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Leicester IgA Nephropathy Research Group

Future Clinical Trials in IgA Nephropathy

Professor Jonathan Barratt

University of Leicester

&

John Walls Renal Unit, Leicester

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Leicester IgA Nephropathy Research Group

Future Clinical Trials in IgA Nephropathy

How long have we got……

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&

John Walls Renal Unit, Leicester

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Future Clinical Trials in IgA Nephropathy

15 minutes!

Professor Jonathan Barratt

University of Leicester

&

John Walls Renal Unit, Leicester

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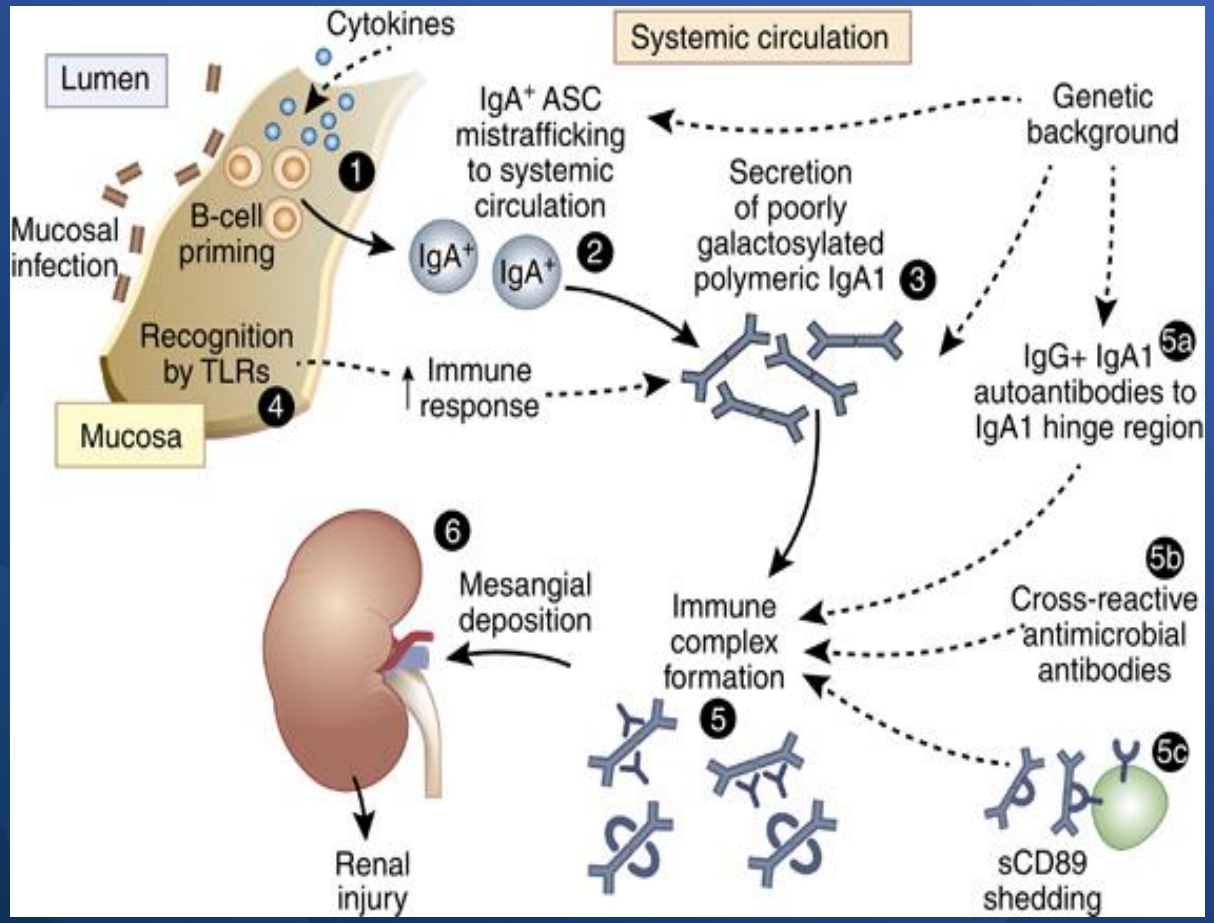
Speaker Declarations

Jonathan Barratt	
Consulting and Speaker Fees	Alnylam, Argenx, Astellas, BioCryst, Calliditas, Chinook, Dimerix, Galapagos, Novartis, Omeros, Travere Therapeutics, Vera Therapeutics, Visterra
Grant Support	Argenx, Calliditas, Chinook, Galapagos, GlaxoSmithKline, Novartis, Omeros, Travere Therapeutics, Visterra
Clinical trials	ADU-CL-19 & ALIGN (Chinook), APPLAUSE (Novartis), ARTEMIS-IGAN (Omeros), ENVISION (Visterra), NeflgARD (Calliditas), ORIGIN (Vera Therapeutics)
Research projects	Argenx, Calliditas, Chinook, Galapagos, GlaxoSmithKline, Novartis, Omeros, Travere Therapeutics, Visterra


Cytokines
Systemic circulation
Lumen
IgA+ ASC mistrafficking to systemic circulation
Genetic background
Mucosal infection
B-cell priming
1
IgA+
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Secretion of poorly galactosylated polymeric IgA1
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Recognition by TLRs
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Immune response
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Mucosa
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Mesangial deposition
5b
Cross-reactive antimicrobial antibodies
Immune complex formation
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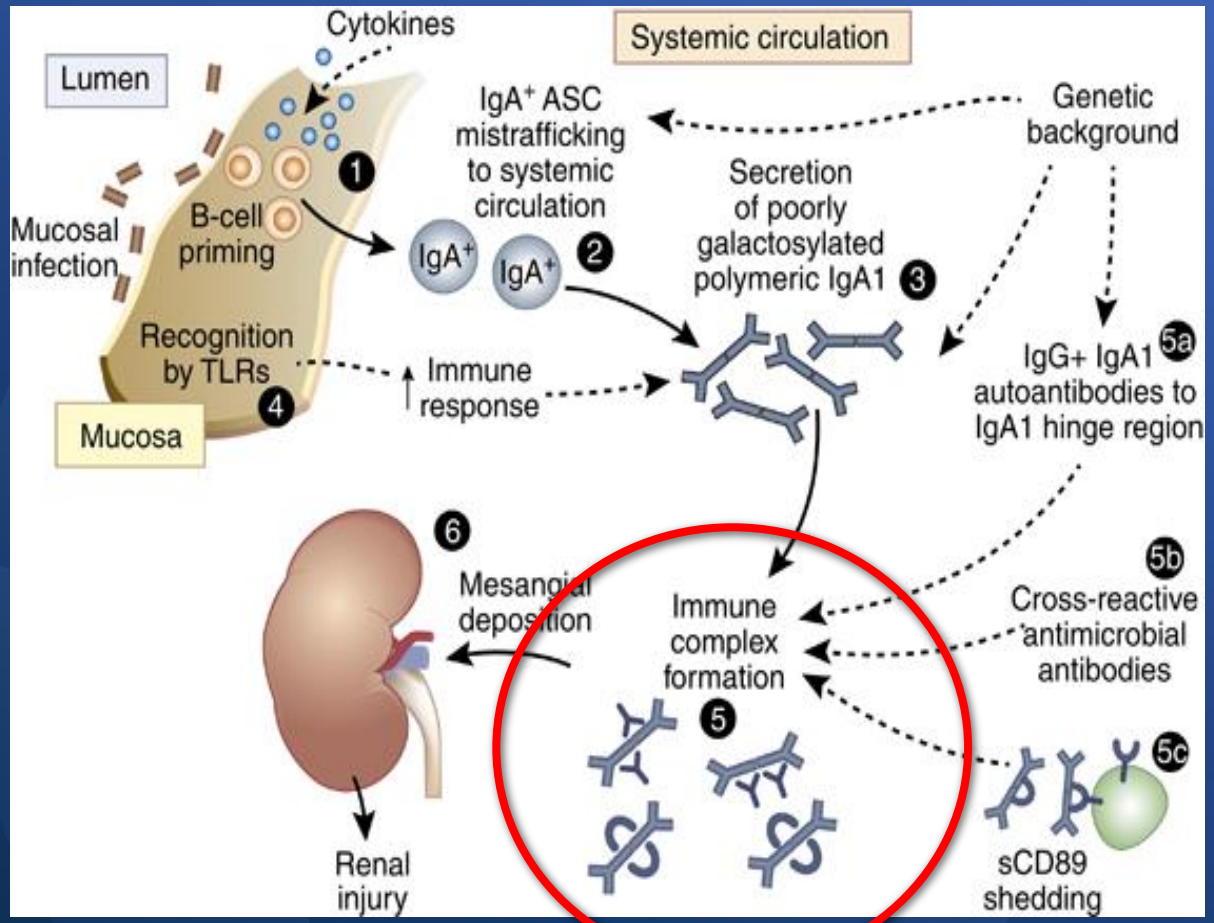
5c
Renal injury
sCD89 shedding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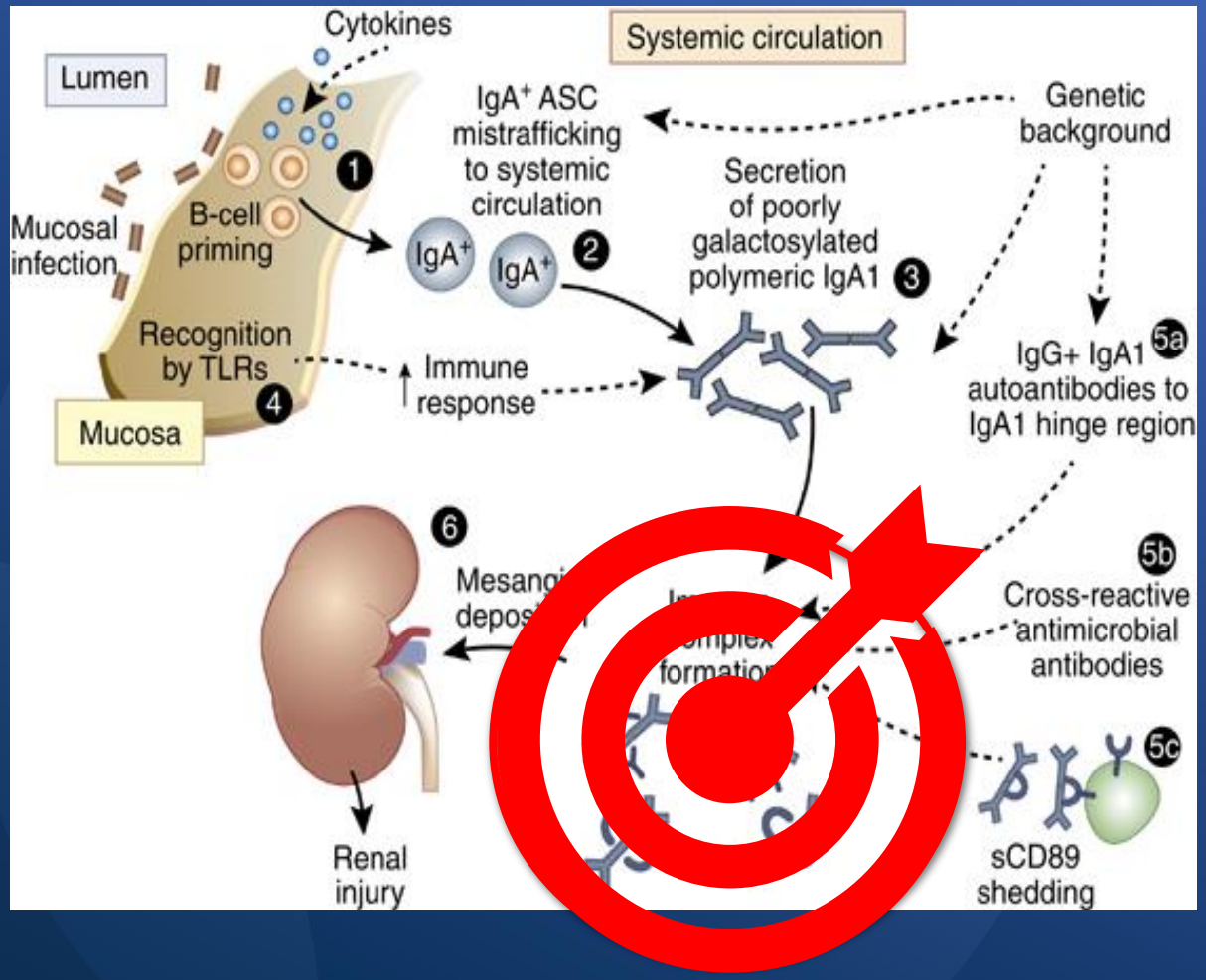

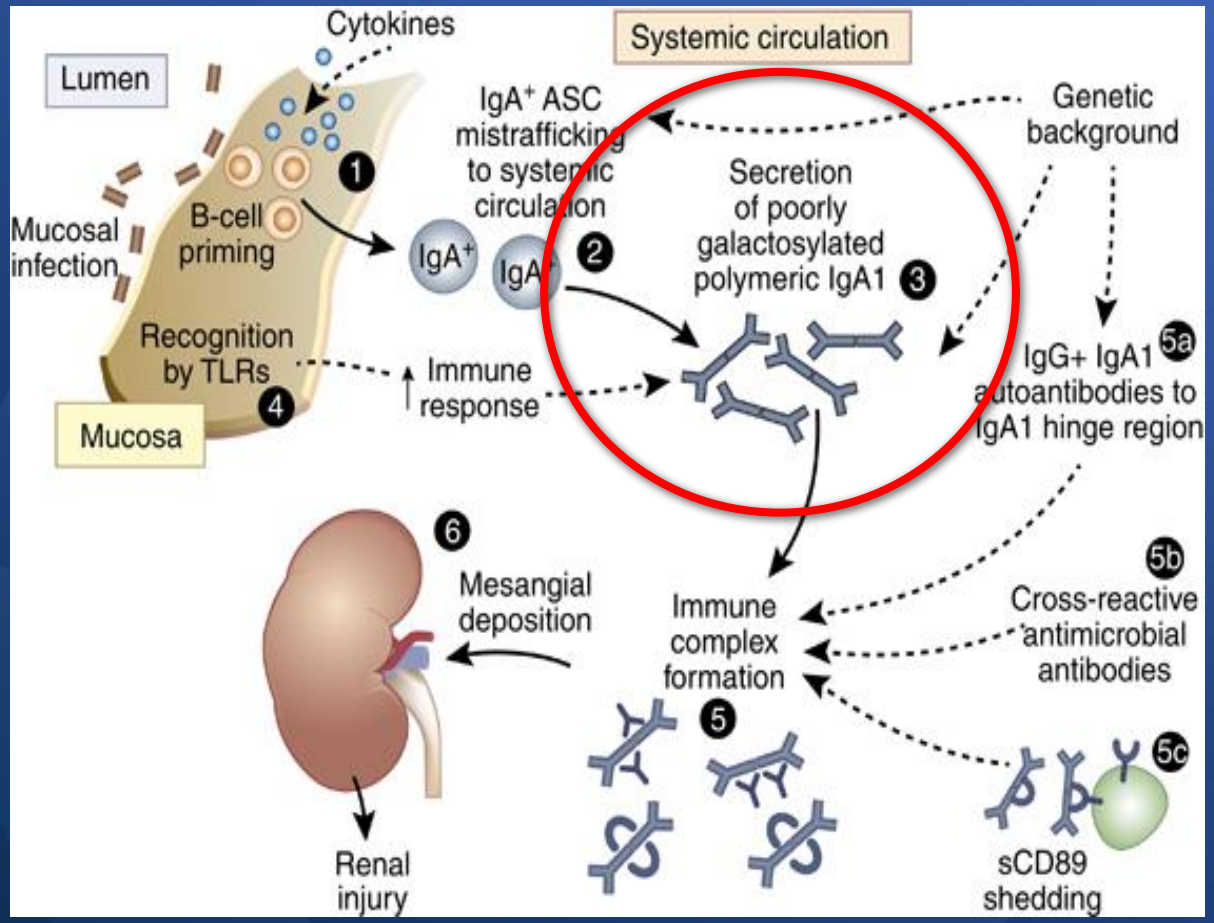
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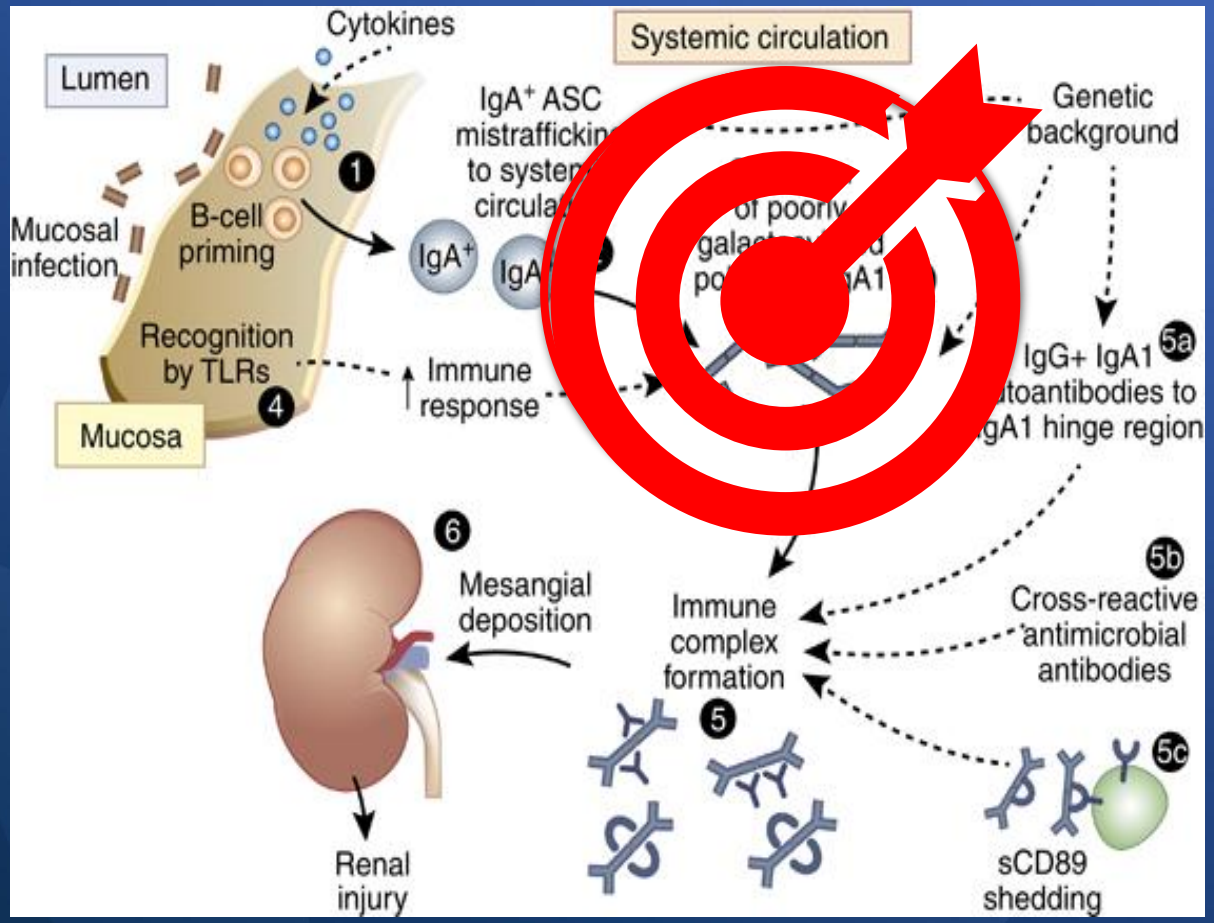

