Updates of IgA Nephropathy

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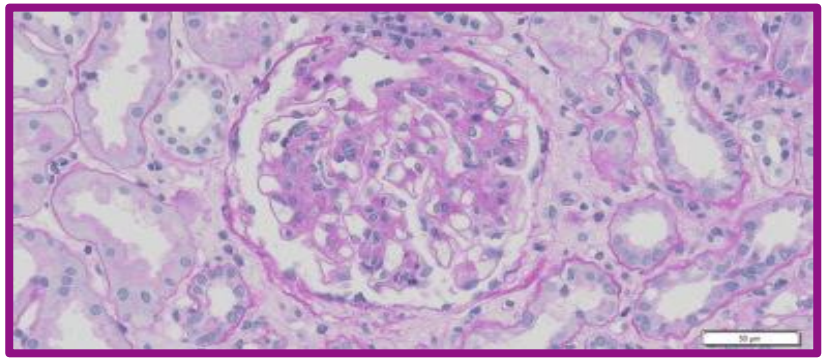
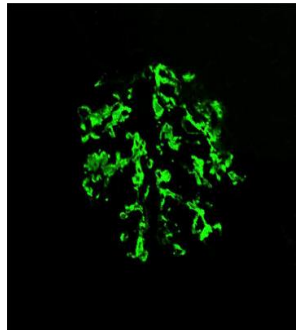
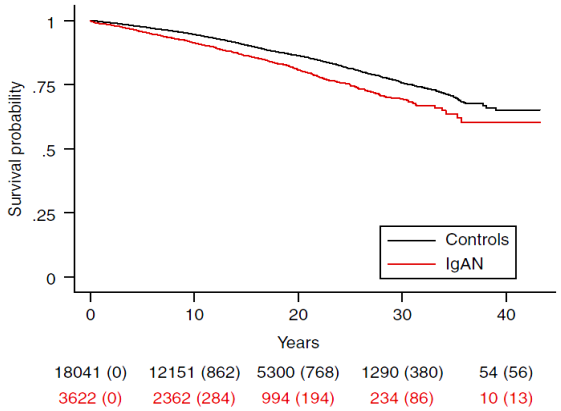


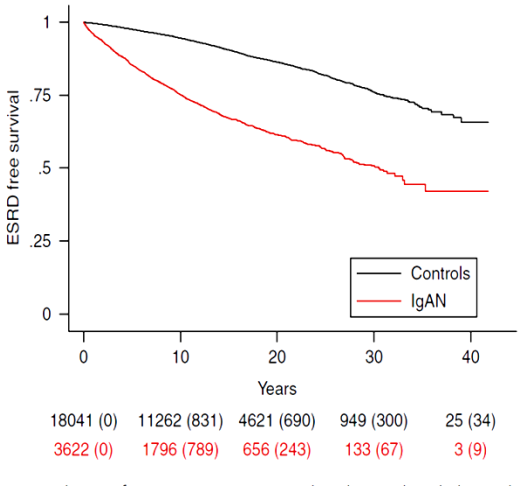


- les dépôts intercapillaires d'IgA-IgG (intercapillary deposits of IgA-IgG) first described by Berger and Hinglais in 1968.
- It was recognized as a most frequent GN in many parts of the world (20-40% Asia, 15-20% in Northern Europe).
- 40% of patients progress to end-stage renal disease over the course of 30-40 years.
- Recently we have new insights in the pathogenesis of IgAN.

Mortality in IgA Nephropathy: A Nationwide Population-Based Cohort Study

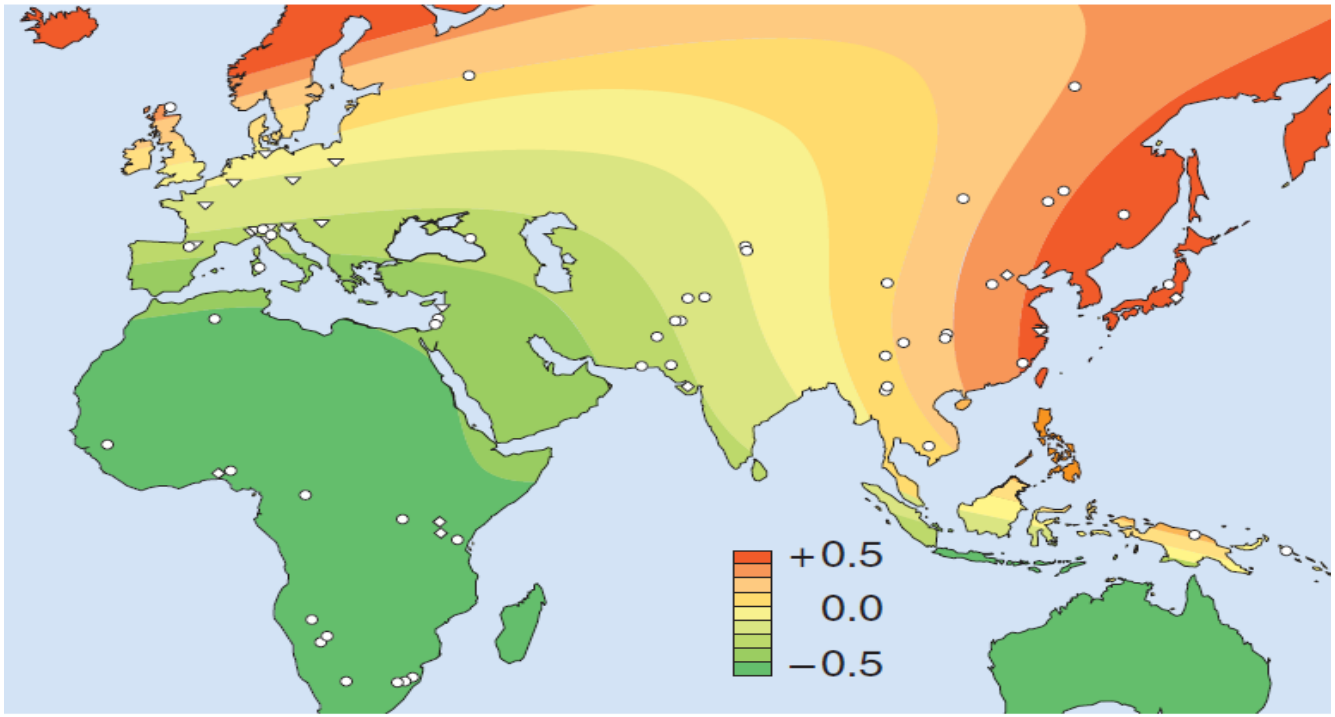
- A population-based cohort study in Sweden, involving patients with biopsy verified IgAN diagnosed in 1974–2011; main outcome measures were death and ESRD.
- 1.53-fold increased risk and an absolute excess mortality of 3.23 per 1000 person-years (equaling one extra death per 310 person-years) and a 6-year reduction in median life expectancy.





