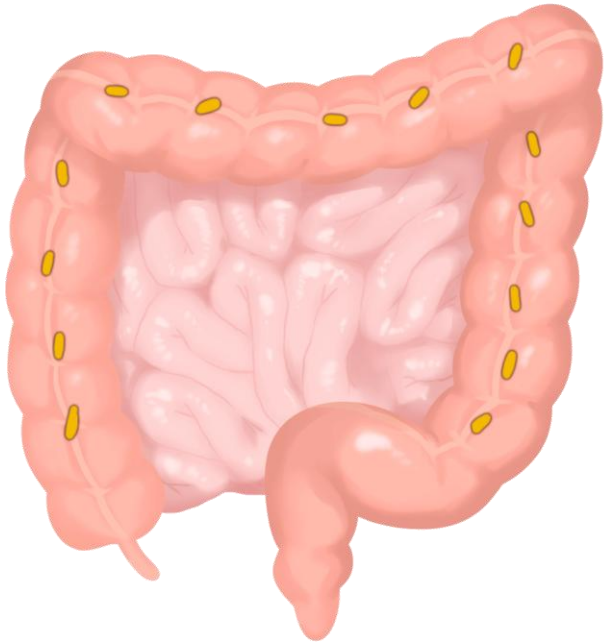
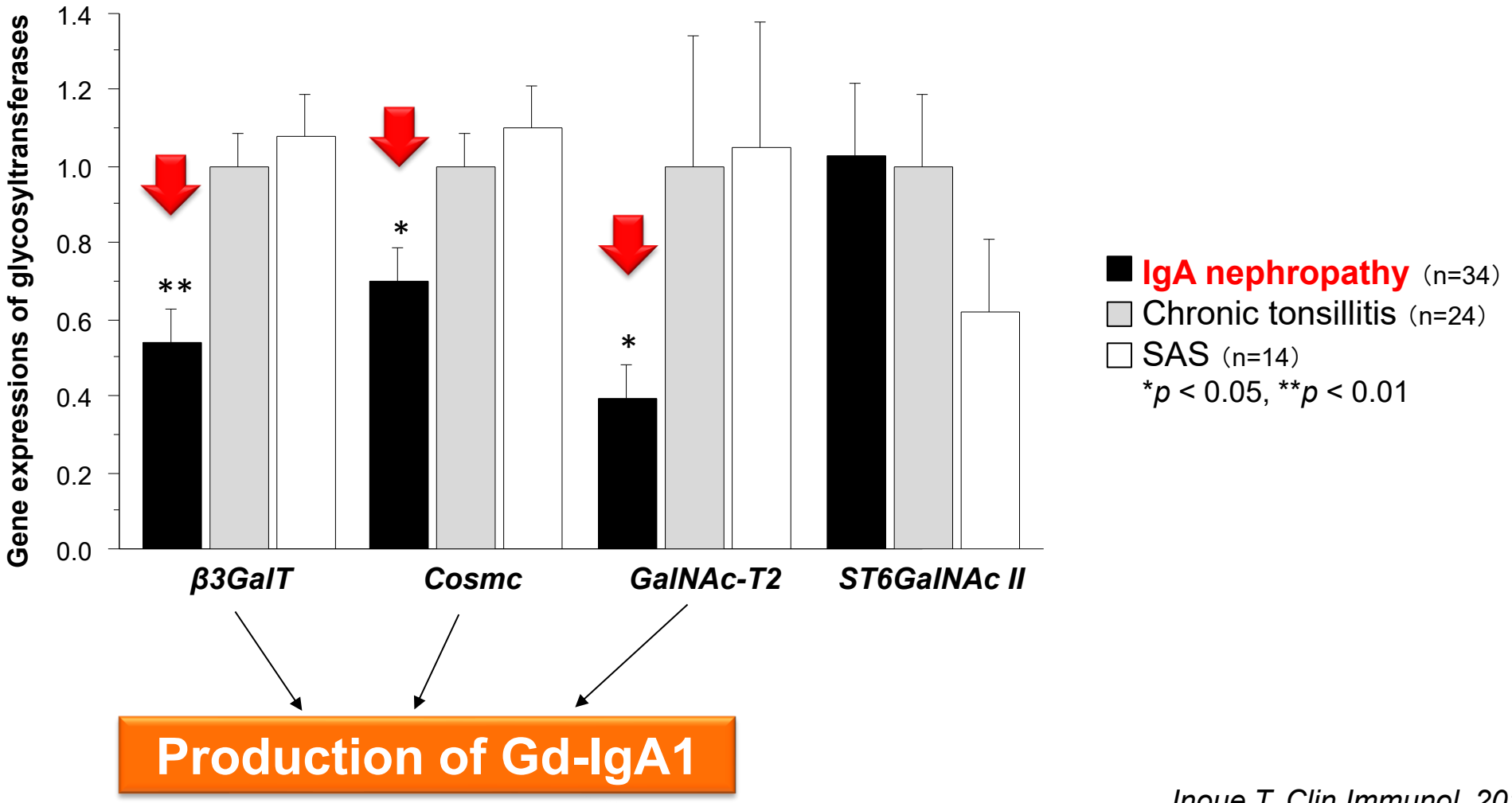
GALT: Gut-associated lymphatic tissue



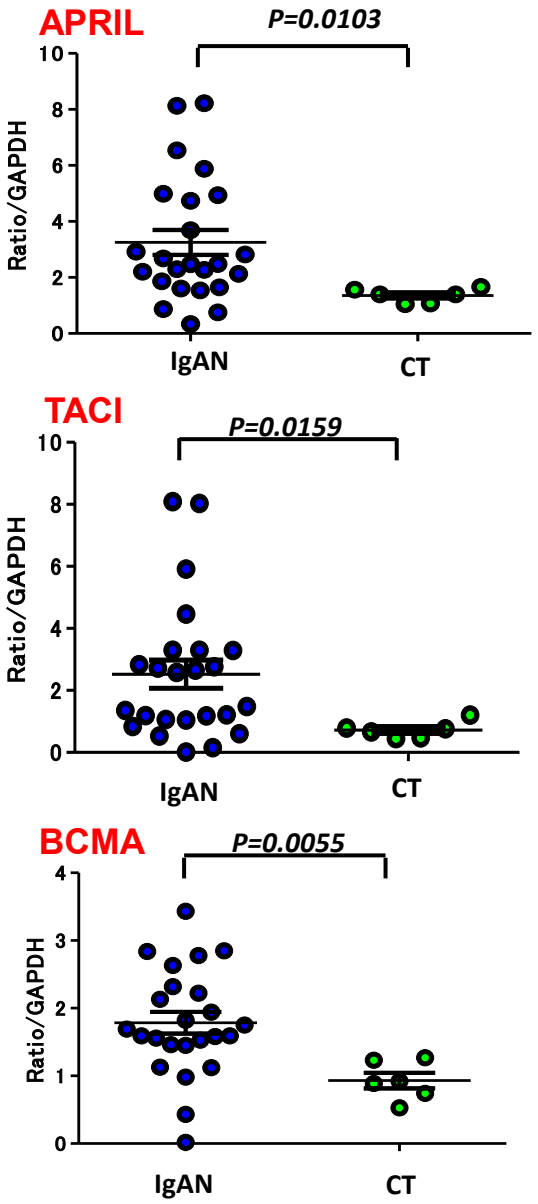
Shikakukaibougaku, Kangoroo

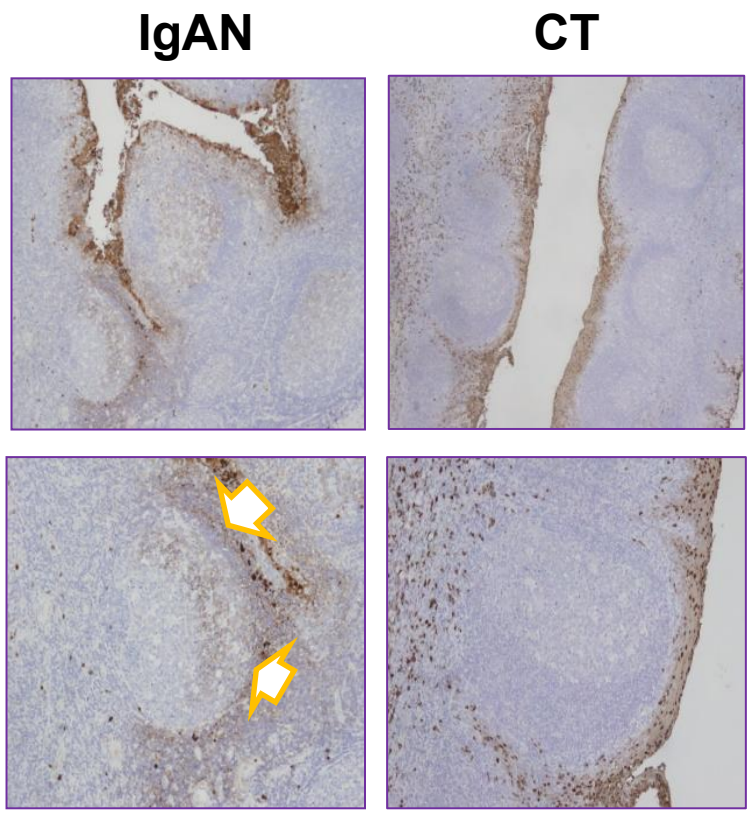
Abnormal expressions of specific glycosyltransferases of IgA1 in tonsillar B cell of IgAN



Inoue T. Clin Immunol, 2010

APRIL and its receptors are overexpressed in tonsils of IgAN



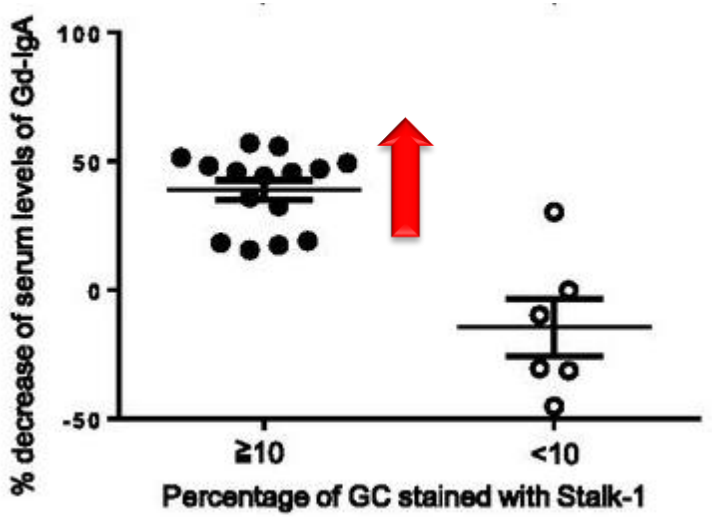


APRIL: a proliferation inducing ligand

B lymphocyte development, selection, and homoeostasis, IgA classswitch

APRIL+ cell in GC↑

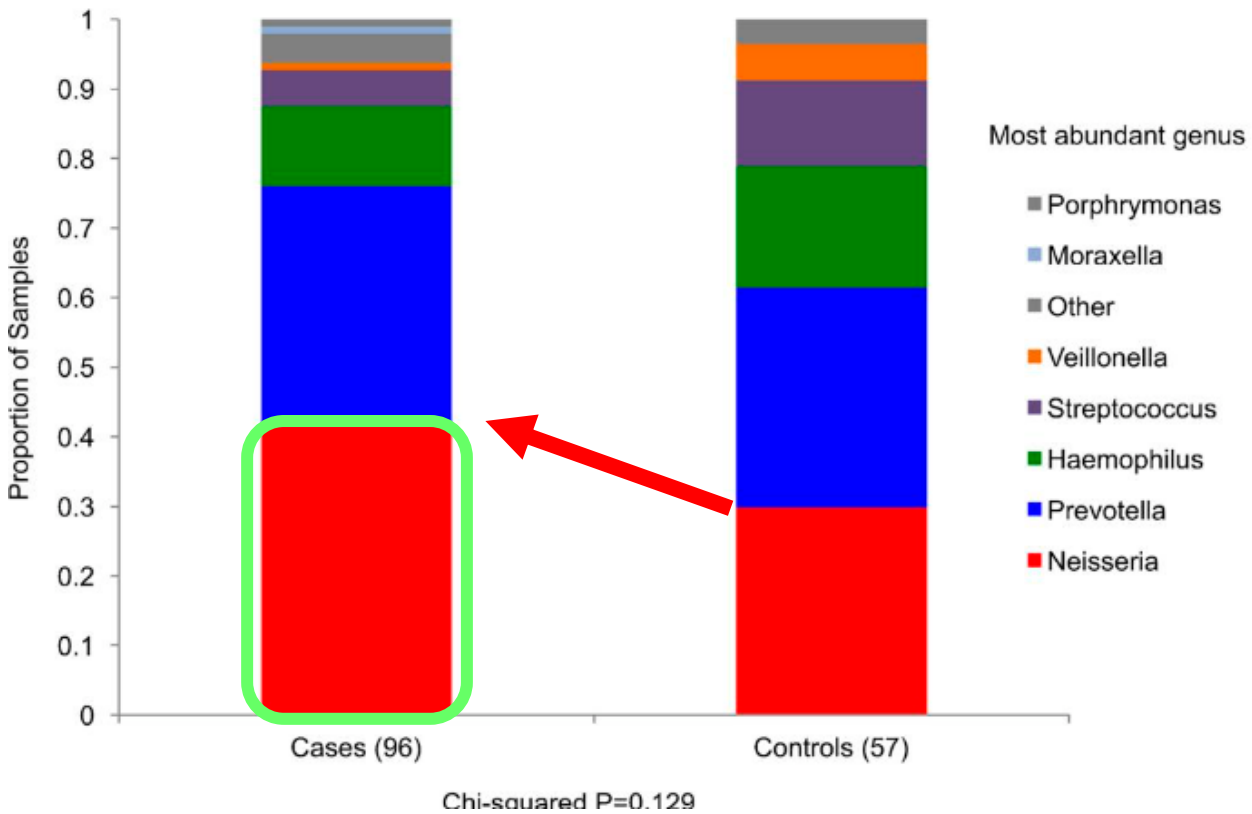
➡ serum Gd-IgA1↑



Percentage of APRIL+ cells in germinal center (GC) links to severity of IgAN

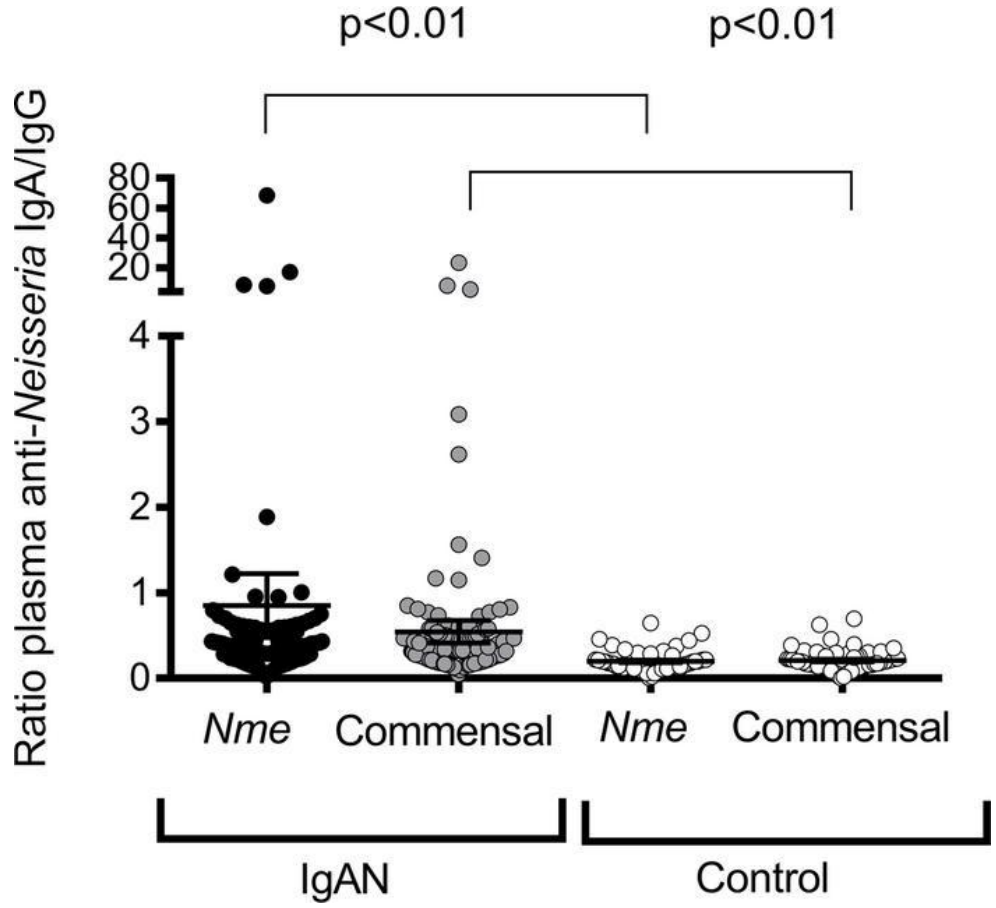
Muto M, et al, J Am Soc Nephrol, 2017

Aberrant mucosal immune responses to oropharyngeal pathobionts, such as Neisseria, in the immunopathogenesis of IgAN



The most abundant genus in tonsil swabs in patients with IgAN was *Neisseria*

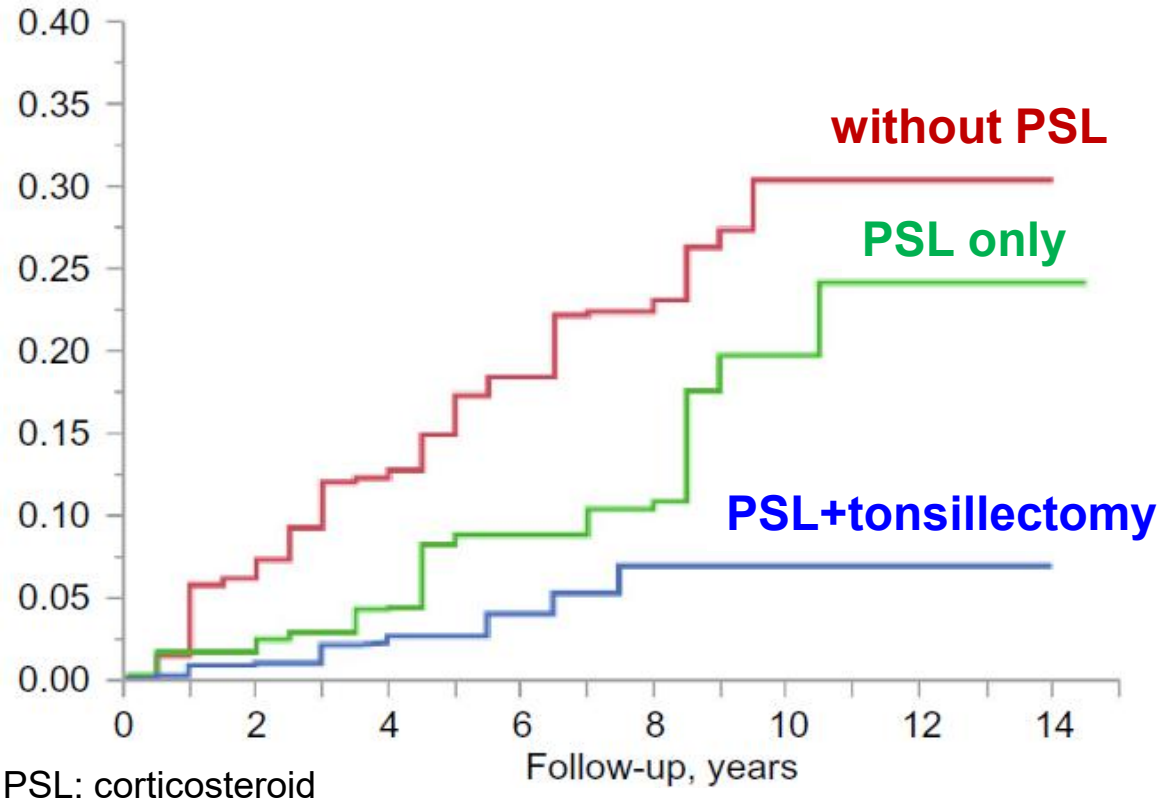
Patients with IgAN exhibited exaggerated IgA-biased anti-*Neisseria* responses to both pathogenic and nonpathogenic *Neisseria* species.