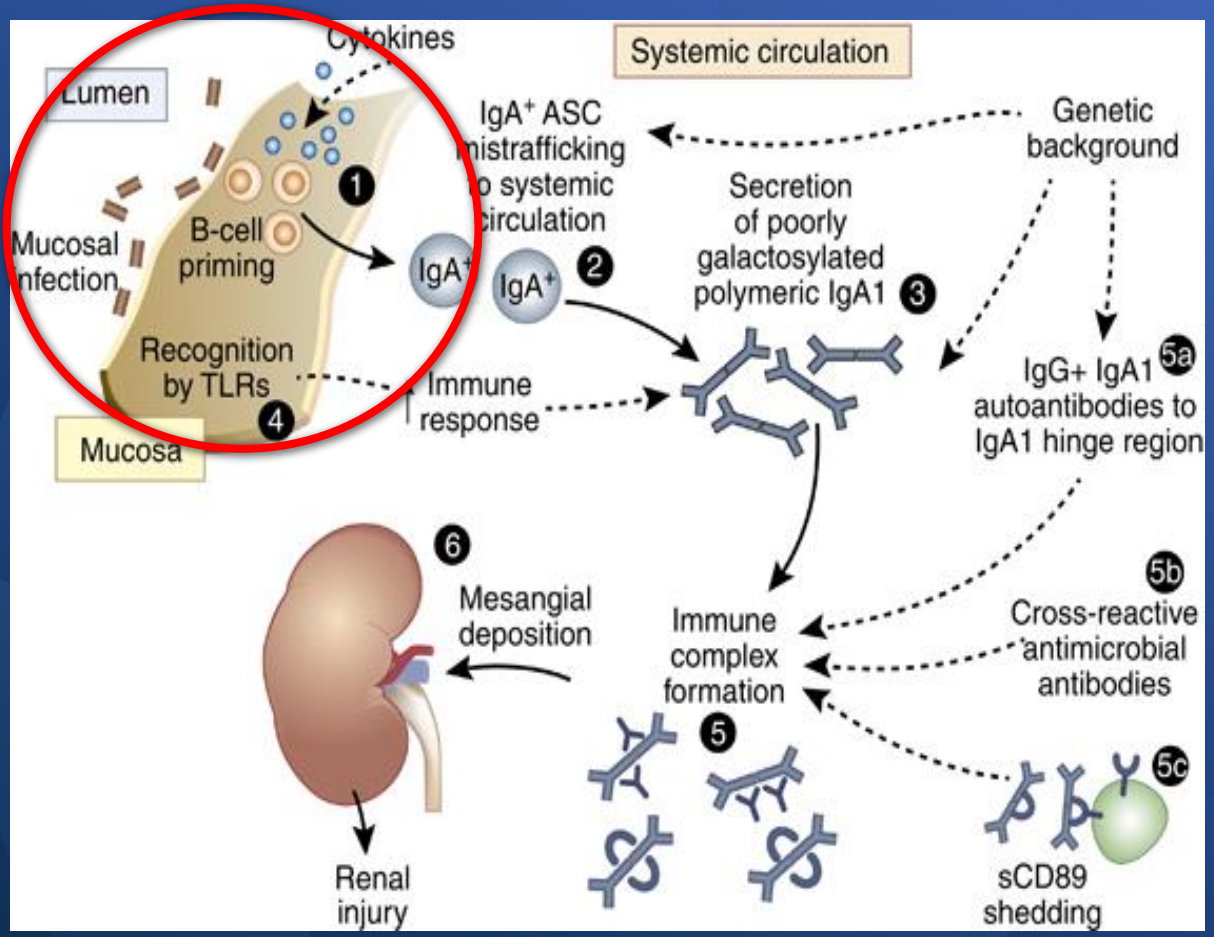
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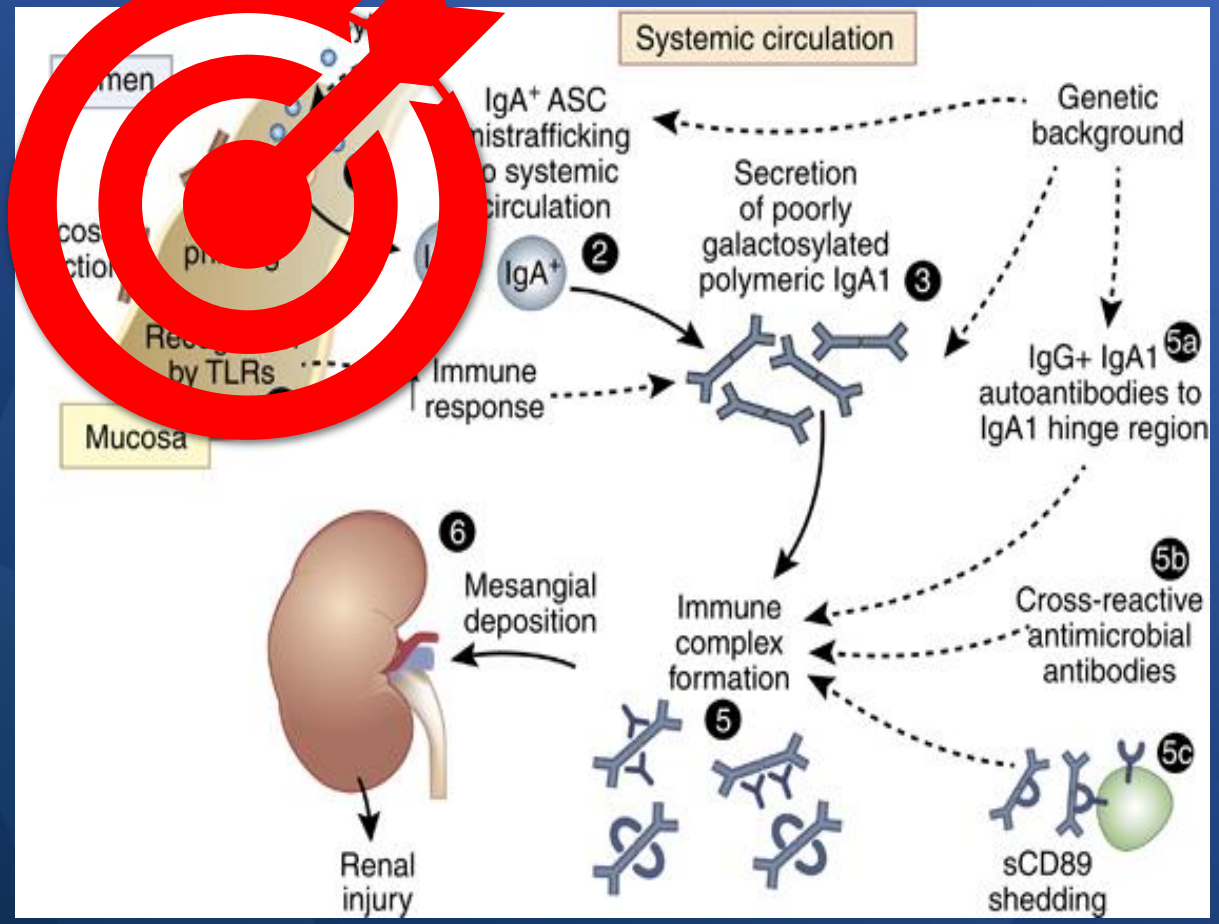

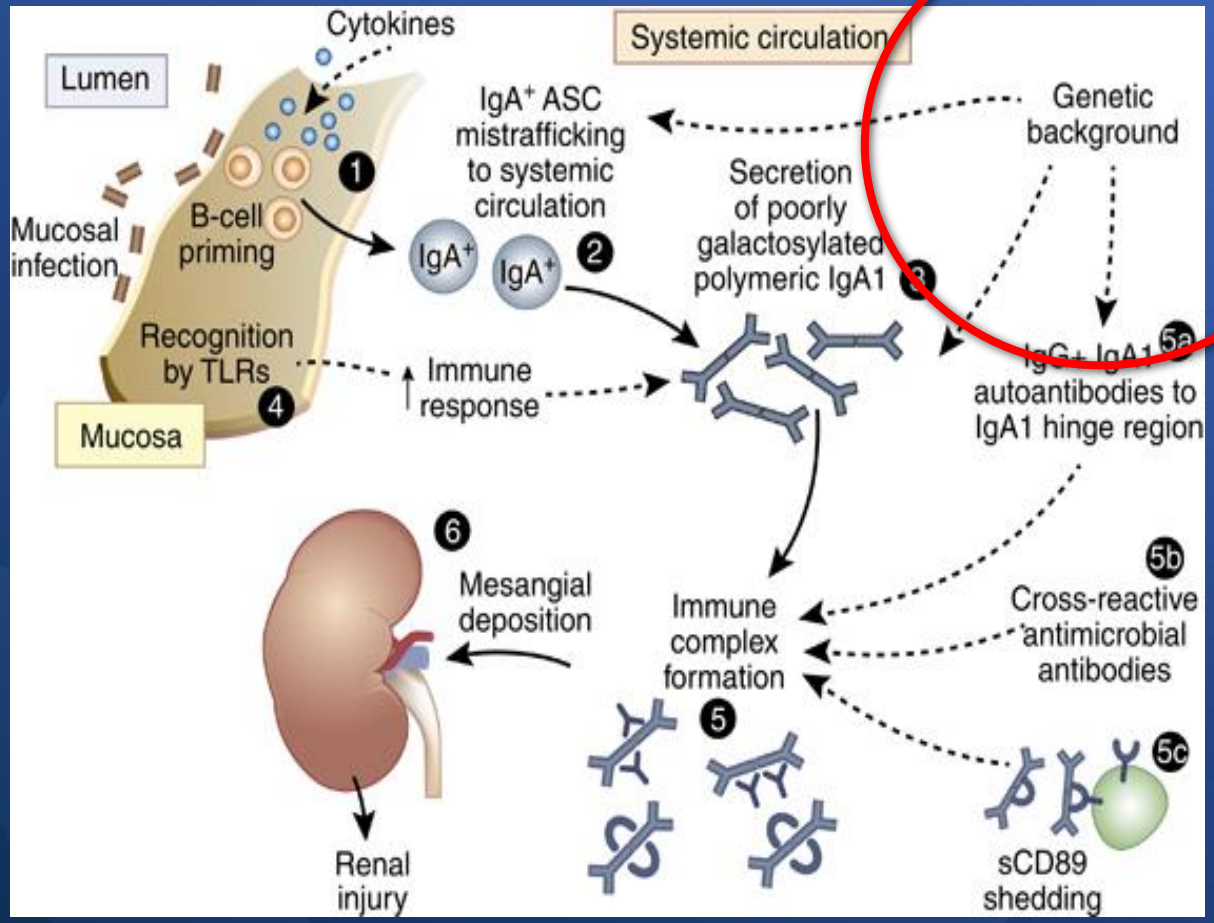
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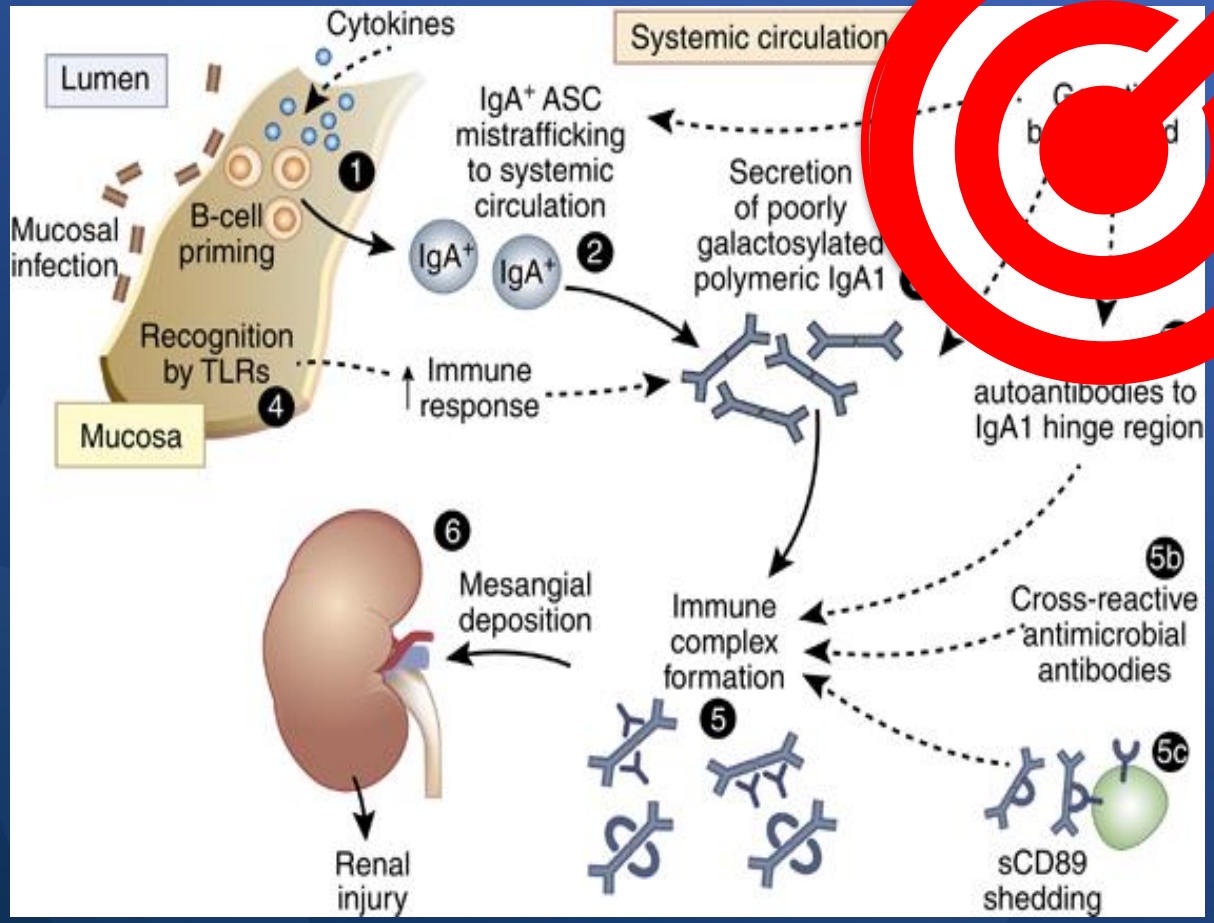

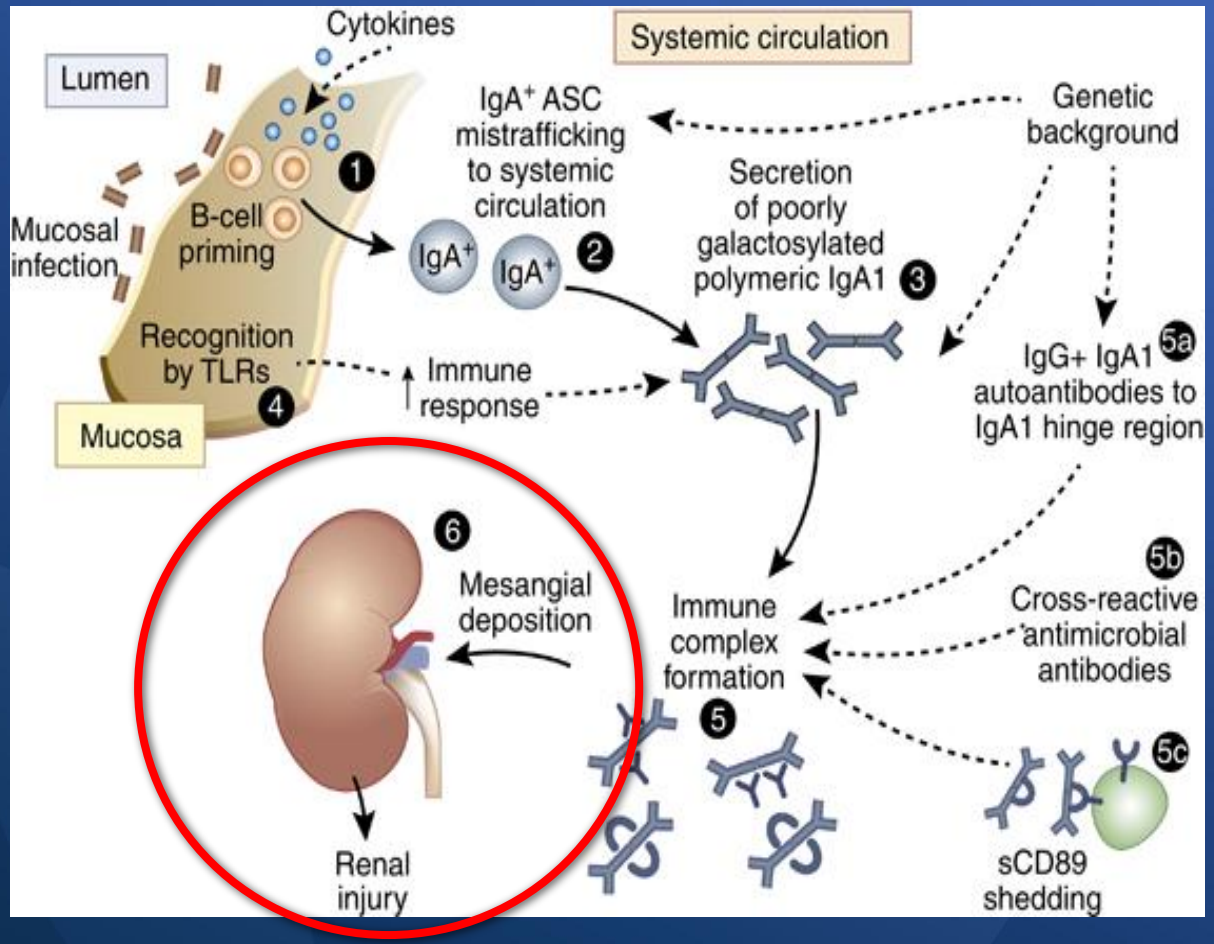
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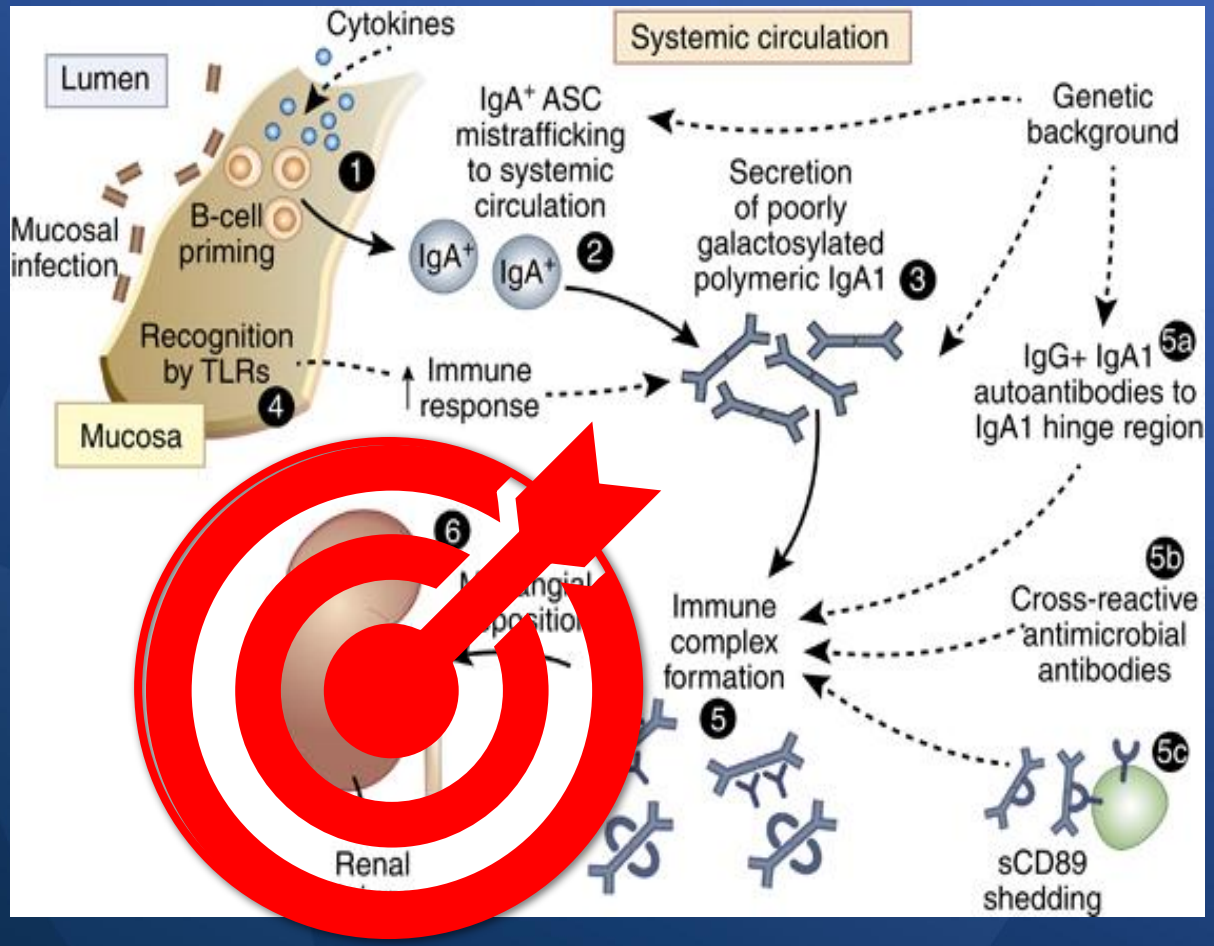

