Complement in IgA nephropathy

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Head of Pediatric Nephrology

Tanta University

Thanks for IPNA

INTERNATIONAL PEDIATRIC NEPHROLOGY ASSOCIATION

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Dr. Maher Ahmed Ahmed Abdel-Hafez
Shershaba, Zefta
Gharbia
EGYPT

Freiburg, May 30th, 2007

Dear Dr. Abdel-Hafez,

We would like to come back to your application for fellowship in pediatric nephrology. The IPNA committee on fellowships evaluated your application and we are pleased to inform you that it has been approved. An amount of US $ 7,500.- (plus the economy airfare for your trip from Egypt to the US and back) will be granted to support your 6-months fellowship at the University of Florida, Division of Pediatric Nephrology, under the guidance of Dr. Eduardo Garin.
A detailed report on your activities will be due upon termination of the fellowship and you shall receive a certificate from us confirming its completion as well as a copy of the textbook "Pediatric Nephrology", 5th edition.

We look forward to hearing from you regarding the starting date of your fellowship and wish you a fruitful training in Florida already now.

Sincerely,

Prof. Dr. M. Brandis
(Secretary General IPNA)

Thanks for IPNA

The International Pediatric Nephrology Association

CERTIFICATE

Is hereby granted to

Dr. Maher Abdel-Hafez

For completing a 6 months fellowship (November 1, 2007 – April 30, 2008) in Pediatric Nephrology at the University of Florida in the United States of America, under the guidance of Dr. Eduardo Garin.

July 20, 2008

Isidro B. Salusky, M.D.
Secretary General

AfPNA IPNA ESPNT

IPNA TEACHING COURSE

Under Patronage of

Prof. Hosam Salah

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COMPLEMENT-MEDIATED KIDNEY DISEASES (CMKDs)

Course Coordinator

Prof. Happy Sawires

Professor of Pediatric Nephrology
Cairo University

11th - 12th Feb, 2026

LRC,- Kasr Al-Aini
School of Medicine

Agenda

- IgA nephropathy
- How complement works in IgA nephropathy
- Potential therapeutic targets

IgA nephropathy (IgAN) is the most common primary glomerular disease world- wide

Table 2. Frequency of IgAN in European Countries

Country	PGD, %*	Study
Level 1	(31-50)	
Czech Republic	37.4	Maixnerova et al,[9] 2015
Estonia	35.4	Riispere et al,[66] 2012
France	52.7	Moranne et al,[67] 2008
Germany	50.7	Braun et al,[68] 2011
Italy	35.2	Schena et al,[10] 1997
Lithuania	35.0	Beitnaraite et al,[69] 2007
Sweden	40.6	Peters et al,[70] 2015
United Kingdom	39.0	McQuarrie et al,[18] 2014
Level 2	(21-30)	
Belgium	21.2	Mesquita et al,[71] 2011
Croatia	18.1	Batinić et al,[72] 2007
Poland	29.8	Kurnatowska et al,[73] 2012
Romania	28.9[†]	Covic et al,[74] 2006
The Netherlands	27.8	van Passen et al,[75] 2004
Level 3	(10-20)	
Macedonia	11.8	Polenakovic et al,[76] 2003
Level 4	(<10)	
Serbia and Montenegro	8.5	Naumovic et al,[77] 2009

*The frequency is expressed as the percentage of patients with a biopsy-proven diagnosis of PGD. The numbers in parentheses indicate the range of percentages.

[†]Includes mesangial proliferative glomerulonephritis.

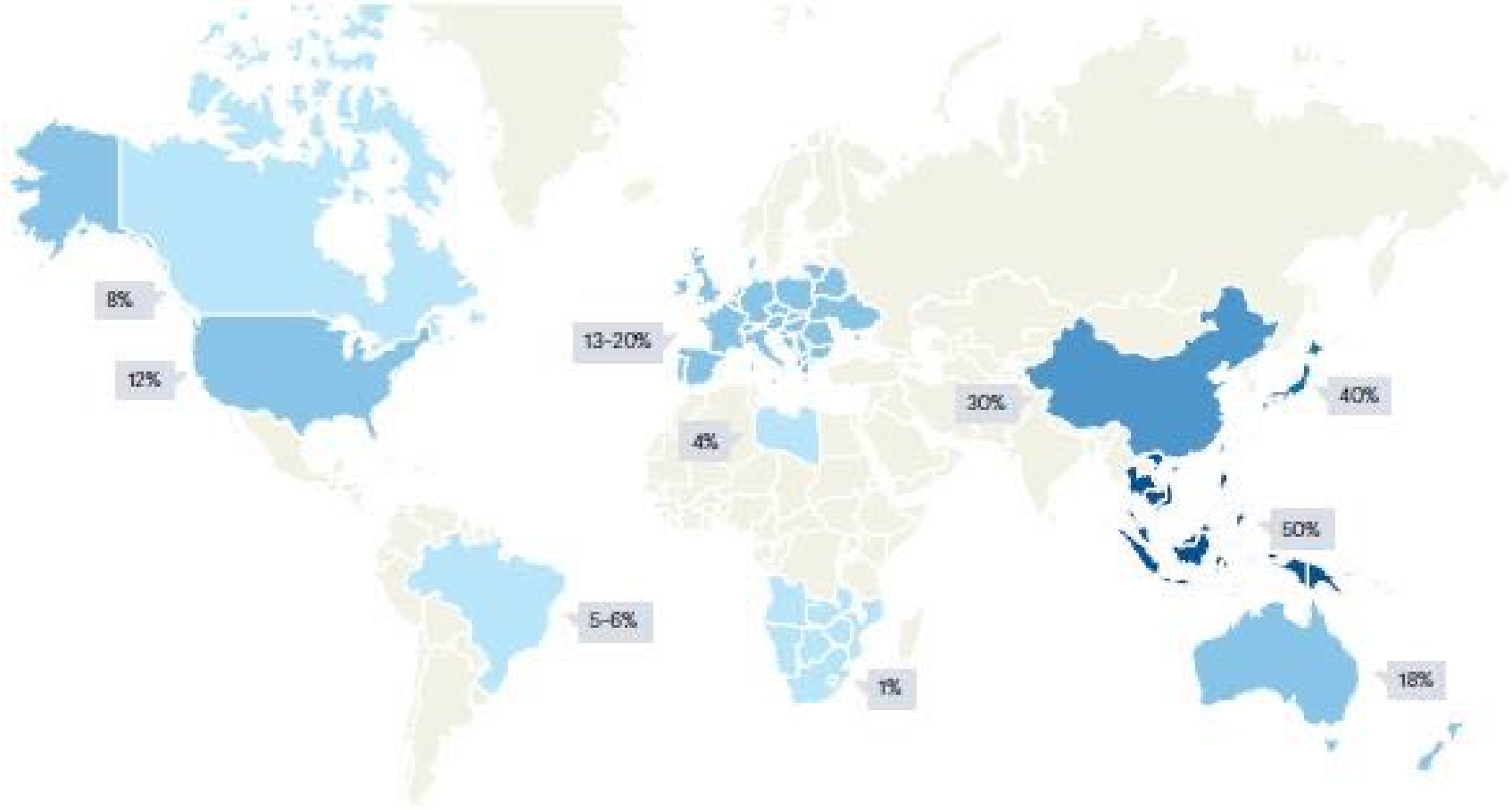
Table 1. Frequency of IgAN in Asian Countries