Simmon Jarrick et al, CJASN 2019

GWAS Loci Associated With IgAN or Serum Gd-IgA1 Levels

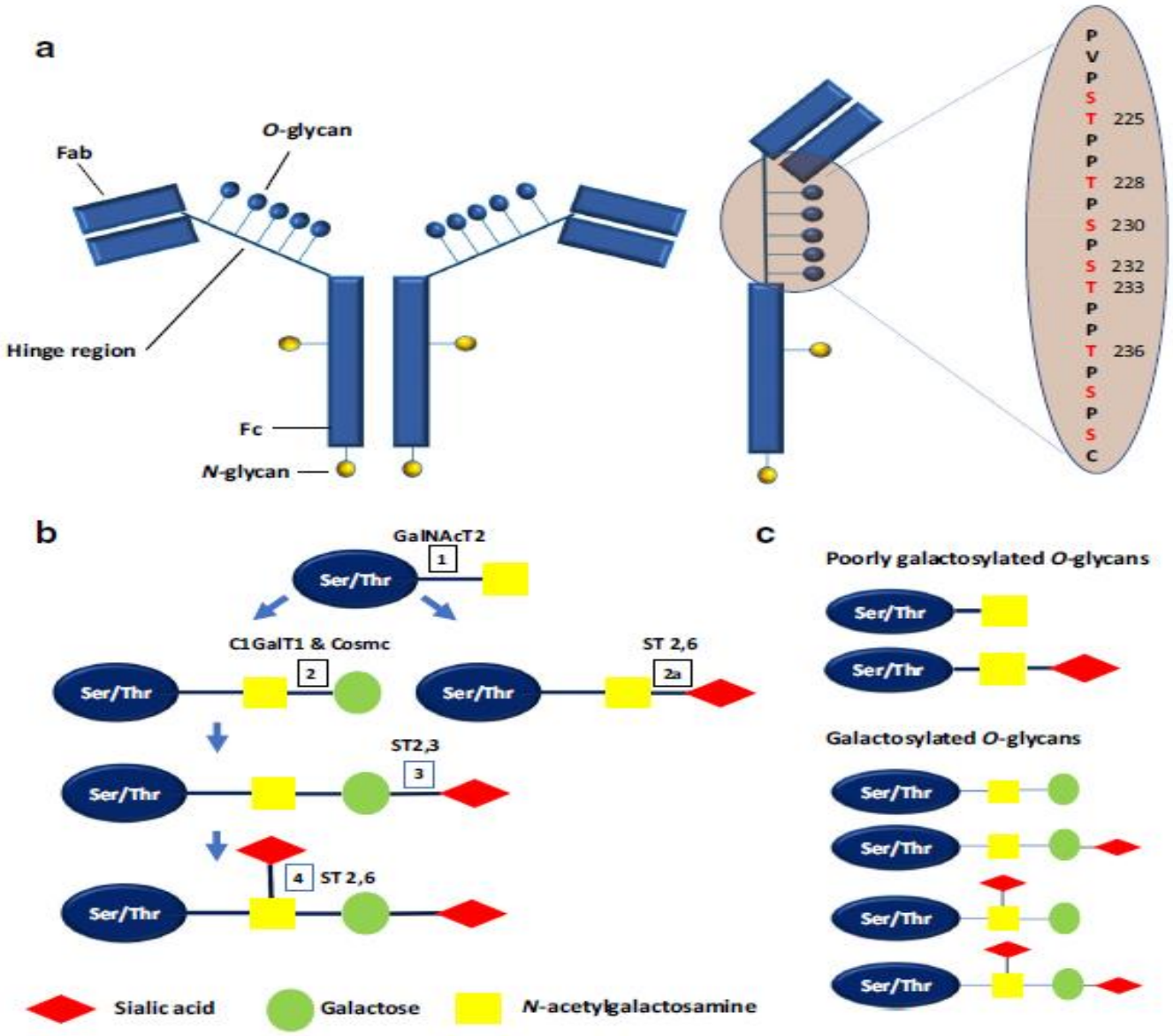


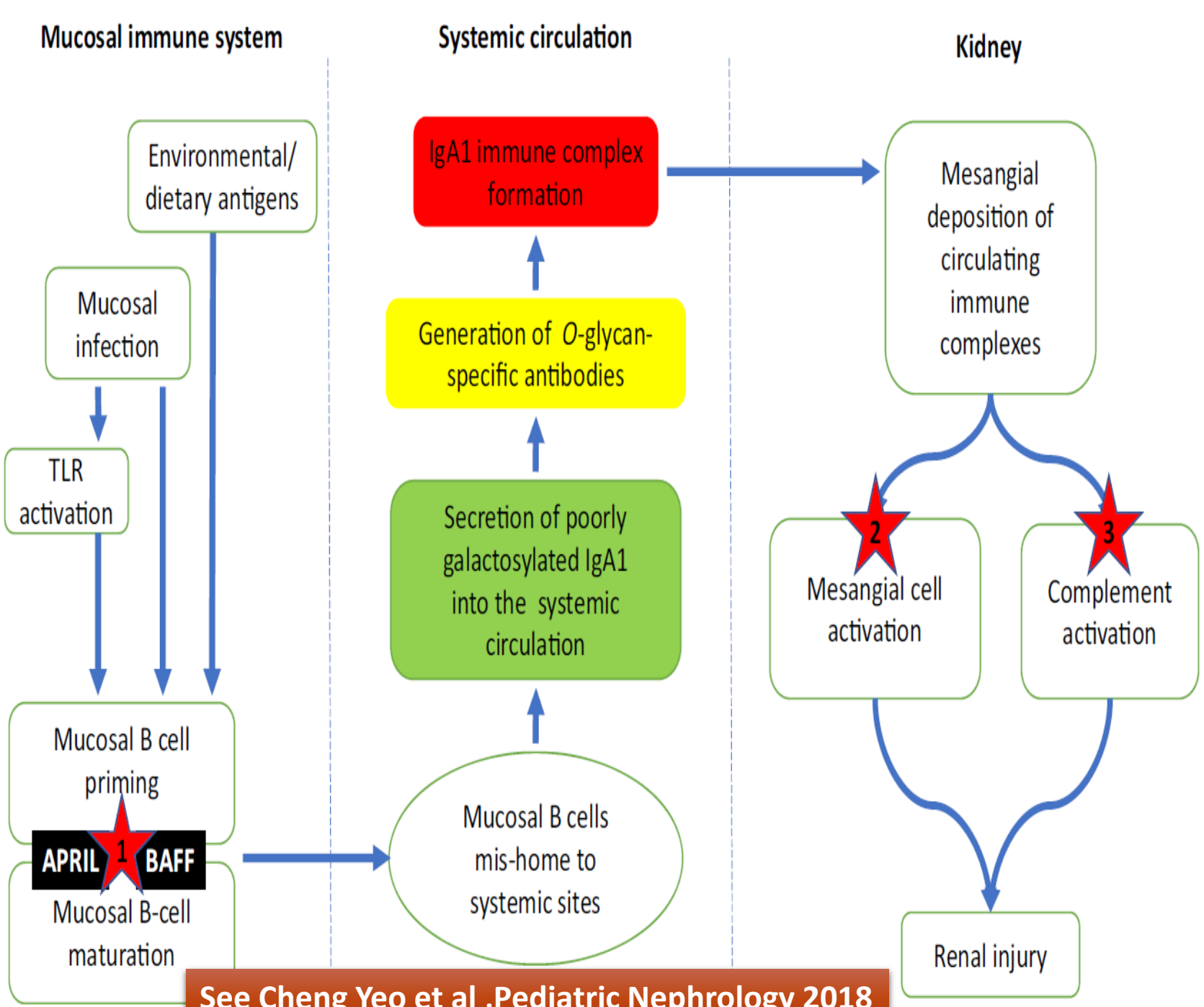
Locus	Notable Genes at a Locus
1p13	*VAV3*
1q32	*CFHR1*, *CFHR3*
3q27.3	*ST6GAL1*
6p21	Multiple *HLA* genes
8p23	*DEFA1*, *DEFA3*
8q22.3	*ODF1-KLF10*
9q34	*CARD9*
11p11.2	*ACCS*
16p11	*ITGAM*, *ITGAX*
17p13	*TNFSF13*
22q12	*LIF*, *OSM*
7p21.3	*C1GALT1*
Xq24	*C1GALT1C1*

These loci encode multiple proteins that play a role in innate immunity, including the pathways of nuclear factor kB signaling, complement activation, and, in particular, intestinal mucosal barrier maintenance and regulation of mucosal IgA production.