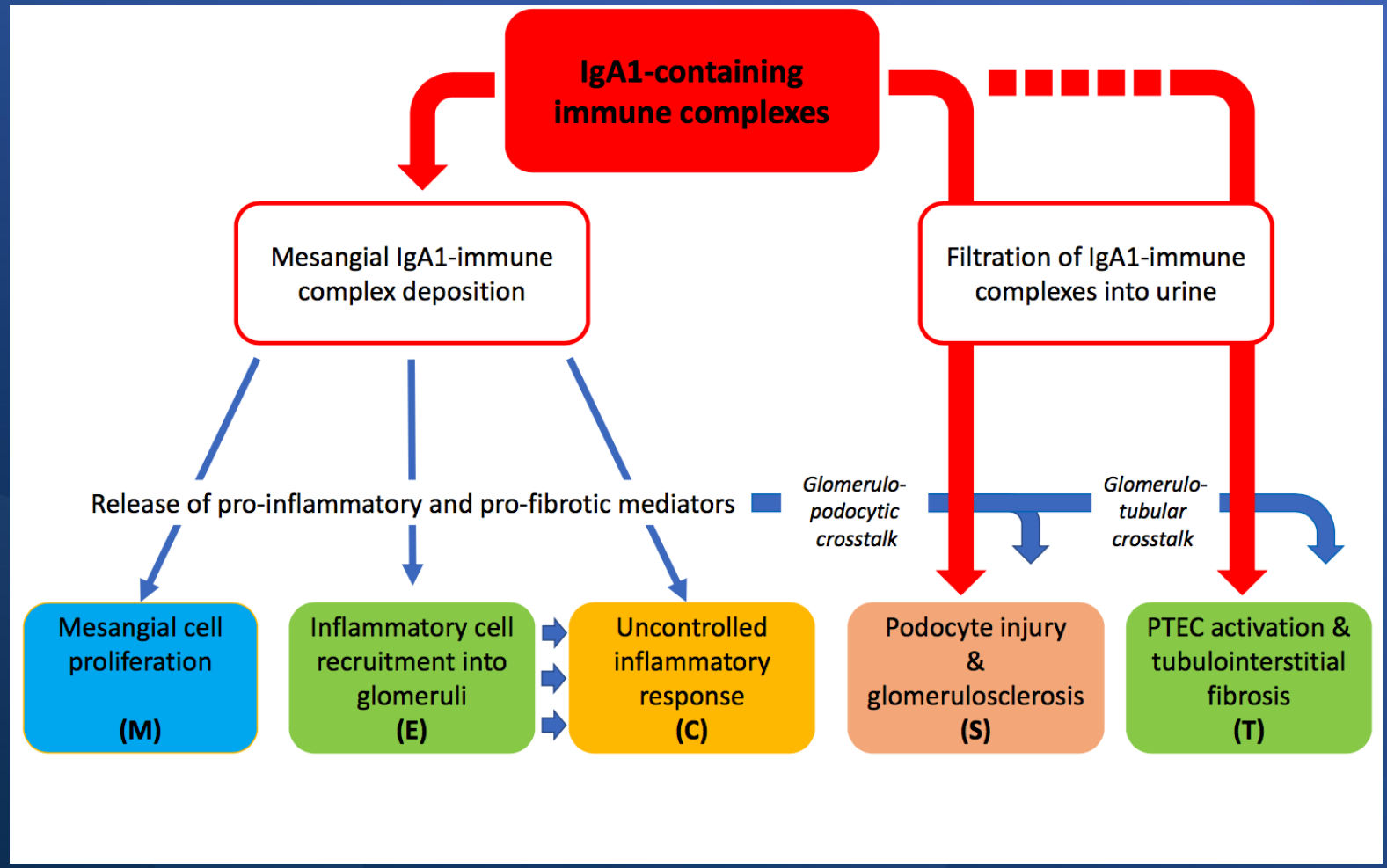
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Mesangial IgA1-immune complex deposition
Filtration of IgA1-immune complexes into urine
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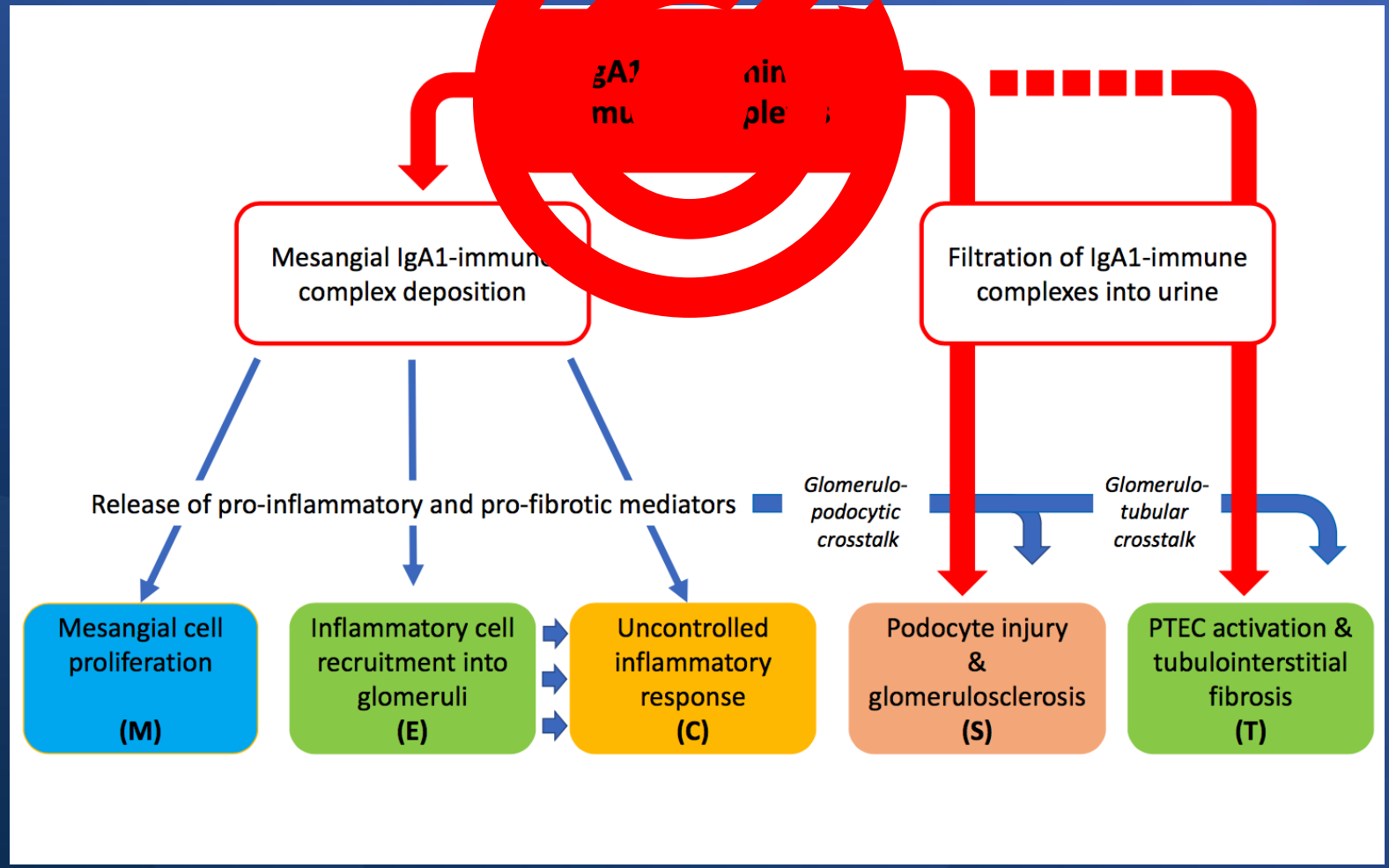
Glomerulo-tubular crosstalk
Mesangial cell proliferation (M)
Inflammatory cell recruitment into glomeruli (E)
Uncontrolled inflammatory response (C)
Podocyte injury & glomerulosclerosis (S)
PTEC activation & tubulointerstitial fibrosis (T)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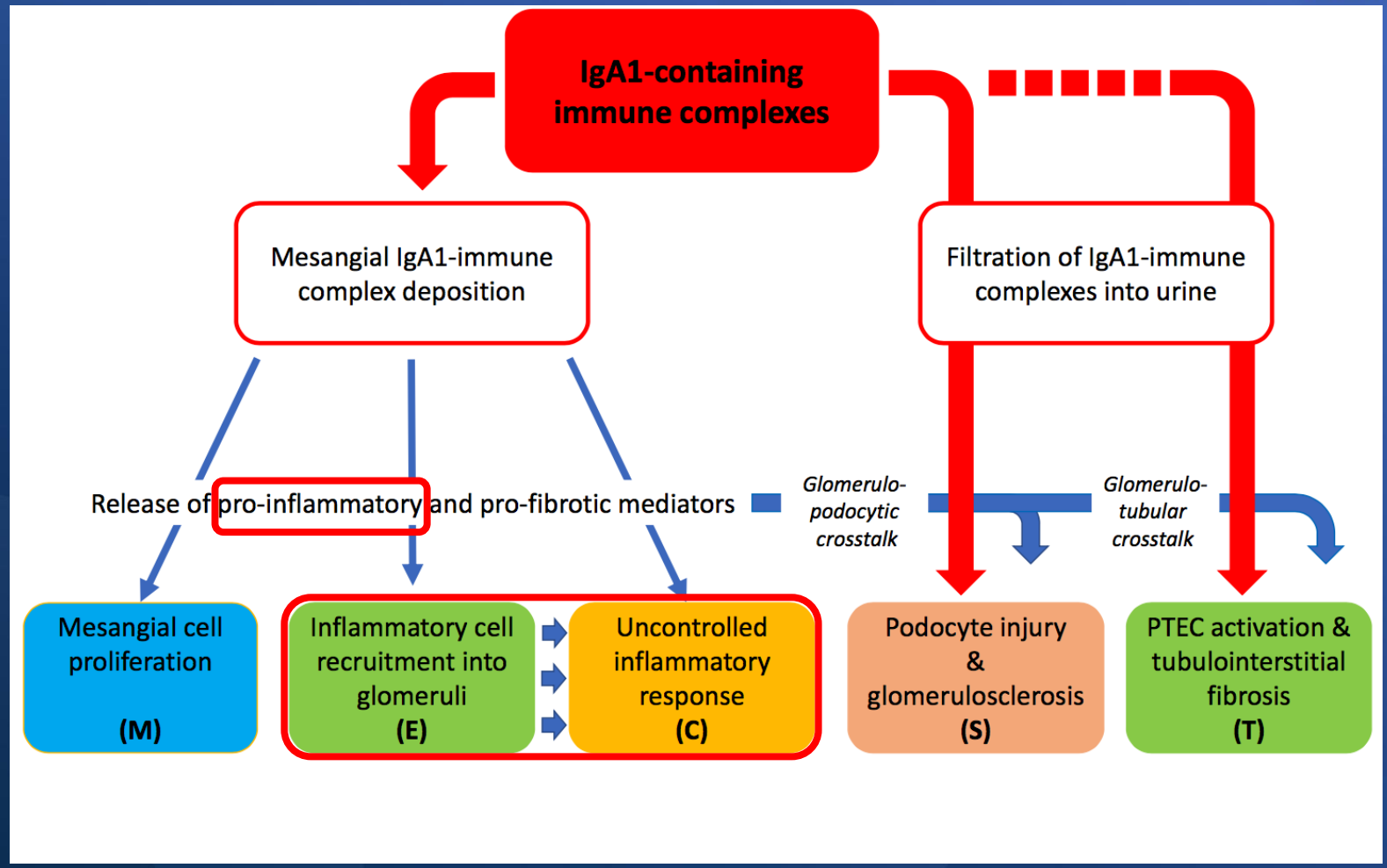
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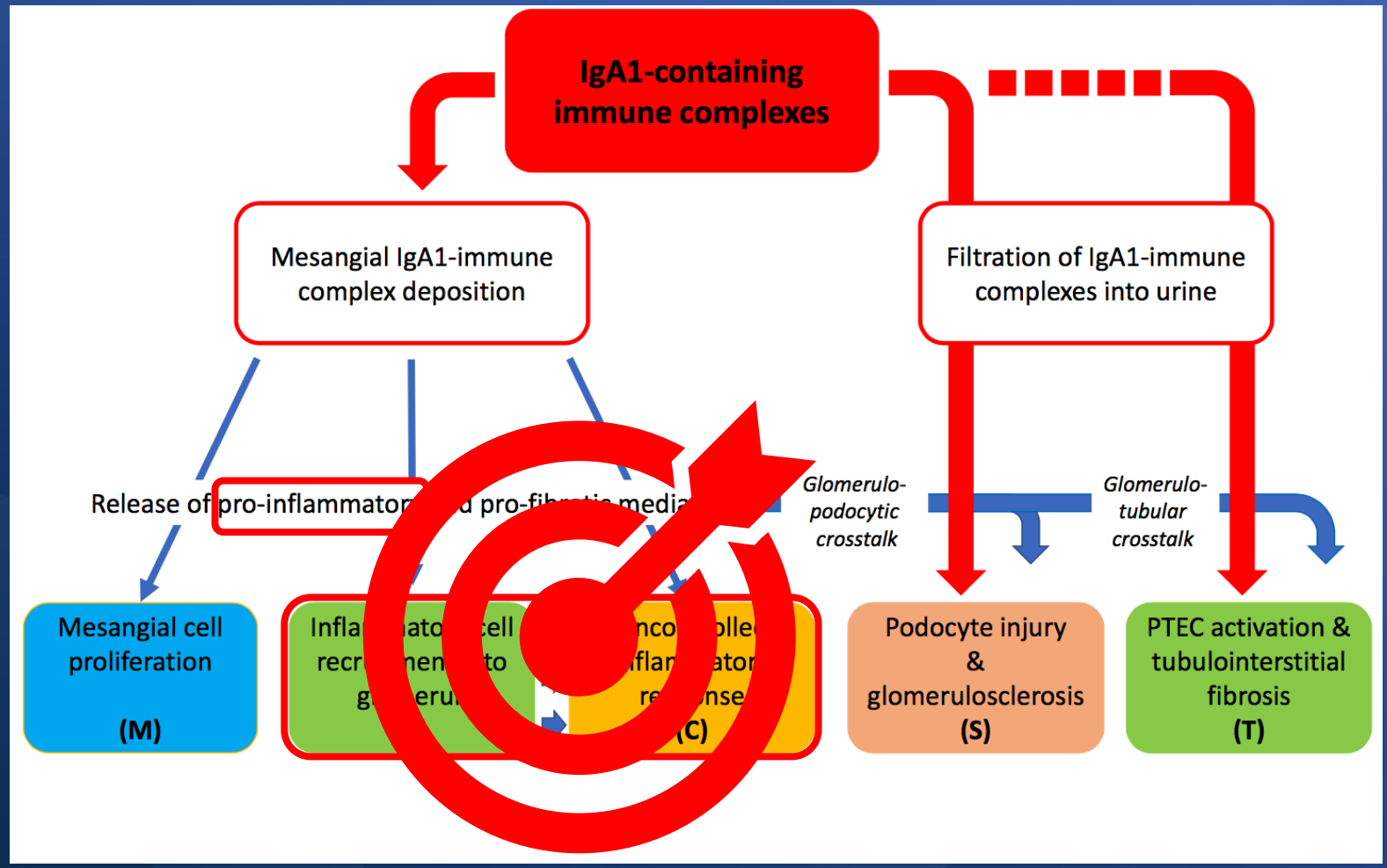
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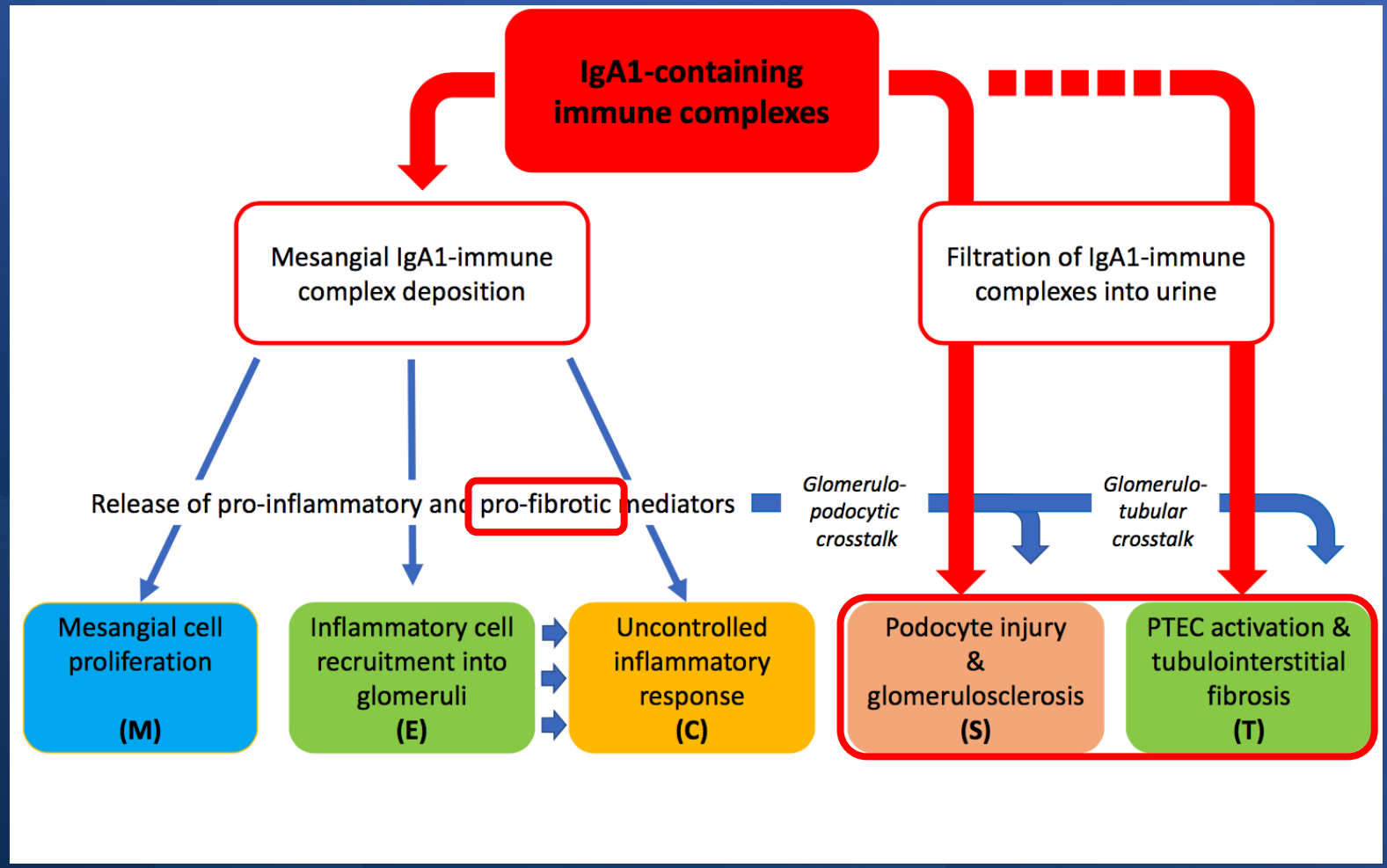
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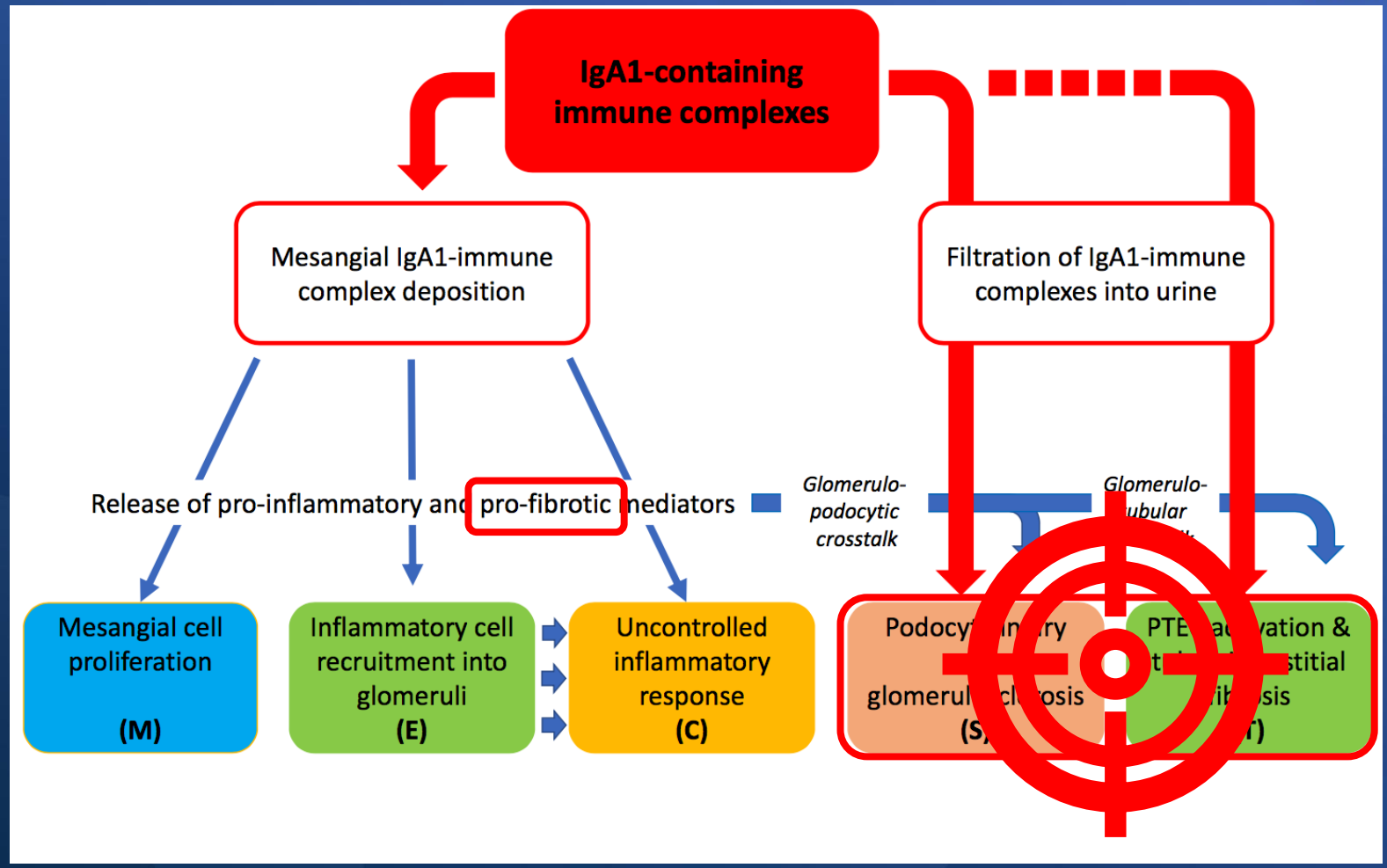
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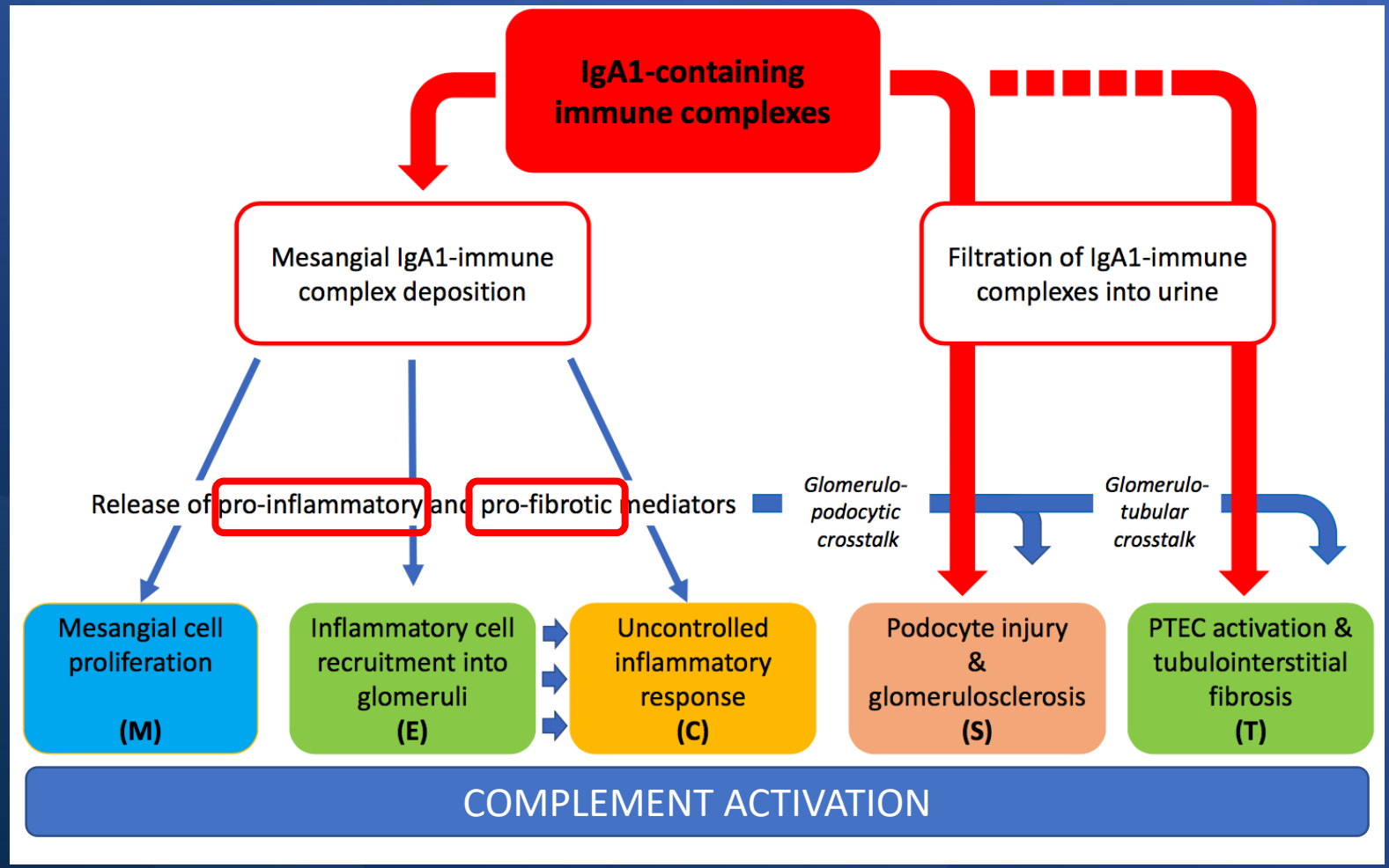
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COMPLEMENT ACTIVATION