Country	PGD, %*	Study
Level 1	(31-50)	
China	54.3	Zhou et al,[55] 2009
	45.2	Li et al,[56] 2004
	36.6	Pan et al,[57] 2013
Japan	47.4	Research Group on Progressive Chronic Renal Disease,[7] 1999
	31.0	Sugiyama et al,[8] 2013
Singapore	43.2	Woo et al,[5] 2010
Level 2	(21-30)	
Korea	28.2	Chang et al,[58] 2009
Taiwan	22.4	Chou et al,[41] 2012
Level 3	(10-20)	
Bahrain	14.8	Al Arrayed et al,[59] 2007
Iran	14.7	Ossareh et al,[60] 2010
Saudi Arabia	10.8	Mitwalli et al,[61] 1996
Thailand	17.9	Parichatikanond et al,[62] 2006
Level 4	(<10)	
Bangladesh	6.9	Habib et al,[63] 2012
India	6.3	Das et al,[64] 2011
United Arab Emirates	6.3	Yahya et al,[65] 1998

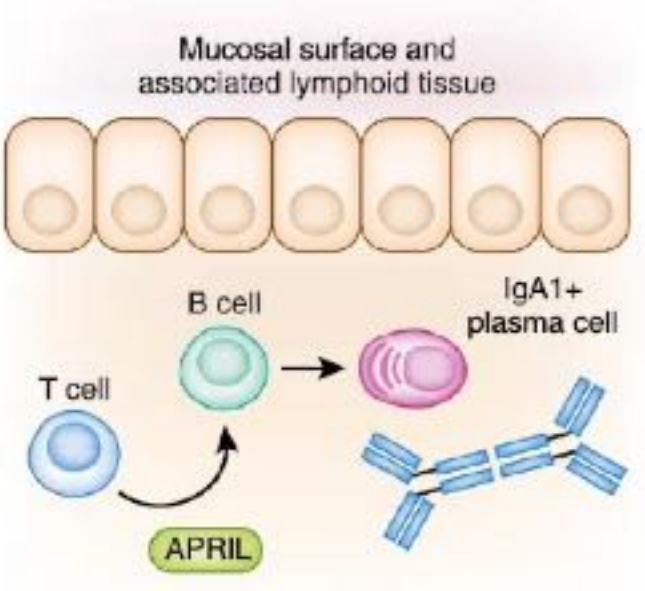
*The frequency is expressed as the percentage of patients with a biopsy-proven diagnosis of PGD. The numbers in parentheses indicate the range of percentages.

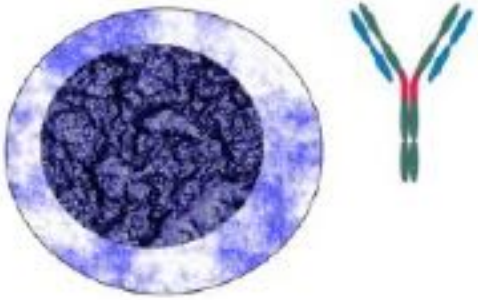
More common and aggressive in East and South East Asia,

Prevalence of IgAN worldwide



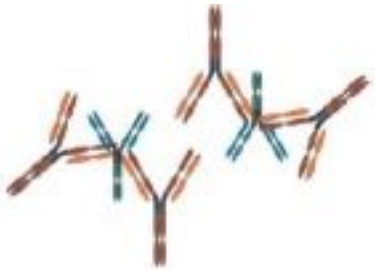
Multi-Hit Hypothesis for Pathogenesis of IgAN.



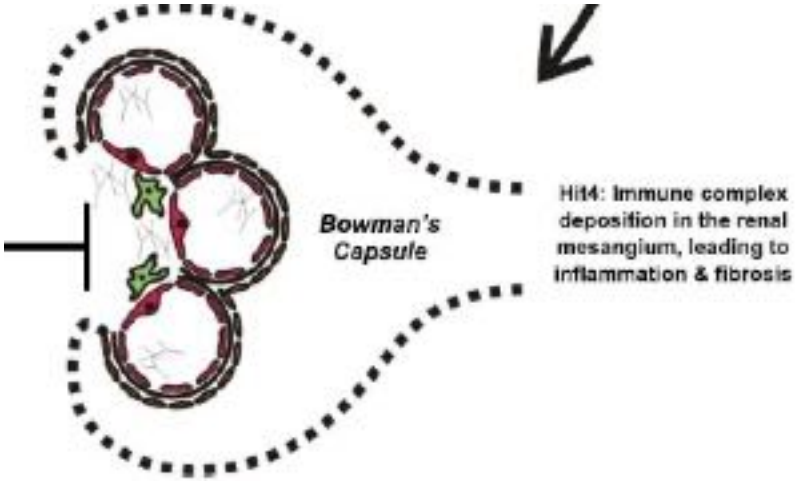


Hit 1: B-cell production of Galactose deficient IgA (Gd-IgA)

Hit 2: B-cell production of Anti-Gd-IgA (IgG)



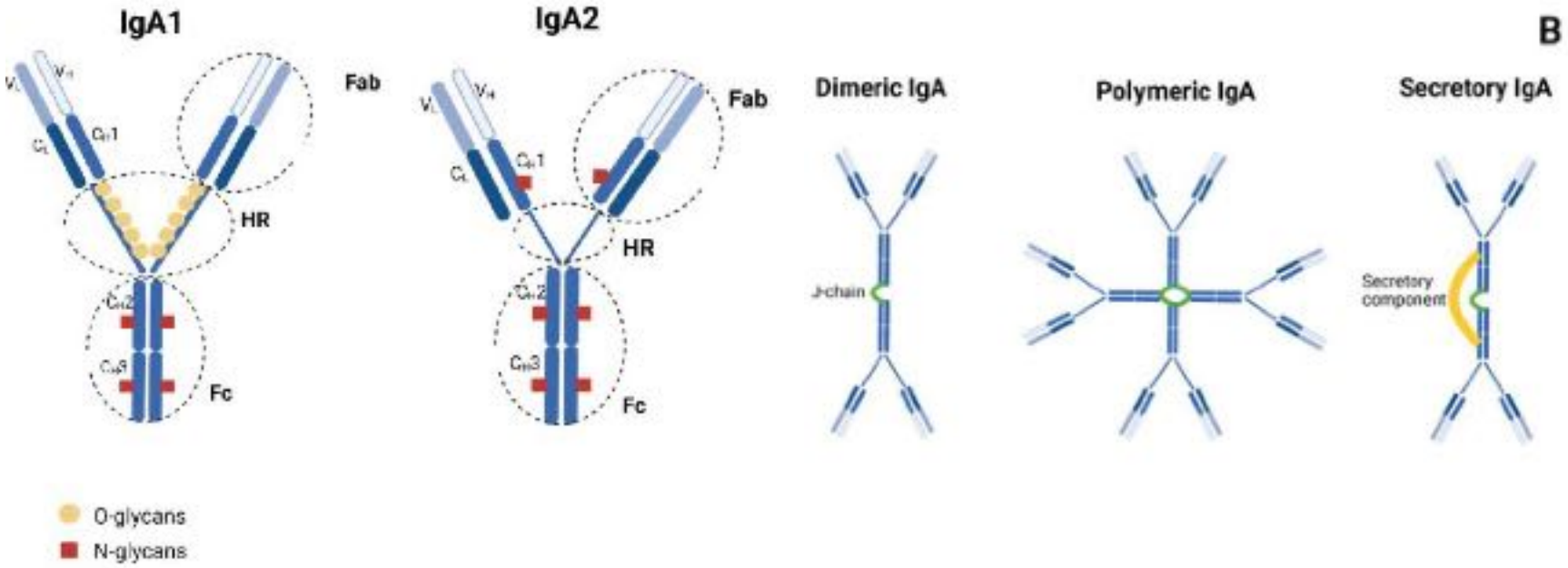
Hit 3: Anti-Gd-IgA/Gd-IgA complex formation