Currie EG. JCI Insight 8: e141289, 2022

Tonsillectomy with corticosteroid therapy is effective for kidney survival in a multicenter prospective study for IgAN

Renal outcome



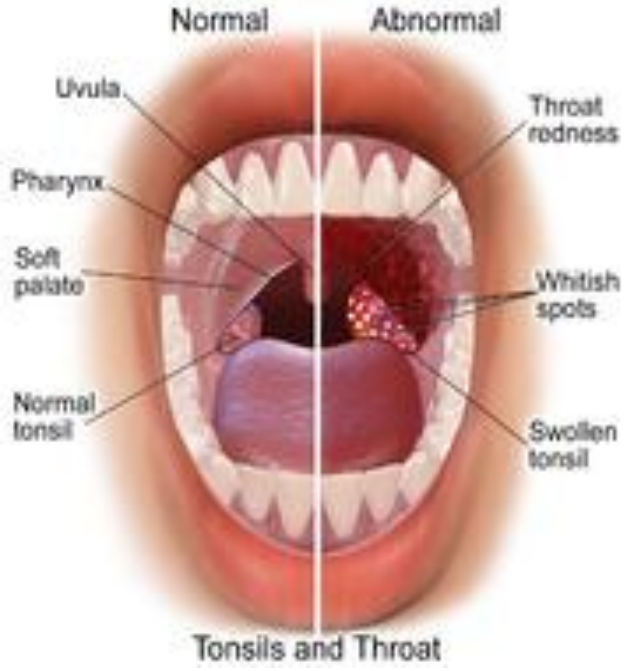
PSL: corticosteroid

Subgroups		Initial treatment	Overlap weighting analyses N	Events per 1,000 PY (95%CI)
MAP	≥90	non-CS	169.0	48.3 (32.4-74.6)
		CS	157.6	28.9 (18.0-48.8)
		CS+Tx	146.1	7.9 (2.6-34.9)
	<90	non-CS	145.5	20.2 (11.2-39.8)
		CS	156.9	8.1 (3.2-26.6)
		CS+Tx	168.3	6.8 (2.7-21.8)
eGFR	<60	non-CS	100.7	86.1 (57.7-131.9)
		CS	104.0	36.8 (21.6-66.2)
		CS+Tx	87.0	20.3 (8.4-61.8)
	≥60	non-CS	213.8	16.9 (9.2-34.5)
		CS	210.5	10.1 (4.9-24.5)
		CS+Tx	227.5	2.7 (1.0-9.5)
Proteinuria	≥1.0	non-CS	105.8	80.5 (52.2-126.6)
		CS	110.2	39.5 (24.1-67.6)
		CS+Tx	92.6	18.8 (8.1-54.0)
	<1.0	non-CS	208.7	14.4 (8.3-27.1)
		CS	204.3	7.4 (3.0-24.4)
		CS+Tx	221.9	2.4 (0.8-9.7)
Hematuria	>20	non-CS	162.9	37.1 (23.2-62.9)
		CS	165.0	9.9 (4.8-23.0)
		CS+Tx	160.4	1.0 (ND)
	≤20	non-CS	151.5	33.5 (21.0-56.5)
		CS	149.4	27.8 (16.6-49.6)
		CS+Tx	154.1	15.4 (7.4-37.2)

Kawamura T. Sci Rep 13: 18455, 2023

Which is responsible for the pathogenesis of IgA nephropathy?

NALT: Nasal-associated lymphoid tissue



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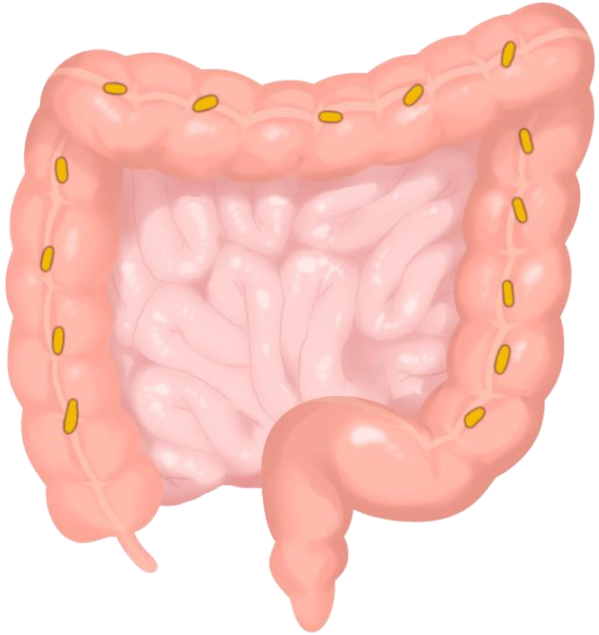
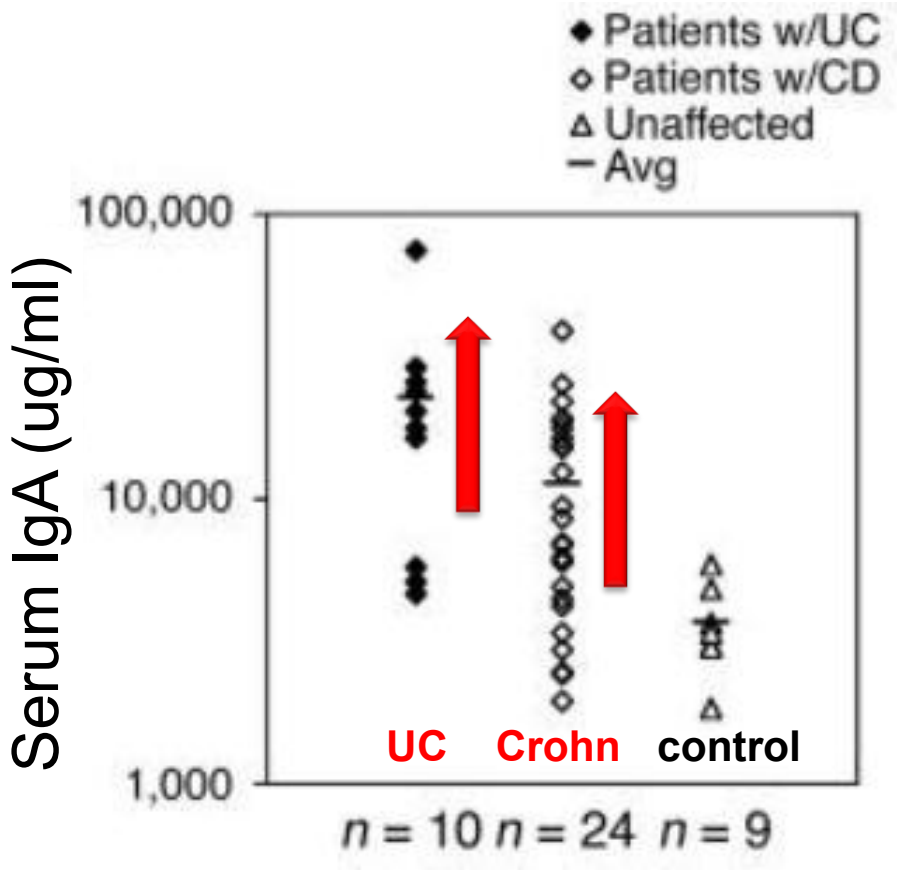
GALT: Gut-associated lymphatic tissue

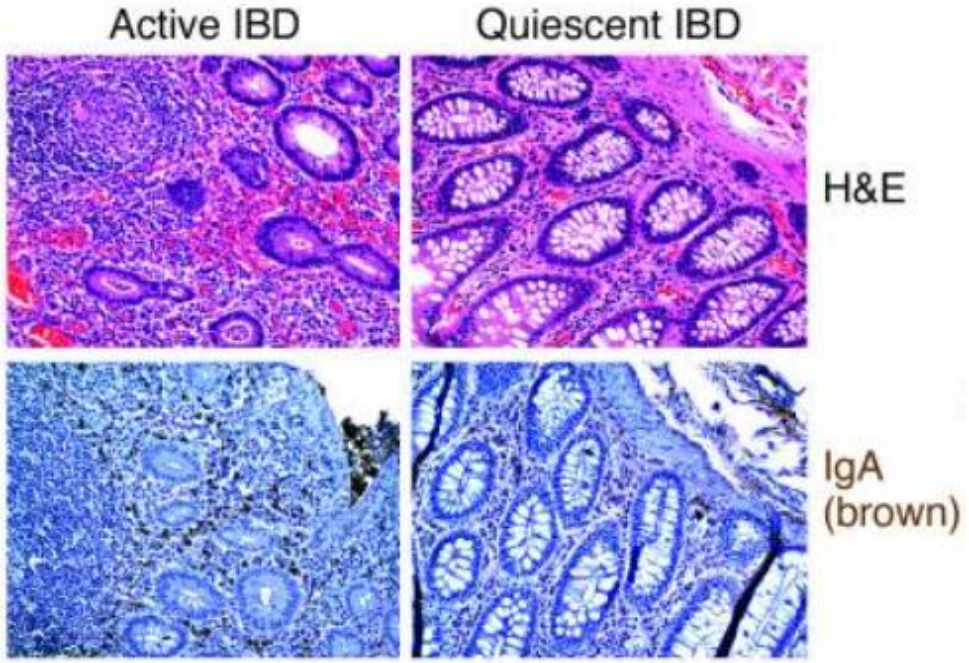


Increased IgA$^+$ PCs in the intestine in patients with inflammatory bowel diseases (IBD)



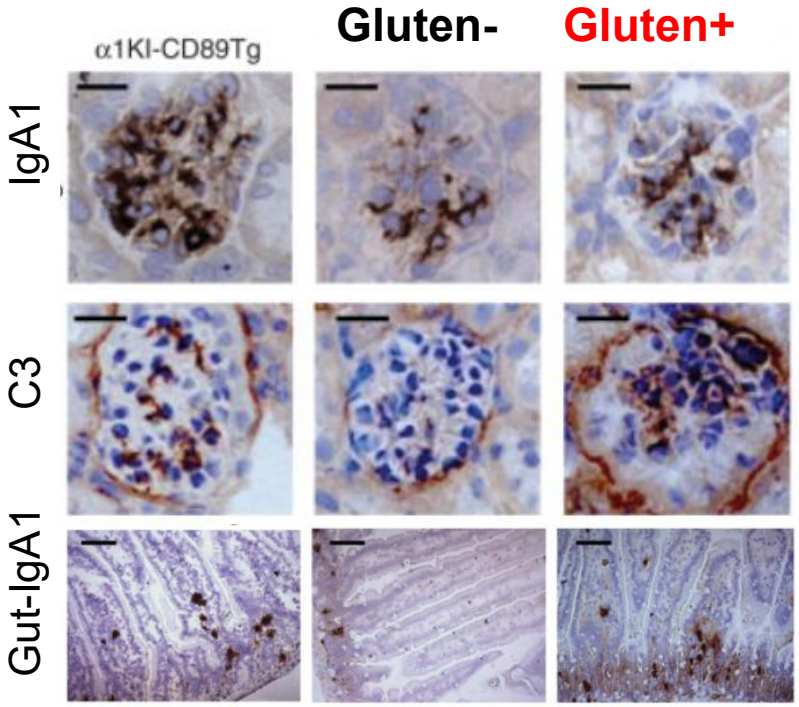
UC: Ulcerative colitis
Crohn: Crohn disease

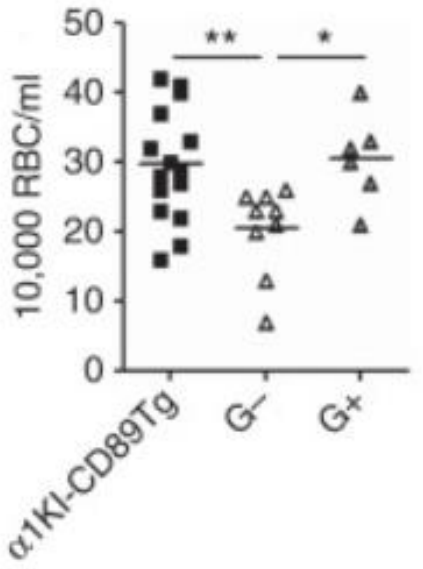
Increased IgA$^+$ Plasma cells in the intestine in patients with active IBD



Wang J, et al. J Clin Invest 113,826-835, 2004

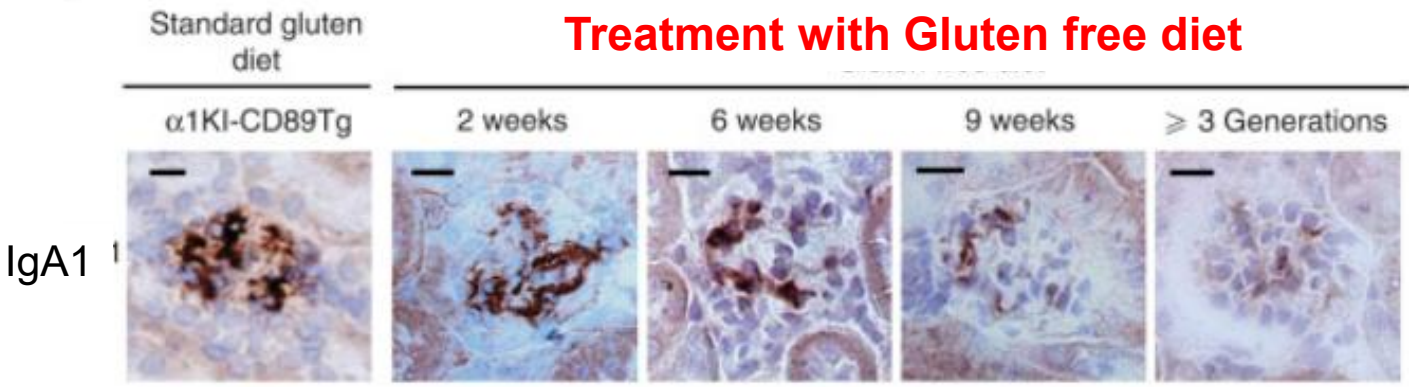
Intestinal mucosal immune response in IgAN





Gluten exacerbates IgAN in IgA1+CD89+ humanized mice

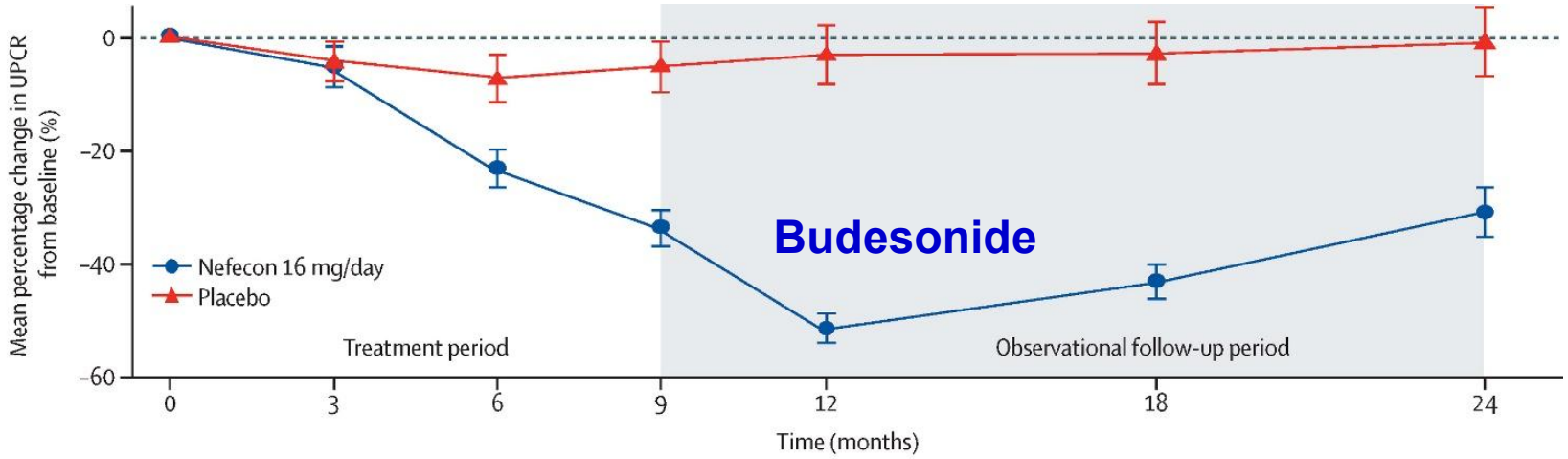
- Deposition of IgA1/C3
- Immune complex
- Hematuria/proteinuria