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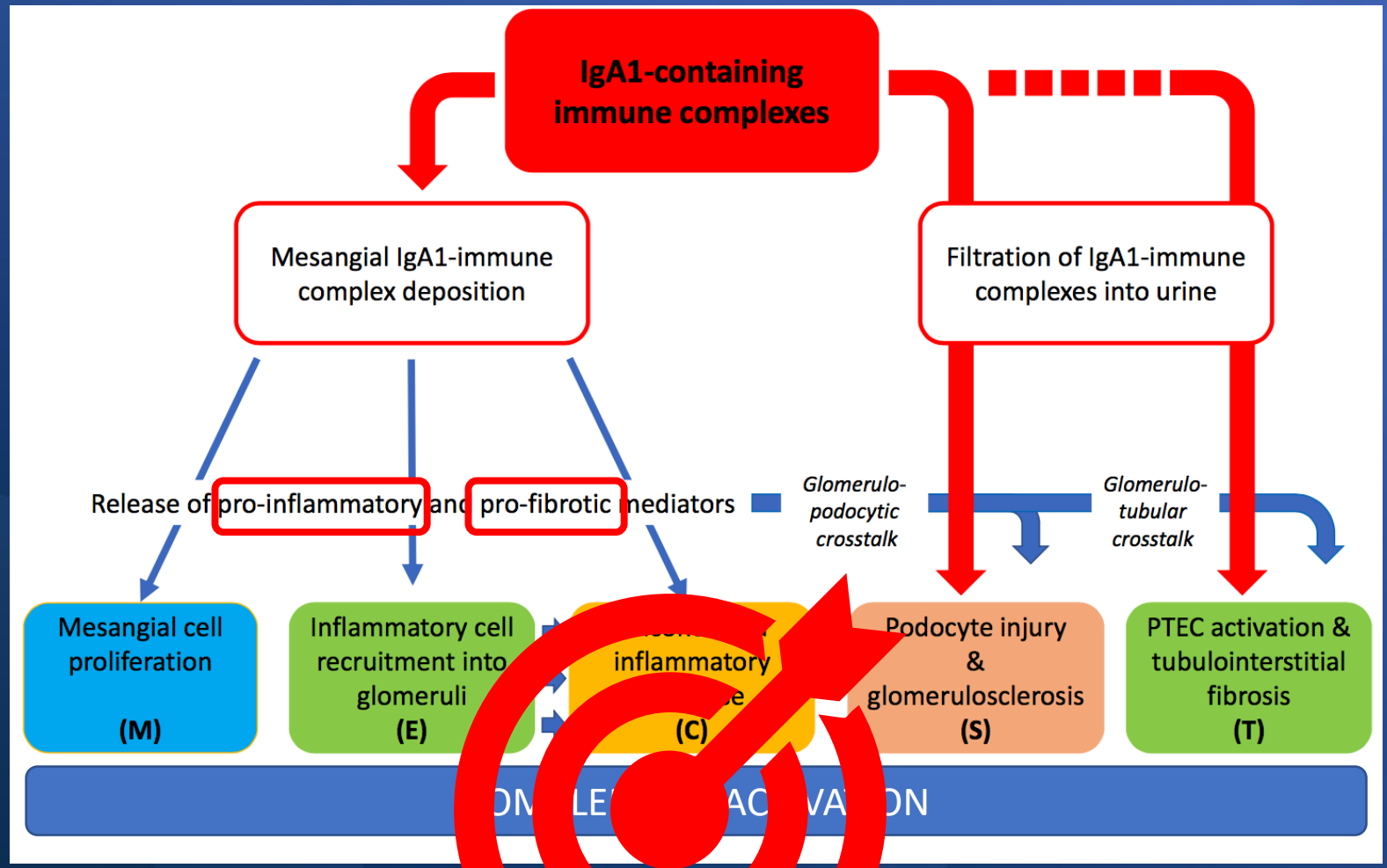

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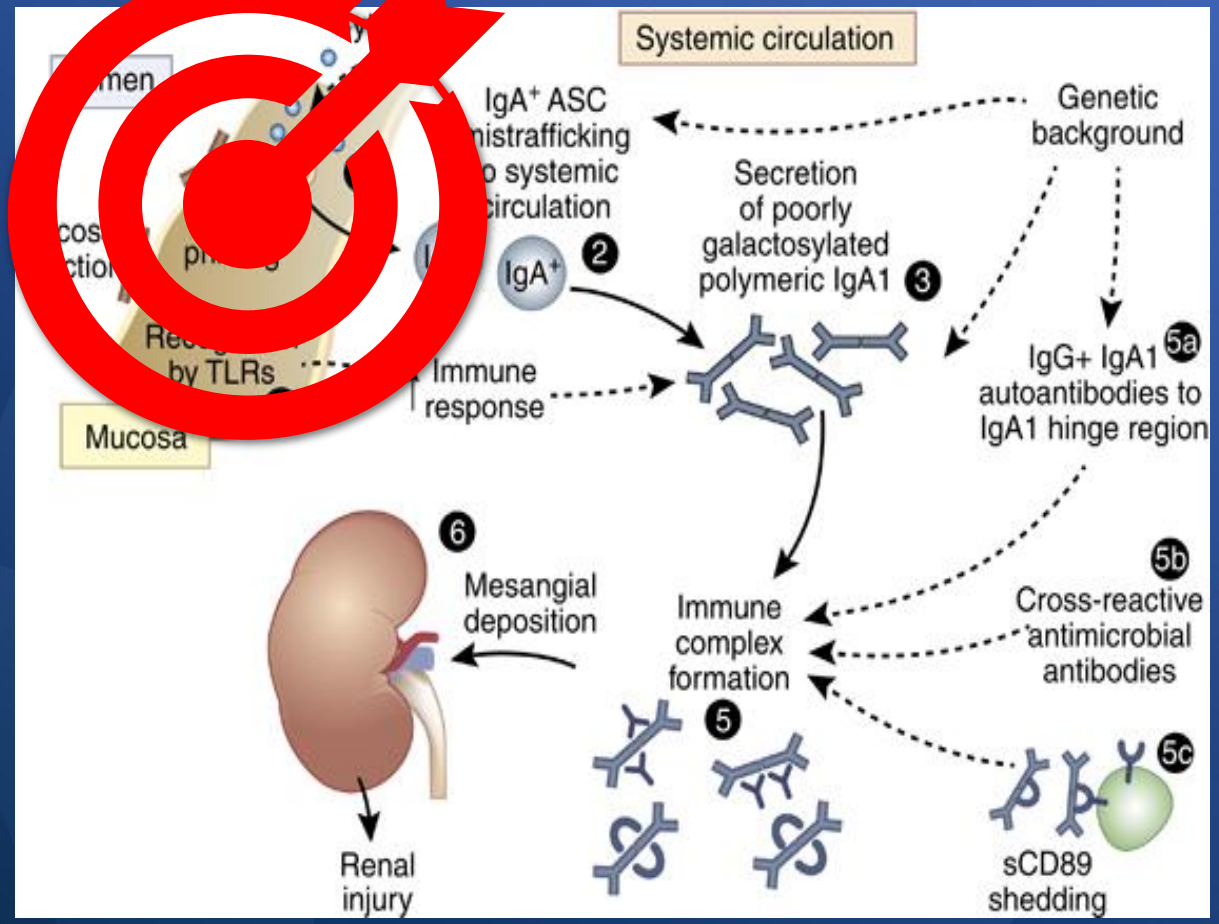

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Articles

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

Benga 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

Summary

Background IgA nephropathy is thought to be associated with mucosal immune system dysfunction, which manifests as renal IgA deposition that leads to impairment and end-stage renal disease in 20–40% of patients within 10–20 years. In this trial (NEFIGAN) we aimed to assess safety and efficacy of a novel targeted-release formulation of budesonide (TRF-budesonide), designed to deliver the drug to the distal ileum in patients with IgA nephropathy.

Methods We did a randomised, double-blind, placebo-controlled phase 2b trial, comprised of 6-month run-in, 9-month treatment, and 3-month follow-up phases at 62 nephrology clinics across ten European countries. We recruited patients aged at least 18 years with biopsy-confirmed primary IgA nephropathy and persistent proteinuria despite optimised renin-angiotensin system (RAS) blockade. We randomly allocated patients with a computer algorithm, with a fixed block size of three, in a 1:3:1 ratio to 16 mg/day TRF-budesonide, 8 mg/day TRF-budesonide, or placebo, stratified by baseline urine protein creatinine ratio (UPCR). Patients self-administered masked capsules, once daily, 1 h before breakfast during the treatment phase. All patients continued optimised RAS blockade treatment throughout the trial. Our primary outcome was mean change from baseline in UPCR for the 9-month treatment phase, which was assessed in the full analysis set, defined as all randomised patients who took at least one dose of trial medication and had at least one post-dose efficacy measurement. Safety was assessed in all patients who received the intervention. This trial is registered with ClinicalTrials.gov, number NCT01738035.

Findings Between Dec 11, 2012, and June 25, 2015, 150 randomised patients were treated (safety set) and 149 patients were eligible for the full analysis set. Overall, at 9 months' TRF-budesonide (16 mg/day plus 8 mg/day) was associated with a 24·4% (SEM 7·7%) decrease from baseline in mean UPCR (change in UPCR vs placebo 0·74; 95% CI 0·59–0·94; p=0·0066). At 9 months, mean UPCR had decreased by 27·3% in 48 patients who received 16 mg/day (0·71; 0·53–0·94; p=0·0092) and 21·5% in the 51 patients who received 8 mg/day (0·76; 0·58–1·01; p=0·0290); 50 patients who received placebo had an increase in mean UPCR of 2·7%. The effect was sustained throughout follow-up. Incidence of adverse events was similar in all groups (43 [88%] of 49 in the TRF-budesonide 16 mg/day group, 48 [94%] of 51 in the TRF-budesonide 8 mg/day, and 42 [84%] of 50 controls). Two of 13 serious adverse events were possibly associated with TRF-budesonide—deep vein thrombosis (16 mg/day) and unexplained deterioration in renal function in follow-up (patients were tapered from 16 mg/day to 8 mg/day over 2 weeks and follow-up was assessed 4 weeks later).

Interpretation TRF-budesonide 16 mg/day, added to optimised RAS blockade, reduced proteinuria in patients with IgA nephropathy. This effect is indicative of a reduced risk of future progression to end-stage renal disease. TRF-budesonide could become the first specific treatment for IgA nephropathy targeting intestinal mucosal immunity upstream of disease manifestation.

Funding Pharmalink AB.

Introduction

Primary IgA nephropathy is the most prevalent chronic glomerular disease worldwide, with patients often diagnosed as young adults.[1] About 20–40% of patients progress to end-stage renal disease within 10–20 years of diagnosis.[2–4] Major risk factors for progression to end-stage renal disease are persistent proteinuria, hypertension, and reduced glomerular filtration rate (GFR).[2,3,5] Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for glomerulonephritis recommend renin-angiotensin system (RAS) blockade with angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) as first-line treatment for patients with IgA nephropathy with proteinuria of more than 1 g/day (recommendation level 1B), and suggest up-titration as far as tolerated to the maximum recommended dose to achieve proteinuria of less than 1 g/day (recommendation level 2D).[6] For patients with persistent proteinuria of more than 1 g/day and GFR greater than 50 mL/min per 1·73 m² despite 6 months' optimised RAS blockade, KDIGO

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Uppsala University Hospital, Uppsala, Sweden (Prof B C Fellström MD); University of Leicester, Leicester, UK (J Barratt FRCP, Prof J Feehally FRCP); Pharmalogic Consulting AB, Stockholm, Sweden (H Cook PhD); Fondazione Ricerca Molinette, Regina Margherita Hospital, Turin, Italy (R Coppo MD); Leiden University Medical Center, Netherlands (Prof J W de Fijter MD); RWTH University Aachen, Germany (Prof J Floege MD); Heinrich-Heine-University, Düsseldorf, Germany (Prof G Hetzel MD); University of Glasgow, Glasgow, UK (Prof A G Jardine MD); Ospedale A Manzoni, Lecco, Italy (F Locatelli FNKF, L Del Vecchio MD); AZ Delta, Roeselare, Belgium (Prof B D Maes PhD); Pharmalink AB, Stockholm, Sweden (A Mercer PhD); Helsinki University Hospital, Helsinki, Finland (F Ortiz PhD); Complutense University, Investigation Institute Hospital 12 de Octubre, Madrid, Spain (Prof M Praga PhD); Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark (Prof S S Sørensen DMSci); and Charles University, Prague, Czech Republic (Prof V Tesar MD)

Correspondence to: Prof Bengt Fellström, Department of Nephrology, University Hospital, SE-75185 Uppsala, Sweden bengt.fellstrom@medsci.uu.se

Results from part A of the multi-center, double-blind, randomized, placebo-controlled NefIgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy

see commentary on page 258

OPEN

Jonathan Barratt[1], Richard Lafayette[2], Jens Kristensen[3], Andrew Stone[4], Daniel Cattran[5], Jürgen Floege[6], Vladimir Tesar[7], Hernán Trimarchi[8], Hong Zhang[9], Necmi Eren[10], Alexander Paliege[11] and Brad H. Rovin[12]; for the NefIgArd Trial Investigators[13]

[1]College of Medicine Biological Sciences and Psychology, University of Leicester, Leicester, UK; [2]Division of Nephrology, Department of Medicine, Stanford University, Stanford, California, USA; [3]Calliditas Therapeutics AB, Stockholm, Sweden; [4]Stone Biostatistics Ltd., Crewe, UK; [5]Division of Nephrology, Toronto General Hospital Research Institute, University of Toronto, Toronto, Ontario, Canada; [6]Department of Nephrology and Clinical Immunology, Rheinisch Westfälische Technische Hochschule Aachen University Hospital, Aachen, Germany; [7]Department of Nephrology, 1st School of Medicine and General University Hospital, Charles University, Prague, Czech Republic; [8]Nephrology Service, Hospital Británico de Buenos Aires, Buenos Aires, Argentina; [9]Renal Division, Peking University First Hospital, Peking University Institute of Nephrology, Beijing, China; [10]Department of Nephrology, Kocaeli University, Kocaeli, Turkey; [11]Division of Nephrology, Department of Internal Medicine III, University Hospital Carl Gustav Carus at the Technische Universität Dresden, Dresden, Germany; and [12]Division of Nephrology, the Ohio State University Wexner Medical Center, Columbus, Ohio, USA

The therapeutic potential of a novel, targeted-release formulation of oral budesonide (Nefecon) for the treatment of IgA nephropathy (IgAN) was first demonstrated by the phase 2b NEFIGAN trial. To verify these findings, the phase 3 NefIgArd trial tested the efficacy and safety of nine months of treatment with Nefecon (16 mg/d) versus placebo in adult patients with primary IgAN at risk of progressing to kidney failure (ClinicalTrials.gov: NCT03643965). NefIgArd was a multicenter, randomized, double-blind, placebo-controlled two-part trial. In Part A, 199 patients with IgAN were treated with Nefecon or placebo for nine months and observed for an additional three months. The primary endpoint for Part A was 24-hour urine protein-to-creatinine ratio (UPCR) after nine months. Secondary efficacy outcomes evaluated included estimated glomerular filtration rate (eGFR) at nine and 12 months and the UPCR at 12 months. At nine months, UPCR was 27% lower in the Nefecon group compared with placebo, along with a benefit in eGFR preservation corresponding to a 3.87 ml/min/1.73 m² difference versus placebo (both significant). Nefecon was well-tolerated, and treatment-emergent adverse events were mostly mild to moderate in severity and reversible. Part B is ongoing and will be reported on later. Thus, NefIgArd is the first phase 3 IgA nephropathy trial to show clinically important improvements in UPCR and eGFR and confirms the findings from the phase 2b NEFIGAN study.

Kidney International (2023) **103**, 391–402; https://doi.org/10.1016/j.kint.2022.09.017

KEYWORDS: glomerular disease; glucocorticoids; gut-associated lymphoid tissue; IgA nephropathy

IgA nephropathy (IgAN) is a mesangioproliferative glomerulonephritis, characterized by the deposition of galactose-deficient IgA1 (Gd-IgA1)–containing immune complexes in the glomerular mesangium.[1] These immune complexes initiate a cascade of inflammatory events, eventually causing irreversible glomerulosclerosis and tubulointerstitial inflammation and fibrosis with loss of kidney function; in patients with progressive disease (i.e., proteinuria >1 g/24 h), the risk of kidney failure may be up to 50% within 20 years.[2–5] At the time the present study was initiated, no IgAN-specific treatments were available, and guidelines recommended goal-directed supportive care comprising lifestyle change, optimal blood pressure control, and renin-angiotensin system (RAS) blockade to reduce proteinuria.[5–8]

There is accumulating evidence for the gut mucosal immune system and mucosal-derived Gd-IgA1 in the pathogenesis of primary IgAN. Peyer's patches are aggregations of lymphoid follicles, located in the mucosal layer of the intestine, and concentrated in the ileum. They are part of the gut-associated lymphoid system and serve as antigen sampling

Correspondence: *Brad H. Rovin, Division of Nephrology, the Ohio State University Wexner Medical Center, 410 W 10th Avenue, Columbus, Ohio 43210, USA. E-mail: Brad.Rovin@osumc.edu*

[13]The NefIgArd Trial Investigators are listed in the Appendix.

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

Richard Lafayette, Jens Kristensen, Andrew Stone, Jürgen Floege, Vladimir Tesař, Hernán Trimarchi, Hong Zhang, Necmi Eren, Alexander Paliege, Heather N Reich, Brad H Rovin, Jonathan Barratt, *on behalf of the NefIgArd trial investigators*

Summary

Background IgA nephropathy is a chronic immune-mediated kidney disease and a major cause of kidney failure worldwide. The gut mucosal immune system is implicated in its pathogenesis, and Nefecon is a novel, oral, targeted-release formulation of budesonide designed to act at the gut mucosal level. We present findings from the 2-year, phase 3 NefIgArd trial of Nefecon in patients with IgA nephropathy.

Methods In this phase 3, multicentre, randomised, double-blind, placebo-controlled trial, adult patients (aged ≥18 years) with primary IgA nephropathy, estimated glomerular filtration rate (eGFR) 35–90 mL/min per 1·73 m², and persistent proteinuria (urine protein–creatinine ratio ≥0·8 g/g or proteinuria ≥1 g/24 h) despite optimised renin-angiotensin system blockade were enrolled at 132 hospital-based clinical sites in 20 countries worldwide. Patients were randomly assigned (1:1) to receive 16 mg/day oral capsules of Nefecon or matching placebo for 9 months, followed by a 15-month observational follow-up period off study drug. Randomisation via an interactive response technology system was stratified according to baseline proteinuria (<2 or ≥2 g/24 h), baseline eGFR (<60 or ≥60 mL/min per 1·73 m²), and region (Asia-Pacific, Europe, North America, or South America). Patients, investigators, and site staff were masked to treatment assignment throughout the 2-year trial. Optimised supportive care was also continued throughout the trial. The primary efficacy endpoint was time-weighted average of eGFR over 2 years. Efficacy and safety analyses were done in the full analysis set (ie, all randomly assigned patients). The trial was registered on ClinicalTrials.gov, NCT03643965, and is completed.

Findings Patients were recruited to the NefIgArd trial between Sept 5, 2018, and Jan 20, 2021, with 364 patients (182 per treatment group) randomly assigned in the full analysis set. 240 (66%) patients were men and 124 (34%) were women, and 275 (76%) identified as White. The time-weighted average of eGFR over 2 years showed a statistically significant treatment benefit with Nefecon versus placebo (difference 5·05 mL/min per 1·73 m² [95% CI 3·24 to 7·38], p<0·0001), with a time-weighted average change of −2·47 mL/min per 1·73 m² (95% CI −3·88 to −1·02) reported with Nefecon and −7·52 mL/min per 1·73 m² (−8·83 to −6·18) reported with placebo. The most commonly reported treatment-emergent adverse events during treatment with Nefecon were peripheral oedema (31 [17%] patients, vs placebo, seven [4%] patients), hypertension (22 [12%] vs six [3%]), muscle spasms (22 [12%] vs seven [4%]), acne (20 [11%] vs two [1%]), and headache (19 [10%] vs 14 [8%]). No treatment-related deaths were reported.

Interpretation A 9-month treatment period with Nefecon provided a clinically relevant reduction in eGFR decline and a durable reduction in proteinuria versus placebo, providing support for a disease-modifying effect in patients with IgA nephropathy. Nefecon was also well tolerated, with a safety profile as expected for a locally acting oral budesonide product.

Funding Calliditas Therapeutics.

Introduction

IgA nephropathy is a chronic immune-mediated kidney disease characterised by IgA deposition in the glomeruli.[1] IgA nephropathy is the most common primary glomerular disease globally and has serious consequences, including reduced life expectancy; most patients with IgA nephropathy are expected to develop kidney failure, with up to 50% doing so within 20 years of presentation.[1,2] Therefore, IgA nephropathy places a substantial burden on patients and health-care services worldwide. With no cure for IgA nephropathy, current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, published in 2021, recommend providing optimised supportive care (blood pressure management, lifestyle modification, maximally tolerated renin-angiotensin system [RAS] inhibition to reduce proteinuria, and addressing cardiovascular risk).[3] After supportive care, patients who remain at high risk for a clinical trial, or for systemic glucocorticoids (if they

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Targeted-release budesonide modifies key pathogenic biomarkers in immunoglobulin A nephropathy: insights from the NEFIGAN trial

OPEN

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Nefecon is the first approved treatment for patients with immunoglobulin A nephropathy (IgAN) at high risk of progression to kidney failure (accelerated approval: US Food and Drug Administration; conditional approval: European Medicines Agency).[1–3] Nefecon delivers budesonide, in a targeted formulation, to the gut-associated lymphoid tissue (GALT) of the ileum directly addressing immune dysregulation within this Peyer's patches–rich area of the GALT and downregulating the local production of the polymeric poorly O-galactosylated form of IgA1 or galactose-deficient IgA1 (Gd-IgA1) and generation of pathogenic IgA-containing immune complexes (IgA-IC).[4] The aim of the current analysis is to explore the biochemical pathways through which Nefecon exerted its effects in patients treated in the NEFIGAN study.