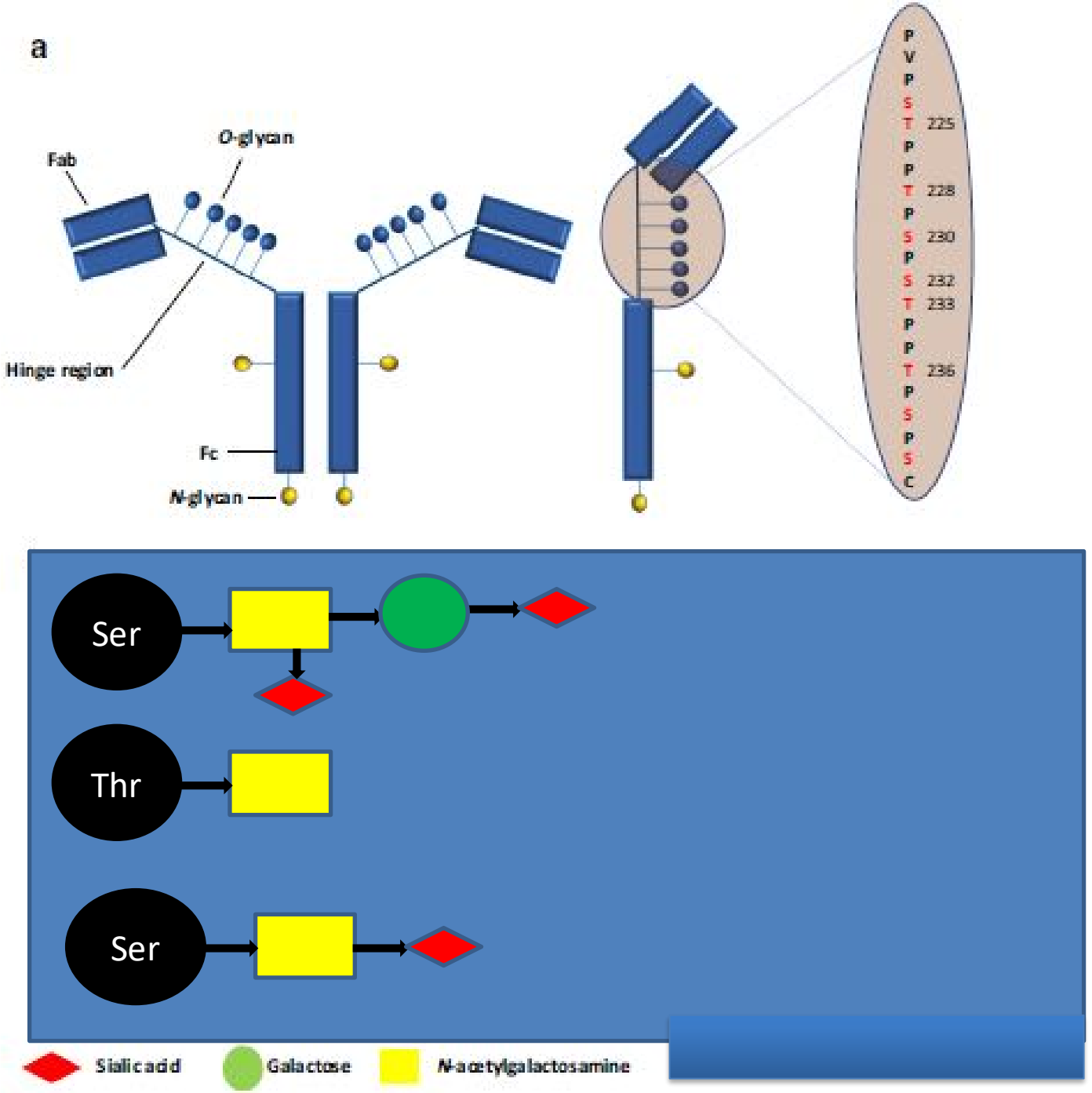


Hit4: Immune complex deposition in the renal mesangium, leading to inflammation & fibrosis

Types of IgA

Mucosal IgA




a
Fab
O-glycan
Hinge region
Fc
N-glycan
P
V
P
S
T 225
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T 228
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S 230
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S 232
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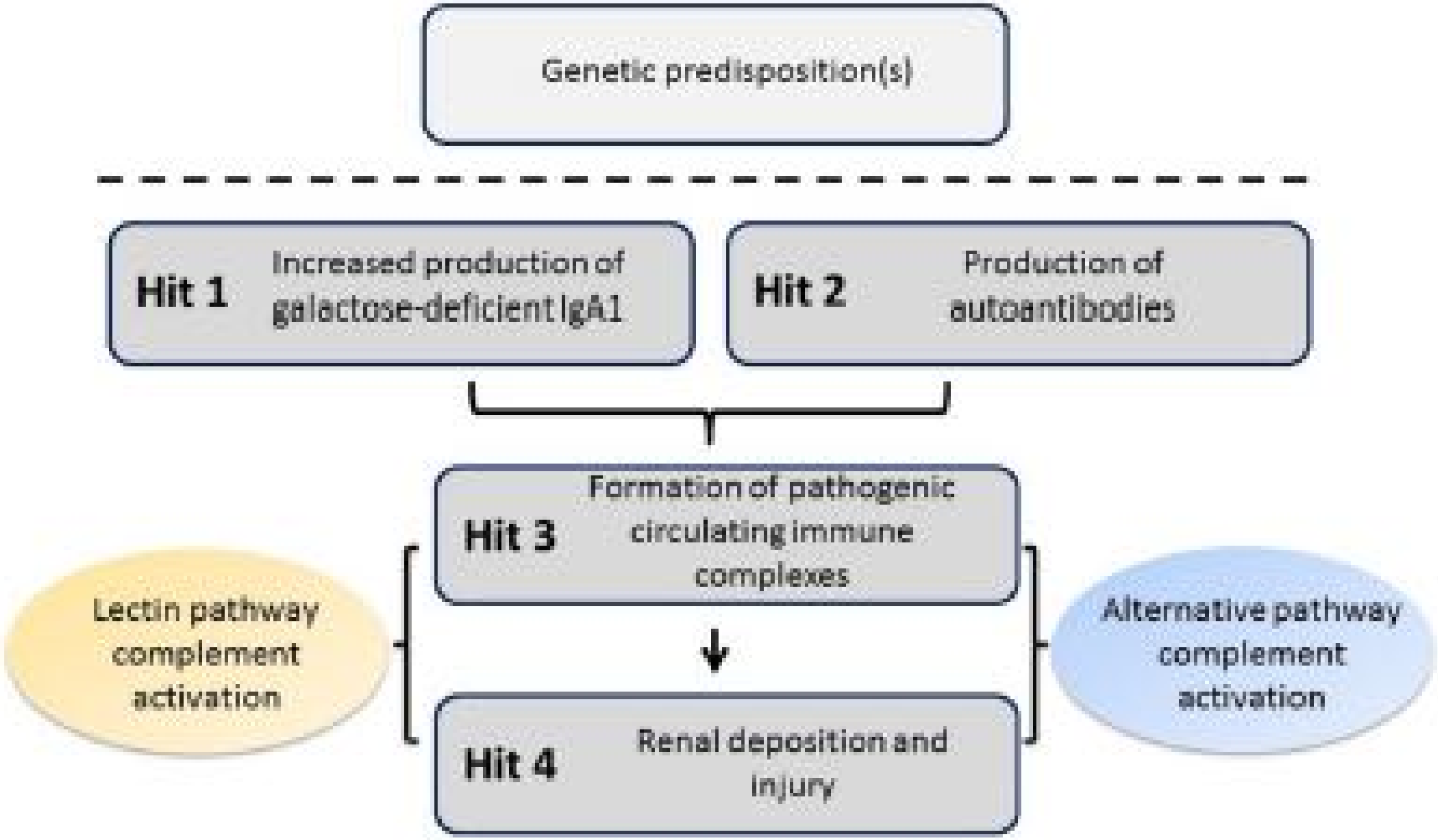
S
C
Ser
Thr
Ser
Sialic acid
Galactose
N-acetylgalactosamine