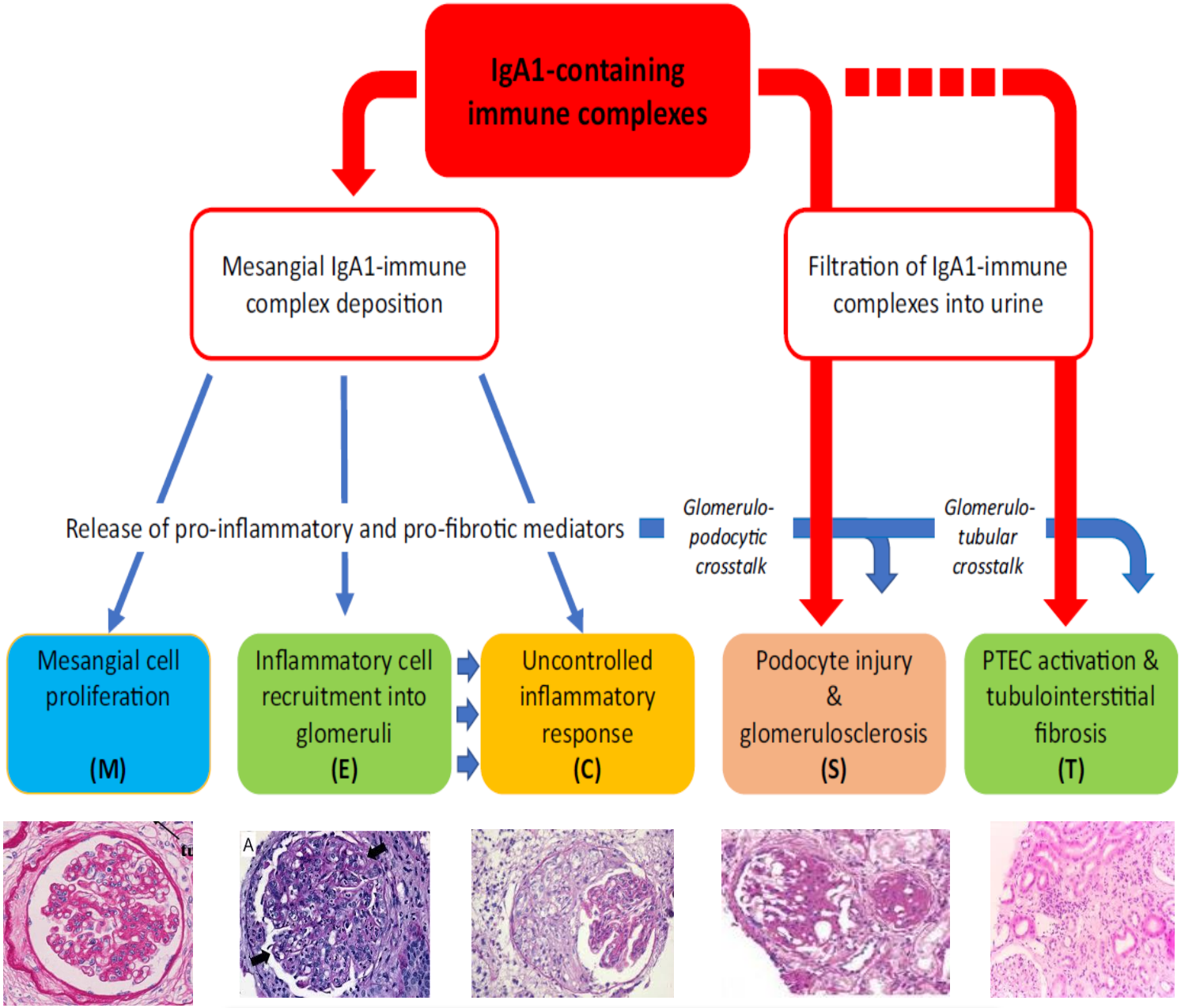
Y. Dana Neugut et al , Seminars in nephrology, 2018

First Hit
Poorly Glycosylated IgA1





See Cheng Yeo et al ,Pediatric Nephrology 2018



See Cheng Yeo et al ,Pediatric Nephrology 2018

Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments

- The VALIGA study examined 1147 patients from 13 European countries that encompassed the whole spectrum of IgAN.
- M, S, and T lesions independently predicted the loss of estimated glomerular filtration rate (eGFR) and a lower renal survival.
- The addition of M, S, and T lesions to clinical variables significantly enhanced the ability to predict progression only in those who did not receive immunosuppression.
- The independent predictive value of pathology MEST score is reduced by glucocorticoid/immunosuppressive therapy.

Coppo et al , kidney International 2014

Oxford Classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group

- MEST criteria continue to be applied to cases of IgAN .
- The predictive value of E in patients not treated with immunosuppression.
- C score be added to the MEST score in all cases of IgAN to indicate the frequency of cellular and/or fibrocellular crescents. C0 (no crescents) or C1 (crescent in a least 1 glomerulus) or 2 (crescents in at least 25% of glomeruli)
- No change in the definition of S1, but adding text to indicate whether there are podocytopathic features.
- MEST criteria are not yet applied to cases of Henoch-Schönlein purpura nephritis (IgA vasculitis).

Trimarchi Hernan et al , Kidney International 2016

Evaluating a New International Risk-Prediction Tool in IgA Nephropathy

- How can we better predict, at the time of kidney biopsy, the risk of a 50% decline in kidney function or end-stage renal disease ?
- Large international multiethnic cohorts including 3927 patients were enrolled to validate 2 prediction models, one included patient race/ethnicity, and one that did not. Both models outperformed clinical measures for prediction of kidney disease progression and patient risk stratification.