METHODS

NEFIGAN (ClinicalTrials.gov: NCT01738035) was a randomized, double-blind, placebo-controlled, phase 2b trial to assess the safety and efficacy of Nefecon in patients (≥18 years) with IgAN and overt proteinuria despite optimized renin-angiotensin-aldosterone system blockade therapy.[2] Patients (n = 150) were stratified according to the baseline urine protein creatinine ratio (≥0.8 g/g and >0.9 g/g) and were randomized (1:1:1) to Nefecon 8 mg/d, Nefecon 16 mg/d, or placebo. After a 6-month run-in phase, patients underwent a 9-month treatment phase followed by a 3-month follow-up phase. Blood and urine samples were collected during the trial and exploratory analyses of a range of IgAN-related biomarkers were conducted, using in-house enzyme-linked immunosorbent assays, commercial enzyme-linked immunosorbent assay duo kits, and multiplex immunoassays. A full description of the methods is provided in Supplementary Methods. All ELISAs are listed in Supplementary Table S1, and the Luminex assays used for the biomarker analyses are shown in Supplementary Table S2.

RESULTS

Patient demographics and baseline characteristics are given in Supplementary Table S3.[2] Changes from baseline in multiple biomarkers were observed at 9 months, as described below,

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Effects of nefecon on Hits 1, 2, and 3 of the IgAN pathogenic cascade: a full NefIgArd analysis

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I. KHAN[1], N. NAWAZ[1], A.A.A. JAMA[1], W.A. BARRATT[1], R.C. THOMAS[1], R. JONES[2], and J. BARRATT[1]
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INTRODUCTION

IgAN follows a multihit model: elevated Gd-IgA1 (**Hit 1**) levels trigger IgA and IgG autoantibody production (**Hit 2**), leading to the formation of IgA-IC (**Hit 3**), which deposits in the mesangium, causing inflammation and injury.[1] GALT is the main site for Gd-IgA1 production. The NefIgArd clinical trial, which investigated nefecon (a gut-targeted budesonide formulation), showed eGFR stabilization during 9 months of treatment and durable proteinuria reduction vs placebo.[2]

AIM

To assess the changes in markers of Hits 1, 2, and 3 of the IgAN pathogenic cascade with nefecon in patients from the Phase 3 clinical trial at different exploratory time points.

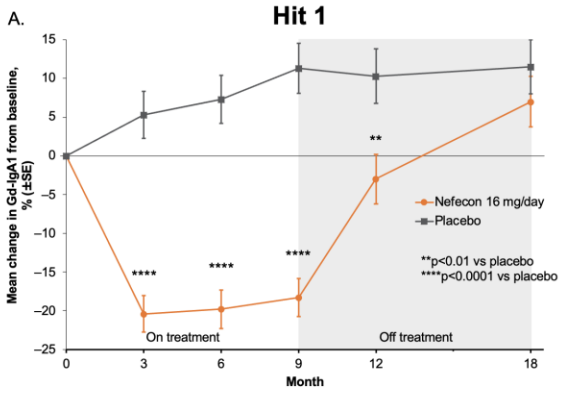
METHOD

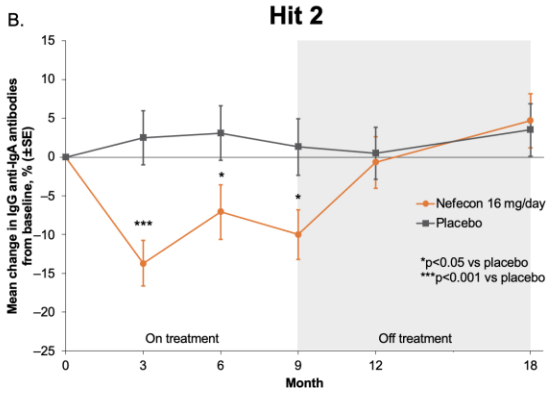
- In the NefIgArd trial (NCT0364396), patients received 9 months of treatment with either placebo or nefecon 16 mg/day, before entering a 15-month off-drug observational period
- Gd-IgA1, IgG anti-IgA autoantibody, and IgA-IC levels in 216 consenting NefIgArd participants (n=108 per group) were measured using serum samples collected at baseline, 3, 6, 9, 12, and 18 months
- Gd-IgA1 levels were assessed using a commercial assay, and IgG anti-IgA autoantibody and IgA-IC levels using in-house sandwich ELISAs

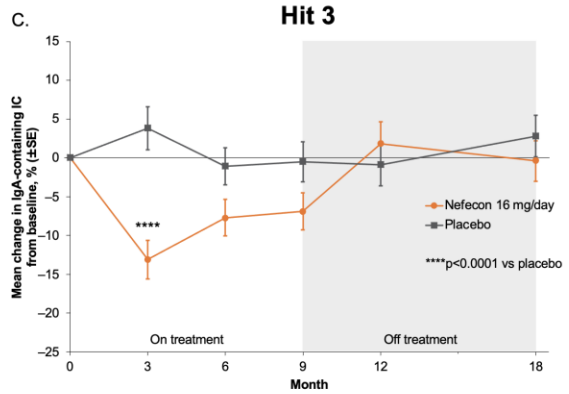
RESULTS

Figure: Relative changes from baseline over time for **(A)** Gd-IgA1 (Hit 1), **(B)** IgG anti-IgA autoantibodies (Hit 2), and **(C)** IgA-ICs (Hit 3), using robust regression with multiple imputations.

- Significant reductions in Gd-IgA1 levels were seen with nefecon vs placebo, showing the efficacy of nefecon in addressing Hit 1 of IgAN pathogenesis
- IgG anti-IgA autoantibodies were also reduced significantly with nefecon, tackling Hit 2 of IgAN pathogenesis
- As a result, we also observed a significant reduction in IgA-ICs (Hit 3 of the IgAN pathogenesis) with nefecon







CONCLUSIONS

- Nefecon 16 mg/day was the first fully approved treatment for IgAN based on the Phase 3 NefIgArd trial findings
- The 18-month NefIgArd biomarker data represent the complete analysis of the effects of the drug on the IgAN pathogenic cascade, showing clear reductions in markers of Hits 1, 2, and 3, compared with standard of care alone
- These findings, coupled with other previously published data, demonstrate that nefecon has a direct disease-modifying effect in IgAN

ACKNOWLEDGMENTS

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DISCLOSURES

J. Barratt is a consultant to Calliditas Therapeutics and reports grants and consultancy and personal fees from Calliditas Therapeutics, Everest Medicines, and STADA Arzneimittel. **R. Jones** is an employee of Calliditas Therapeutics. **I. Khan**, **N. Nawaz**, **A.A.A. Jama**, **W.A. Barratt**, and **R.C. Thomas** have nothing to disclose.

REFERENCES

1. **Cheung CK et al.** The pathogenesis of IgA nephropathy and implications for treatment. *Nat Rev Nephrol* 2025; 21: 9-23.

2. **Lafayette R et al. NefIgArd trial investigators**. Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NefIgArd): 2-year results from a randomised phase 3 trial. *Lancet* 2023; 402: 859-870.

ABBREVIATIONS

eGFR, estimated glomerular filtration rate; ELISA, enzyme-linked immunosorbent assay; GALT, gut-associated lymphoid tissue; Gd-IgA1, galactose-deficient IgA1; IgA, immunoglobulin A; IgA-IC, IgA-containing immune complex; IgAN, immunoglobulin A nephropathy; IgG, immunoglobulin G; SE, standard error.

CONTACT INFORMATION

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

Richard J Lafayette, Jens Kristensen, Andrew Stone, Jürgen Floege, Vladimir Tesař, Hernán Trimarchi, Hong Zhang, Necmi Eren, Alexander Paliege, Heather N Reich, Brad H Rovin, Jonathan Barratt, on behalf of the NefIgArd trial investigators

Summary

Background IgA nephropathy is a chronic immune-mediated kidney disease and a major cause of kidney failure worldwide. The gut mucosal immune system is implicated in its pathogenesis, and Nefecon is a novel, oral, targeted-release formulation of budesonide designed to act at the gut mucosal level. We present findings from the 2-year, phase 3 NefIgArd trial of Nefecon in patients with IgA nephropathy.

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158 (87%) of 182 patients in the Nefecon group and 165 (91%) of 182 in the placebo group received 9 months of randomised treatment. Compliance with study treatment was high (171 [94%] patients in each treatment group took at least 80% of the total capsules). The overall rate of study completion was high and similar in both

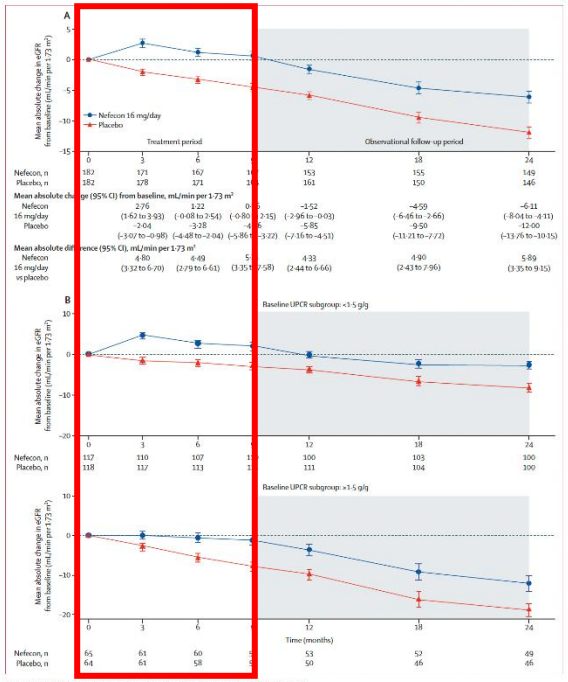

Figure 1: **Mean absolute change in eGFR from baseline to 24 months (full analysis set)**
All patients (A) and patients stratified according to baseline UPCR, <1·5 g/g and ≥1·5 g/g (B). Estimated mean absolute change (and standard error) was calculated from multiple-imputation robust regression analysis of log-transformed post-baseline to baseline ratios at 3, 6, 9, 12, 18, and 24 months, and transformed back into the original scale. eGFR was calculated by the central laboratory with the Chronic Kidney Disease Epidemiology Collaboration formula.[16] Data included at baseline and 24 months are the log of the geometric mean of the two replicate values recorded at each timepoint, respectively. eGFR=estimated glomerular filtration rate. UPCR=urine protein–creatinine ratio.

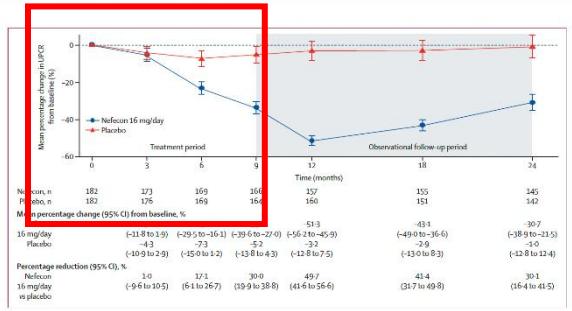

Figure 2: **Mean percentage change in UPCR (g/g) from baseline to 24 months (full analysis set)**
Estimated geometric mean percentage change (and standard error) was calculated from a mixed-effects model for repeated measures of log-transformed post-baseline to baseline ratios at 3, 6, 9, 12, 18, and 24 months. Data included at baseline and 24 months are the log of the geometric mean of the two replicate values recorded at each timepoint, respectively. The corresponding percentage reduction and confidence interval was derived from (1− ratio of geometric least squares means) × 100. UPCR=urine protein–creatinine ratio.

12 months, with a reduction in UPCR of 49·7% (41·6–56·6).

Results from the UACR analysis were consistent with those for UPCR, with the Nefecon group showing a 46·3% (36·5–54·5) reduction in time-averaged UACR between 12 and 24 months compared with the placebo group (p<0·0001; appendix p 11). The proportion of patients without microhaematuria during the observational follow-up period was significantly higher in the Nefecon group than in the placebo group (in patients with two or more urine dipstick results during the observational period, 94 [59%] of 158 *vs* 59 [39%] of 152; odds ratio for Nefecon *vs* placebo 2·5 [95% CI 1·6–4·1], p=0·0001; appendix p 12). Results of other secondary efficacy analyses were generally supportive of the overall beneficial effect of Nefecon treatment (appendix pp 13–14).

During the 9-month treatment period, Nefecon 16 mg/day was well tolerated, with a safety profile as expected for a locally acting oral budesonide product. Discontinuations due to treatment-emergent adverse events occurred in 17 (9%) of 182 patients in the Nefecon group and three (2%) of 182 in the placebo group (table 3). Treatment-emergent serious adverse events were reported in 18 (10%) patients in the Nefecon group and nine (5%) patients in the placebo group, with most considered unrelated to study treatment (table 3), and no discernible patterns in terms of body system or organ (appendix p 15). During the 15-month observational follow-up, the incidence of treatment-emergent adverse events and treatment-emergent serious adverse events was similar between the groups.

One death due to SARS-CoV-2 infection was reported during Nefecon treatment in a patient with several risk factors for COVID-19 mortality, and another patient treated with Nefecon died from a cerebral haemorrhage 10·5 months after their last dose. Neither death was considered to be related to study treatment. No treatment-emergent adverse events leading to death were reported in the placebo group.

The most commonly reported treatment-emergent adverse events during treatment with Nefecon were peripheral oedema (31 [17%] of 182 patients *vs* placebo, seven [4%] of 182 patients), hypertension (22 [12%] *vs* six [3%]), muscle spasms (22 [12%] *vs* seven [4%] patients), acne (20 [11%] *vs* two [1%]), and headache (19 [10%] *vs* 14 [8%]); appendix p 15). These were generally non-serious adverse events and were of mild severity, and reversible during or after treatment. In the Nefecon group, two patients had hypertension events, and one patient had both peripheral and face oedema events, all of which were classed as serious; a fourth patient had a peripheral oedema event that was graded as severe (appendix p 15). During the observational follow-up, frequencies of the most commonly reported treatment-emergent adverse events were similar in both treatment groups, including of SARS-CoV-2 infection, which was the most frequently reported event (26 [15%] of 175 patients in the Nefecon group and 30 [17%] of 174 in the placebo group), among patients who had a study visit during the observational follow-up; appendix p 16).

The incidence of infections during treatment was similar between treatment groups (63 [35%] of 182 patients

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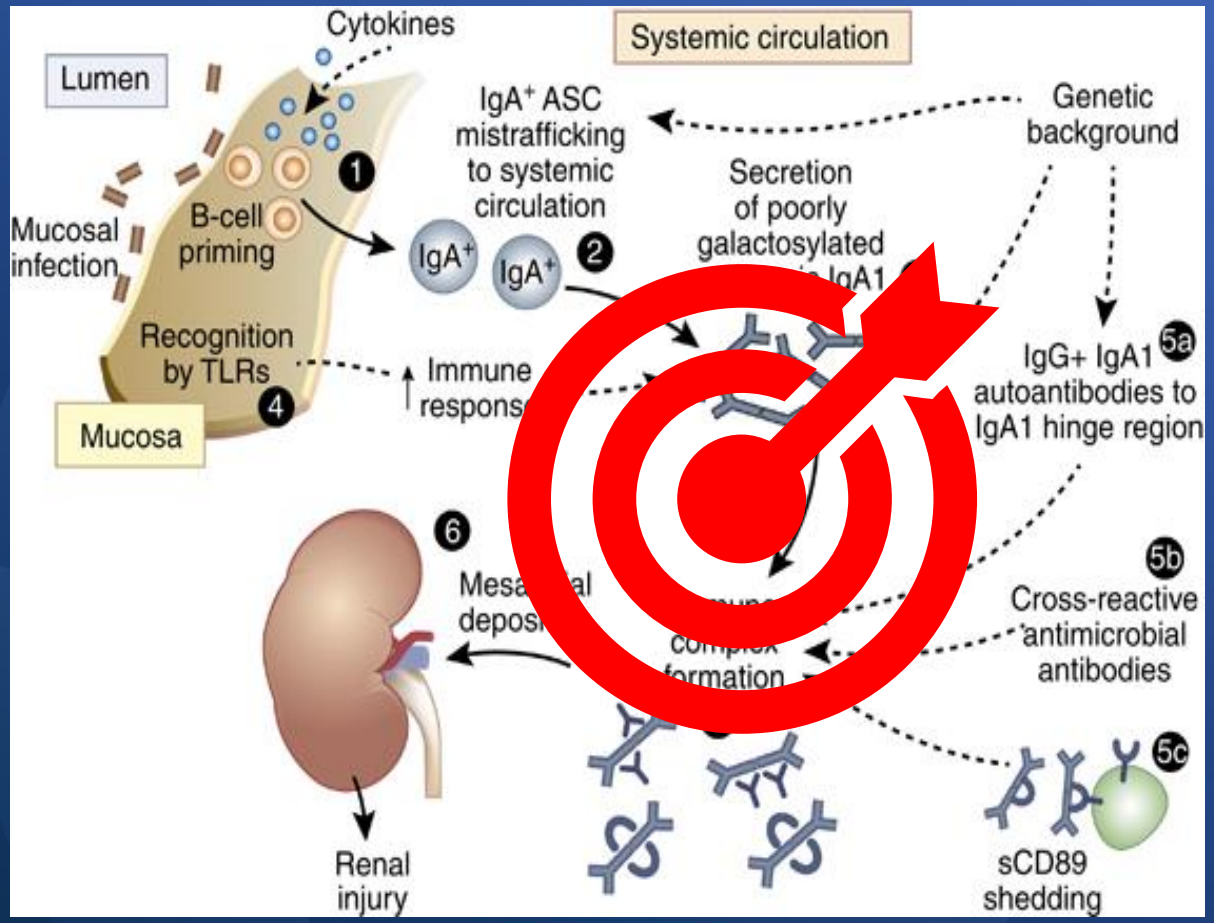

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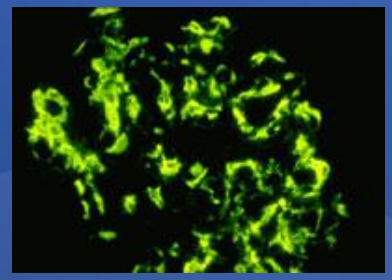

Pathogenic IgA Synthesis & IgA immune complex formation

B cell depletion

B cell modulation

IgA degraders

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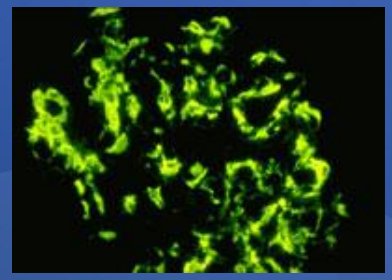

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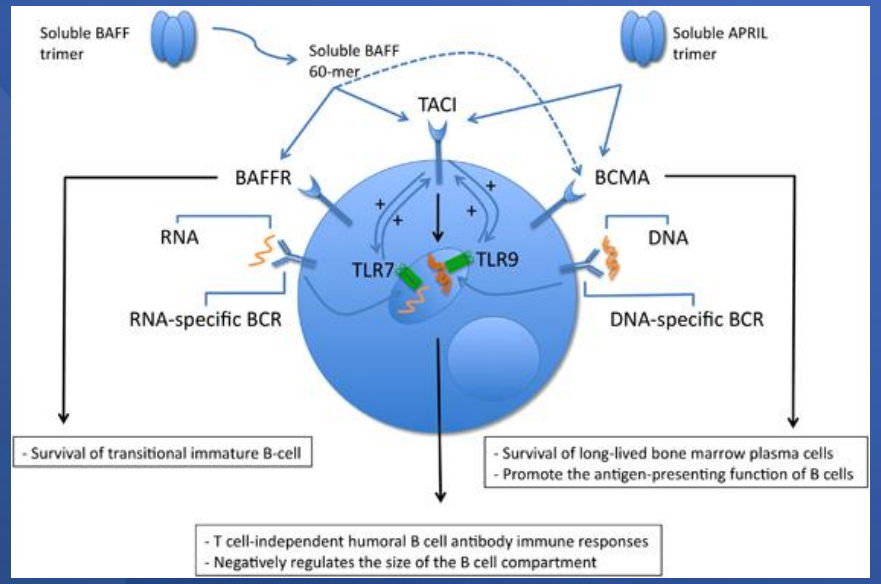

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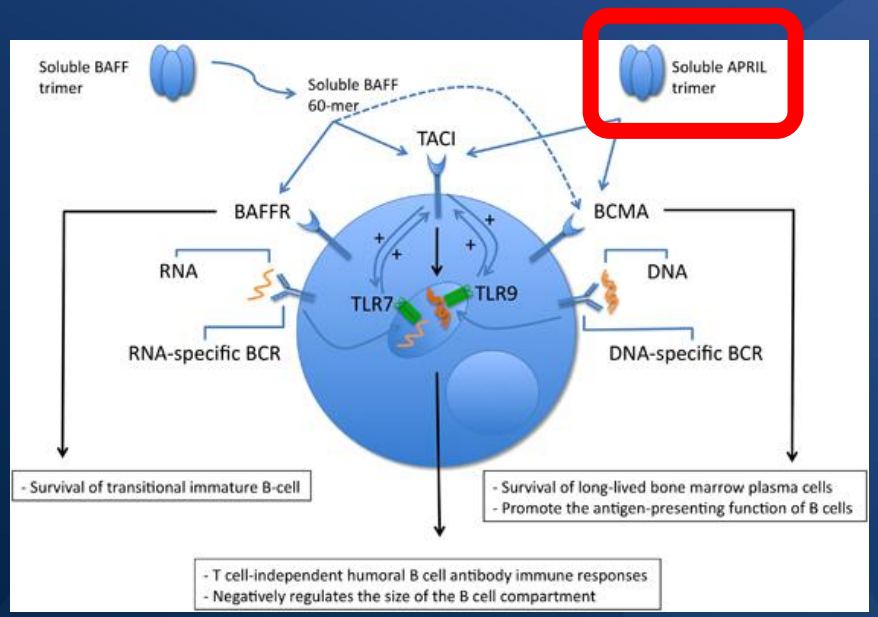

ACTIVE, NOT RECRUITING

Visionary Study: Phase 3 Trial of Sibeprenlimab in Immunoglobulin A Nephropathy (IgAN)

ClinicalTrials.gov ID NCT05248646

Sponsor Otsuka Pharmaceutical Development & Commercialization, Inc.

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RECRUITING

A Study of BION-1301 in Adults With IgA Nephropathy

ClinicalTrials.gov ID NCT05852938

Sponsor Chinook Therapeutics, Inc.