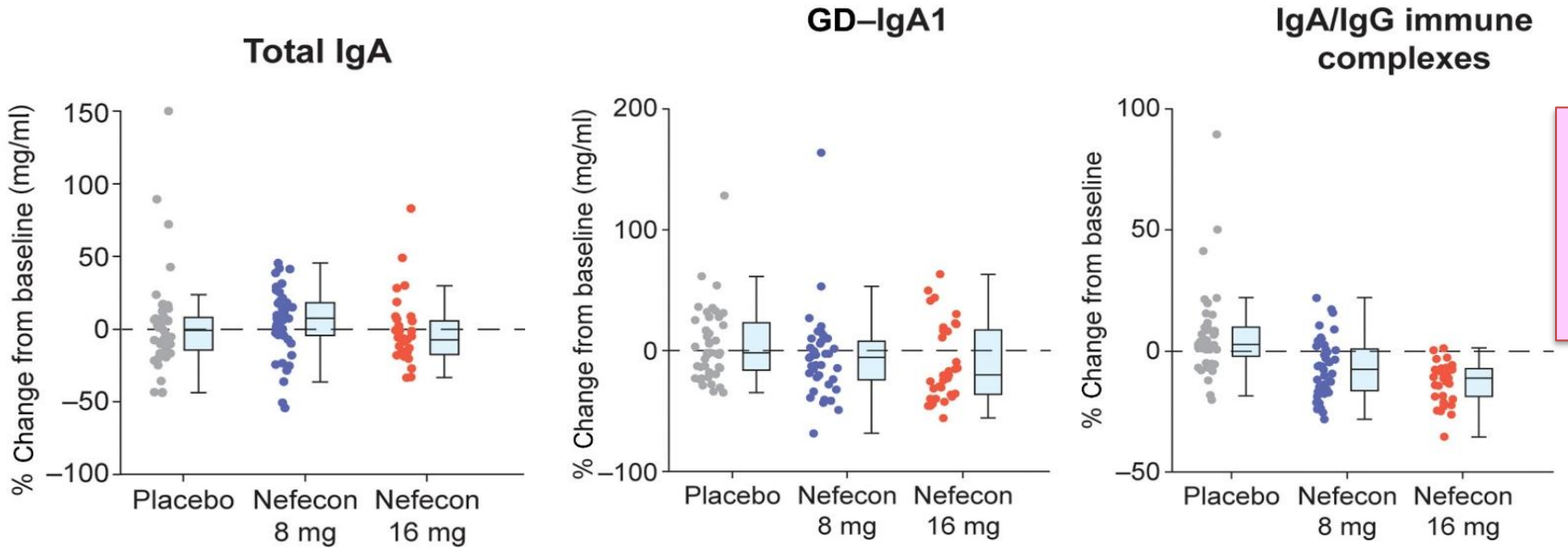
Treatment with a gluten-free diet could be beneficial to prevent progression of IgAN

Christina P et al,: kidney Int 88,276-285, 2015

Efficacy and safety of a targeted-release formulation of budesonide in patients with IgAN (NefIgArd): 2-year results from a randomised phase 3 trial



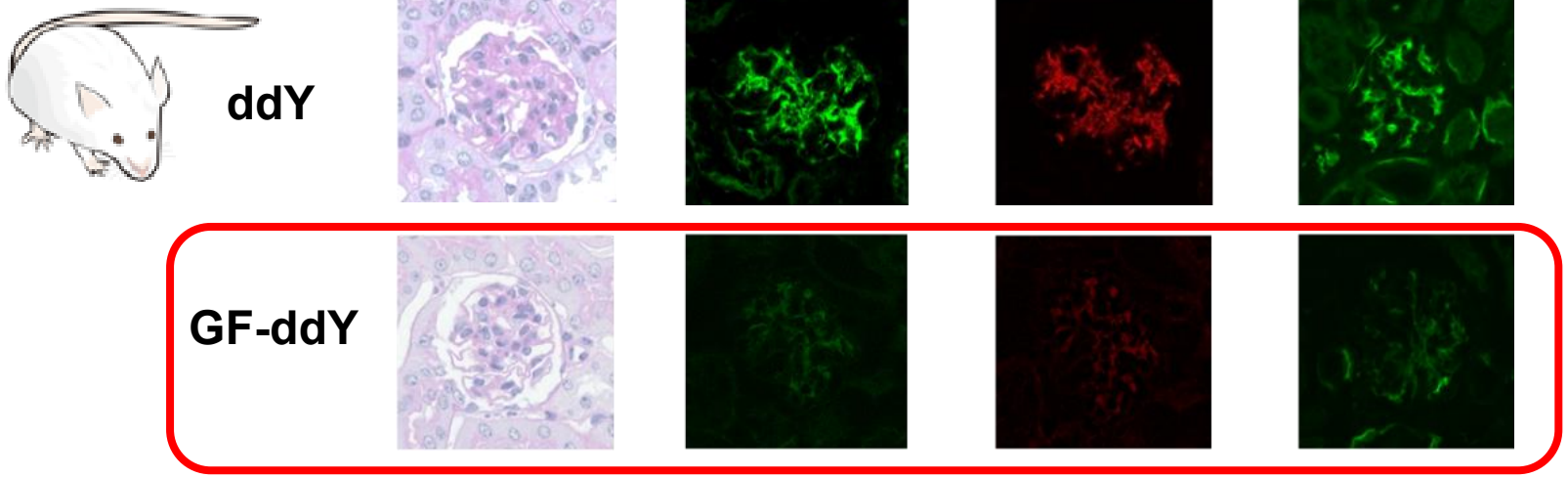
Lafayette R. Lancet 402: 859, 2023



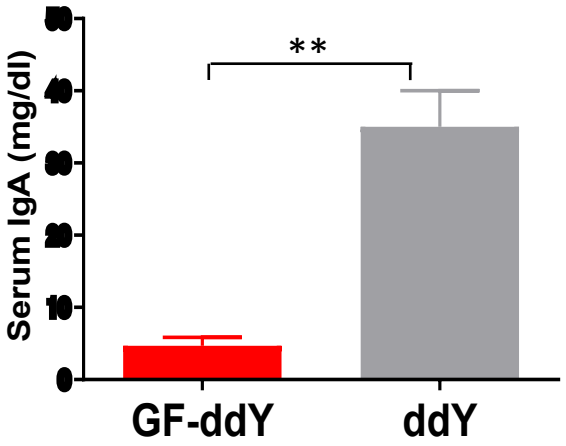
Budesonide →Gd-IgA1 →IgA-IgG IC

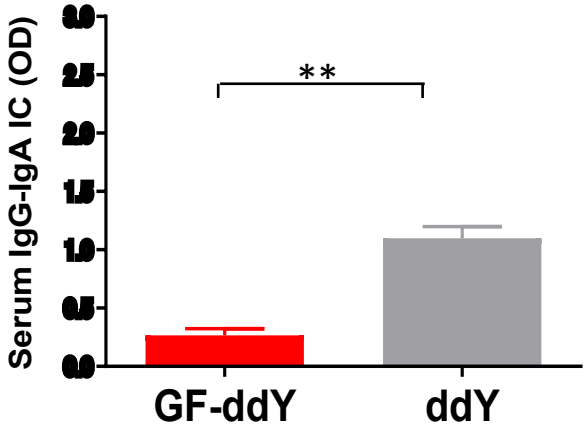
Kidney Int 105:381, 2024

Germ free condition markedly decreased proteinuria and IgA, IgG, C3 deposits in the mesangium



Bacteria?
Virus?
- Oral?
- Pharynx?
- Gut?





Kano T, Kidney Int 2021

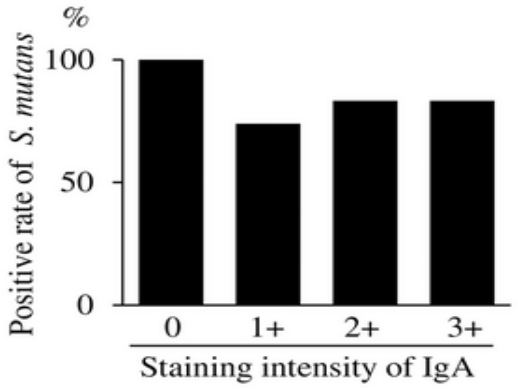
RESEARCH ARTICLE

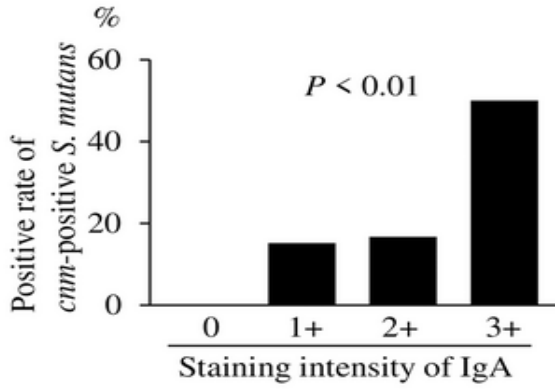
cnm-positive *Streptococcus mutans* is associated with galactose-deficient IgA in patients with IgA nephropathy

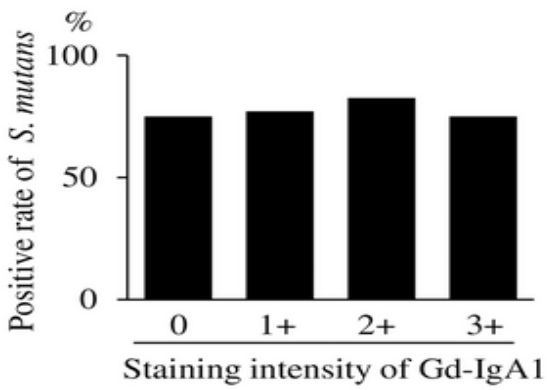
Taro Misaki[1,2]*, Shuhei Naka[3], Hitoshi Suzuki[4], Mingfeng Lee[4], Ryosuke Aoki[4], Yasuyuki Nagasawa[5], Daiki Matsuoka[3], Seigo Ito[6], Ryota Nomura[7,8], Michiyo Matsumoto-Nakano[3], Yusuke Suzuki[4], Kazuhiko Nakano[8]

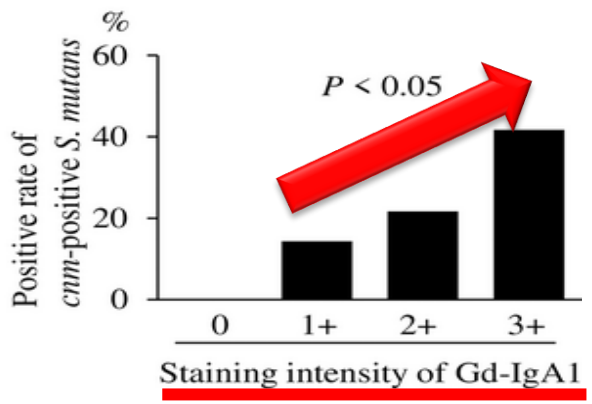
Several bacterial species have been reported to be potential contributors to the pathogenesis of IgAN, including
--periodontitis-related and
--dental caries-related bacteria

Association between glomerular IgA and Gd-IgA1 and the rate of *cnm*-positive S. mutans in the oral cavity



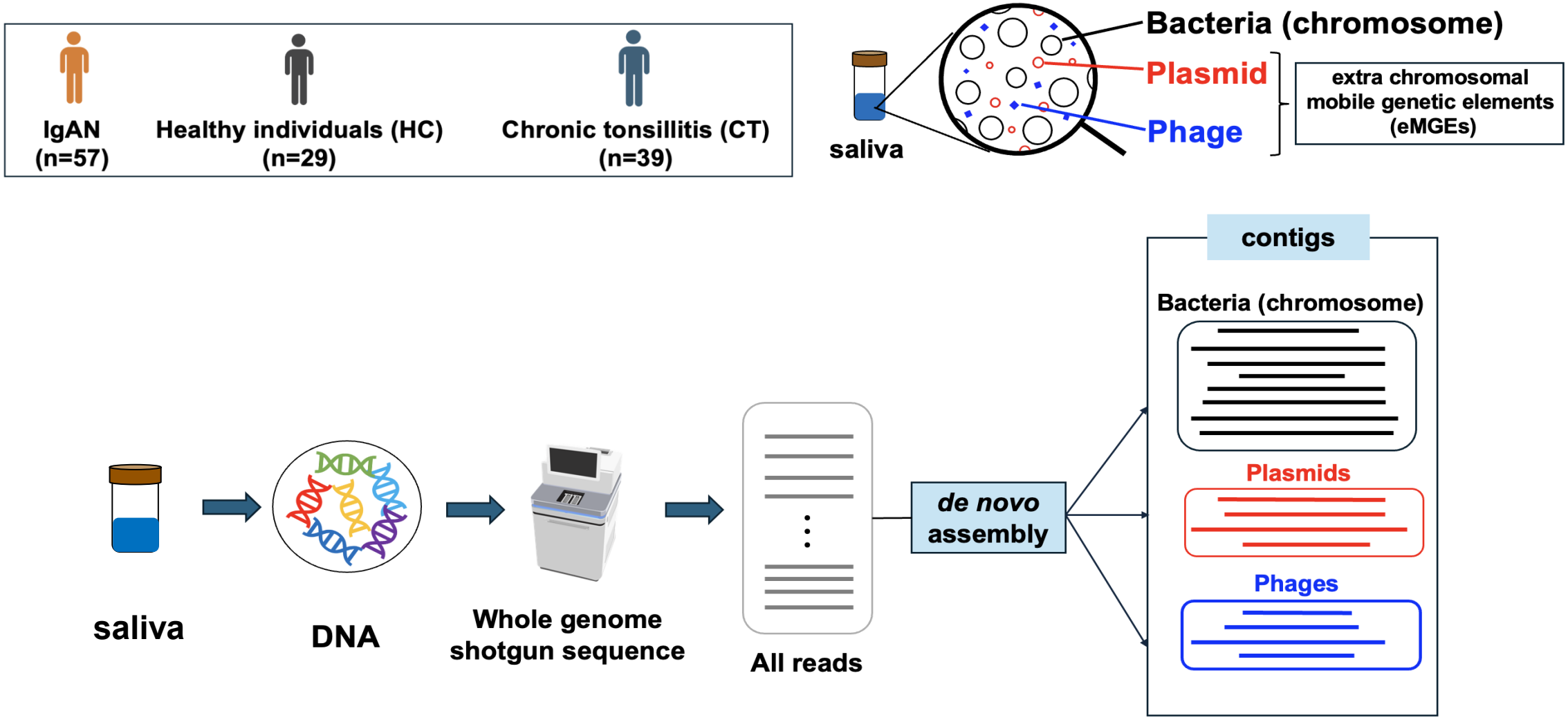




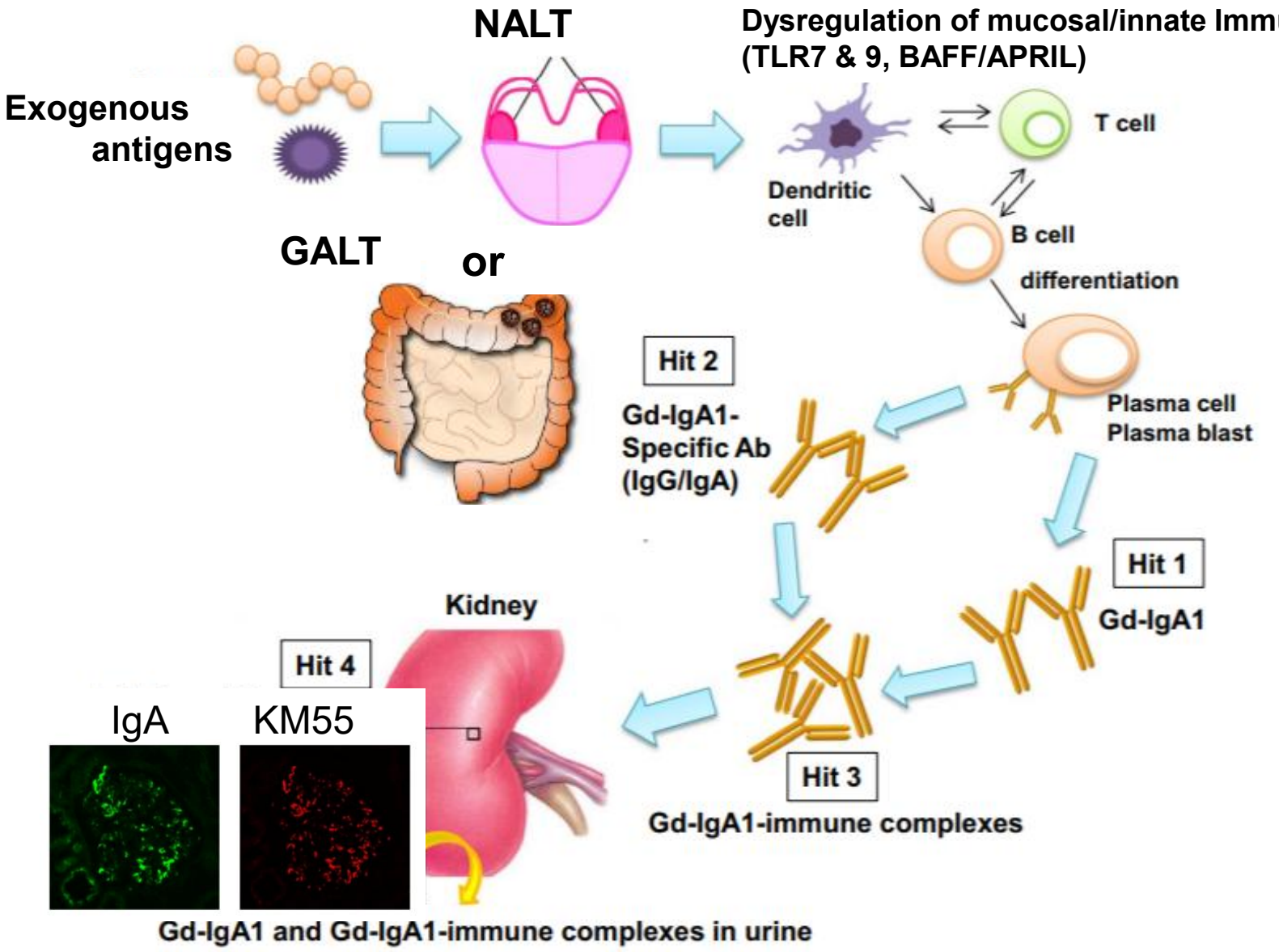


Sho Hamaguchi, et al. Deep shotgun metagenomic analysis of the oral microbiome identifies certain bacterial plasmids associated with IgAN.