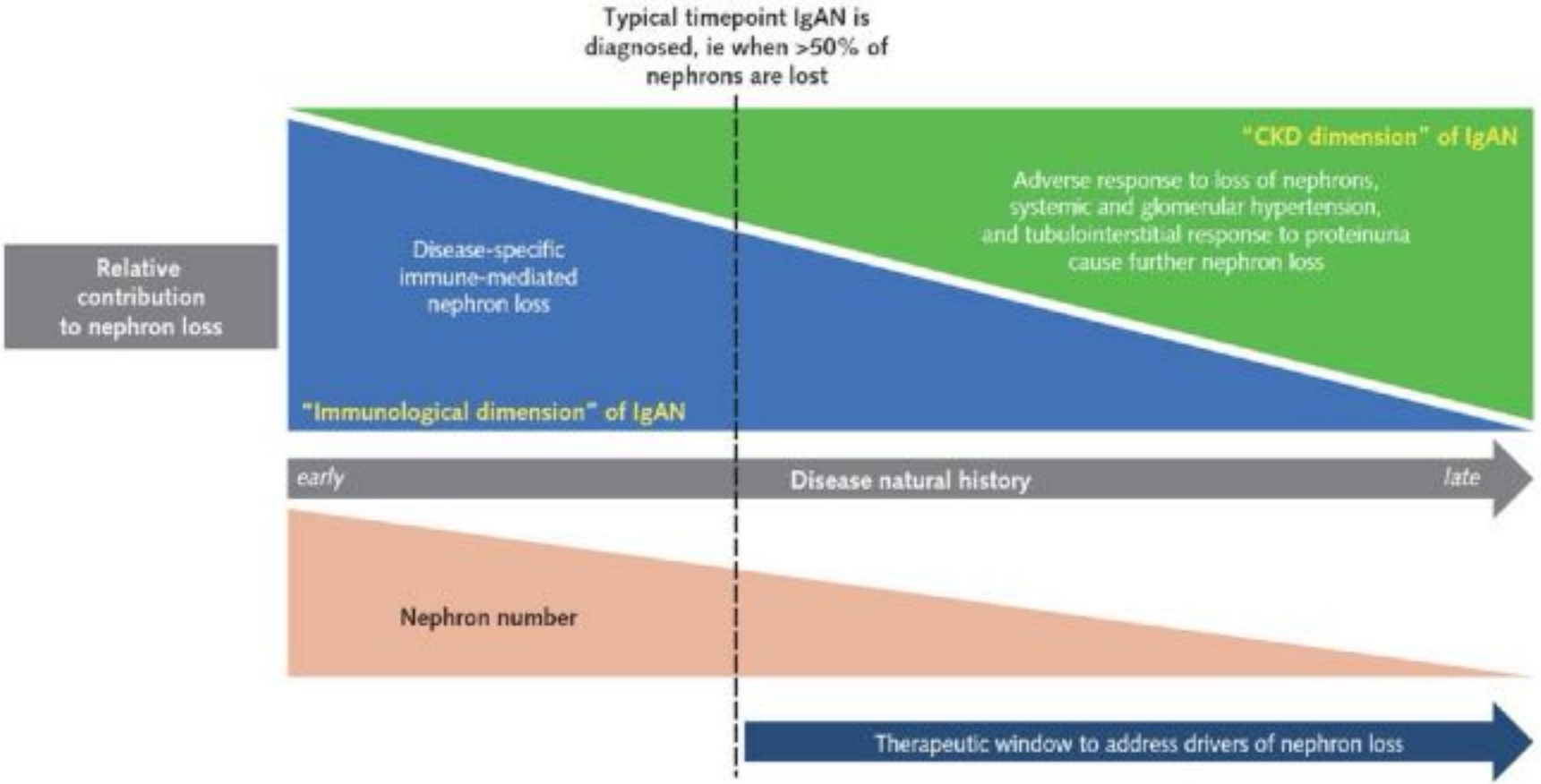
Pathophysiology of the disease



Clinical presentation

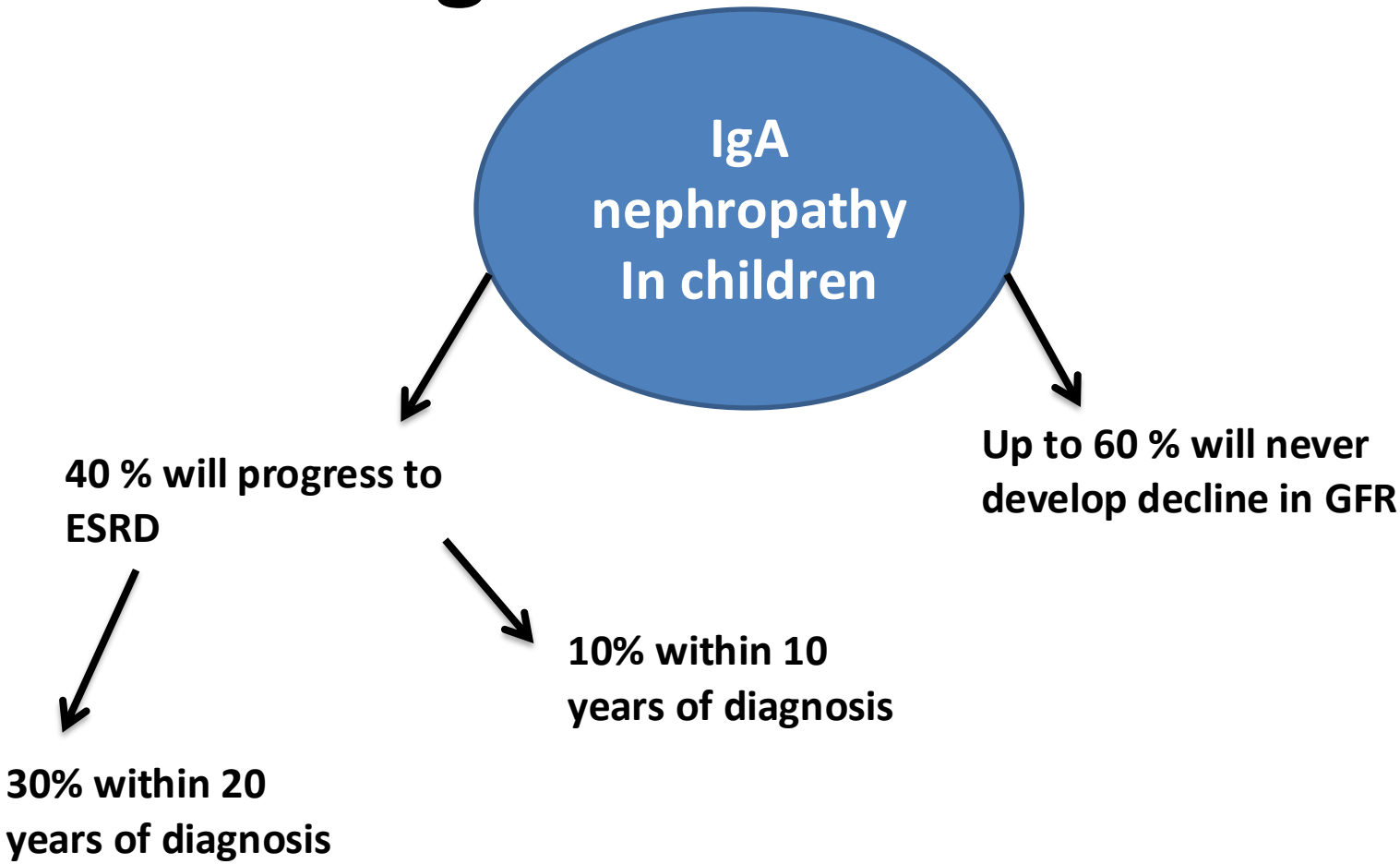
- **Synpharengitic recurrent gross hematuria**
- **Acute nephritis wit normal serum C3 level**
- **Proteinuria, hypertention and decline of GFR in progressive disease**