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Last Update Posted 2024-04-19

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Recruiting

Trial of the Impact of Sibeprenlimab on Immunoglobulin A Nephropathy Kidney Tissue

ClinicalTrials.gov ID NCT06740526

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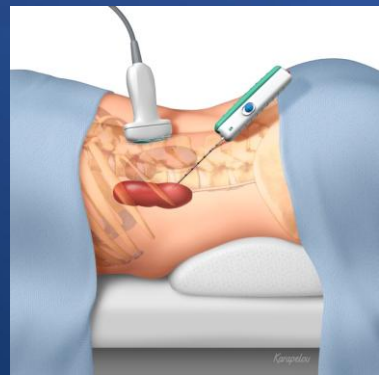

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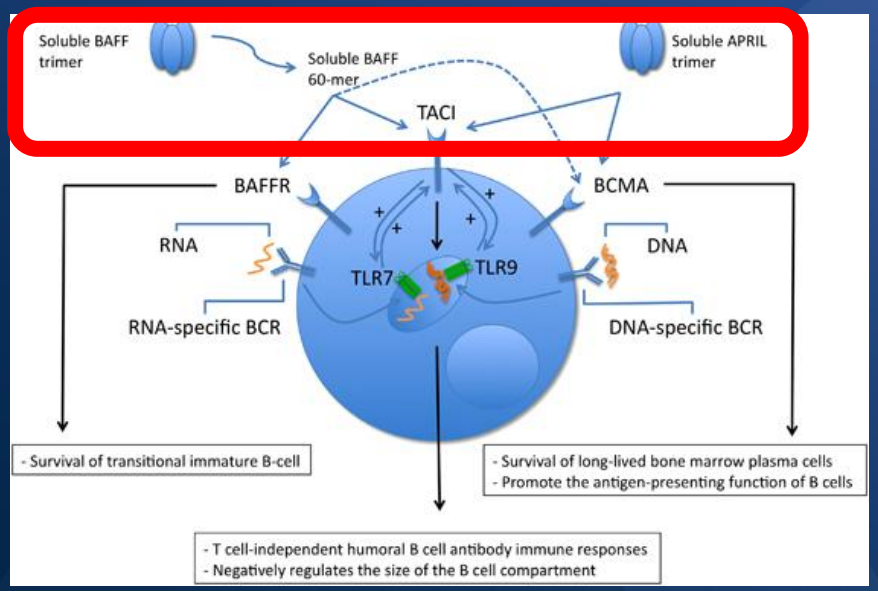

RECRUITING

Atacicept in Subjects With IgA Nephropathy (ORIGIN 3)

ClinicalTrials.gov ID NCT04716231

Sponsor Vera Therapeutics, Inc.

Information provided by Vera Therapeutics, Inc. (Responsible Party)

Last Update Posted 2023-11-29

RECRUITING

A Study of Telitacicept in Patients With Primary IgA Nephropathy

ClinicalTrials.gov ID NCT05799287

Sponsor RemeGen Co., Ltd.

Information provided by RemeGen Co., Ltd. (Responsible Party)

Last Update Posted 2023-09-06

Recruiting

Evaluation of Efficacy of Povetacicept in Adults With Immunoglobulin A Nephropathy (IgAN)

ClinicalTrials.gov ID NCT06564142

Sponsor Alpine Immune Sciences Inc, A Subsidiary of Vertex

Information provided by Alpine Immune Sciences, Inc. (Alpine Immune Sciences Inc, A Subsidiary of Vertex) (Responsible Party)

Last Update Posted 2024-12-05

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pioneer

pioneer

Population 1
Expanded IgAN populations*
- Adults with biopsy-proven IgAN or IgAVN
  - Minimum eGFR 20 mL/min/1.73m^2
  - Minimum UPCR 0.5 g/g
- Children (age 10 to <18 y) with biopsy-proven IgAN or IgAVN (UPCR ≥1 g/g)
- Adults with recurrent IgAN post-transplant

Population 2
Anti-PLA2R membranous nephropathy

Population 3
Anti-nephrin podocytopathy (MCD/FSGS)

Recruiting

Monthly Dosing of Atacicept in IgAN

ClinicalTrials.gov ID NCT07020923

Sponsor Vera Therapeutics, Inc.

Information provided by Vera Therapeutics, Inc. (Responsible Party)

Last Update Posted 2025-06-24

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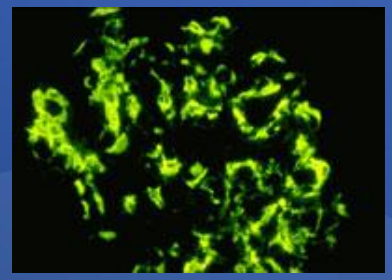

Pathogenic IgA Synthesis & IgA immune complex formation

B cell depletion

B cell modulation

IgA degraders

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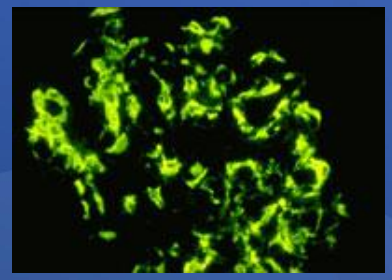

CLINICAL RESEARCH www.jasn.org

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‖

*Division of Nephrology and Hypertension, Stanford University, Stanford, California; †Division of Nephrology and Hypertension, Columbia University Medical Center, New York, New York; ‡Division of Nephrology, Ohio State University, Columbus, Ohio; Departments of §Microbiology and ††Medicine, University of Alabama at Birmingham, Birmingham, Alabama; ‖Division of Nephrology and Hypertension, ¶Department of Laboratory Medicine and Pathology, and ‡‡Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota; **Division of Nephrology, University of Tennessee, Chattanooga, Tennessee; and §§§Department of Immunology, Faculty of Medicine and Dentistry, Palacky University and University Hospital, Olomouc, Czech Republic

Pathogenic IgA Synthesis & IgA immune complex formation

B cell depletion

B cell modulation

IgA degraders

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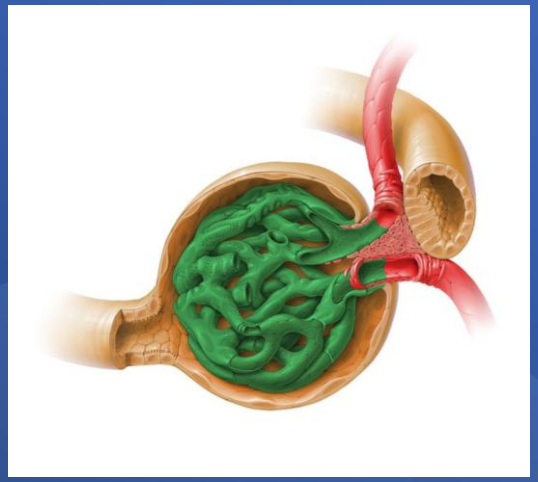

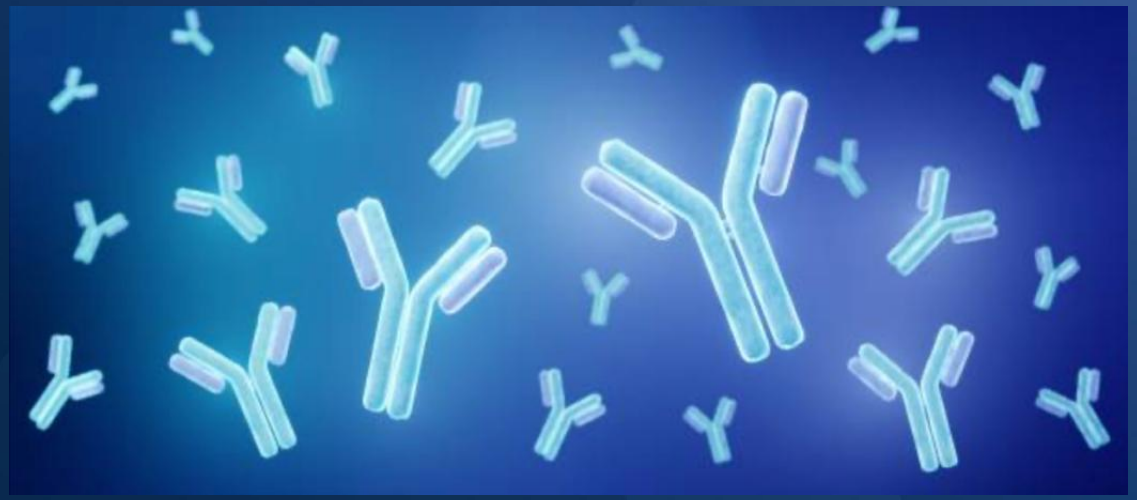

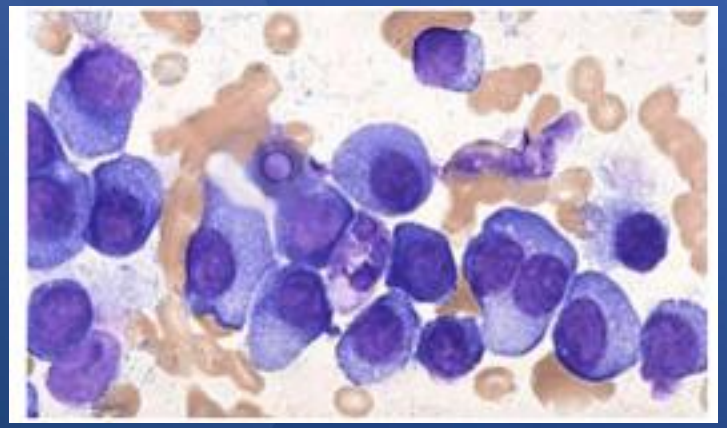

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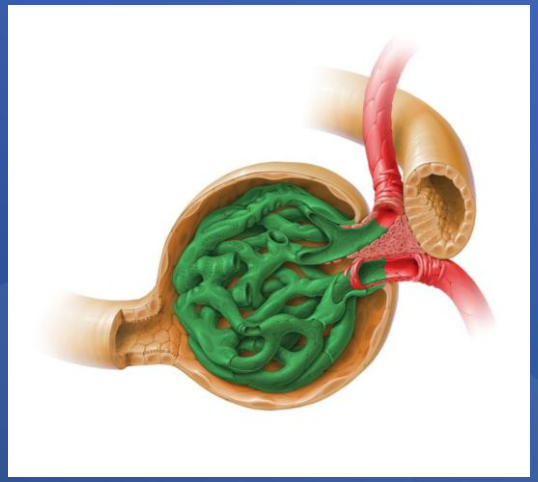

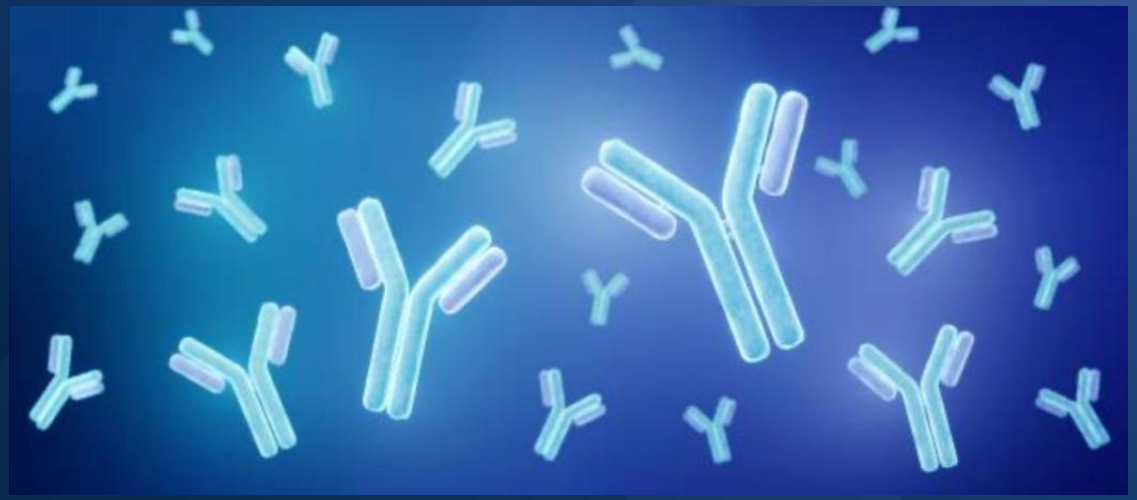

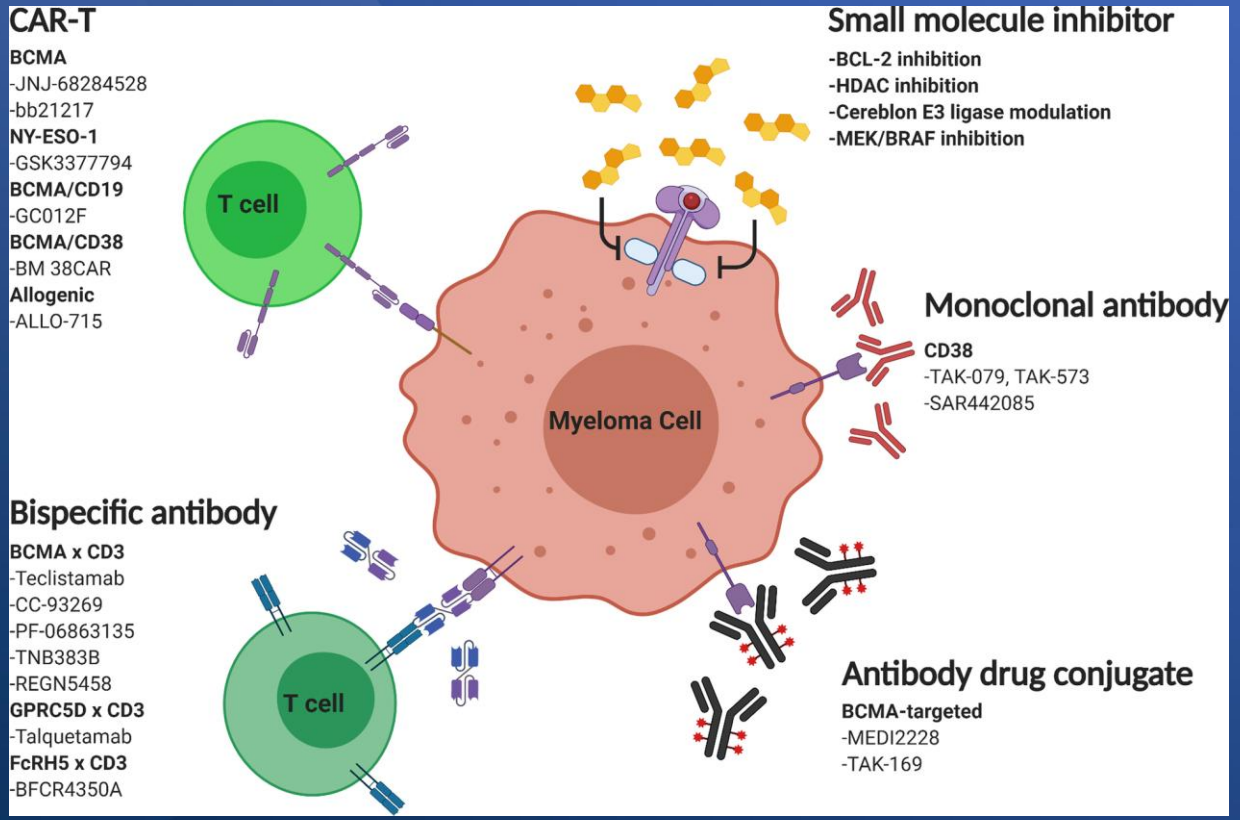

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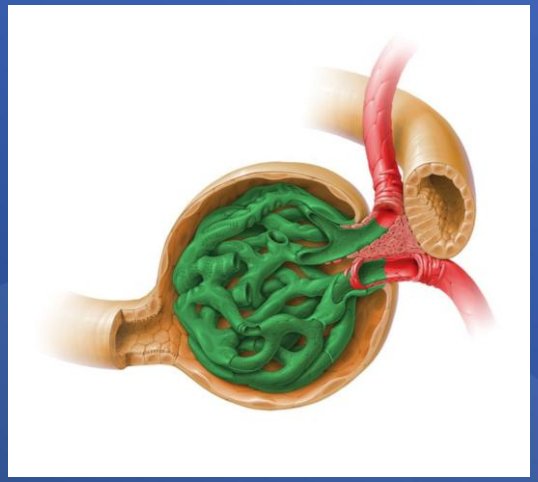

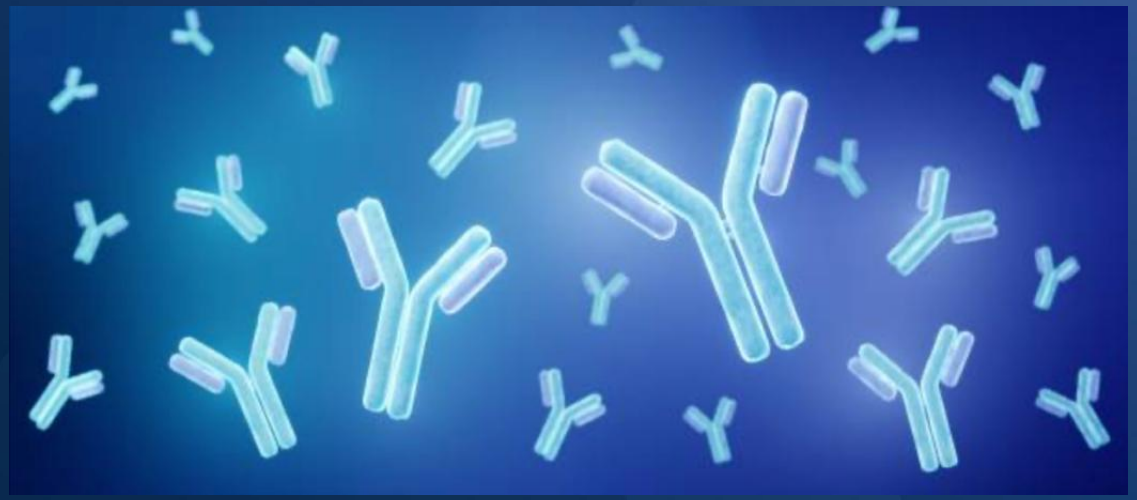

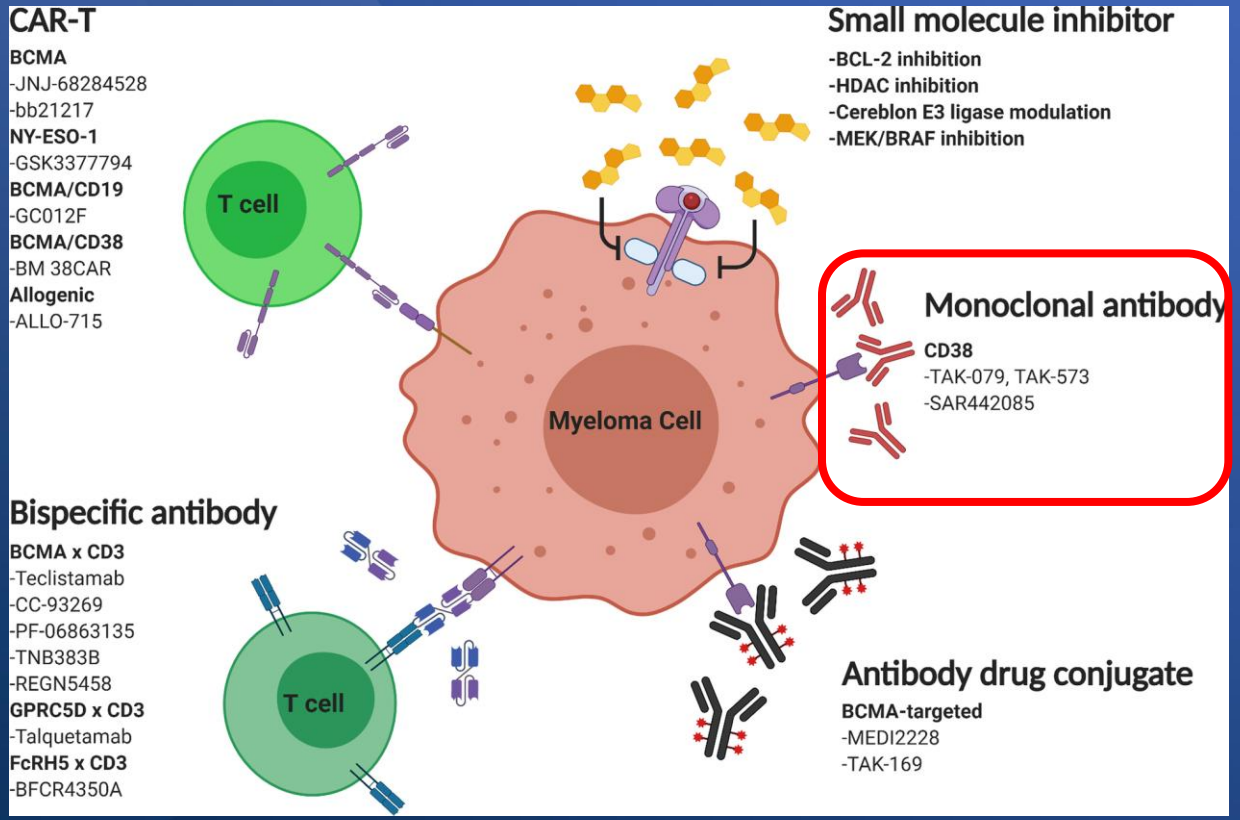

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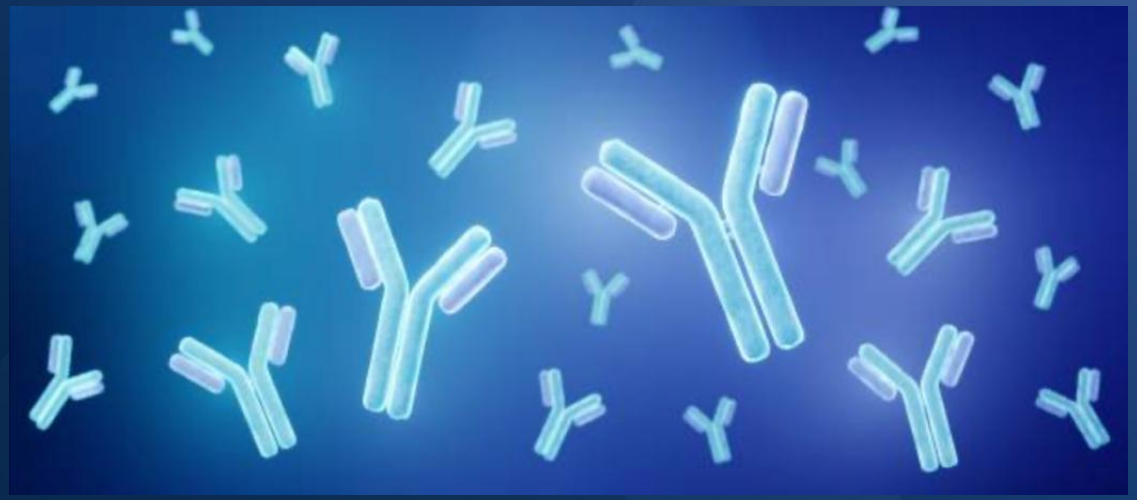