Please see the Oral Communications 7: Basic Research, Oral 5-4, 5th Dec, 2025



Multi-Hit model of pathogenesis of IgA nephropathy



Suzuki H, et al. Semin Immunopathol, 2021

Plasmacytoid dendritic cells (pDC) modulate the pathogenesis of IgA nephropathy by facilitating aberrantly glycosylated IgA production

Focus of study was to investigate the role of plasmacytoid dendritic cells (pDCs) in the synthesis of aberrantly glycosylated IgA in IgAN

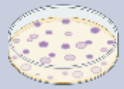
Methods

tonsillar mononuclear cells from IgAN patients

ddY mice nasally immunized with CpG-oligonucleotide

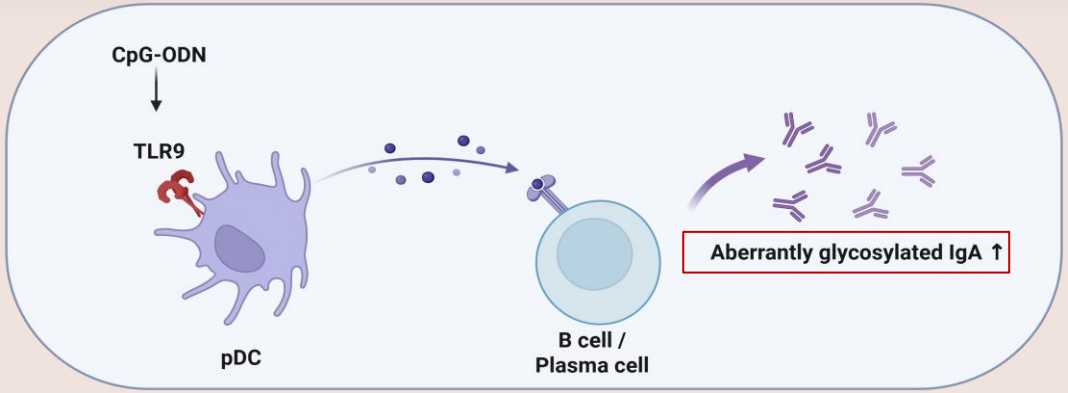
Exposures:
pDC isolation

Outcomes:

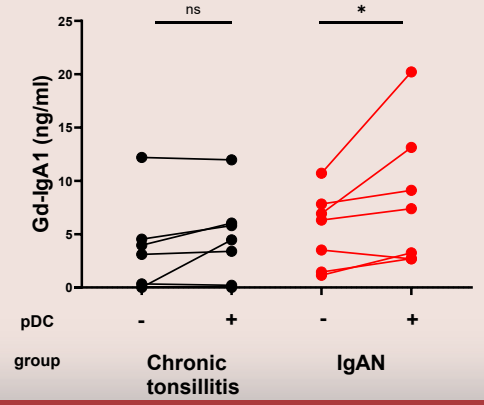


Analysis of the level of aberrantly glycosylated IgA in culture supernatant of tonsillar cells and serum of the ddY mice

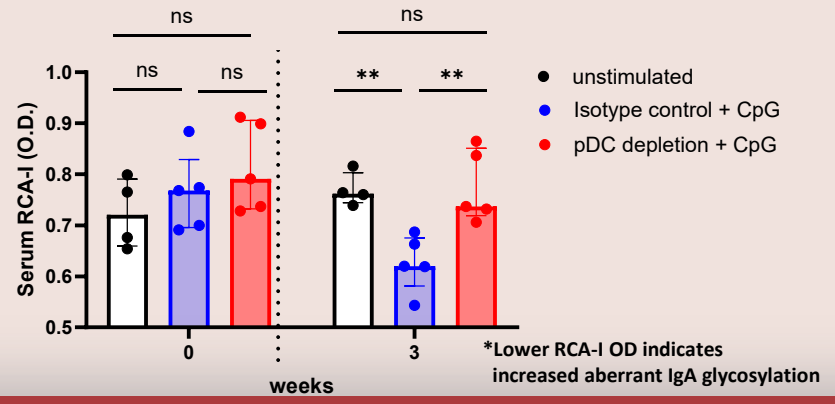
Results



Tonsillar pDCs modulates the production of Gd-IgA1 in patients with IgAN



pDC depletion abrogates CpG-induced aberrantly glycosylated IgA production in murine model



*Lower RCA-I OD indicates increased aberrant IgA glycosylation

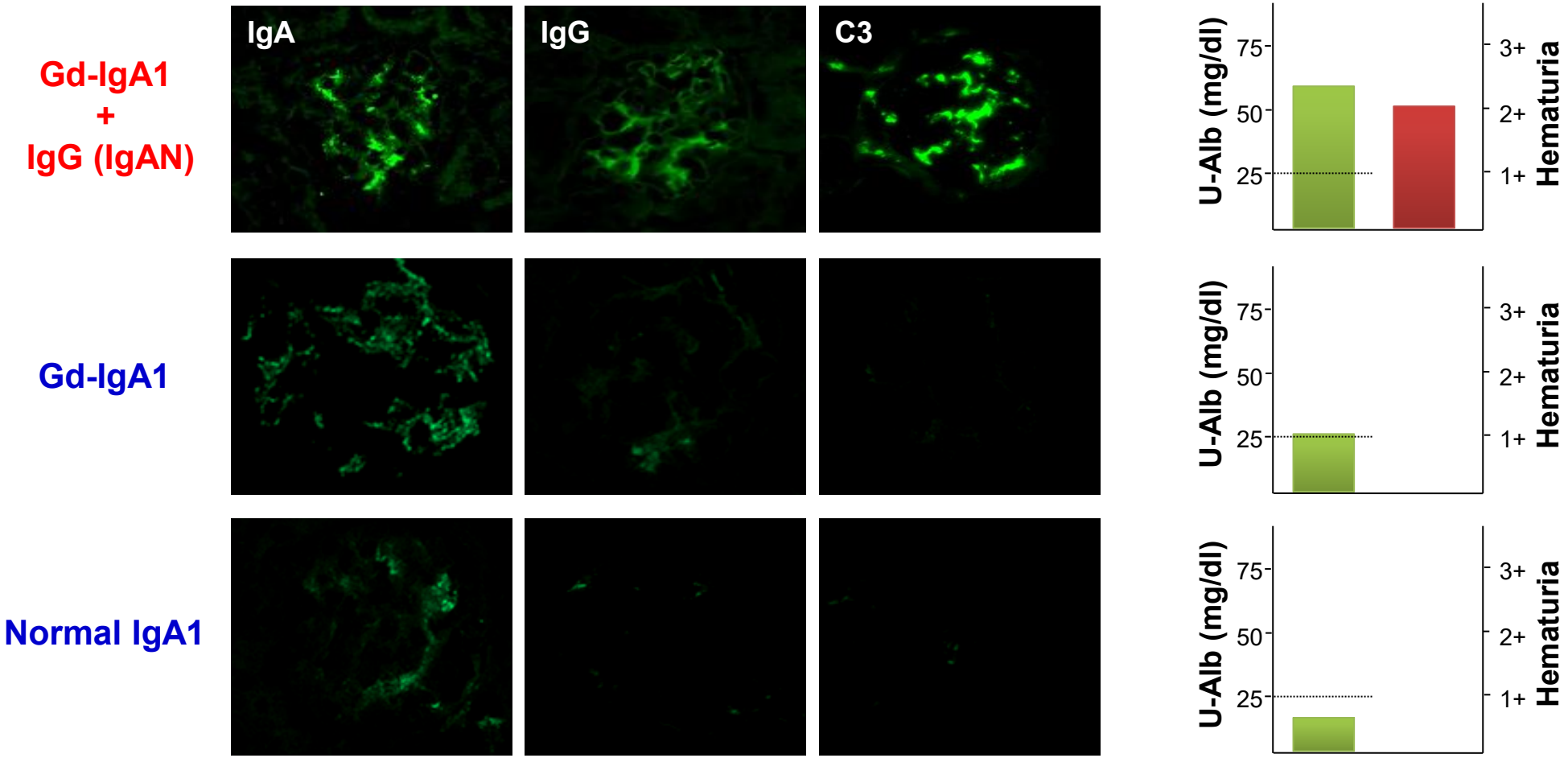
Fukao, Y. *et al.*
Nephrol Dial Transplant
NDT (2025)

pDCs promote production of aberrantly-glycosylated IgA in IgAN *via* TLR9 signaling, highlighting a novel target of treatment for IgAN

Outline

- Mucosal immunity of IgA nephropathy
- **Mechanisms of glomerular deposition of IgA**
- Development of new treatment

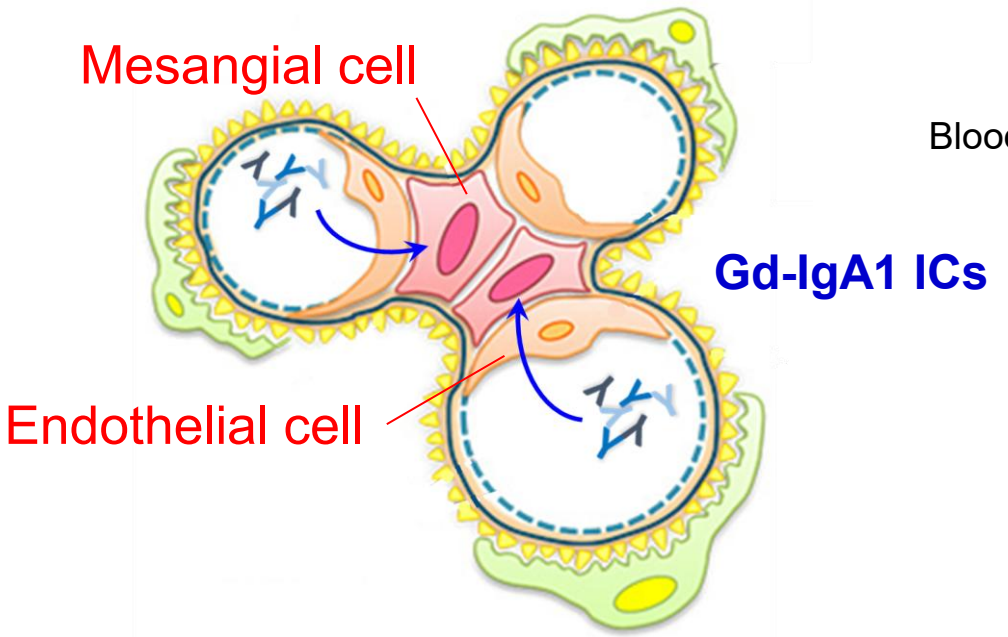
Gd-IgA1-IgG IC-injected mice showed mesangial deposits of IgA, IgG, and C3 with albuminuria and hematuria



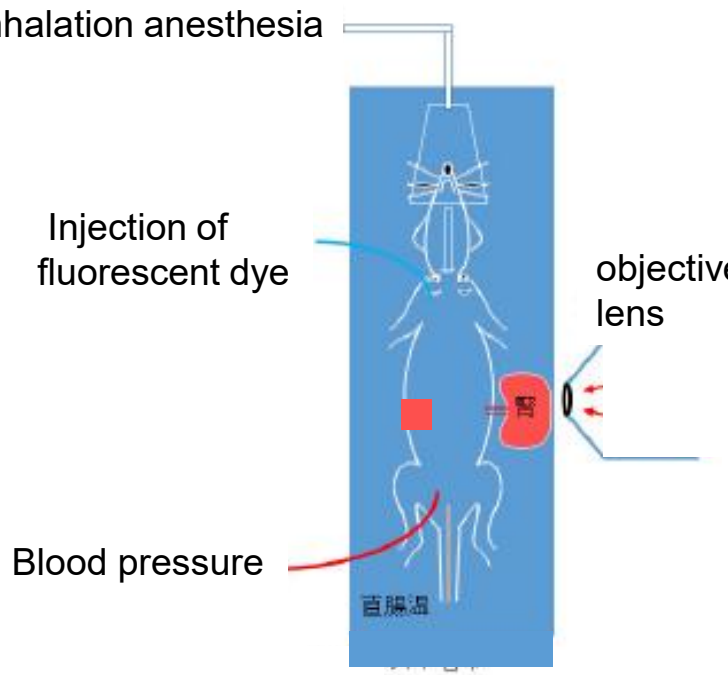
Moldoveanu Z, et al. J Autoimmun, 2021

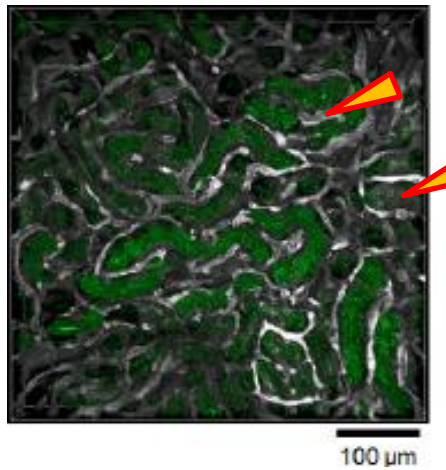
Real-time glycocalyx imaging

How Gd-IgA1 ICs deposit in mesangium?



Gd-IgA1 ICs





Renal tubule

Microvascular

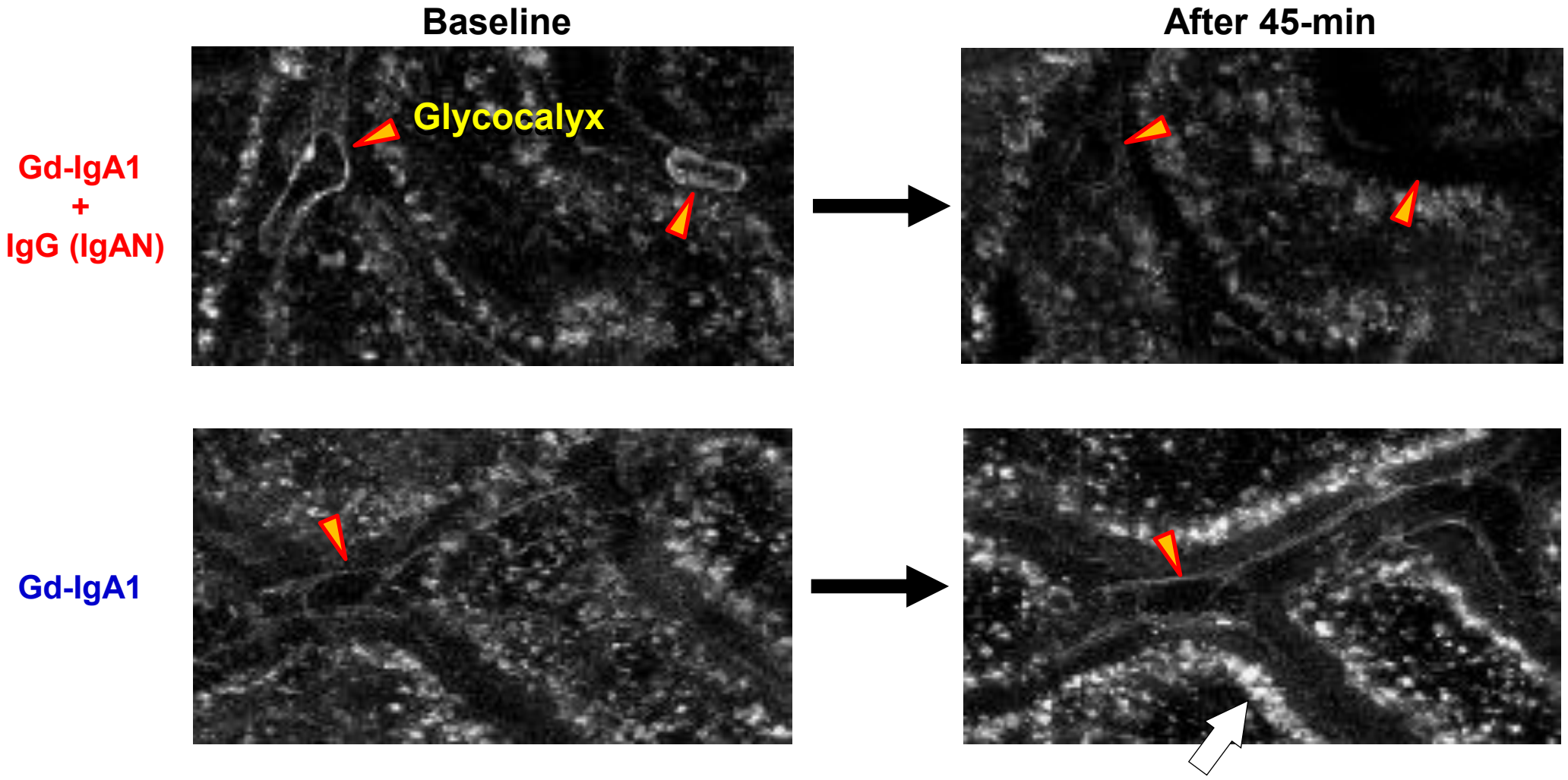
Gd-IgA1 + IgG (IgAN)

Gd-IgA1 + PBS

Balb/cAJcl-*nu/nu*

Makita Y, Nephrol Dial Transplant, 2022

Gd-IgA1-IgG IC damaged renal microvascular glycocalyx immediately after injection