Dimensions of IgAN



Barratt et al. Frontiers in medicine 2024

Prognosis in Pediatrics



Prediction of progression

Current clinical markers of disease progression namely proteinuria, hypertension, and impaired renal function, are non-specific and manifest only when significant renal injury and scarring have occurred. (often irreversible)

MEST C score

Histological Feature	Definition	Score
Mesangial hypercellularity	Percentage of glomeruli with > 3 mesangial cells per mesangial area	M0: ≤ 50% M1: > 50%
Endocapillary hypercellularity	Increased number of cells within glomerular capillary lumina causing narrowing of the lumina	E0: Absent E1: Present
Segmental glomerulosclerosis	Any amount of the glomerular tuft involved in sclerosis, but not involving the whole tuft, or the presence of an adhesion	S0: Absent S1: Present
Tubular atrophy / Interstitial fibrosis	Percentage of cortical area involved by tubular atrophy or interstitial fibrosis, whichever is greater	T0: 0–25% of cortical area T1: 26–50% of cortical area T2: > 50% of cortical area
Cellular or fibrocellular crescent	Percentage of glomeruli with cellular or fibrocellular crescent	C0: Absent C1: < 25% of glomeruli C2: ≥ 25% of glomeruli

M: Mesangial hypercellularity; E: Endocapillary hypercellularity; S: Segmental glomerulosclerosis; T: Tubular atrophy/Interstitial fibrosis;

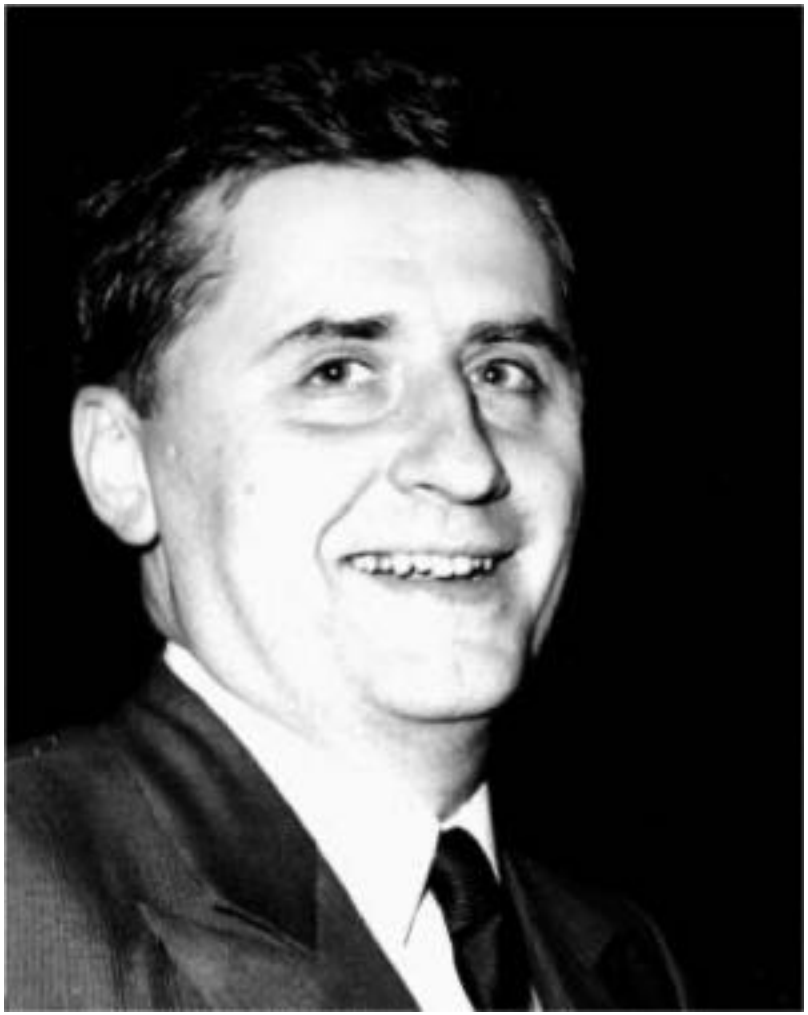
C: Cellular or fibrocellular crescents

New markers

- **Serum IgA/C3 ratio**
- **Glomerular staining of C3 and or C4d**
- **Serum and urinary galactose-deficient IgA1 (gd-IgA1)**
- **Autoantibodies against gd-IgA1**
- **Urinary cytokines, such as IL-6 and TGF-β1**

IgA nephropathy

Dr. Jean Berger



- **Since its first description by Berger and his colleague Dr. Nicole Hinglais**

in 1968. there is no breakthrough in diagnosis or therapy of the disease

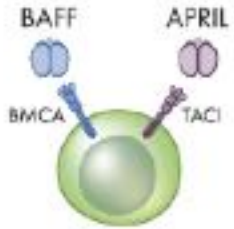
Current treatment of IgAN

remains generic and applicable to many kidney diseases, focusing on modulating downstream immune and inflammatory events, and is not specific to IgAN

Clinical Kidney Journal

Immune abnormalities in IgA nephropathy

B cells



Increased BAFF and APRIL serum levels

Higher expression of BMCA and TACI

Higher levels of gut-homing ($CCR9^+$ $\beta7integrin^+$) B cells

T cells

Th1/Th2 imbalance

Decreased Treg

Increased Th22 and Th17

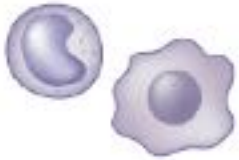
Positive correlation between $CXCR5^+$ $PD\text{-}1^+$Tfh and serum gd-IgA1

Toll-like receptors

Higher expression of TLRs in the kidney

Increased expression of TLR mRNA in PBMCs with positive correlation with proteinuria

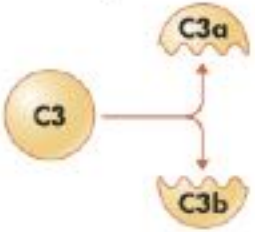
Monocytes/ macrophages



Increase in non-classical monocytes

Increased expression of $TIM\text{-}3^+$ with positive correlation with proteinuria

Complement



Activation of alternative and lectin pathways

Glomerular C3b deposition correlates with the progression of IgAN

Conclusion: Although several key questions about the production of gd-IgA1 and the formation of anti-gd-IgA1 antibodies remain unanswered, a growing body of evidence is shedding light on the innate and adaptive immune mechanisms involved in this complex pathogenic process and how they could be therapeutically targeted.