NCT06935357 Recruiting

A Study to Learn About the Effects of Felzartamab Infusions on Adults With Immunoglobulin A Nephropathy (IgAN)

Conditions

Immunoglobulin A Nephropathy (IgAN)

Locations

Little Rock, Arkansas, United States
Apple Valley, California, United States
Oxnard, California, United States
San Dimas, California, United States

Show all 59 locations

PREVAIL

NCT06963827 Recruiting

A Study of Mezagitamab in Adults With Primary IgA Nephropathy Kidney Condition

Conditions

Kidney Disease

Locations

Montgomery, Alabama, United States
Los Angeles, California, United States
Lauderdale Lakes, Florida, United States
Miami, Florida, United States

Show all 33 locations

AMIgA STUDY

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Pathogenic IgA Synthesis & IgA immune complex formation

B cell depletion

B cell modulation

IgA degraders

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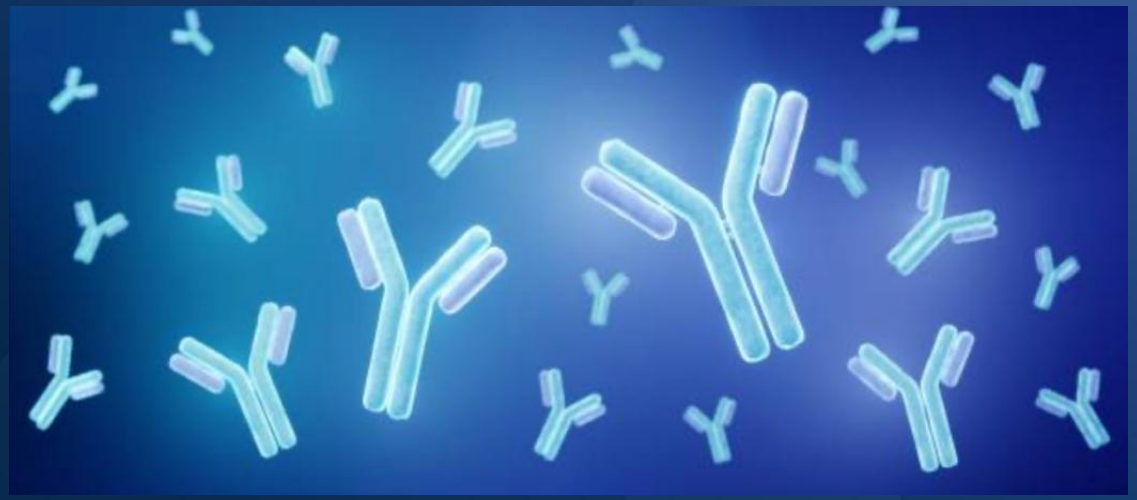
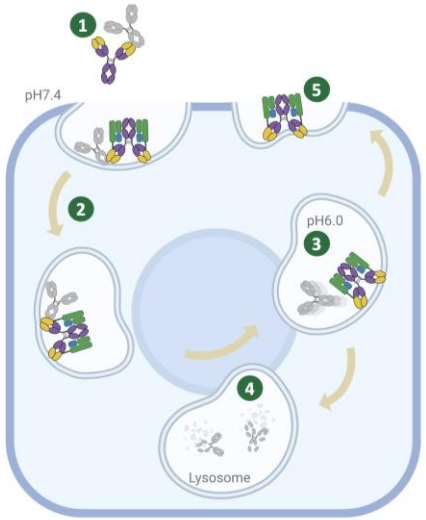
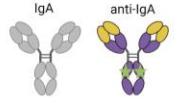


Development of a sweeping and blocking anti-IgA antibody

FcRn-mediated removal of circulating IgA





1. Anti-IgA binds to circulating IgA
2. Receptor-mediated endocytosis of anti-IgA in complex with IgA
3. Complex dissociates in endosomes
4. IgA is degraded in the lysosomes
5. Anti-IgA recycles back through enhanced FcRn binding and remains bound to FcRn

★ LALAPG mutations to avoid FcγR and C1q binding

8

argenx

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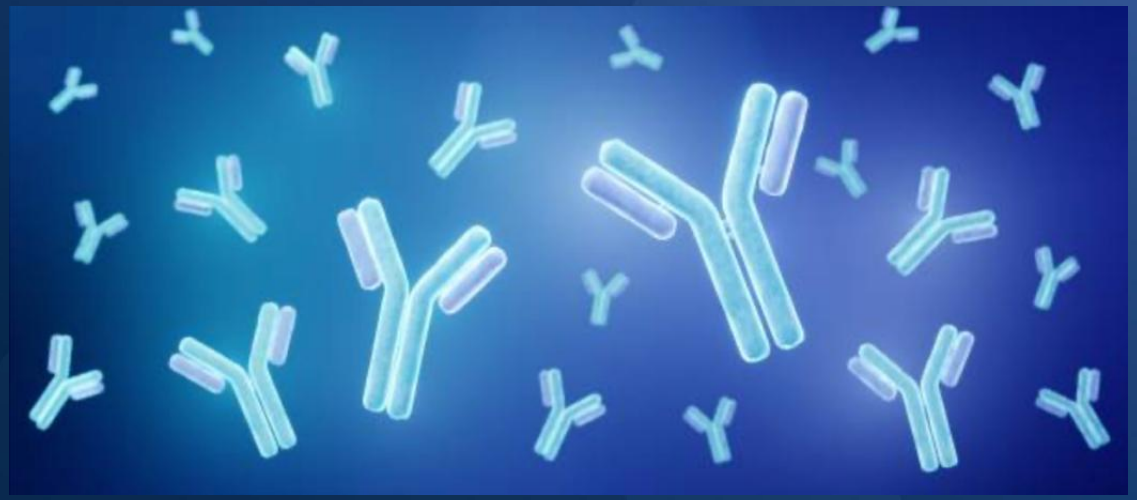
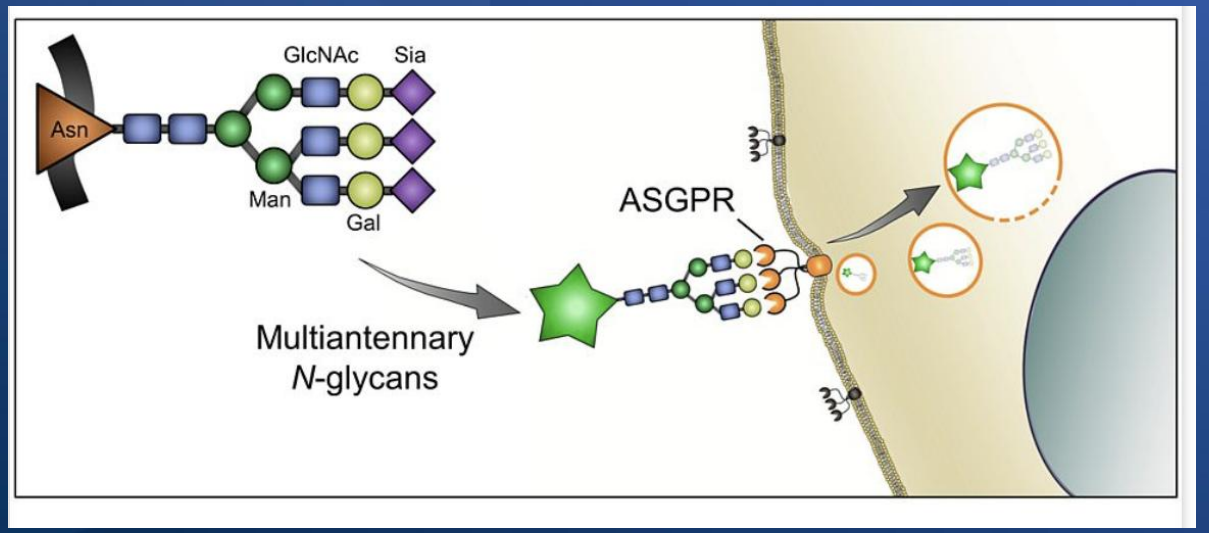


biohaven

Biohaven Highlights Portfolio Progress, Innovation, and Anticipated Milestones at the 43rd Annual J.P. Morgan Healthcare Conference; Reports Positive Degrader Data with Rapid, Deep, and Selective Lowering of Galactose-Deficient IgA1 with Next Generation Potential Therapy for IgA Nephropathy

January 13, 2025



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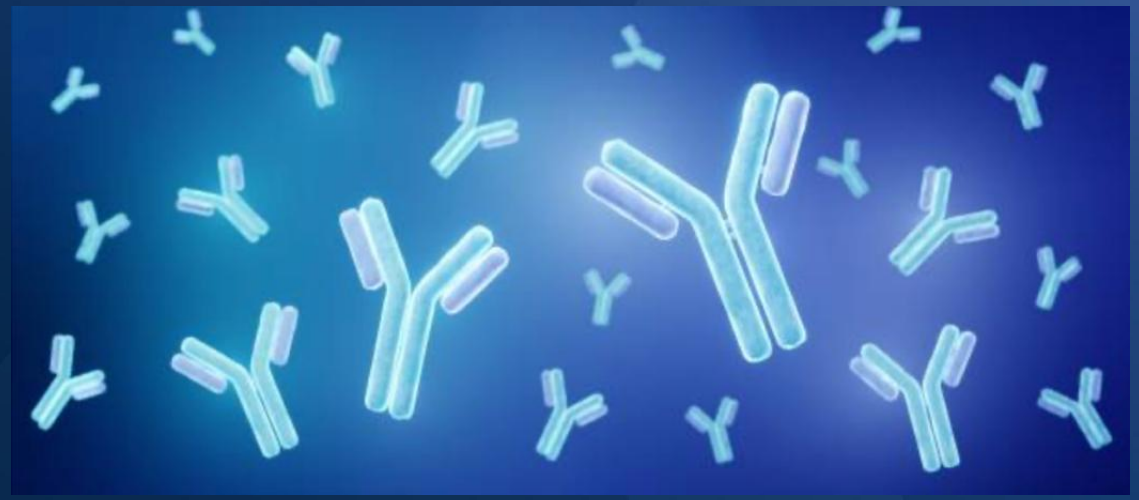

biohaven

Biohaven Highlights Portfolio Progress, Innovation, and Anticipated Milestones at the 43rd Annual J.P. Morgan Healthcare Conference; Reports Positive Degrader Data with Rapid, Deep, and Selective Lowering of Galactose-Deficient IgA1 with Next Generation Potential Therapy for IgA Nephropathy

January 13, 2025

☐ **NCT07054684** Recruiting New

Study of BHV-1400 in IgA Nephropathy

Conditions

IgA Nephropathy

Locations

Miami Lakes, Florida, United States

Pembroke Pines, Florida, United States

Chesterfield, Missouri, United States

Dakota Dunes, South Dakota, United States

Show all 5 locations

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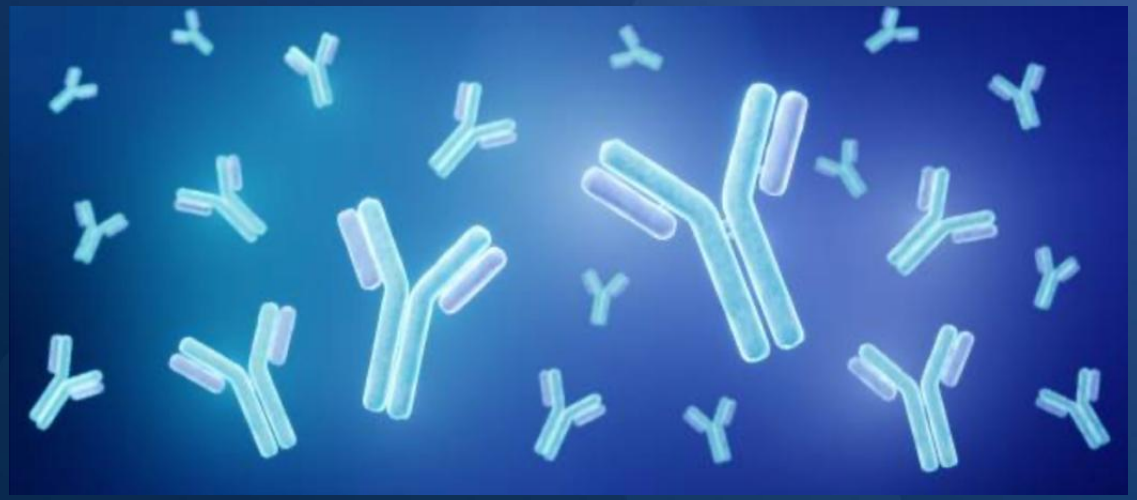

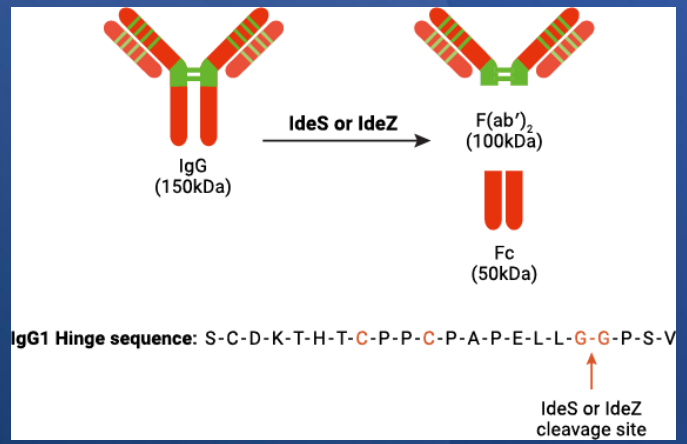

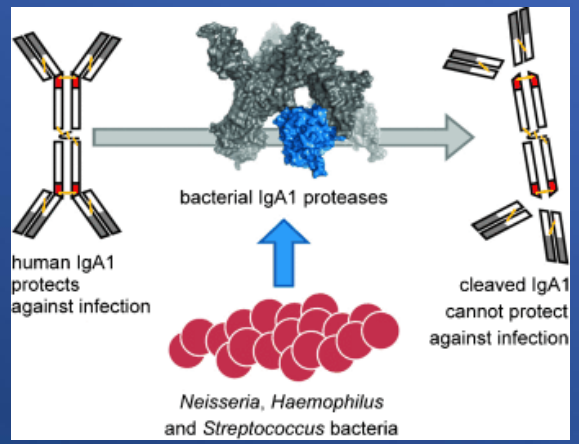

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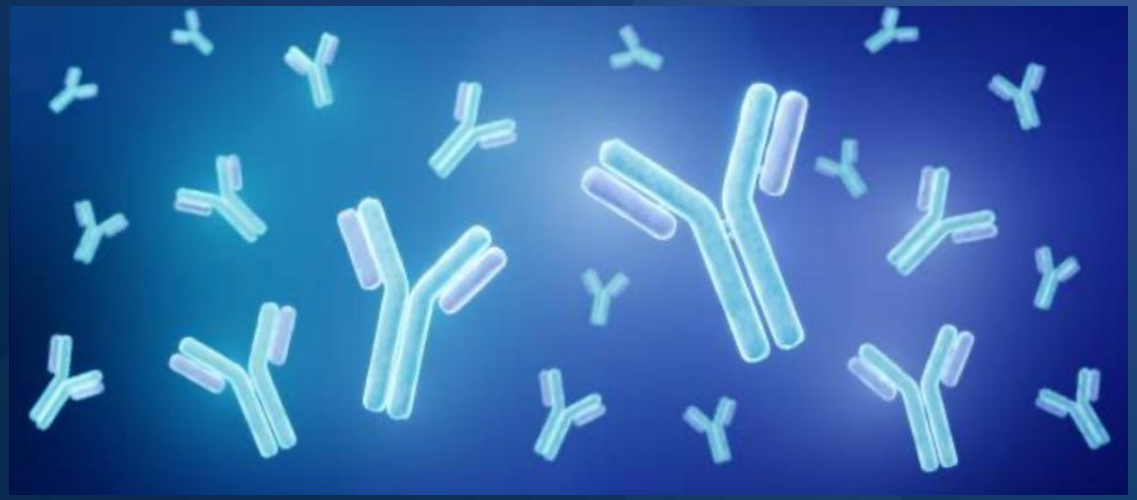

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

IgG Endopeptidase in Highly Sensitized Patients Undergoing Transplantation

S.C. Jordan, T. Lorant, J. Choi, C. Kjellman, L. Winstedt, M. Bengtsson, X. Zhang, T. Eich, M. Toyoda, B.-M. Eriksson, S. Ge, A. Peng, S. Järnum, K.J. Wood, T. Lundgren, L. Wennberg, L. Bäckman, E. Larsson, R. Villicana, J. Kahwaji, S. Louie, A. Kang, M. Haas, C. Nast, A. Vo, and G. Tufveson

ABSTRACT

BACKGROUND

Donor-specific antibodies create an immunologic barrier to transplantation. Current therapies to modify donor-specific antibodies are limited and ineffective in the most highly HLA-sensitized patients. The IgG-degrading enzyme derived from *Streptococcus pyogenes* (IdeS), an endopeptidase, cleaves human IgG into $F(ab')_2$ and Fc fragments inhibiting complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity, which suggests that IdeS might be useful for desensitization. We report on the combined experience of two independently performed open-label, phase 1–2 trials (conducted in Sweden and the United States) that assessed the efficacy of IdeS with regard to desensitization and transplantation of a kidney from an HLA-incompatible donor.

METHODS

We administered IdeS to 25 highly HLA-sensitized patients (11 patients in Uppsala or Stockholm, Sweden, and 14 in Los Angeles) before the transplantation of a kidney from an HLA-incompatible donor. Frequent monitoring for adverse events, outcomes, donor-specific antibodies, and renal function was performed, as were renal biopsies. Immunosuppression after transplantation consisted of tacrolimus, mycophenolate mofetil, and glucocorticoids. Patients in the U.S. study also received intravenous immune globulin and rituximab after transplantation to prevent antibody rebound.

RESULTS

Recipients in the U.S. study had a significantly longer cold ischemia time (the time elapsed between procurement of the organ and transplantation), a significantly higher rate of delayed graft function, and significantly higher levels of class I donor-specific antibodies than those in the Swedish study. A total of 38 serious adverse events occurred in 15 patients (5 events were adjudicated as being possibly related to IdeS). At transplantation, total IgG and HLA antibodies were eliminated. A total of 24 of 25 patients had perfusion of allografts after transplantation. Antibody-mediated rejection occurred in 10 patients (7 patients in the U.S. study and 3 in the Swedish study) at 2 weeks to 5 months after transplantation; all these patients had a response to treatment. One graft loss, mediated by non-HLA IgM and IgA antibodies, occurred.

CONCLUSIONS

IdeS reduced or eliminated donor-specific antibodies and permitted HLA-incompatible transplantation in 24 of 25 patients. (Funded by Hansa Medical; ClinicalTrials .gov numbers, NCT02224820, NCT02426684, and NCT02475551.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Jordan at the Comprehensive Transplant Center, Cedars–Sinai Medical Center, 8900 Beverly Blvd., Los Angeles, CA 90048, or at sjordan@cshs.org.

Drs. Jordan and Lorant, and Drs. Vo and Tufveson, contributed equally to this article.

This article was last updated on October 6, 2017, at NEJM.org.

N Engl J Med 2017;377:442-53.
DOI: 10.1056/NEJMoa1612562

BRIEF COMMUNICATION www.jasn.org

IgA1 Protease Treatment Reverses Mesangial Deposits and Hematuria in a Model of IgA Nephropathy

Sebastian M. Lechner,*†‡§ Lilia Abbad,*†‡§ Erwan Boedec,*†‡§ Christina Papista,*†‡§ Marie-Bénédicte Le Stang,*†‡§ Christelle Moal,*†‡§ Julien Maillard,*†‡§ Agnès Jamin,*†‡§ Julie Bex-Coudrat,*†‡§ Yong Wang,‖ Aiqun Li,‖ Paolo G.V. Martini,‖ Renato C. Monteiro,*†‡§¶ and Laureline Berthelot*†‡§

*National French Institute of Health and Medical Research (INSERM) Unit 1149, Center of Research on Inflammation, Paris, France; †Laboratory of Inflamex Excellency, Faculty of Medicine, Xavier Bichat Site, Paris, France; ‡Paris Diderot University, Sorbonne Paris Cité, Paris, France; §National French Center of Scientific Research (CNRS) ERL8252, Paris, France; ‖Shire, Bioprocess Development and Discovery Biology and Translational Research, Lexington, Massachusetts; and ¶Immunology Department, Bichat Hospital, Paris Public Assistance Hospitals, Department of Hospital and University (DHU) Fire, Paris, France

ABSTRACT

IgA nephropathy (IgAN), characterized by mesangial IgA1 deposits, is a leading cause of renal failure worldwide. IgAN pathogenesis involves circulating hypogalactosylated IgA1 complexed with soluble IgA Fc receptor I (sCD89) and/or anti–hypogalactosylated-IgA1 autoantibodies, but no specific treatment is available for IgAN. The absence of IgA1 and CD89 homologs in the mouse has precluded *in vivo* proof-of-concept studies of specific therapies targeting IgA1. However, the α1KI-CD89Tg mouse model of IgAN, which expresses human IgA1 and human CD89, allows *in vivo* testing of recombinant IgA1 protease (IgA1-P), a bacterial protein that selectively cleaves human IgA1. Mice injected with IgA1-P (1–10 mg/kg) had Fc fragments of IgA1 in both serum and urine, associated with a decrease in IgA1–sCD89 complexes. Levels of mesangial IgA1 deposits and the binding partners of these deposits (sCD89, transferrin receptor, and transglutaminase 2) decreased markedly 1 week after treatment, as did the levels of C3 deposition, $CD11b^+$ infiltrating cells, and fibronectin. Antiprotease antibodies did not significantly alter IgA1-P activity. Moreover, hematuria consistently decreased after treatment. In conclusion, IgA1-P strongly diminishes human IgA1 mesangial deposits and reduces inflammation, fibrosis, and hematuria in a mouse IgAN model, and therefore may be a plausible treatment for patients with IgAN.