Barbour et al , JAMA Intern Med, 2019

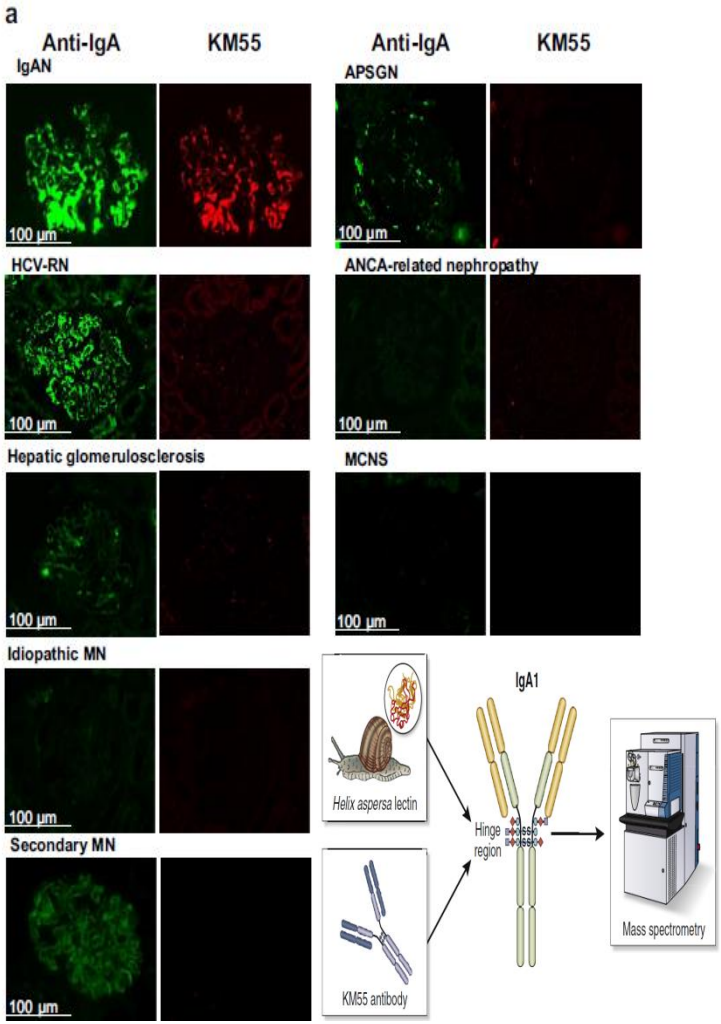
- Cohort of 2781 patients: included eGFR, blood pressure, and proteinuria at biopsy the MEST histologic score, age, medication use, and either racial/ethnic characteristics (white, Japanese, or Chinese)
- 2 prediction models were shown to be accurate and validated methods to help clinicians improve management and treatment of IgA nephropathy in multi-ethnic cohorts.

https://qxmd.com/calculate/calculator_499/international-igan-prediction-tool

Biomarkers in IgA nephropathy

Serum IgA Diagnosis & Progression	Maeda et al , J Clin Lab Anal, 2003
Serum Gd-IgA1-specific IgG (Diagnosis)	Yasutake J et al , Nephrol Dial Transplant , 2015
Serum IgA/C3	Gong et al BMC Nephrology 2019
Urinary membrane attack complex and Factor H (interstitial fibrosis, glomerular sclerosis)	Onda et al , BMC Nephrology 2011
TNF Receptors 1 and 2 (serum and urine) (markers of Kidney injury)	Sonda et al Plos one 2015
Urinary podocalyxin and podocytes (Predict Histological Changes)	Asao et al , Clin J Am Soc Nephrol , 2012
Kit –IgA (Urinary biomarkers of cell free DNA, methylated cell-free DNA , DMAIMO, AMIMO, Clusterin, CXCL10) Diagnosis , Progression	Joshua Y.C. Yang et al .Int. J. Mol. Sci. 2019
Phosphatidylethanolamine binding protein-4 (PEBP 4, Diagnosis)	Taylor et al, Journal of Immunology 2019

IgA nephropathy and IgA vasculitis with nephritis have a shared feature involving galactose-deficient IgA1-oriented pathogenesis



Immunostaining of gd-IgA1 with KM55 performed in renal biopsy of 48 IgAN and 49 patients with other renal diseases.

Gd-IgA1 was specifically detected in IgA nephropathy patients.

This study strongly suggests Gd deficient IgA1 in IgAN pathogenesis.

Suzuki et al , Kidney International, 2018

Significance of serum galactose deficient IgA1 as a potential biomarker for IgA nephropathy: A case control study

- They measured serum Gd-IgA1 levels (ELISA) in 136 primary IgAN and 110 controls.
- Considering a cut-off value of serum **Gd-IGA1:7982.1ng/ml**, the sensitivity for diagnosing IgAN compared to healthy controls was **74.3%** and specificity was **72.0%** with a positive predictive value of **87.8%** and negative predictive value of **50.7%**.
- The serum Gd-IgA1 level did not co-relate with baseline estimated glomerular filtration rate, urine protein creatinine ratio and the M, E,S, T and C scores on renal biopsy.

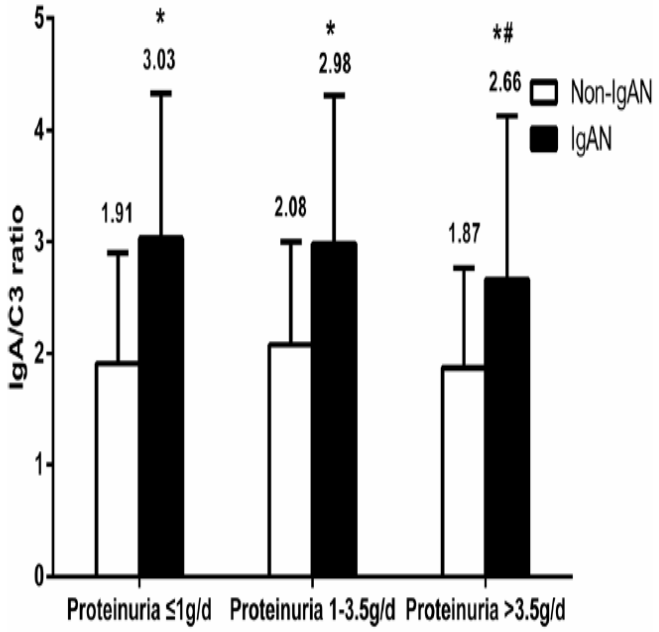
Bagchi et al, PLOS ONE , March 27, 2019

Complement System In IgA Nephropathy

- There is strong evidence that glomerular injury in IgA nephropathy is associated with activation of complement system .
- The presence of C3 and absence of C1q is consistent with the activation of Lectin/or alternative pathway
- There are components properdin , factor H , MBL –associated serine protease 1 , 2 and C4d which supports non classical pathway activity.
- Lectin pathway components C4d and MBL have been associated with increased disease activity and development of ESRD.

High serum IgA/C3 ratio better predicts a diagnosis of IgA nephropathy among primary glomerular nephropathy patients with proteinuria ≤ 1 g/d: an observational cross-sectional study

- A Cohort of 1095 biopsy-diagnosed primary glomerular nephropathy patients, including 757 IgAN patients and 338 non-IgAN patients.
- the IgA/C3 ratio in the IgAN group was significantly higher than that of the non-IgAN group.
- This cut-off assumes that patients with an **IgA/C3 ratio > 3.5304** are predicted to be IgAN, and patients with an **IgA/C3 ratio < 1.0546** are non-IgAN.