Gentile, M., et al.
Clinical Kidney Journal (2023)
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How complement is activated in IgA nephropathy

- In contrast to IgG and IgM, human IgA does not activate complement in the fluid phase and is considered anti-inflammatory.
- IgA is traditionally regarded as non-complement fixing.
- GdIgA was able to trigger C3 cleavage via the AP but not CP and can bind MBL-MASP complexes in vitro

Complement in pathology

- **In IgAN. Immunohistochemical findings of C3, properdin, C4d, MBL and C5b-9 deposits in mesangium of IgAN biopsy samples, coupled with the general absence of C1q, confirm activation of alternative and lectin pathways rather than classical pathway**

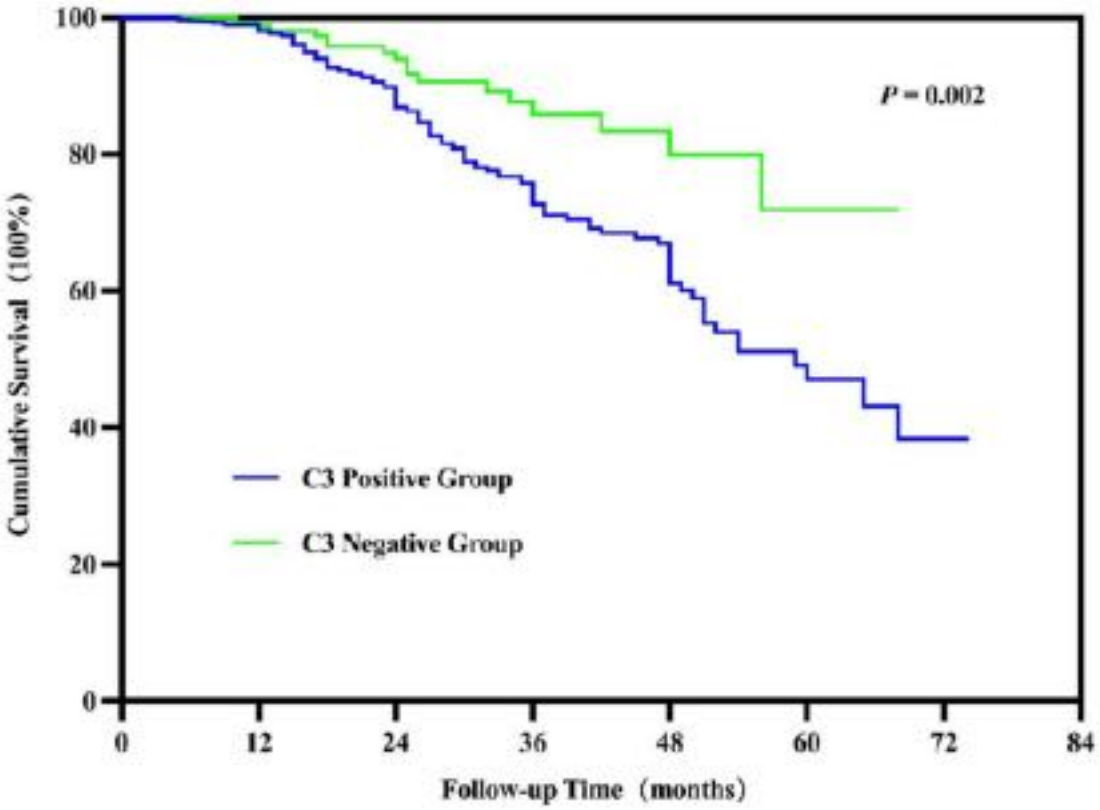
Seminars in Immunopathology (2021) 43:679–690

Sub-clinical mesangial IgA deposition is a relatively common finding in the general population.

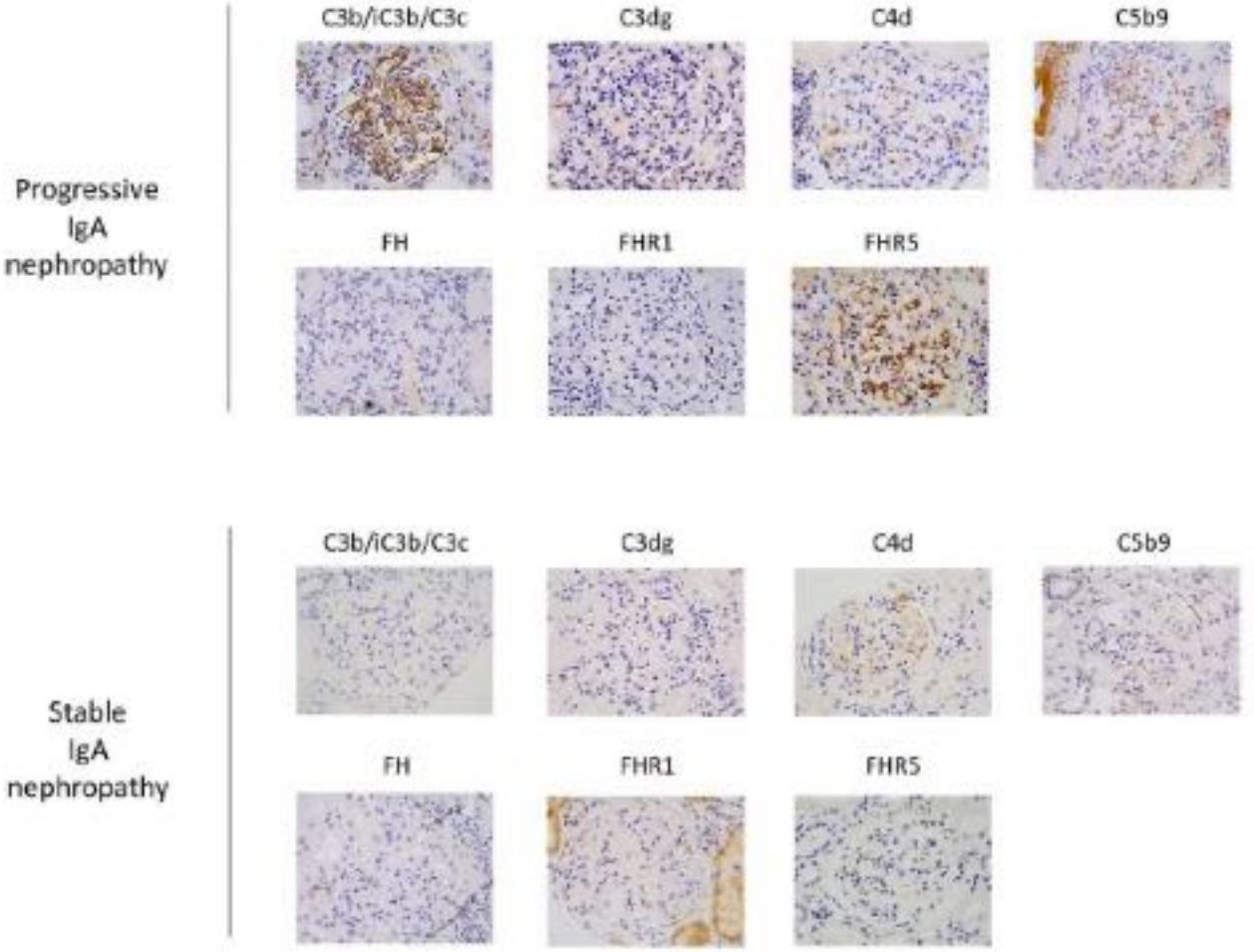
In autopsy series and allograft biopsy series, IgA deposition without overt clinical disease has been observed in up to 16% of subjects