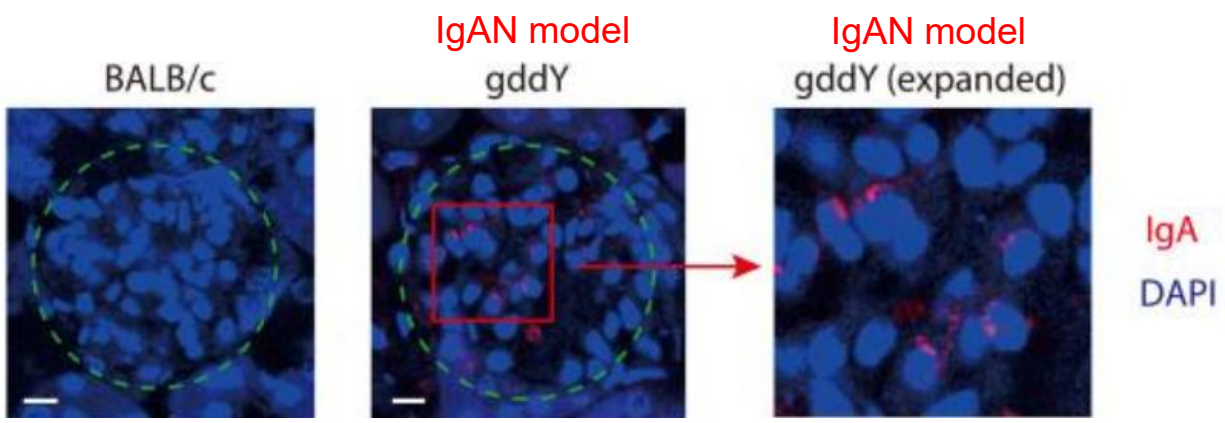
Makita Y. Nephrol Dial Transplant, 2022

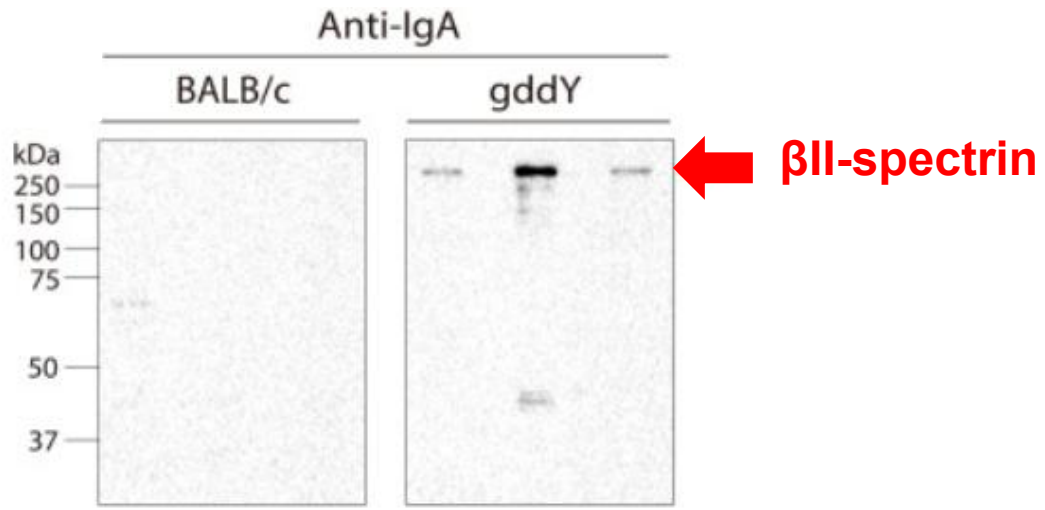
SCIENCE ADVANCES | RESEARCH ARTICLE

DISEASES AND DISORDERS

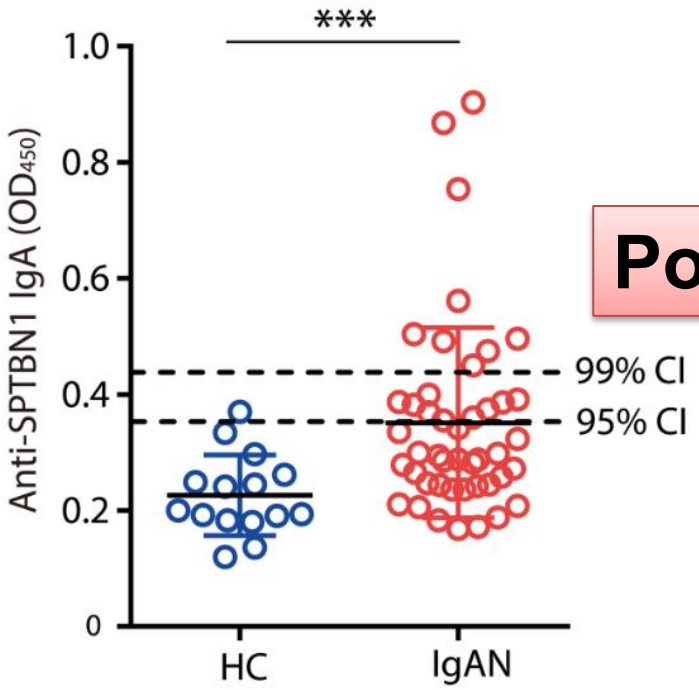
Identification of IgA autoantibodies targeting mesangial cells redefines the pathogenesis of IgA nephropathy

Yoshihito Nihei[1,2], Kei Haniuda[2†], Mizuki Higashiyama[2], Shohei Asami[2], Hiroyuki Iwasaki[1,2], Yusuke Fukao[1], Maiko Nakayama[1], Hitoshi Suzuki[1], Mika Kikkawa[3], Saiko Kazuno[3], Yoshiki Miura[3], Yusuke Suzuki[1*], Daisuke Kitamura[2*]

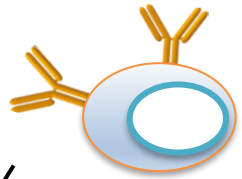




Serum anti–βII-spectrin IgA

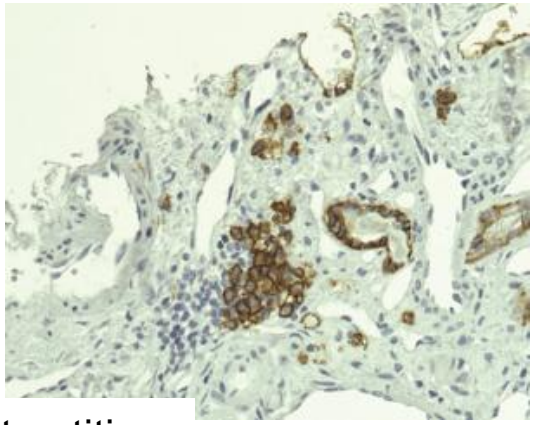


anti–βII-spectrin IgA produsing plasma cells

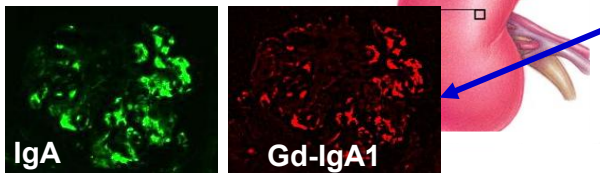


Potential novel biomarker

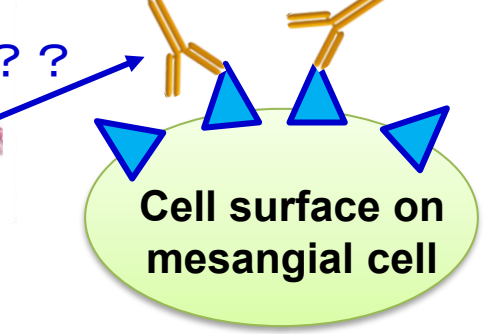
Homing to inflammation site（Kidney）



anti–βII-spectrin IgA

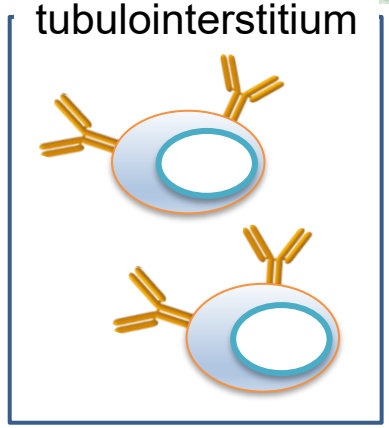


Mesangial deposition



βII-spectrin

tubulointerstitium



Nihei Y, et al. Sci Adv, 2023

Gd-IgA1 producing cell targeting therapeutic Intervention

Multi-Hit model of pathogenesis of IgA nephropathy

Hit1

Increased circulating galactose-deficient IgA1

Hit2

Production of unique anti-glycan antibodies

(IgG, IgA)

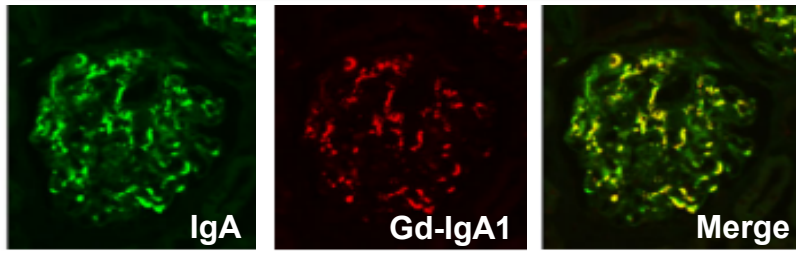
Rituximab?

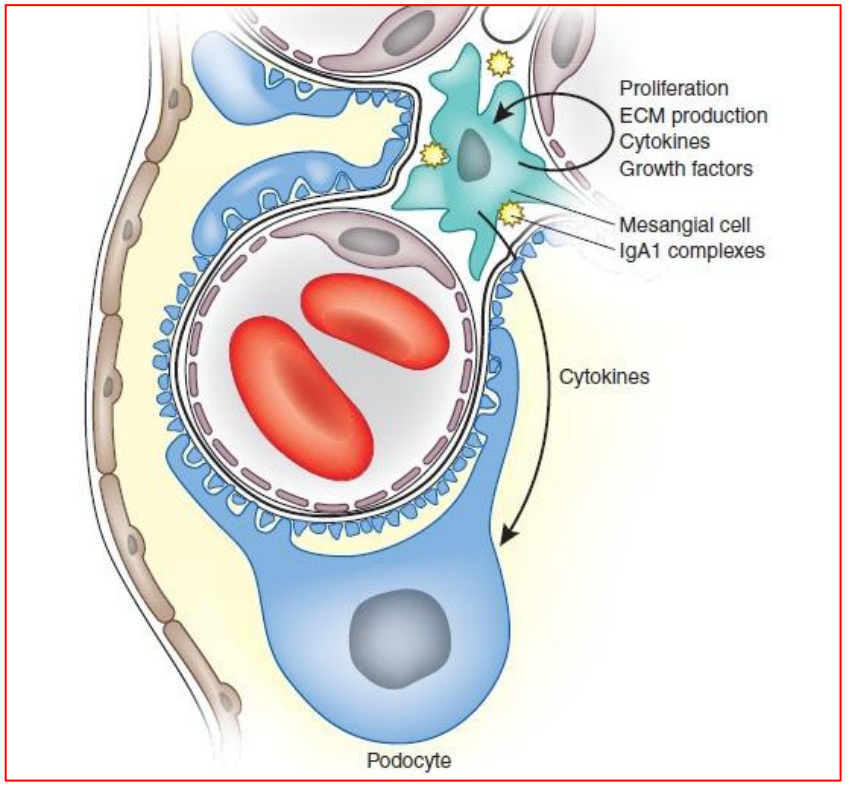
Hit3

Formation of pathogenic IgA1-containing circulation immune complexes

Hit4

Mesangial deposition and activation of mesangial cells resulting in glomerular injury

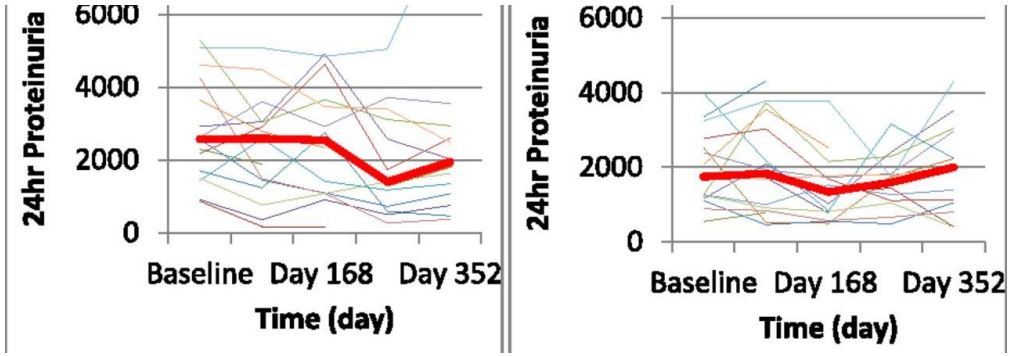




Suzuki H, et al: J Am Soc Nephrol, 2011

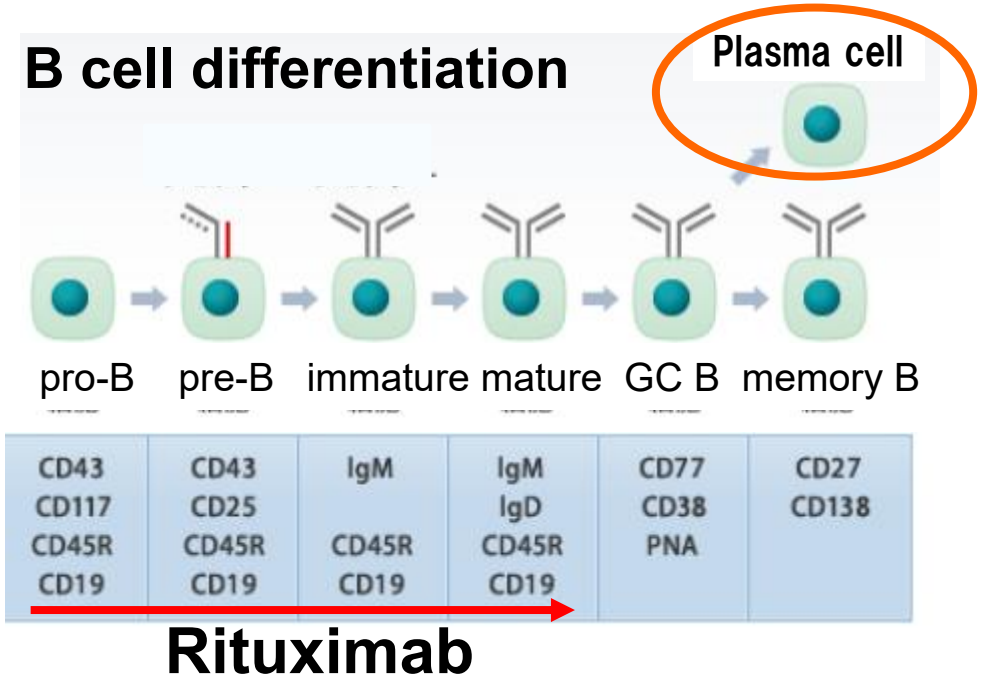
Controlled trial of Rituximab in IgA nephropathy

rituximab versus control



No effect for proteinuria

no favorable effect of rituximab on Gd-IgA1 or autoantibodies to Gd-IgA1



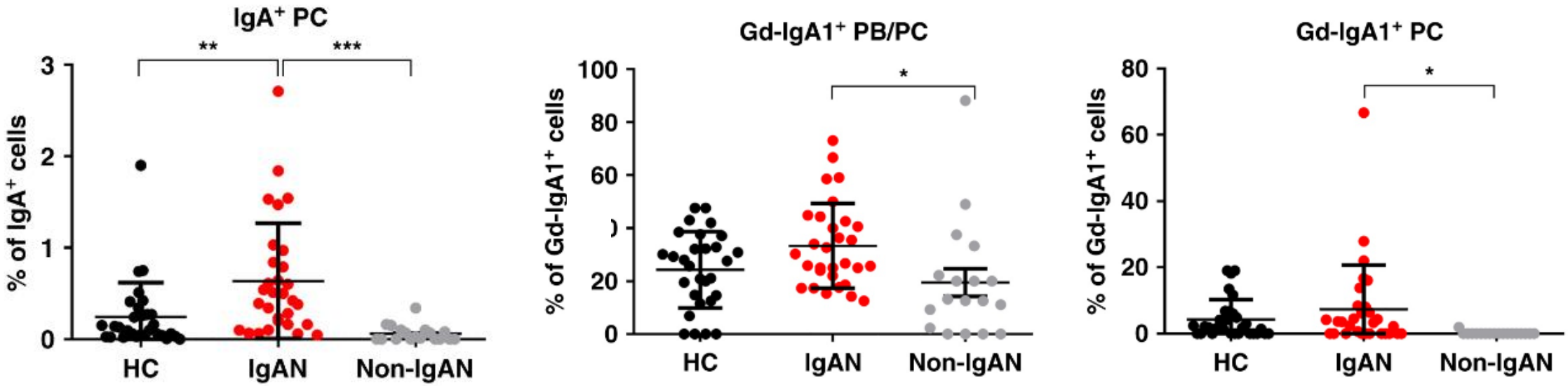
	Baseline	after treatment (1yr)
Total IgA (mg/mL)	5.0	4.4
Gd-IgA1 (U)	54.8	60.5
Anti-Gd-IgA1 IgG (U/mL)	1492.5	1751.3

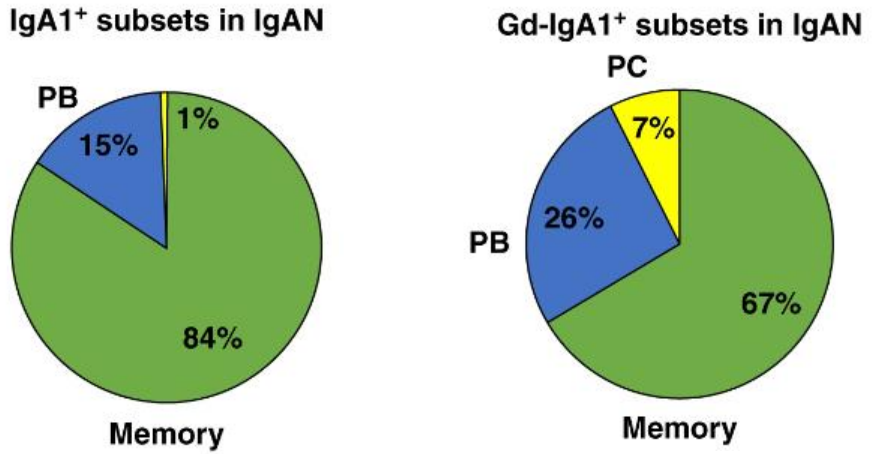
No change

Gd-IgA1 and anti Gd-IgA1 IgG may originate from plasma cells.