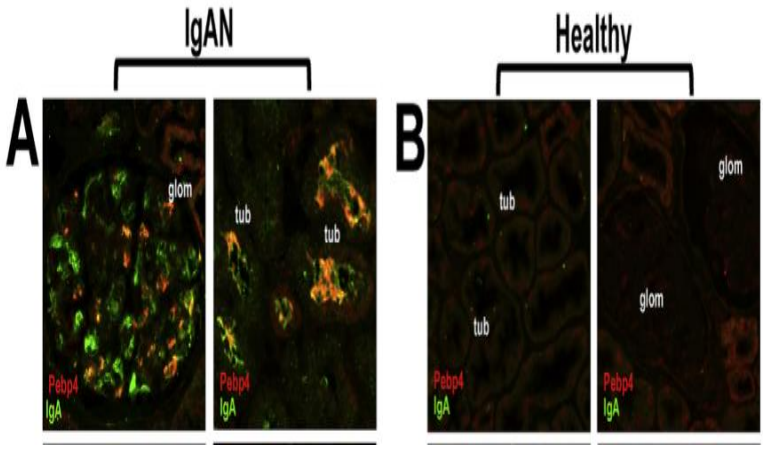
Gong et al BMC Nephrology 2019

Phosphatidylethanolamine binding protein-4 (PEBP4) is increased in IgA nephropathy and is associated with IgA-positive B-cells in affected kidneys

Scott Taylor, Kyriaki Pieri, Paolo Nanni, Jure Tica, Jonathan Barratt, Athanasios Didangelos*

University of Leicester, Mayer IgA Nephropathy Laboratory, University Road, LE1 7RH, Leicester, United Kingdom

- In a survey of **urine proteomics**, they discovered an increase in phosphatidylethanolamine binding protein-4 (PEBP4) in IgAN urine.
- Increased levels of urine and serum PEBP4 were subsequently validated in different cohorts of IgAN patients and PEBP4 was linked **to declining kidney function in IgAN**.
- The function of PEBP4 in IgAN or renal disease is unknown.



Taylor et al, Journal of Immunology 2019

Noninvasive Urinary Monitoring of Progression in IgA Nephropathy

- Multiple urinary biomarkers consisting of cell-free DNA, methylated cell-free DNA, DMAIMO, MAMIMO, total protein, clusterin, creatinine, and CXCL10 were measured by the microwell-based KIT Assay.
- KIT-IgA score was successful in both screening for non-invasive diagnosis of IgAN, and for **predicting risk of progressive renal disease**.
- It should be validated in larger studies.

Joshua Y. C. Yang et al , Int. J. Mol. Sci. 2019

KDIGO Clinical Practice Guideline for Glomerulonephritis August 2018

Treatment	ESRD	Complete Remission
Steroid VS. Placebo	Probably decease	Increase
Tonsillectomy	Lack of data	Decrease proteiniuria and hematuria and relapse (Asian ethnicity)
Cyclophosphamide then AZA +Pred VS. Supportive care	Little or no difference	Increase
AZA+Pred VS. Pred	Lack of enough data	Increase
MMF+ Pred VS. Pred	Uncertain	Little or no difference
CSA+Pred VS. Pred	little or no difference	Uncertain
Leflunomide	Lack of enough data	Little or no difference
Fish Oil	Uncertain	Uncertain

Pilot Study of ACTH in the Treatment of Immunoglobulin A (IgA) Nephropathy at High Risk of Progression

- Approved in treatment of Nephrotic syndrome
- ACTH has renoprotective effects through steroid dependent and independent pathway (through melanocortin 1 receptor **(MC1R)**).
- MC1R effects on glomerular, endothelial, podocytes, mesangial cells and tubular cells.
- Acthar (ACTH) gel injection at a dose of 80 units subcutaneously twice weekly for 6 months is **effective in inducing improvement in proteinuria and renal function**.
- Adverse effects: Infection and metabolic syndrome

ClinicalTrials.gov Identifier: NCT02282930

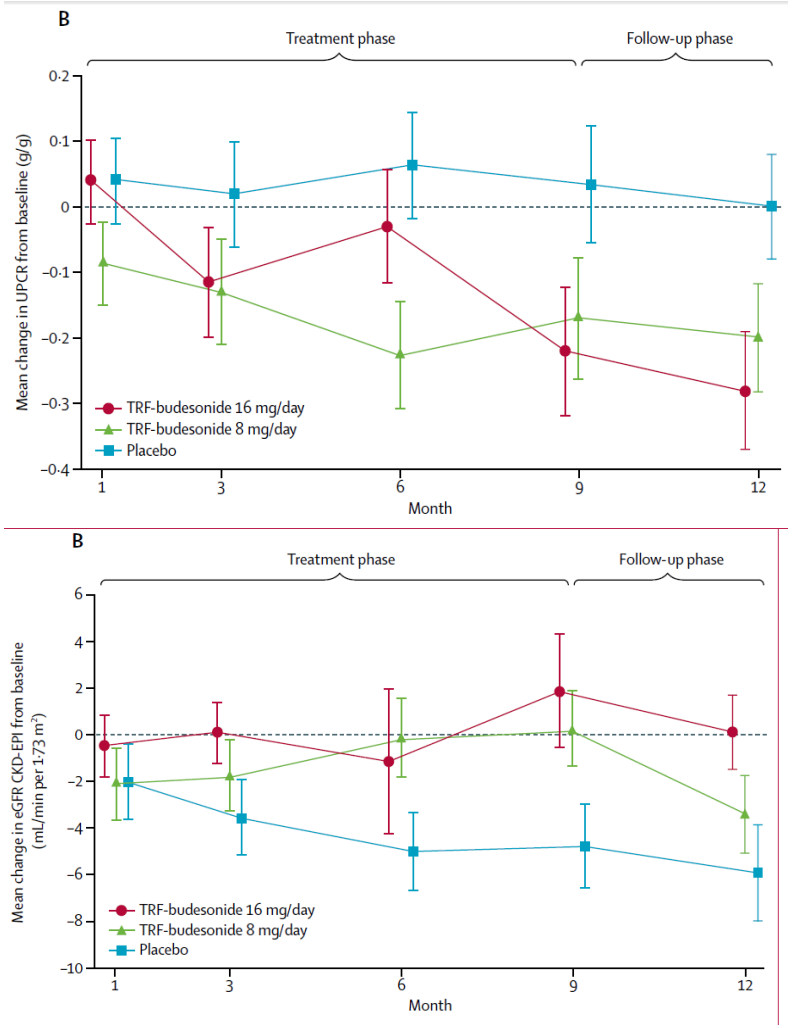
Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial

A randomized , double blind trial around Europe

149 patients were treated in three groups of placebo, 8mg/d budesonide, 16 mg/d budesonide. All received RAS Blockade.

Proteinuria decreased **27.3%** in 16mg/day and **21.5%** in Budesonide group and **2.7%** increase in placebo group .

9 months treatment with budesonide resulted in **<u>reduced proteinuria and stabilized eGFR</u>** in budesonide group.



Bengt C FellstrÖm et al, Lancet 2017

Japanese Clinical Practice Guidelines for IgA Nephropathy (2016): Difference from KDIGO Guidelines

Kazuo Takahashi, Ryohei Yamamoto, and Yukio Yuzawa

Tonsillectomy combined with steroid pulse therapy :[**grade C1**]

Tonsillectomy combined with steroid pulse therapy **may improve** urinary findings in patients with IgAN and inhibit renal dysfunction progression. Considered a treatment option.

Tonsillectomy (alone) :[**grade C1**] Tonsillectomy **may improve** urinary findings in patients with IgAN and inhibit the renal dysfunction progression. Considered as a treatment option.