The degree of mesangial deposition of IgA does not correlate with the severity of renal inflammation and injury

Co-deposits of C3 and other complement particles are considered a biomarker of actual IgAN in comparison to isolated IgA deposition without renal injury



Progressive IgAN was defined as the occurrence of 40% loss of estimated glomerular filtration rate or end-stage kidney disease over 5 years from diagnosis



Medjeral-Thomas et al Kidney Int Rep 2018,3:426–438

Complement in the circulation

- **Despite the presence of normal or elevated C3 levels in the circulation of most Caucasian patients with IgAN, C3 activation fragments are present in about 50% of patients** (Microbiol Immunol Scand C. (1984) 92:213–20.).
- **Subsequently, 70% of pediatric IgAN patients had significantly elevated C3d/C3 ratio in the circulation**(Tanaka C,1991)

Genetics

- **A large GWAS identified a copy number polymorphism of the *CFHR3-1* deletion that is associated with protection against the occurrence of IgAN [Gharavi AG et-al 2011].**
- **This protective effect is due to the fact that *CFHR3 and CFHR1 normally compete with Factor H* for binding sites, reducing its regulatory function. The deletion of *CFHR3-1 enhances Factor H activity, allowing it to* more effectively control C3 convertase production and limit complement activation.**

Genetics

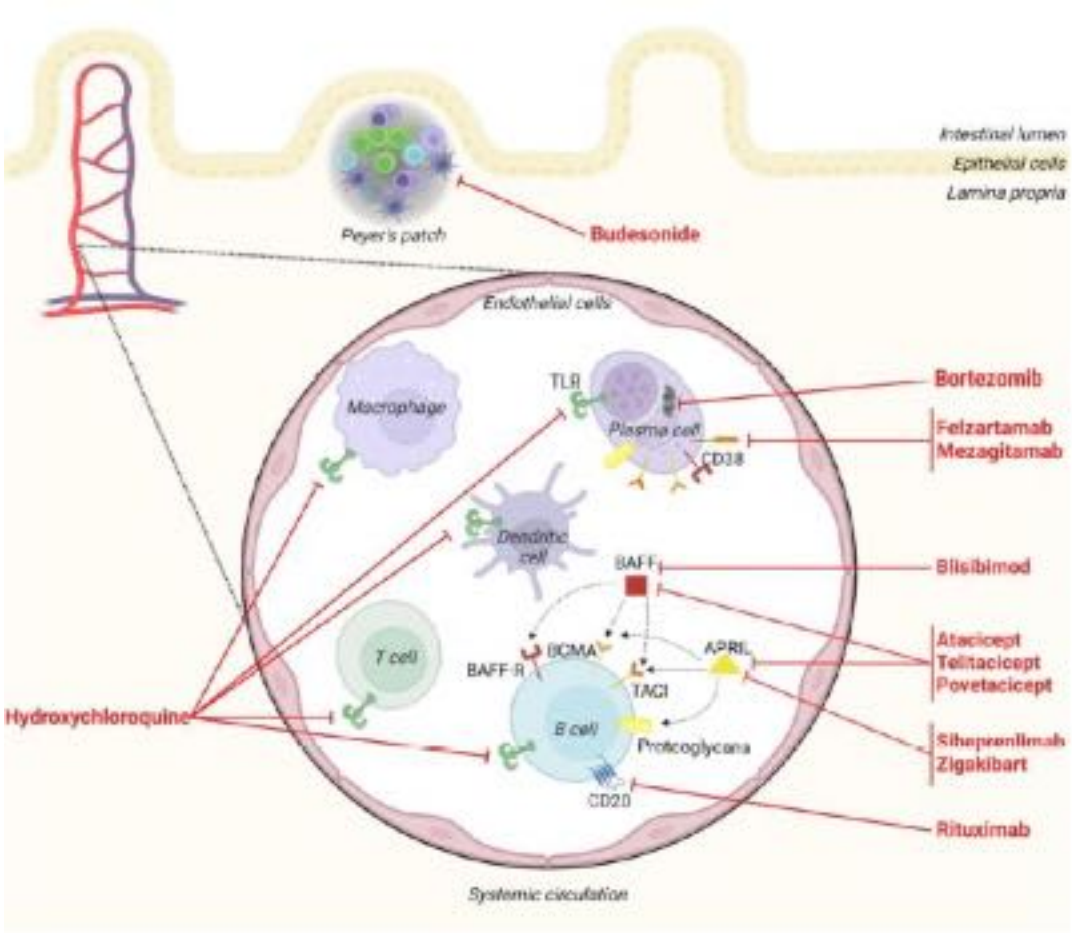
- **The second IgAN GWAS locus related to complement is on chromosome 16p11 that contains ITGAM and ITGAX genes that encode integrins αM and αX, respectively. These integrins have roles in the formation of leukocyte-specific complement receptors 3 and 4 by combining with the integrin ß2 chain**

Therapy of IgA nephropathy

Immunological therapy	CKD therapy
systemic glucocorticoids	RASi
Immunosuppressive drugs, including cyclophosphamide, tacrolimus and MMF azathioprine	sodium–glucose cotransporter-2 inhibitors (SGLT2is
targeted-release formulation budesonide (Nefecon)	endothelin receptor antagonists (ERAs)
Inhibition of BAFF/APRIL (atacicept)	dual endothelin angiotensin receptor antagonists
Compelment inhibitors	mineralocorticoid receptor antagonists (MRAs)

- **Sparsentan is a dual endothelin and angiotensin II receptor antagonist**
- **Received full FDA approval in September 2024**

Therapy of IgA



Cambier A Et-al Pediatric Nephrology 2025

Selection of IgA patients candidate for biological therapy

Types of biological agents	Suitable population
Rituximab or ofatumumab	MCD-like IgAN with hormone dependence or recurrence, progressive IgAN, crescent-type IgAN, MsPGN-IgAN with podocytopathy, recurrent IgAN after kidney transplantation
Belimumab	Progressive IgAN
Telitacicept or atacicept	Progressive IgAN, urinary protein >0.75 g/day on the basis of a sufficient dose of ACEIs or ARBs, and eGFR >30 mL/min/1.73 m^2
BION-1301	Progressive IgAN, urinary protein >0.5 g/day on the basis of a sufficient dose of ACEIs or ARBs, and eGFR >45 mL/min/1.73 m^2
Narsoplimab	Progressive IgAN, urinary protein >1.0 g/day on the basis of a sufficient dose of ACEIs or ARBs, and eGFR >30 mL/min/1.73 m^2
Eculizumab	IgAN with aHUS, crescent-type IgAN