Lafayette RA. JASN 28:1306-1313, 2017

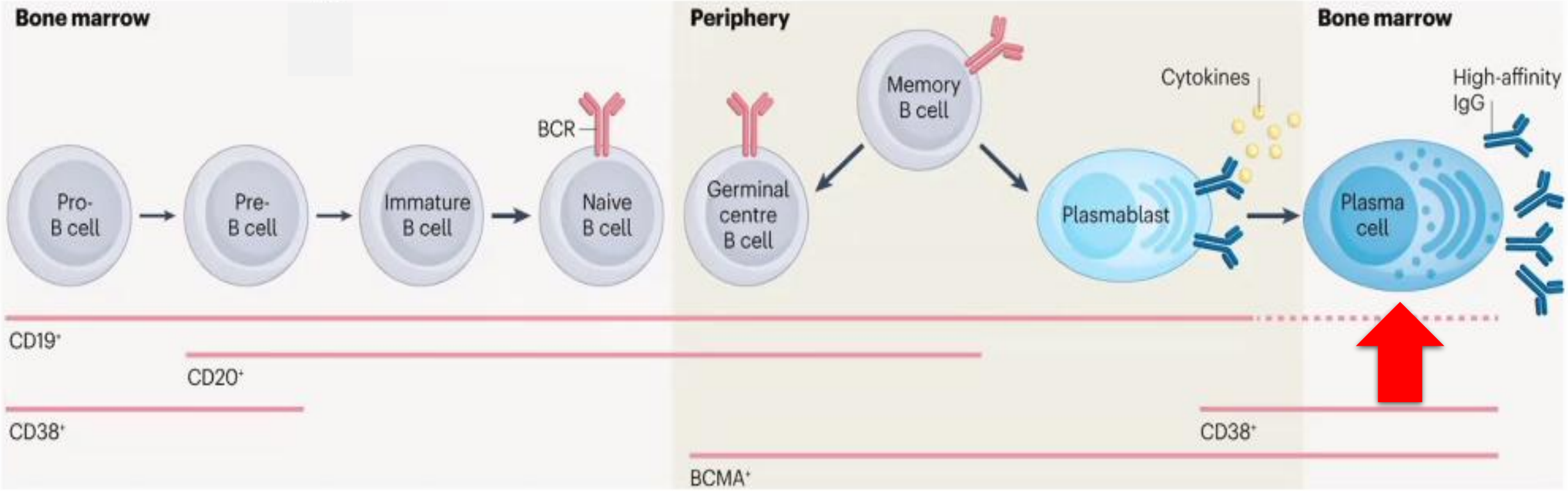
Gd-IgA1$^+$ cell populations in peripheral blood are enriched with plasmablasts/plasma cells





Zachova K, J am Soc Nephrol 33: 908-17, 2022

Anti-CD38 Ab: Targeting plasma cells



Phase 2 clinical trials are underway in patients with IgAN

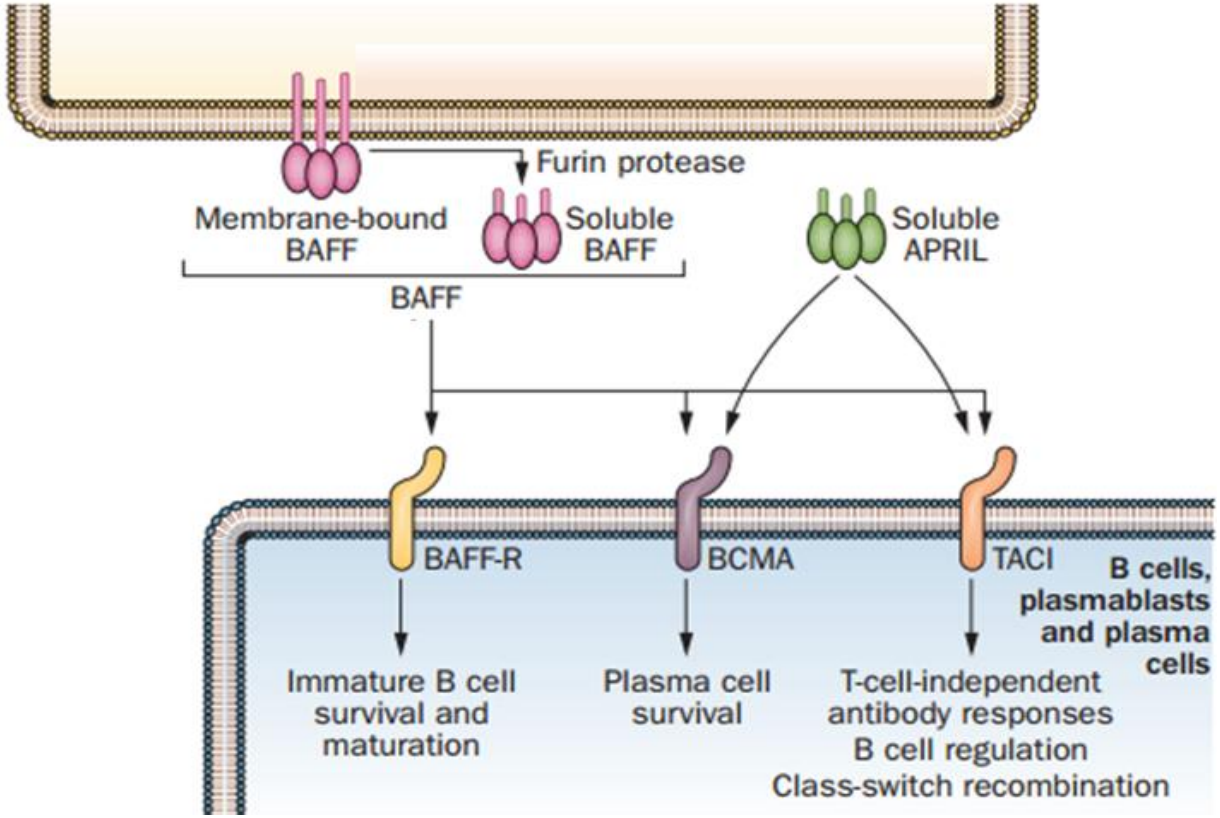
Heeger PS, Nat Rev Nephrol. 2024

B lymphocyte development, selection, and homoeostasis

BAFF and APRIL

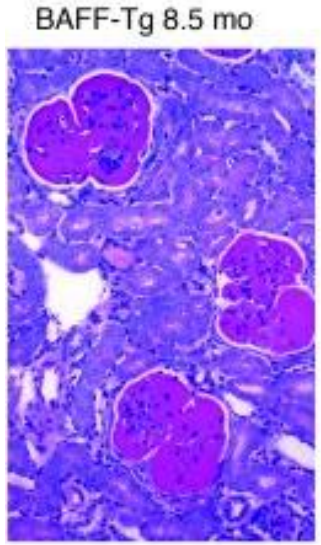
Members of TNFa superfamily ligands
BAFF: B cell activating factor, APRIL: a proliferation inducing ligand

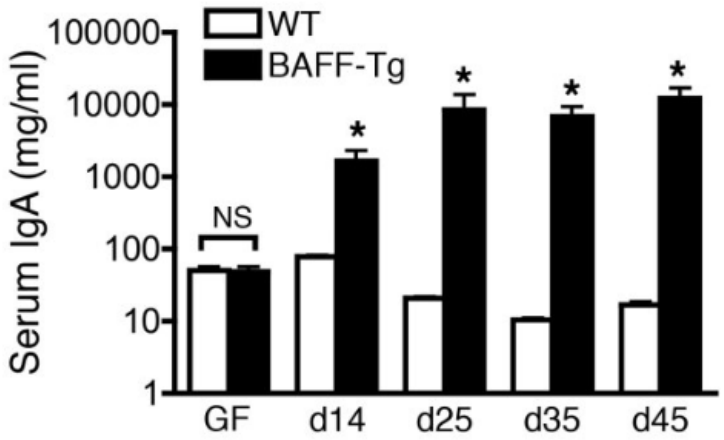
- **BAFF and APRIL play a central role in B lymphocyte development, selection, and homoeostasis**

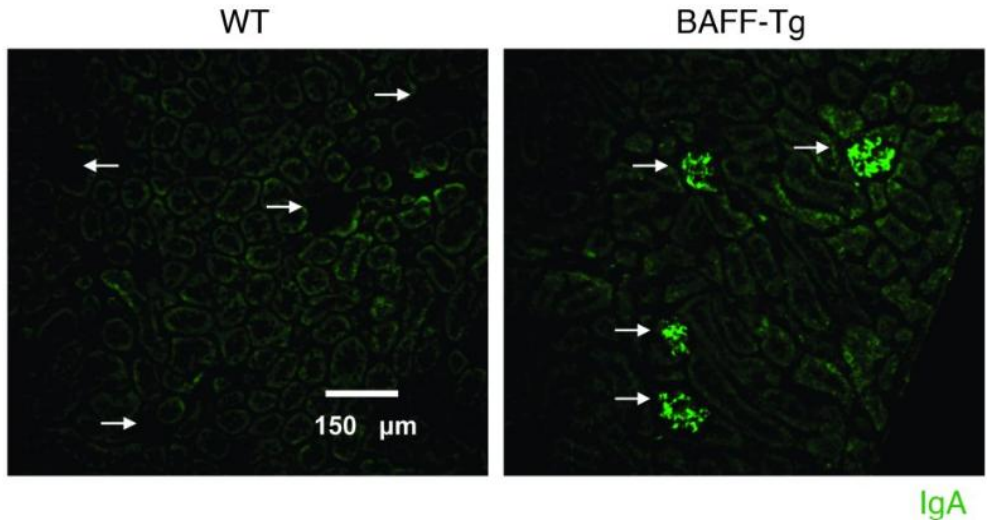


Vincent FB. Nat Rev Rheumatol 10: 365-373, 2014

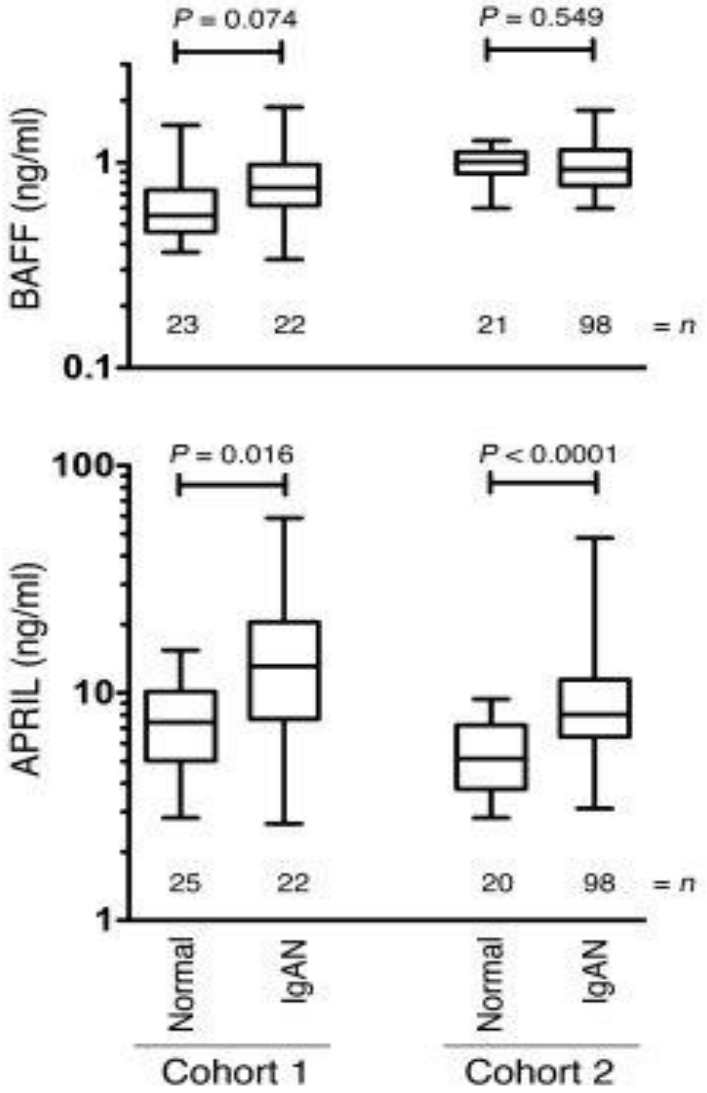
BAFF-Tg mice exhibit IgA-associated nephropathy





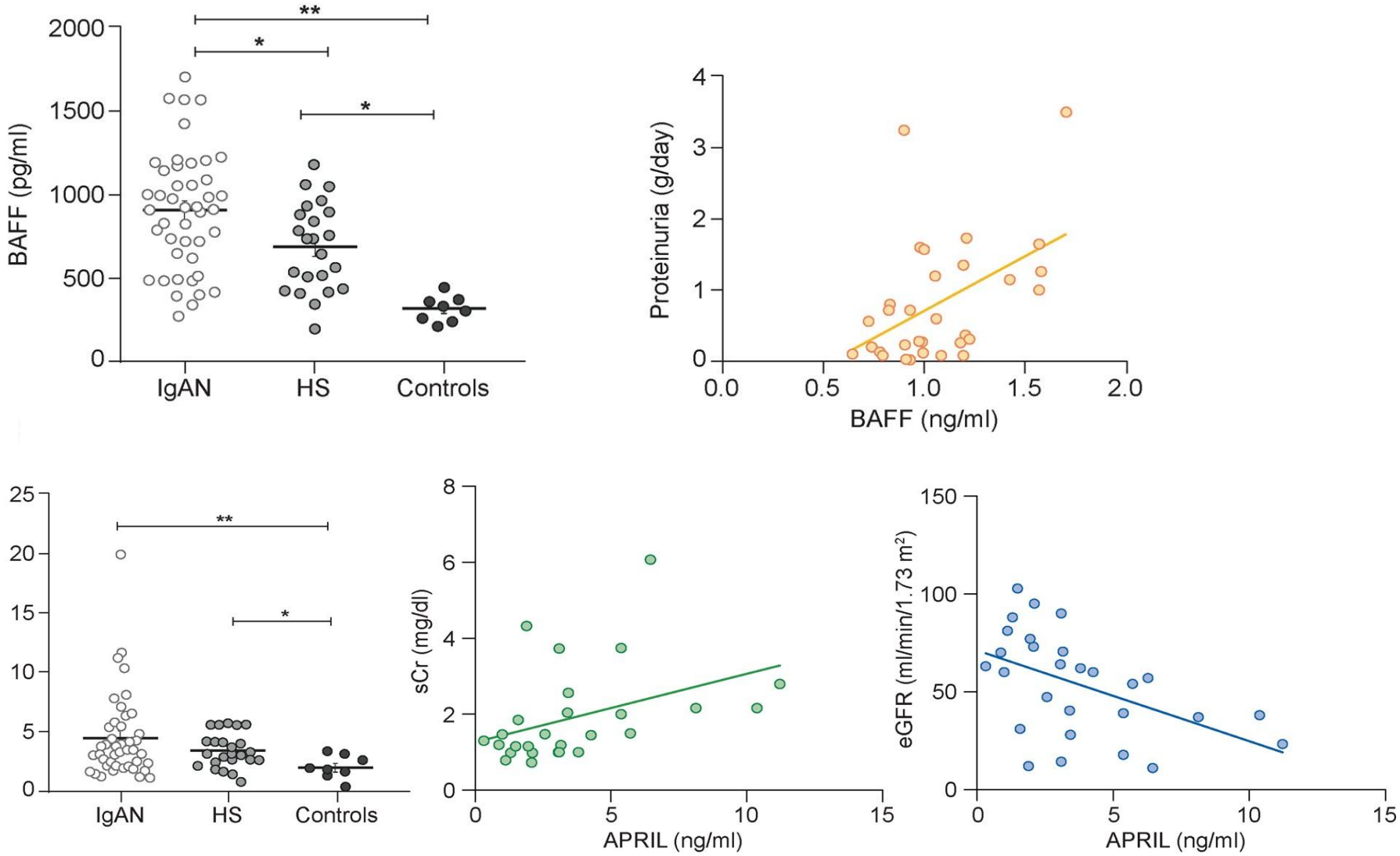


Serum levels of a APRIL and BAFF elevated in patients with IgAN



McCarthy DD. J Clin Invest 121: 3991, 2011

Serum levels of BAFF and APRIL were correlated with proteinuria or eGFR in patients with IgAN



Sallustio F. Nephrol Dial Transplant 27: 1765, 2022

GWAS for IgAN demonstrated strong contribution of TNFSF13 (APRIL) to disease risk

nature genetics

A genome-wide association study in Han Chinese identifies multiple susceptibility loci for IgA nephropathy

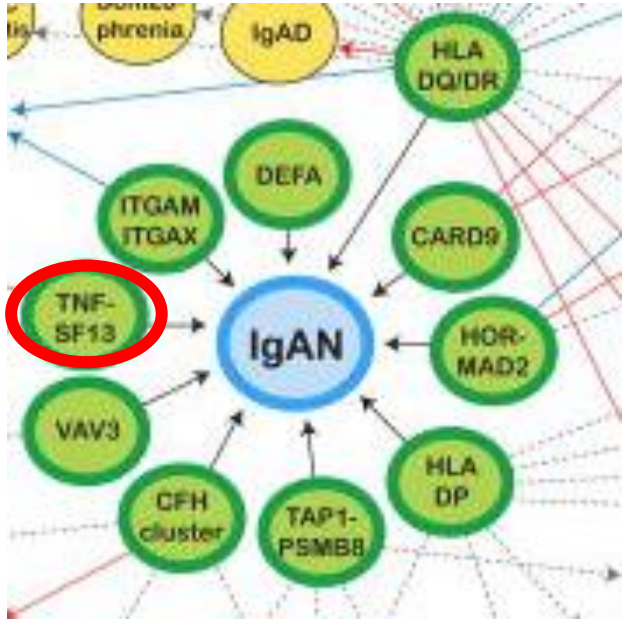
Yu XQ, et al. Nat Genet, 2011

APRIL: candidate genes

nature genetics

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

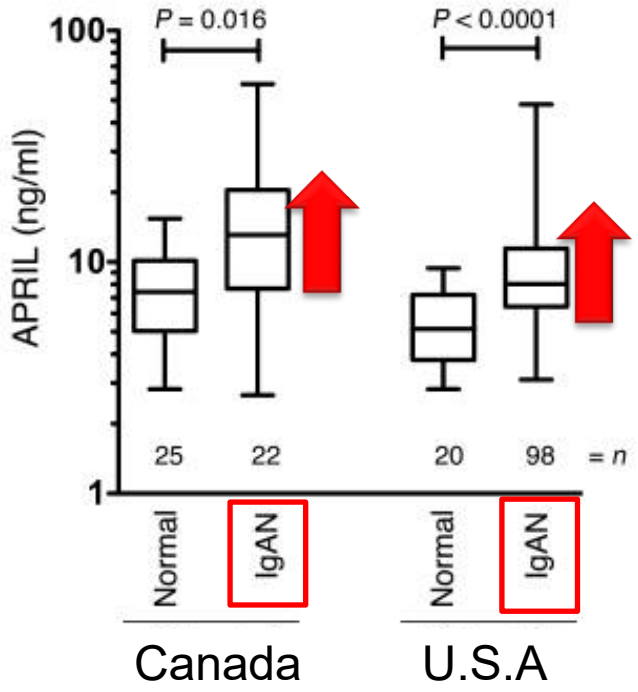
Kiryluk K, et al. Nat Genet, 2014



Kiryluk k, et al. Nat Gent 2014

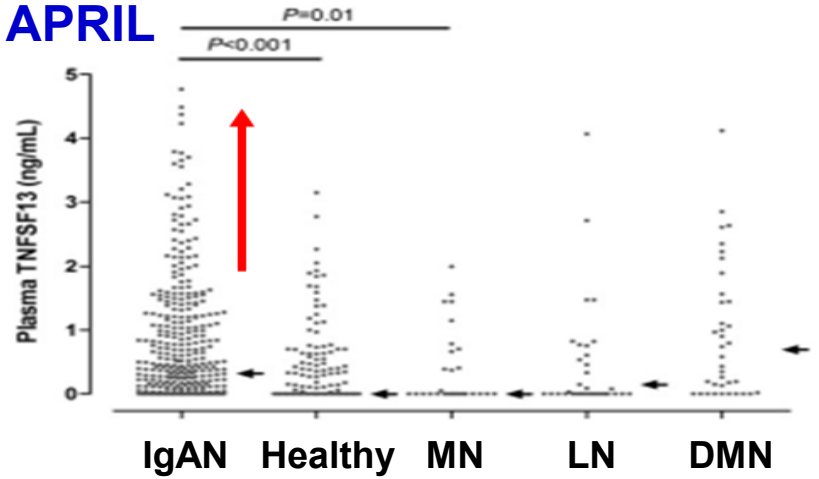
Serum levels of APRIL increased in patients with IgAN
High levels of serum APRIL associated with high risk for ESRD