C1. **Might be implemented in routine clinical practice despite insufficient evidence**

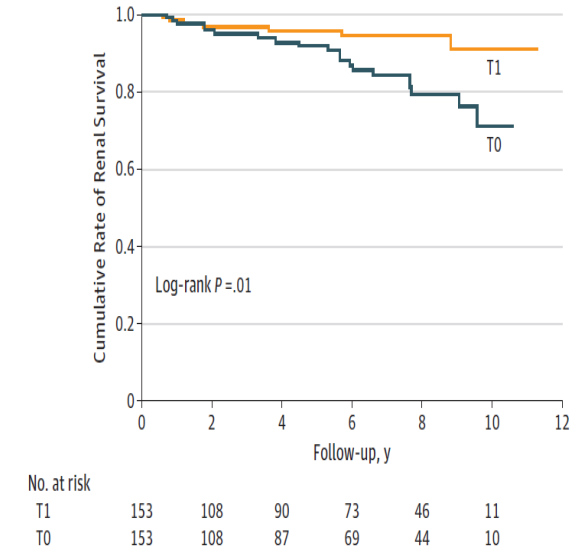
Original Investigation | Nephrology

Association Between Tonsillectomy and Outcomes in Patients With Immunoglobulin A Nephropathy

Keita Hirano, MD; Keiichi Matsuzaki, MD, PhD; Takashi Yasuda, MD, PhD; Masako Nishikawa, PhD; Yoshinari Yasuda, MD, PhD; Kentaro Koike, MD, PhD; Shoichi Maruyama, MD, PhD; Takashi Yokoo, MD, PhD; Seiichi Matsuo, MD, PhD; Tetsuya Kawamura, MD, PhD; Yusuke Suzuki, MD, PhD

- In a Cohort of 1065 IgAN patients in the median follow-up of 5.8 years
- Tonsillectomy vs Non tonsillectomy was associated with primary outcome reduction independent of RAS inhibition. (hazard ratio, 0.34; 95%CI, 0.13-0.77; P = .009)

Figure 1. Comparison of the Cumulative Rates of Renal Survival Between the T1 and T0 Groups After Propensity Score Matching



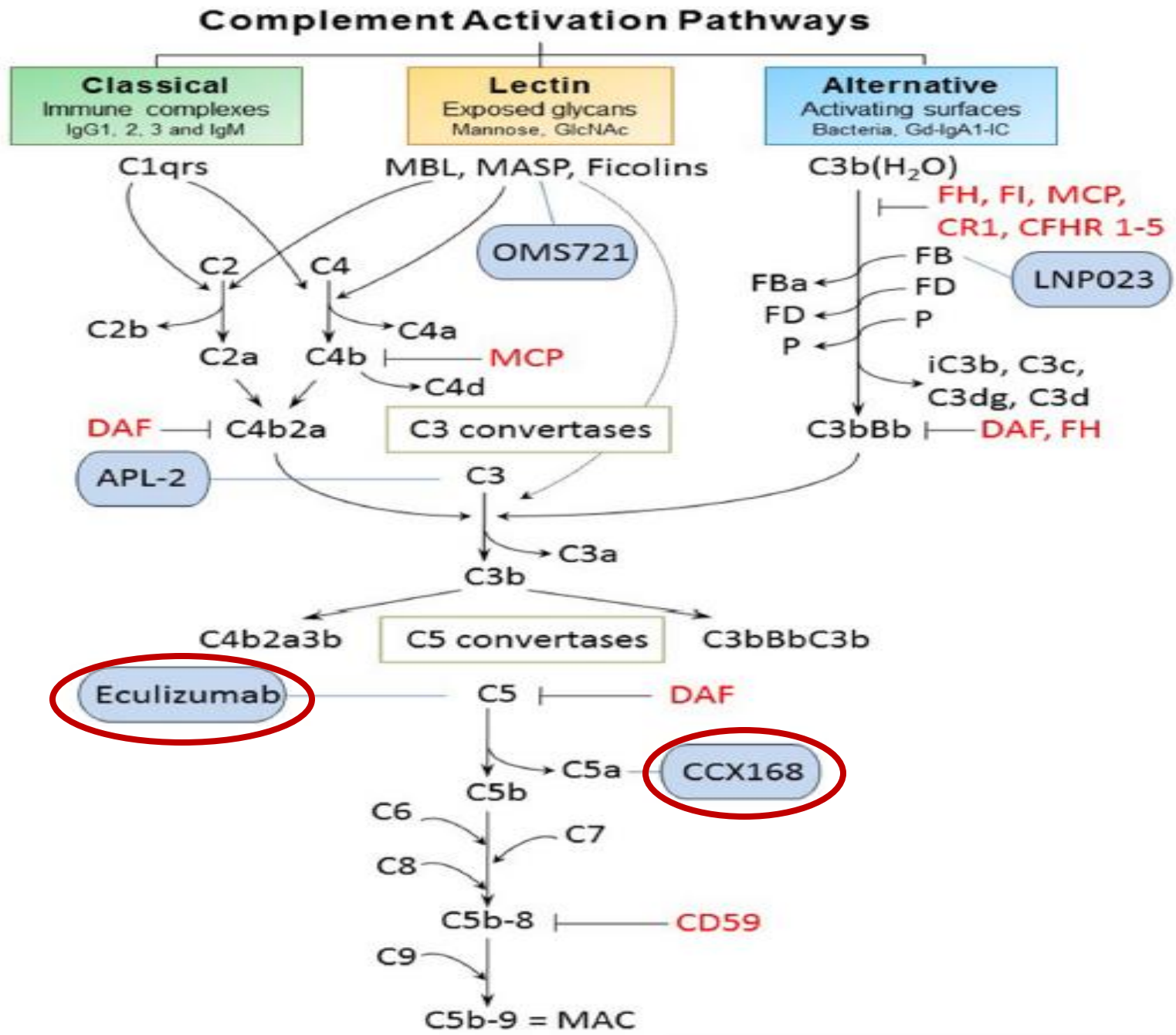
JAMA network open ,2019

A Randomized, Controlled Trial of Rituximab in IgA Nephropathy with Proteinuria and Renal Dysfunction

Richard A. Lafayette,* Pietro A. Canetta,† Brad H. Rovin,‡ Gerald B. Appel,† Jan Novak,§ Karl A. Nath,‖ Sanjeev Sethi,¶ James A. Tumlin,** Kshama Mehta,* Marie Hogan,‖ Stephen Erickson,‖ Bruce A. Julian,§†† Nelson Leung,‖ Felicity T. Enders,‡‡ Rhubell Brown,§ Barbora Knoppova,§§§ Stacy Hall,§ and Fernando C. Fervenza‖

- Randomized 34 adult patients with biopsy–proven IgA nephropathy and proteinuria >1 g/d, on ACE or ARB and eGFR > 90 ml/min to receive standard therapyor rituximab with standard therapy
- Rituximab **did not changed** proteinuria and eGFR in comparison to control group.
- Although Rituximab effectively depleted B cells, it **failed to reduce** serum levels of galactose-deficient IgA1 and antigalactose–deficient IgA1 antibodies.