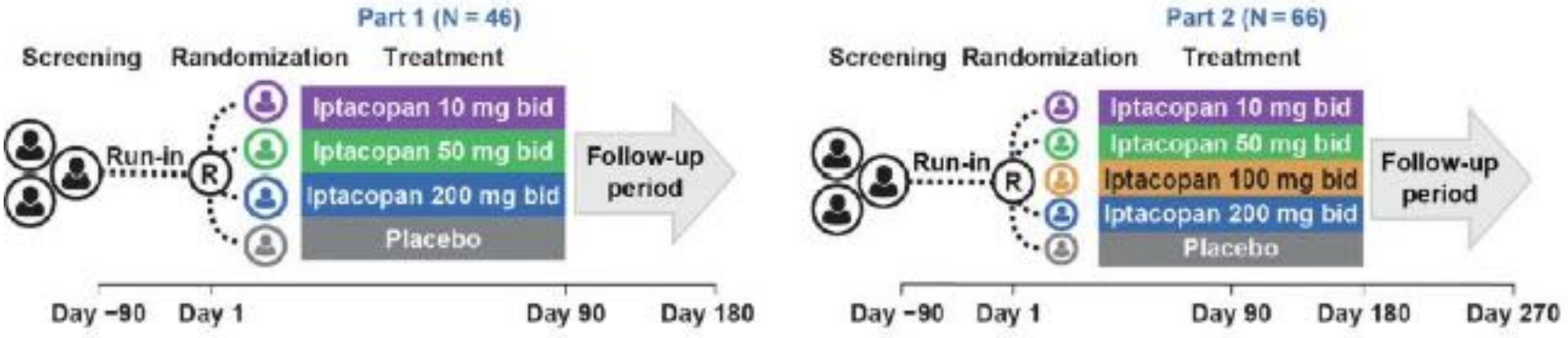
Anti-complement therapy

- **C5 inhibitors: eculizumab**
- **Factor B inhibitors (Iptacopan)**
- **MASP-2 inhibitor (narsoplimab)**
- **Antifactor D (Vemircopan and pelecopan)**
- **Receptor antagonist C5a (avacopan)**

Factor B inhibitor

- Fabhalta (iptacopan) received FDA accelerated approval on August 8, 2024, for reducing proteinuria in adults with primary IgA nephropathy (IgAN) at risk of rapid disease progression

Iptacopan: Study design



Results of a randomized double-blind placebo-controlled Phase 2 study propose iptacopan as an alternative complement pathway inhibitor for IgA nephropathy

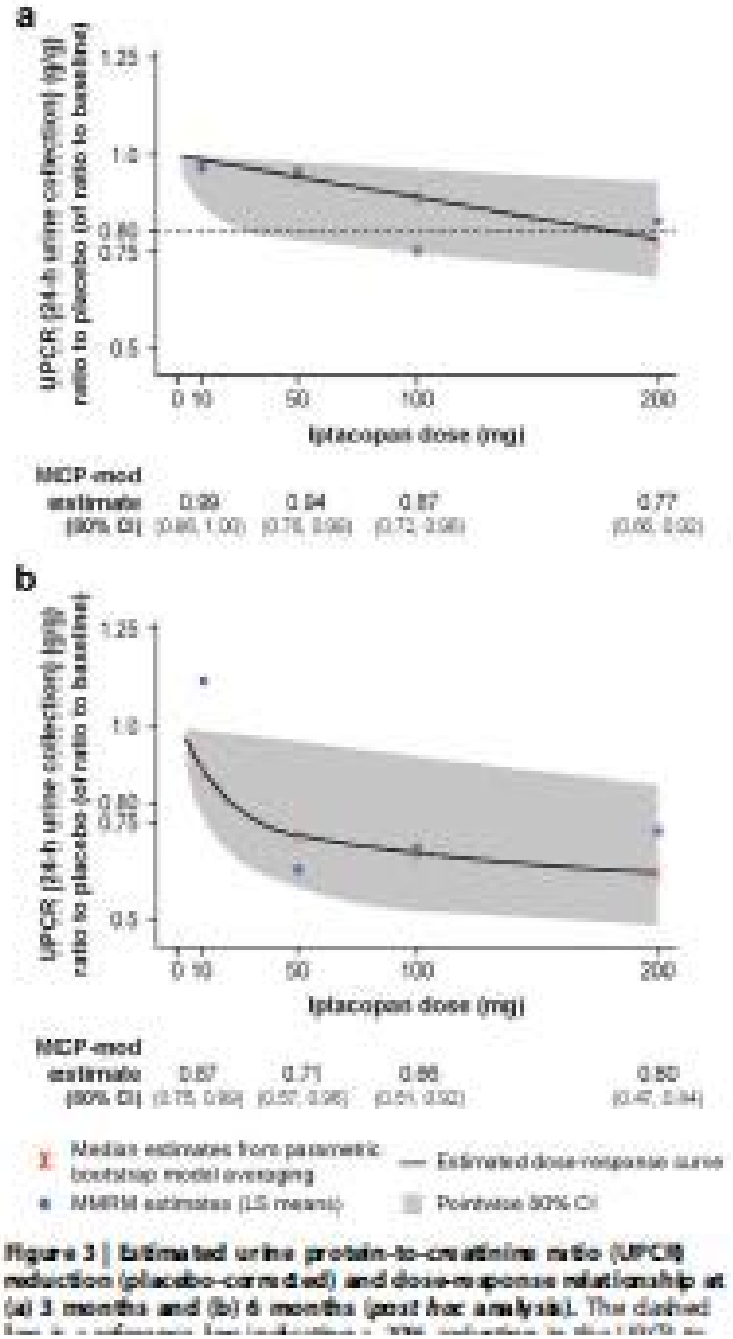


Figure 3 | Estimated urine protein-to-creatinine ratio (UPCR) reduction (placebo-corrected) and dose-response relationship at (a) 3 months and (b) 6 months (*post hoc* analysis). The dashed

Kidney International (2024) 105, 189–199

- **Narsoplimab (Yartemlea) is a human monoclonal antibody approved by the FDA in December 2025 to treat hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA) in adults and children 2 years and older. As a MASP-2 inhibitor, it targets the lectin pathway of the complement system to treat this life-threatening, often fatal, post-transplant complication**

Anti-complement factor D

- **Vemircopan and pelecopan are investigational, potent, oral, small-molecule inhibitors of complement factor D (FD) that block the alternative complement pathway to treat hemolytic diseases. While both aimed to treat paroxysmal nocturnal hemoglobinuria (PNH) and IgA nephropathy, Astrazeneca terminated development of vemircopan due to lack of efficacy, while pelecopan (BCX9930) is being studied as a selective inhibitor**

C5a Receptor antagonist

- **Avacopan (brand name TAVNEOS) was approved by the FDA on October 7, 2021, as an adjunctive treatment for adults with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis. It is the first orally administered C5a receptor inhibitor for this condition**

Take home message

- **IgA nephropathy is not uncommon**
- **The disease spectrum in children is different than adults**
- **Alternate and lectin pathways play an important role in disease progression.**
- **The progressive forms are still in need for specific treatments, that hopefully will be available in the near future.**

Thank you