Serum APRIL

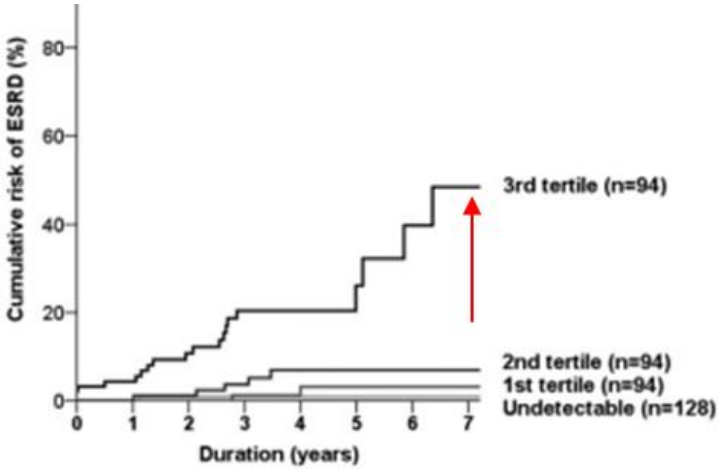


McCarthy DD. J Clin Invest 121:3991-4002, 2011

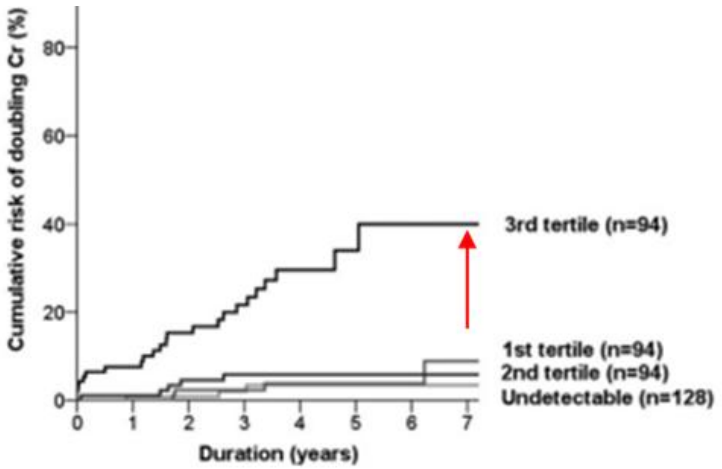
Serum APRIL



Risk for ESRD (%)

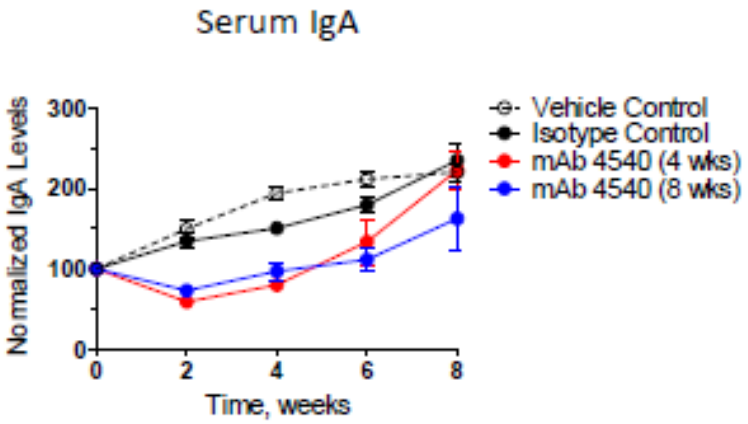


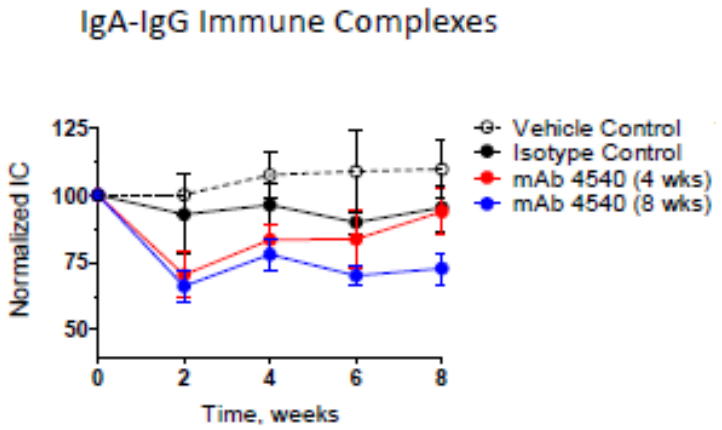
Risk for doubling sCr (%)

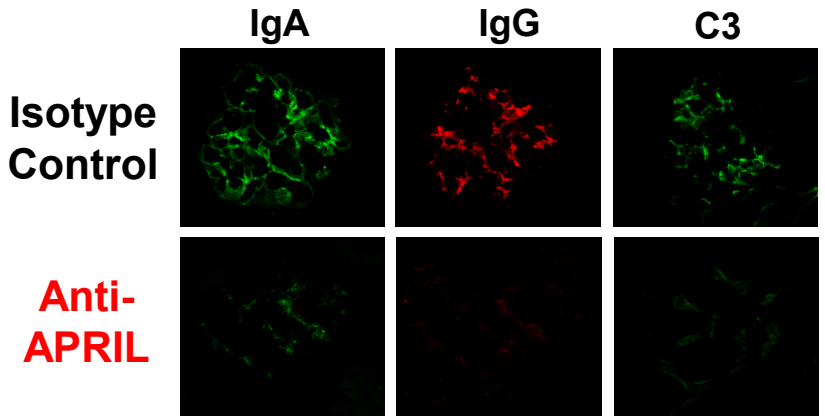


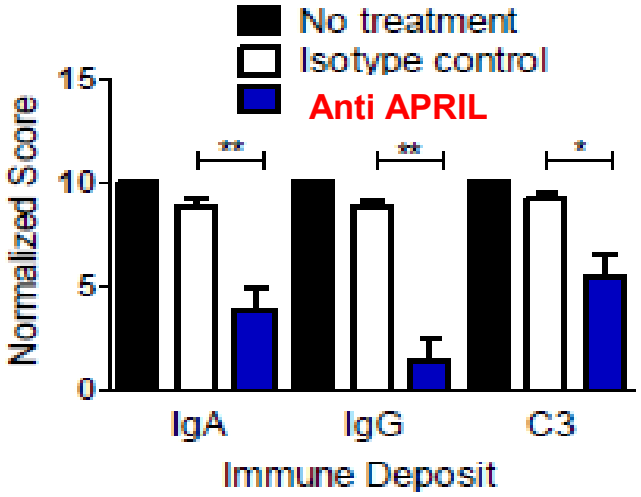
Han SS, et al: J Am Soc Nephrol, 2016

Anti-APRIL antibody treatment effectively reduces key IgA related disease mechanisms in the mouse model of IgAN









Clinical trials

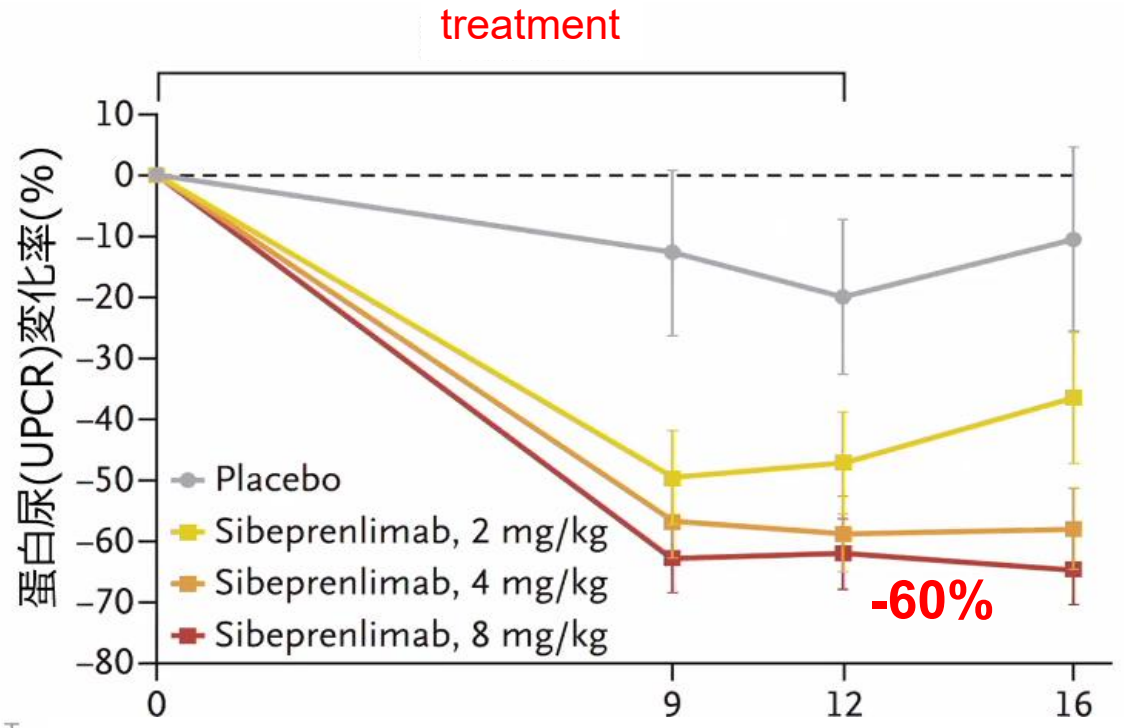
Myette J, Kano T, Suzuki H, Suzuki Y. et al. Kidney Int, 2019

ORIGINAL ARTICLE

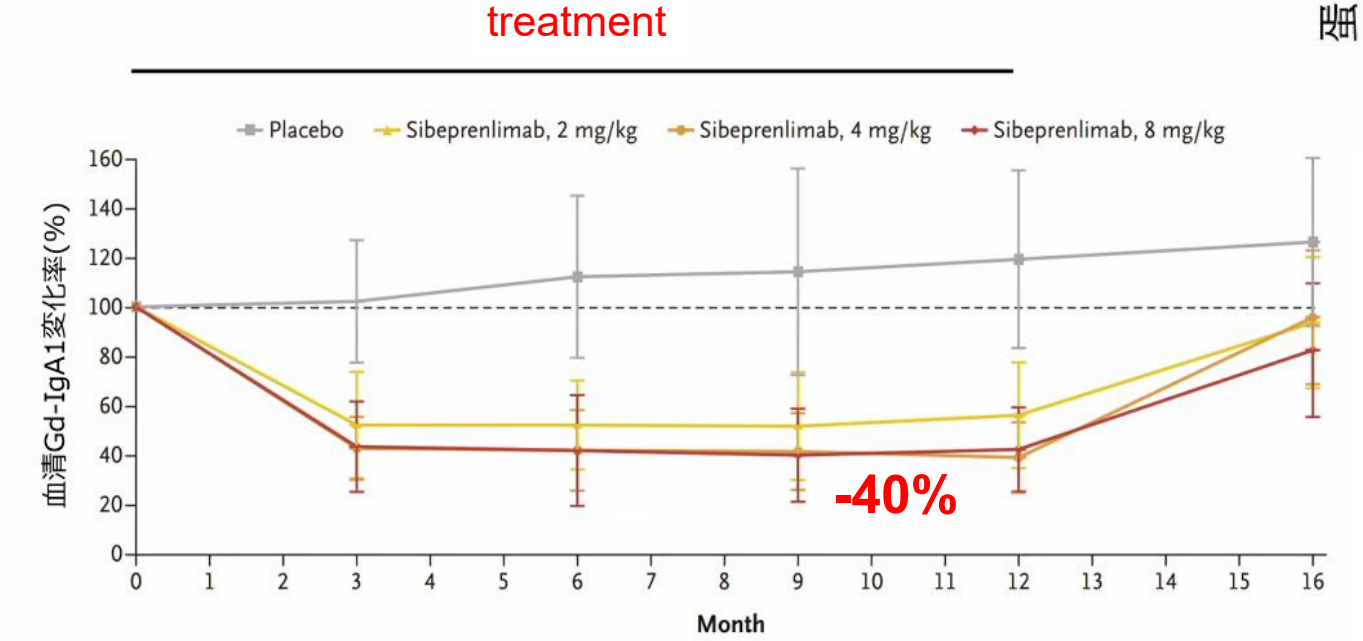
A Phase 2 Trial of Sibeprenlimab in Patients with IgA Nephropathy

Authors: Mohit Mathur, M.D., Jonathan Barratt, Ph.D., Bobby Chacko, M.D., D.M., Tak Mao Chan, M.D., D.Sc., Laura Kooienga, M.D., Kook-Hwan Oh, M.D., Ph.D., Manisha Sahay, M.D., Yusuke Suzuki, M.D., Ph.D., Muh Geot Wong, M.B., B.S., Ph.D., Jill Yarbrough, B.A., Jing Xia, Ph.D., and Brian J.G. Pereira, M.D., for the ENVISION Trial Investigators Group* -5 Author Info & Affiliations

Decrease of proteinuria



Decrease of serum Gd-IgA1



N Engl J Med 390: 20-31, 2024

The NEW ENGLAND JOURNAL of MEDICINE

Sibeprenlimab in IgA Nephropathy — Interim Analysis of a Phase 3 Trial

At 9 months

- UPCR: **50.2%** reduction

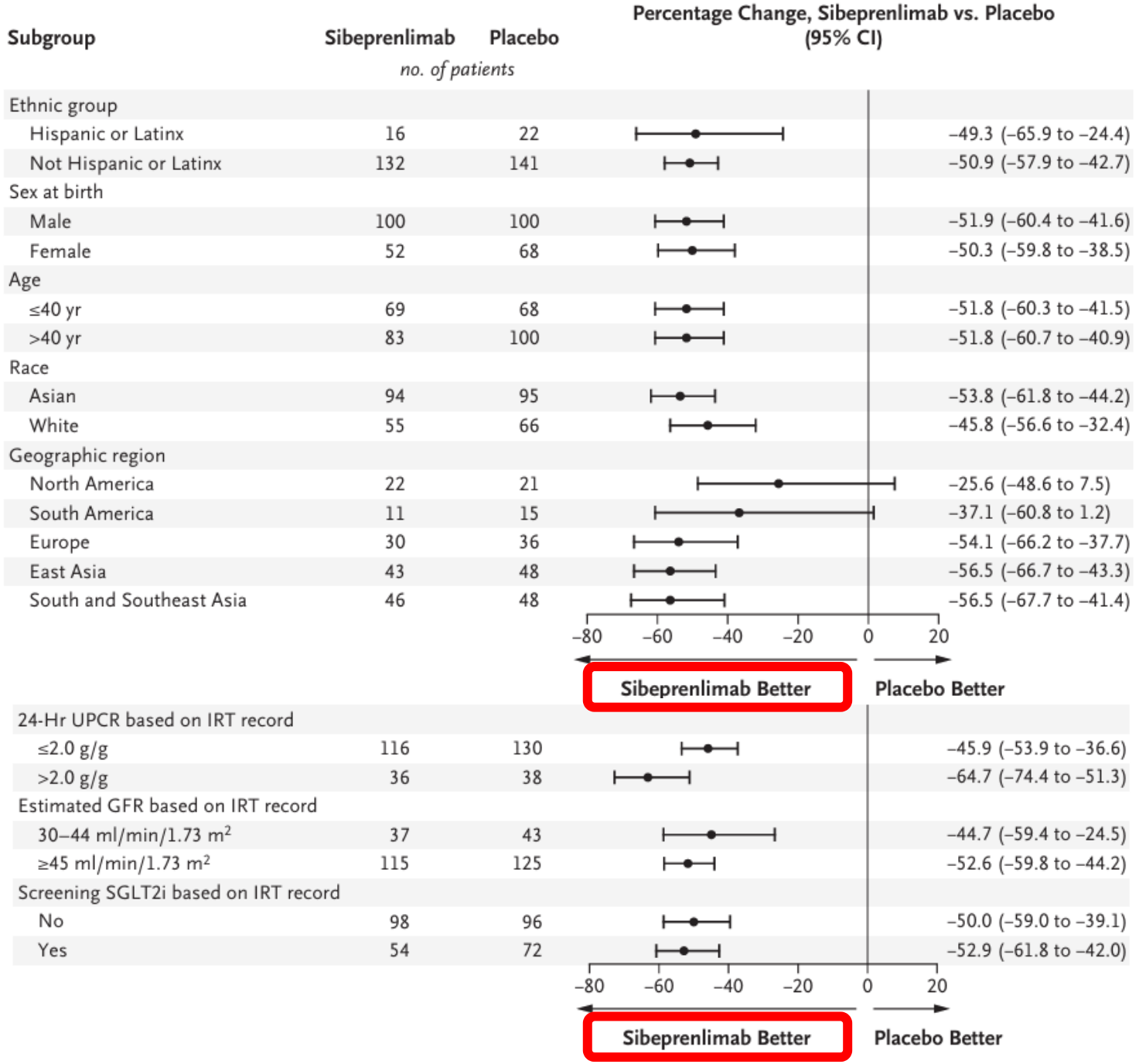
At 12 months,

- Hematuria positive ratio:

  78.3 → 19.8%

- Gd-IgA1: **67.1 %** reduction

Consistency was observed in baseline histopathologic activity and medication history



N Engl J Med 2025

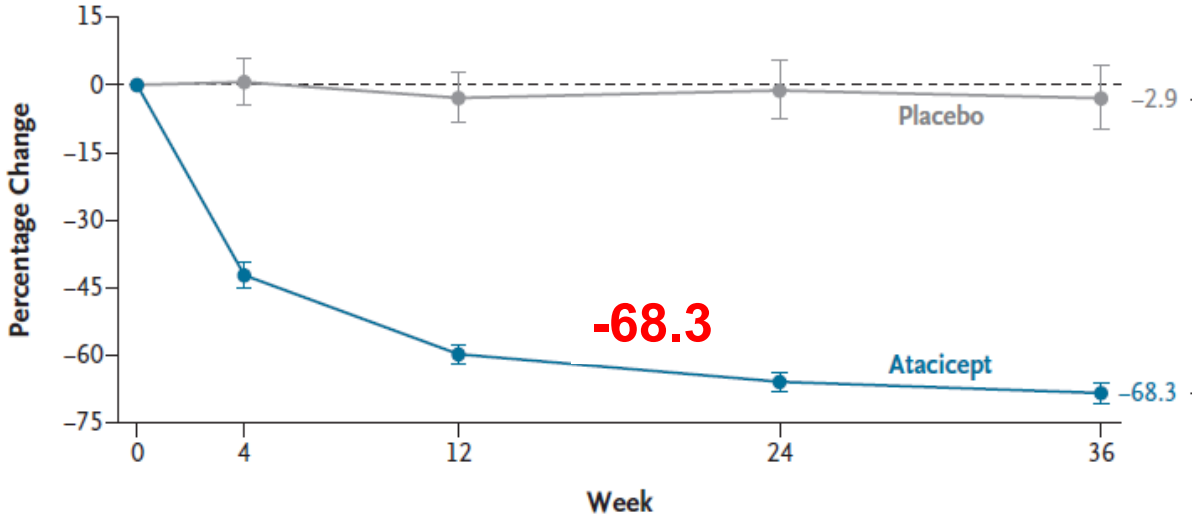
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