J AmSoc Nephrol 28: 1306–1313, 2017



Rizk et al, Frontiers in Immunology 2019

Pediatr Nephrol
DOI 10.1007/s00467-014-2863-y

BRIEF REPORT

Eculizumab treatment for rescue of renal function in IgA nephropathy

Therese Rosenblad · Johan Rebetz · Martin Johansson · Zivile Békássy · Lisa Sartz · Diana Karpman

ckj
OXFORD
Leading European Nephrology

Clinical Kidney Journal, 2015, vol. 8, no. 5, 489–491
doi: 10.1093/ckj/sfv076
Advance Access Publication Date: 27 August 2015
Exceptional Case

EXCEPTIONAL CASE

Use of eculizumab in crescentic IgA nephropathy: proof of principle and conundrum?

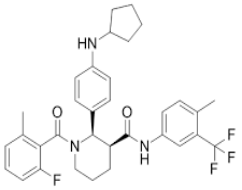
Troels Ring[1], Birgitte Bang Pedersen[1], Giedrius Salkus[2], and Timothy H.J. Goodship[3]

First Treatment of Relapsing Rapidly Progressive IgA Nephropathy With Eculizumab After Living Kidney Donation: A Case Report

A.L. Herzog[a,*], C. Wanner[a], K. Amann[b], and K. Lopau[a]

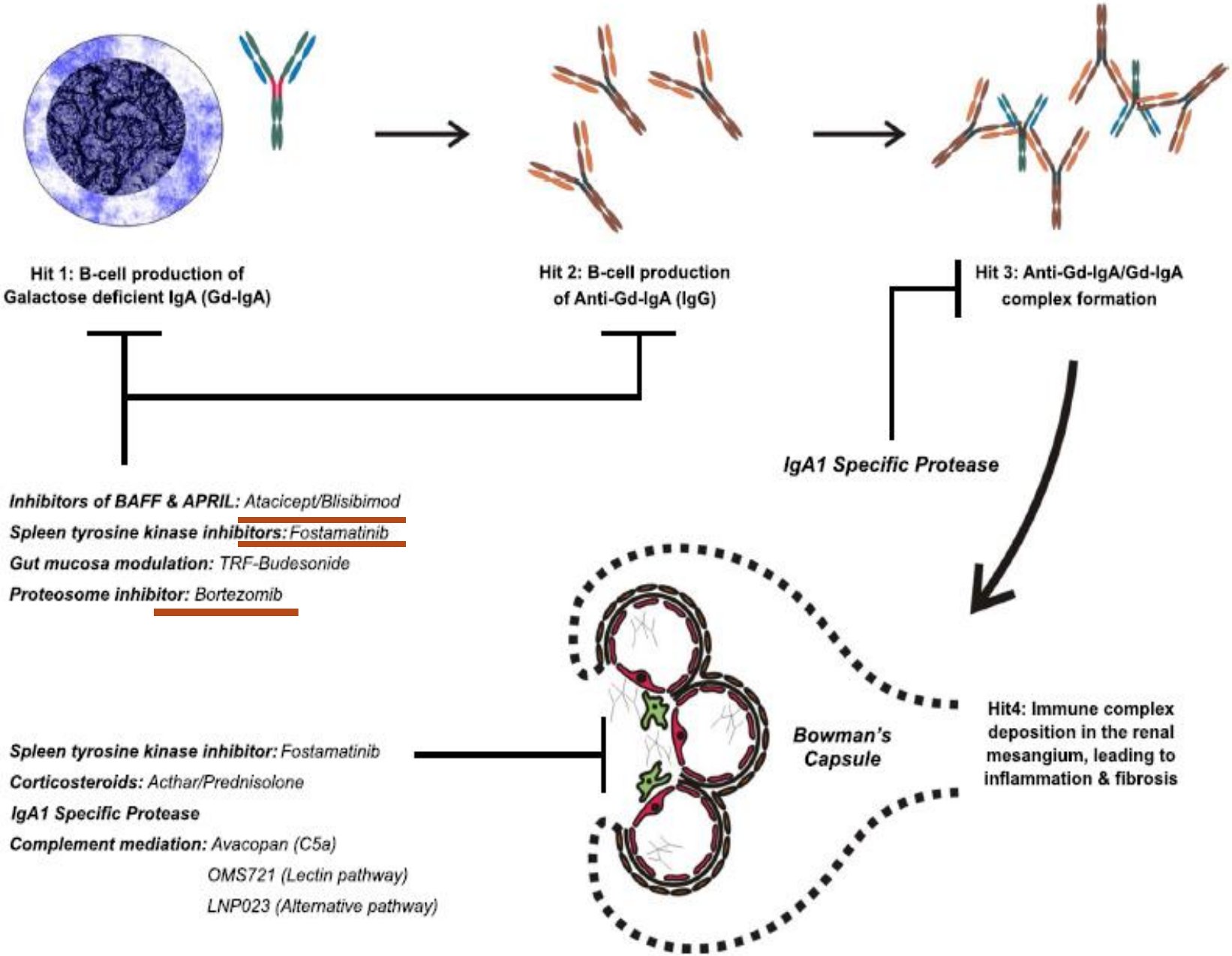
[a]Division of Nephrology, Medizinische Klinik I, Transplantationszentrum, University of Würzburg, Universitätsklinikum, Würzburg, Germany; and [b]Department of Nephropathology, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany

Open-Label Study to Evaluate Safety and Efficacy of CCX168 (Avacopan) in Subjects With Immunoglobulin A Nephropathy on Stable RAAS Blockade



- Complement activation plays important role in the final pathway of IgA nephropathy .
- **C5a correlates histological severity and proteinuria**.
- Targeting C5a offers opportunity to suppress the local inflammation to progressive renal disease.
- An open-label phase II trial on a C5a receptor blocker (**Avacopan**)in **twelve weeks showed decrease proteinuria** in 6 of 7 patients .
- The adverse effects in another study was **hepatic dysfunction and infection**.

ClinicalTrials.gov Identifier: NCT02384317, Daha MR, J nephrology 2016



Selvaskandan et al. Clinical and Experimental Nephrology (2019)

Bortezomib for Reduction of Proteinuria in IgA Nephropathy

- Immunoproteasome axis has been shown in mononuclear cells in IgAN with over expression of the immunoproteasome, increased nuclear translocation of factors related to the NF-kB pathway, and more severe disease manifestations including increased proteinuria.
- 8 IgA nephropathy patient with proteinuria > 1gr/d (T0) from 2011-2016 received 4 doses of Bortezomib.
- Proteasome inhibition by **Bortezomib may reduce significant proteinuria** in select cases of IgA nephropathy.

Hartono C ,Kidney Int Rep (2018) ,Coppo R, KI 2009

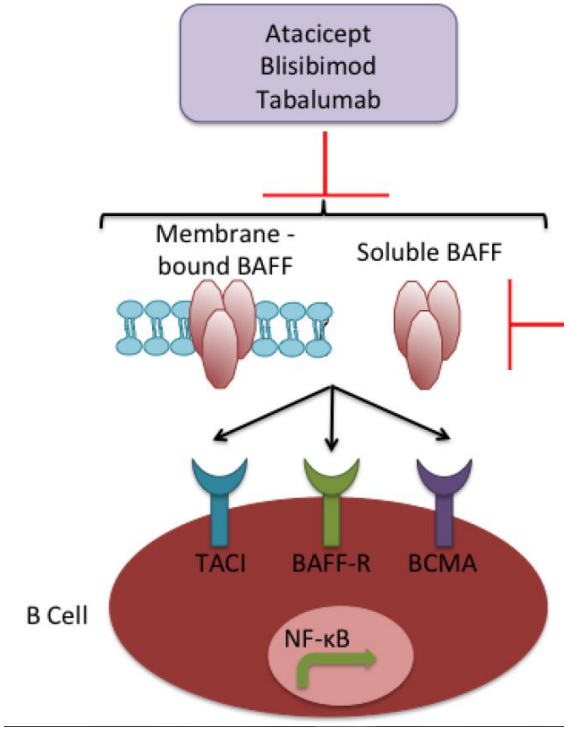
BRIGHT-SC: Blisibimod Response in IgA Nephropathy Following At-Home Treatment by Subcutaneous Administration

BAFF (B cell activating factor) and April (a proliferation inducing ligand) , members of TNF and mediate B- cell function and survival .

They are elevated in the serum of IgA nephropathy patients and correlate with disease activity.

Blisibimod and Atacicept block the action of APRIL and BAFF.

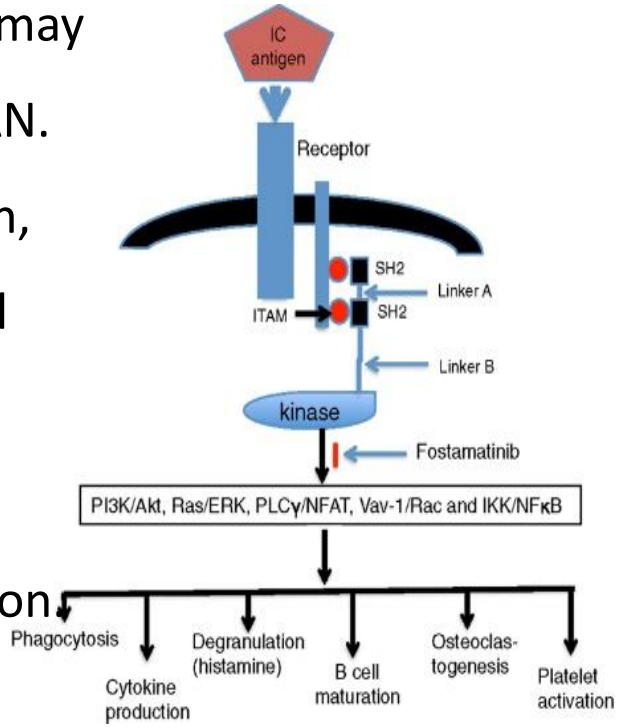
Phase II studies to assess safety and efficacy of these drugs in IgA nephropathy are underway.



Atacicept (NCT02808429) and blisibimod (NCT02062684)

Spleen Tyrosine Kinase (SYK) Inhibition In IgA Nephropathy: A Global, Phase II, Randomised Placebo-Controlled Trial Of Fostamatinib

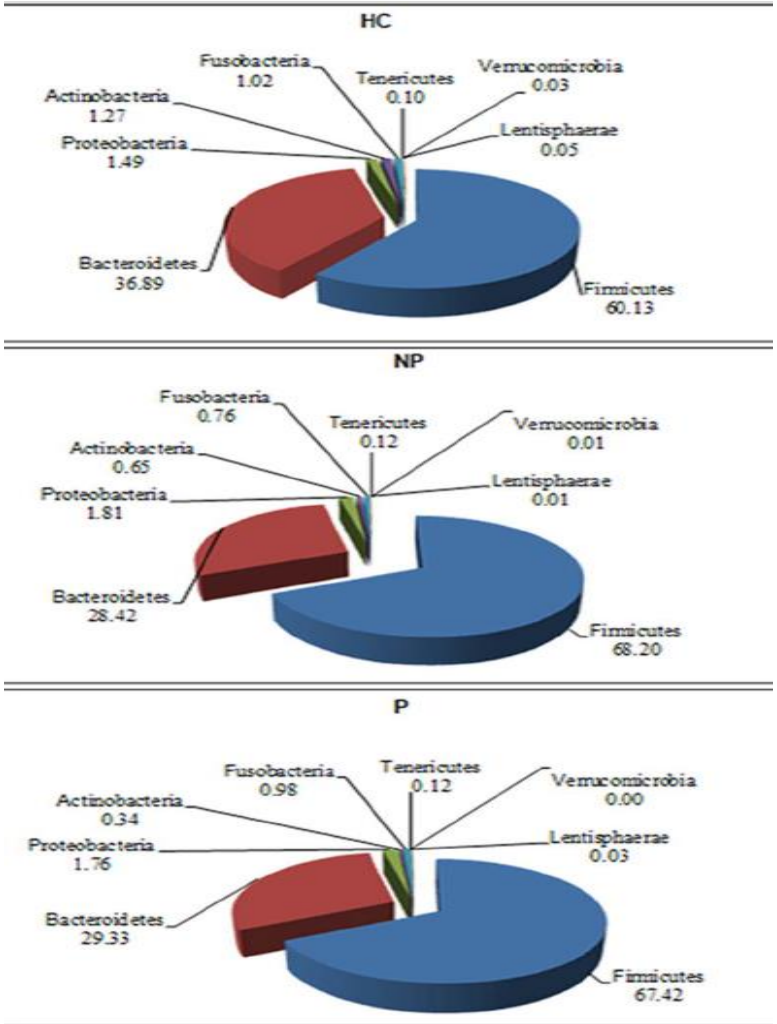
- Spleen tyrosine kinase (SYK) is a non-receptor TK that may modulate a number of key pathogenic pathways in IgAN.
- A signal transducer following B-cell receptor activation, mediating downstream signaling and promoting B-cell maturation and survival.
- Stimulation of mesangial cells in vitro with IgA1 purified from IgAN patients triggers SYK phosphorylation.
- **Fostamatinib** is a selective SYK inhibitor that has been studied in RA.



Tam Wket al, KI 2019

Microbiota and Metabolome Associated with Immunoglobulin A Nephropathy (IgAN)

- Evidence of IgAN flare in conjunction of mucosal infection
- IgAN patients had an altered fecal microbiota.
- Dietary implementation with prebiotics and/or probiotic and mucosal targeted therapy could be a useful therapeutic strategy in IgAN.



P :Progressor, NP: Nonprogressor, HC: Healthy Control, Angelis De Maria et Plos one 2014

IgA Nephropathy in Elderly Patients

- In a retrospective study in 165 elderly patients with IgA nephropathy the outcome was studied.
- Significant increase in diagnosis.
- 34% patients with gross hematuria and AKI were on anticoagulant drug.
- Survival rates were 74%, 48% , 26% at 1, 2 and 5 years.
- Immunosuppressive treatments were not significantly associated with outcome.

Angel M. Sevillano et al CJASN 2019

Conclusion

- The Four-hit pathogenesis of IgA nephropathy has changed to Muli-Hit pathogenesis .
- Risk calculation with the international calculation tool can be used in clinic for personalized treatment.
- New Biomarkers for diagnosis, Risk of progression and response to therapy is forming.
- Better understanding of pathogenesis can lead us to targeted therapy in IgA nephropathy.