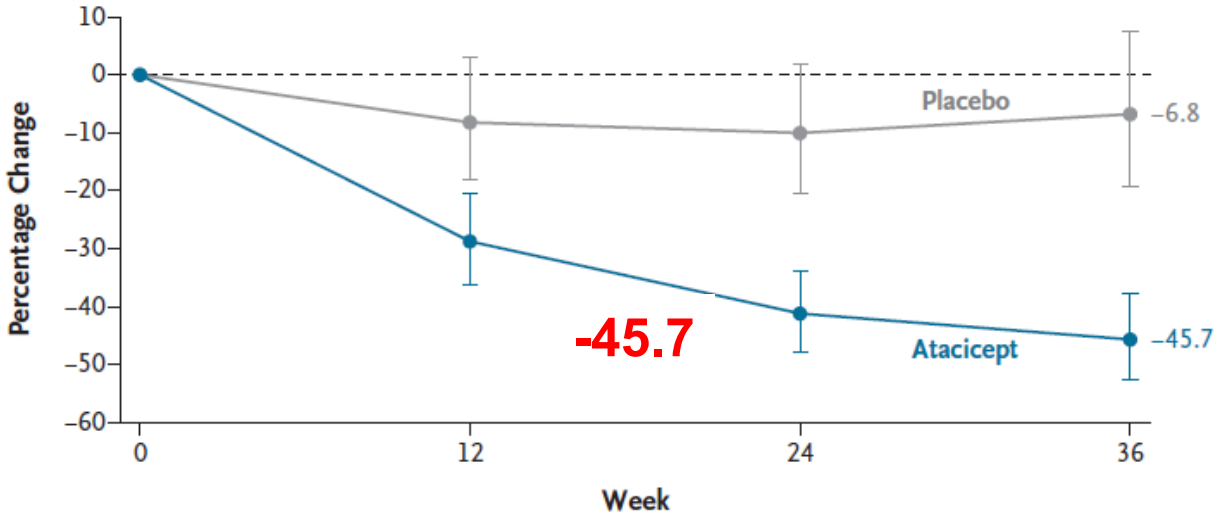
A Phase 3 Trial of Atacicept in Patients with IgA Nephropathy

Richard Lafayette, M.D.,[1] Sean J. Barbour, M.D.,[2] Robert M. Brenner, M.D.,[3] Kirk N. Campbell, M.D.,[4] Tom Doan,[3] Necmi Eren, M.D.,[5] Jürgen Floege, M.D.,[6] Vivekanand Jha, M.B., B.S., M.D., D.M.,[7] Beom Seok Kim, M.D., Ph.D.,[8] Adrian Liew, M.D.,[9] Bart Maes, M.D., Ph.D.,[10] Atanu Pal, M.D., D.M.,[11] Roberto Pecoits-Filho, M.D., Ph.D.,[12,13] Richard K.S. Phoon, M.D.,[14,15] Dana V. Rizk, M.D.,[16] Hitoshi Suzuki, M.D., Ph.D.,[17] Vladimir Tesař, M.D., Ph.D.,[18] Hernán Trimarchi, M.D., Ph.D.,[19] Xuelian Wei, Ph.D.,[3] Hong Zhang, M.D., Ph.D.,[20] and Jonathan Barratt, Ph.D.,[21] for the ORIGIN Phase 3 Trial Investigators*

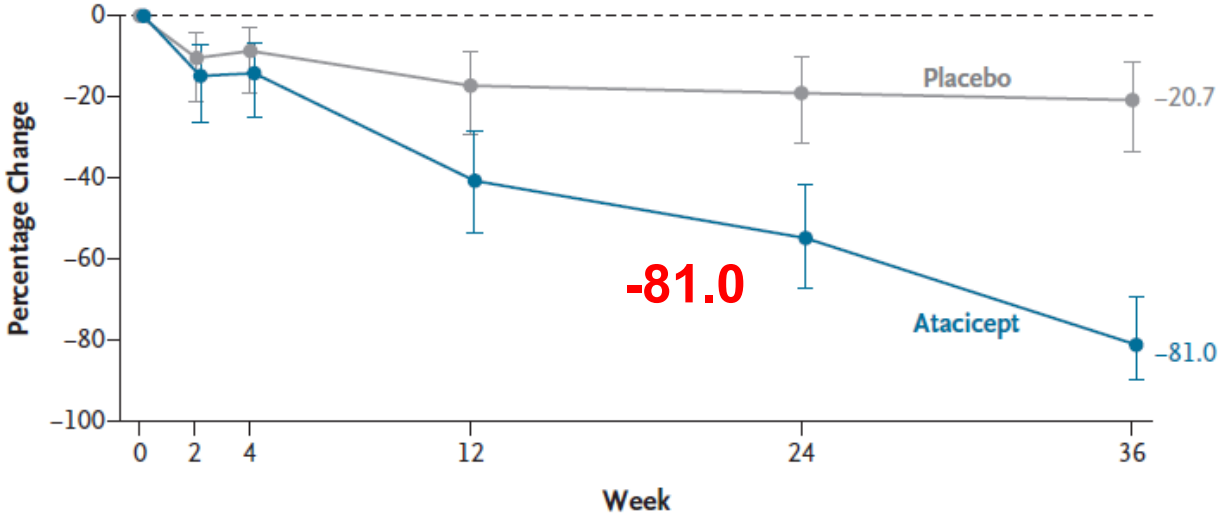
Changes in Gd-IgA1



Changes in UPCR



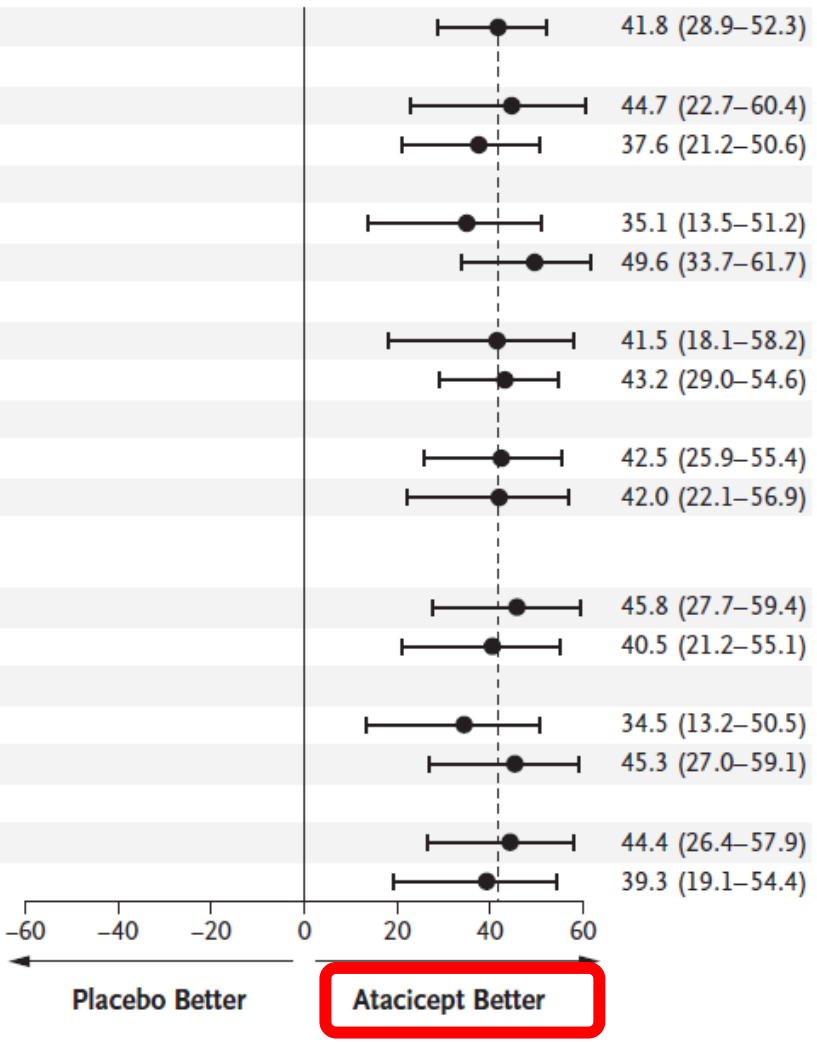
Changes in Hematuria



Atacicept: Dual blockade of BAFF and APRIL

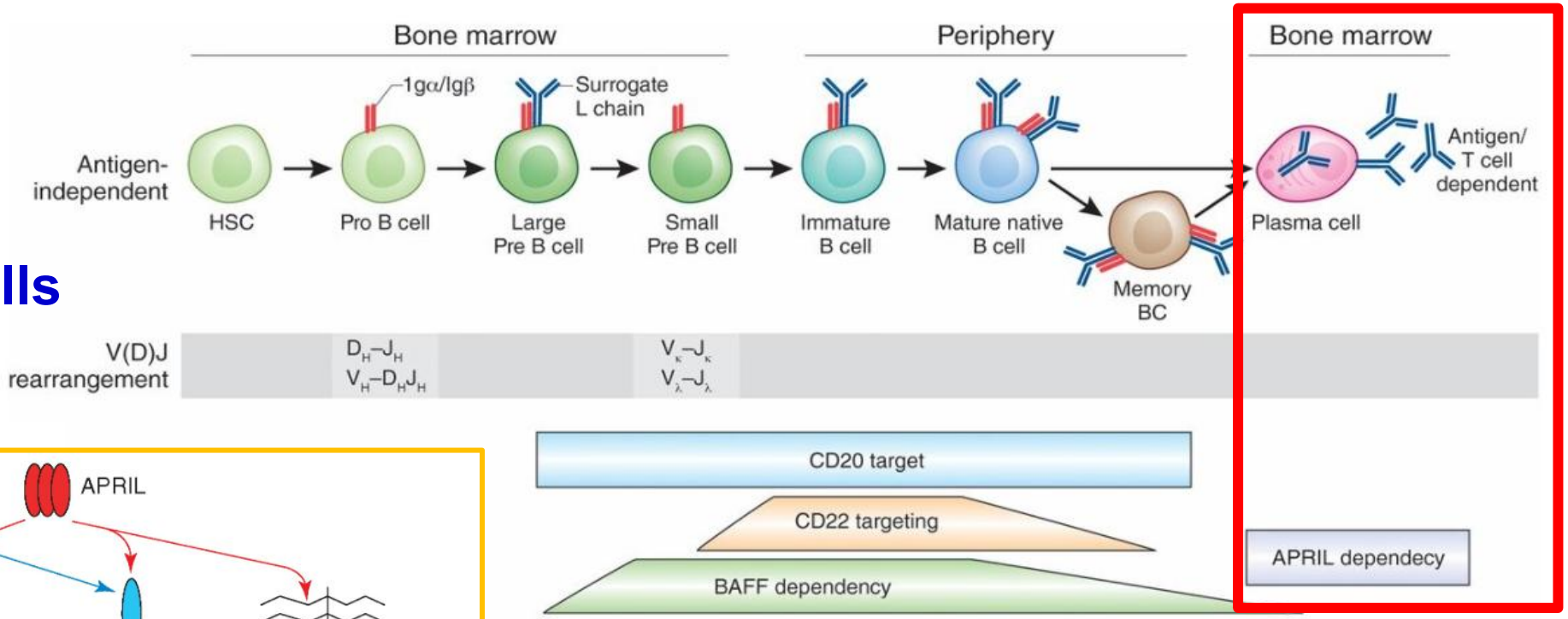
Consistency was observed in baseline histopathologic activity and medication history

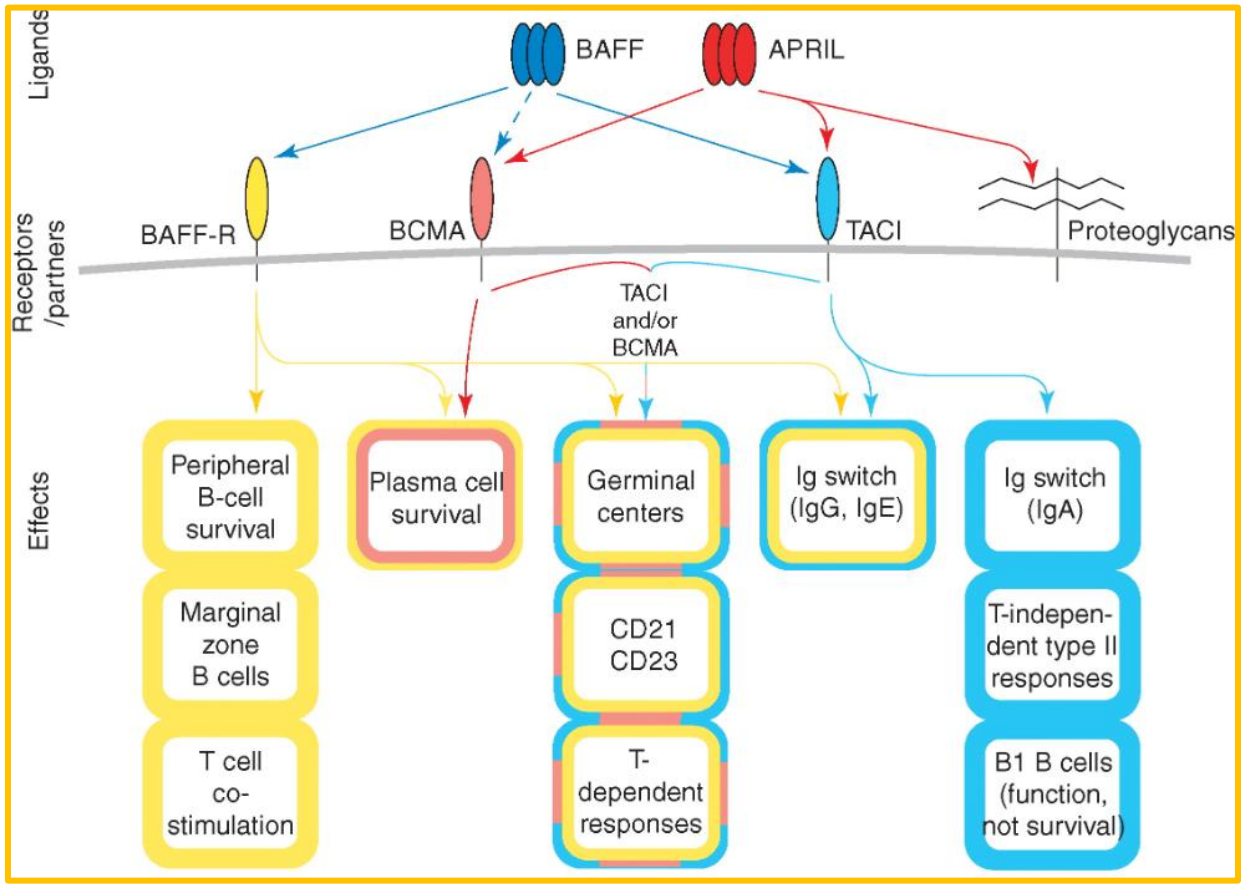
Subgroup	Atacicept	Placebo	Mean Change from Baseline		Mean Reduction vs. Placebo (95% CI)
			Atacicept	Placebo	
	no. of patients (%)		*percent*		*percentage points*
Overall	106 (100)	97 (100)	−45.7	−6.8	41.8 (28.9–52.3)
Age					
<40 yr	48 (45)	49 (51)	−44.5	0.5	44.7 (22.7–60.4)
≥40 yr	58 (55)	48 (49)	−46.4	−14.1	37.6 (21.2–50.6)
Sex					
Male	57 (54)	58 (60)	−41.1	−9.3	35.1 (13.5–51.2)
Female	49 (46)	39 (40)	−50.8	−2.4	49.6 (33.7–61.7)
Geographic region					
Asia	50 (47)	48 (49)	−49.5	−13.7	41.5 (18.1–58.2)
Other	56 (53)	49 (51)	−42.5	1.4	43.2 (29.0–54.6)
Race					
White	46 (43)	42 (43)	−42.4	0.1	42.5 (25.9–55.4)
Non-White	60 (57)	55 (57)	−48.4	−11.1	42.0 (22.1–56.9)
Urinary protein-to-creatinine ratio at baseline					
<1.5	53 (50)	47 (48)	−44.0	3.3	45.8 (27.7–59.4)
≥1.5	53 (50)	50 (52)	−48.5	−13.4	40.5 (21.2–55.1)
Estimated GFR at baseline					
<60 ml/min/1.73 m^2	50 (47)	52 (54)	−35.3	−1.3	34.5 (13.2–50.5)
≥60 ml/min/1.73 m^2	56 (53)	45 (46)	−53.0	−14.0	45.3 (27.0–59.1)
SGLT2 inhibitor use at baseline					
Yes	59 (56)	49 (51)	−48.2	−6.9	44.4 (26.4–57.9)
No	47 (44)	48 (49)	−42.9	−5.9	39.3 (19.1–54.4)



Lafayette R. N Engl J Med, 2025

Interventions and their potential to target distinctly B lineage subsets and plasma cells





- ✓ **BAFF bind strongly to BAFF-R and TACI and weakly to BCMA**
- ✓ **APRIL binds strongly to BCMA and moderately to TACI**

Schrezenmeier E. J Am Soc Nephrol 29: 741-758, 2018
Schneider P. Curr Opin Immunol 17: 282, 2005

Treatment target of IgAN by Multi-Hit pathogenesis

Exogenous antigen

pDC, T cell

Dysregulation of immune response (TLR9 and TLR7)

BAFF/APRIL

Plasma cell
Plasma blast

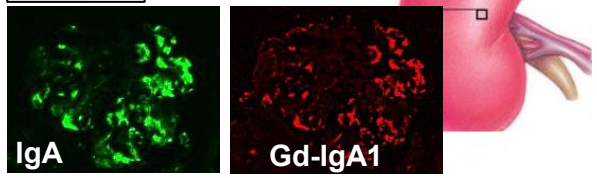
Upper Part:
Reduction of Gd-IgA1 IC production

1st Hit
Gd-IgA1

2nd Hit
Gd-IgA1-specific Ab (IgG, IgA)

3rd Hit
Gd-IgA1 IC

4th Hit



Mesangium

Complement activation

Classical — C1q

Lectin — MBL, MASP, Ficolins

Alternative — $C3b(H_2O)$

C3b
C5

C5b-9

Lower Part:
Anti-inflammation after Gd-IgA1 deposition

Suzuki H, et al. Semin Immunopathol, 2021

Dept. of Nephrology
Juntendo University

Acknowledgment

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23rd Asian Pacific Congress of Nephrology
Gene, Immunology, Vast, MEtabolism at its Finest!

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Rina Kato
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非常感谢您的聆听

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