J Am Soc Nephrol 27: 2622–2629, 2016. doi: 10.1681/ASN.2015080856

IgA nephropathy (IgAN) is the most common primary GN worldwide. The hallmark of the disease is the mesangial deposition of IgA1-immune complexes.[1,2] IgAN patients exhibit circulating galactose-deficient IgA1,[3,4] which can form complexes with its soluble receptor CD89[5–7] and with autoantibodies that specifically recognize galactose-deficient IgA1.[8] Recently, these factors have been identified as valuable biomarkers to predict disease progression and its recurrence after transplantation.[9,10] Human and mouse studies have revealed pathogenic mechanisms by which IgA1 complexes get trapped in the mesangium *via* their interaction with an alternative IgA1 receptor, the transferrin receptor (TfR).[11–13] This induces transglutaminase 2 (TG2) overexpression and activation of mesangial cells, which can be associated with the recruitment of inflammatory cells and the progressive destruction of glomerular filtration.[2,14]

There are no specific treatments for IgAN. Clinicians routinely use angiotensin-converting enzyme inhibitors[15] or angiotensin II receptor antagonists to treat patients with proteinuric or hypertensive IgAN.[16,17] In cases of severe progressive IgAN, immunosuppressive therapies are suggested. Long-term corticosteroid treatments have been shown to be effective in patients with proteinuria and preserved renal function, but their use is still controversial.[18–21] Other treatments, such as tonsillectomy,[22] fish oil,[23] or a gluten-free diet,[24,25] focus on mucosal immunity. Some of these treatments have demonstrated their efficacy

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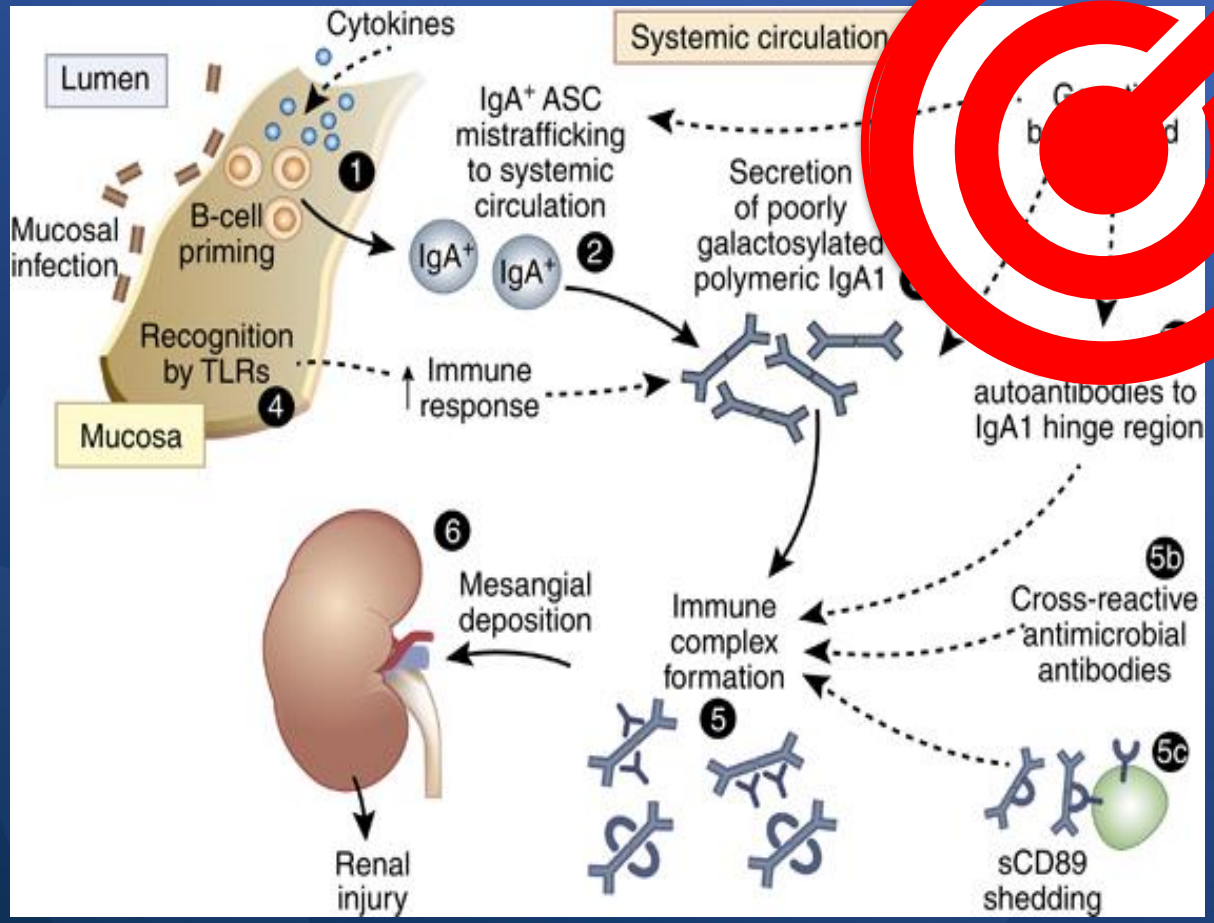

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Leicester IgA Nephropathy Research Group

Not yet recruiting

PS-002 for the Treatment of IgA Nephropathy in Adults

ClinicalTrials.gov ID NCT07182227

Sponsor Purespring Therapeutics Limited

Information provided by Purespring Therapeutics Limited (Responsible Party)

Last Update Posted 2025-09-19

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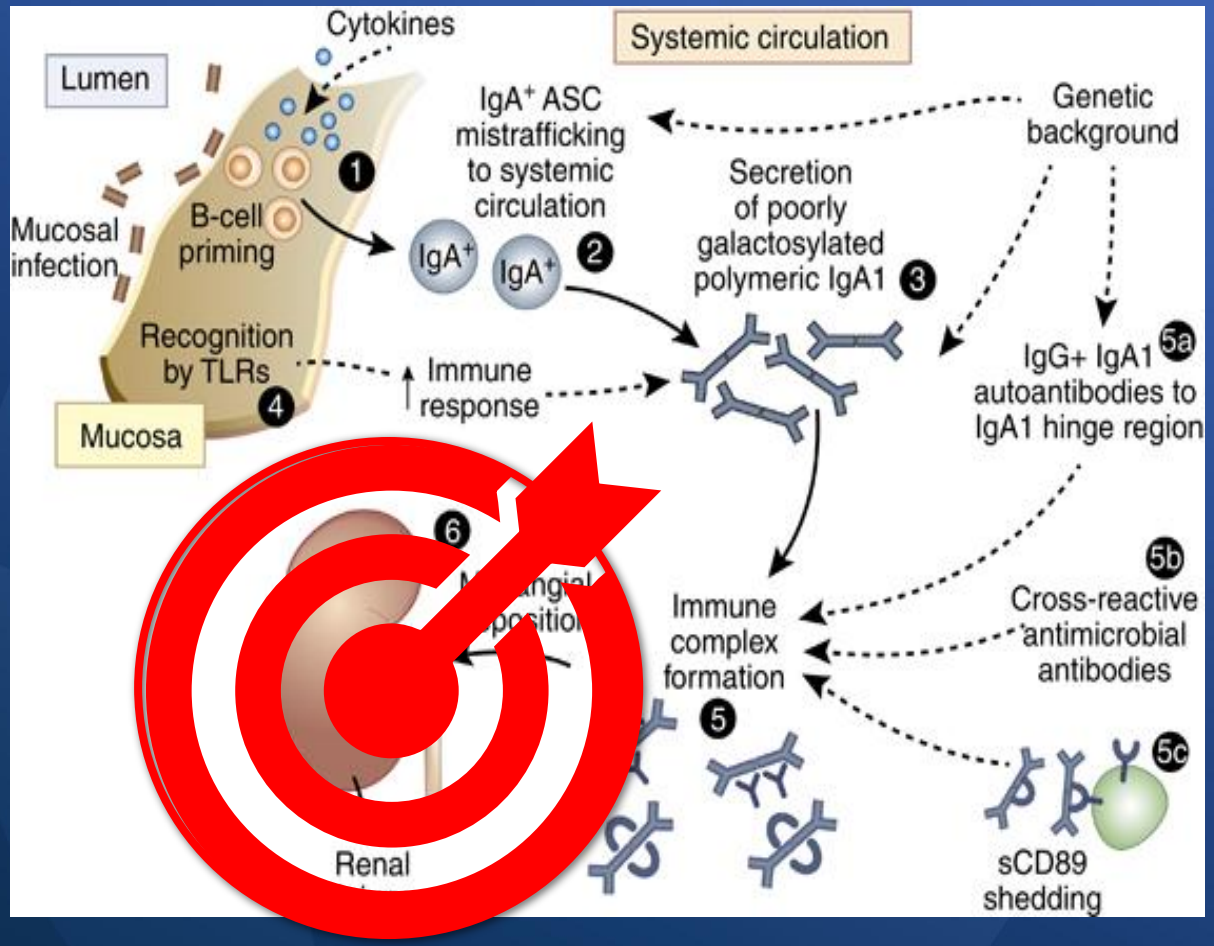

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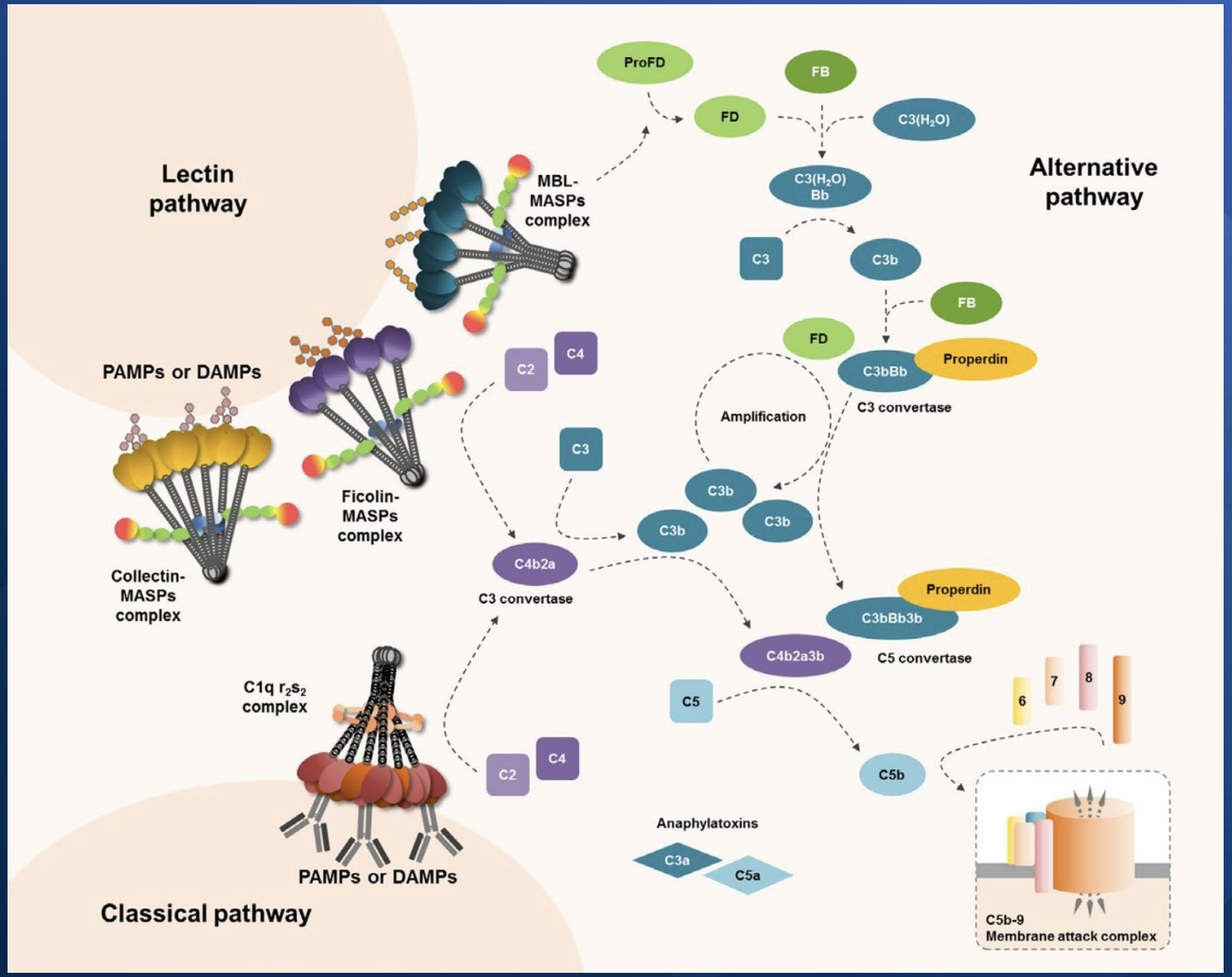

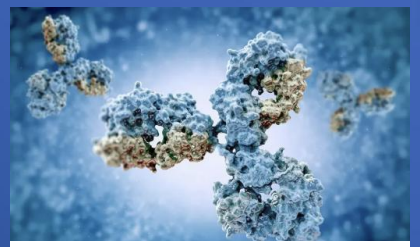

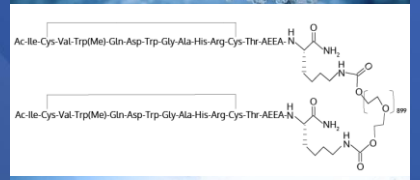

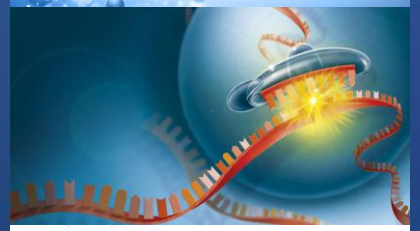

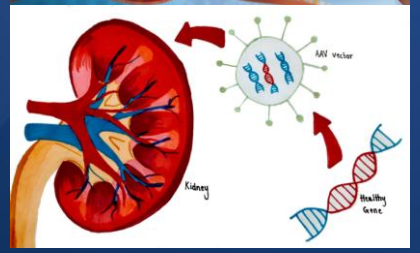

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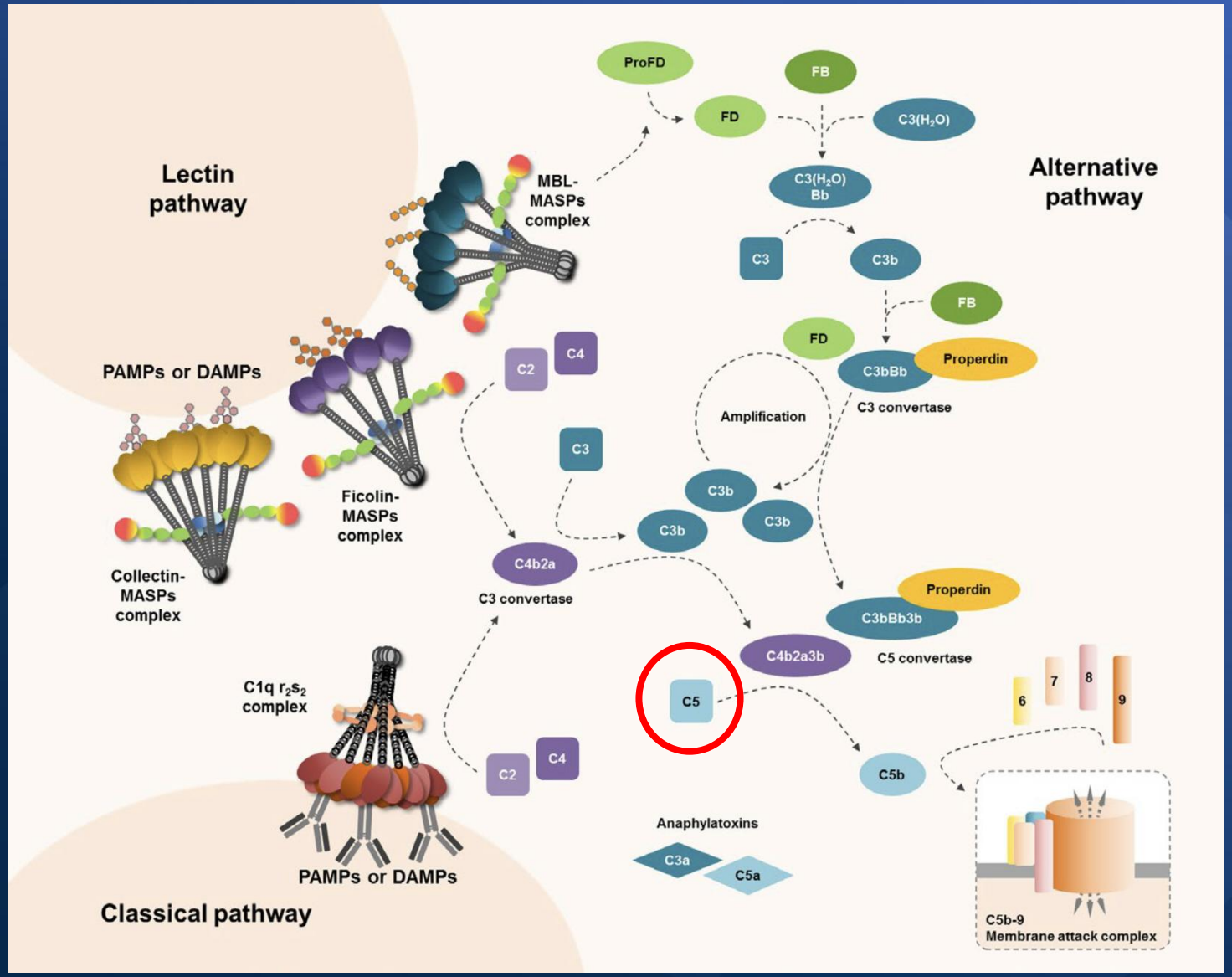

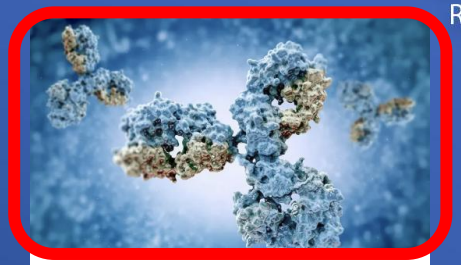

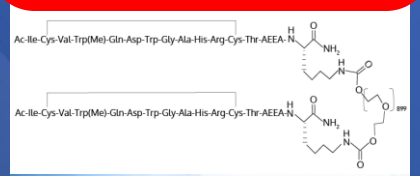

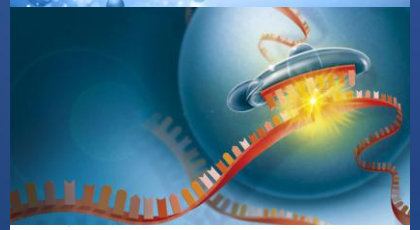

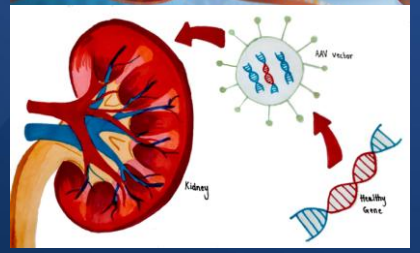

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Clinical Research

OPEN

Efficacy and Safety of Ravulizumab in IgA Nephropathy
A Phase 2 Randomized Double-Blind Placebo-Controlled Trial

Richard Lafayette,[1] James Tumlin,[2] Roberta Fenoglio,[3] Jessica Kaufeld,[4] Miguel Ángel Pérez Valdivia,[5] Mai-Szu Wu,[6] Shih-Han Susan Huang,[7] Eric Alamartine,[8] Sung Gyun Kim,[9] Min Yee,[10] Andreas Kateifides,[10] Kara Rice,[10] Katherine Garlo,[10] Jonathan Barratt,[11] and the SANCTUARY Study Investigators*

Key Points

- This phase 2, double-blind, randomized controlled trial evaluated the complement C5 inhibitor, ravulizumab, in adults with IgA nephropathy.
- A 30.1% (90% confidence interval, 13.7% to 43.5%) relative reduction in proteinuria for ravulizumab versus placebo was observed at approximately 6 months.
- Treatment with ravulizumab was well tolerated.

Abstract

Background The complement system plays a central role in the pathogenesis of IgA nephropathy. We present findings from a phase 2 trial of ravulizumab, a complement C5 inhibitor.

Methods The Study of Ravulizumab in Proliferative Lupus Nephritis or IgA Nephropathy (NCT04564339) was a randomized, double-blind, placebo-controlled trial of ravulizumab in addition to standard of care. Adults with IgA nephropathy, proteinuria ≥1 g/d, and eGFR ≥30 ml/min per 1.73 m^2, and on stable renin-angiotensin blockade were randomized 2:1 to ravulizumab (intravenous every 8 weeks) or placebo for 26 weeks. From week 26–50, all participants received open-label ravulizumab. The primary end point was percentage change in proteinuria from baseline to week 26. Secondary end points included change in proteinuria at week 50 and eGFR. Safety, pharmacokinetics, and pharmacodynamics were evaluated.

Results Forty-three patients were randomized to ravulizumab and 23 to placebo. At week 26, a statistically significant reduction in proteinuria was observed with ravulizumab versus placebo: −41.9% (95% confidence interval [CI], −50.2% to −32.0%) change in urine protein with ravulizumab and −16.8% (95% CI, −31.8% to 1.6%) change with placebo (30.1% treatment effect; $P = 0.005$). At week 50, there was a −44.8% (95% CI, −55.1% to −32.1%) change from baseline in urine protein with ravulizumab, and in patients who crossed over from placebo to ravulizumab at week 26, the change from baseline (week 0) to week 50 was −45.1% (−58.0% to −28.4%). The least squares mean change in eGFR from baseline to week 26 with ravulizumab was 0.2 (95% CI, −2.3 to 2.7) ml/min per 1.73 m^2 and with placebo was −4.5 (−7.9 to −1.1) ml/min per 1.73 m^2. From baseline to week 50, the least squares mean change in eGFR with ravulizumab was −3.9 (95% CI, −6.4 to−1.3) ml/min per 1.73 m^2, and in patients who crossed over from placebo to ravulizumab at week 26, it was −6.3 (−9.7 to −2.9) ml/min per 1.73 m^2. Ravulizumab was well tolerated, with an adverse event profile similar to that for placebo.

Conclusions An early, sustained, and clinically meaningful reduction in proteinuria and trend toward stabilization of eGFR were observed with ravulizumab versus placebo. A phase 3 trial (NCT06291376) is enrolling.

Clinical Trial registry name and registration number: Study of Ravulizumab in Proliferative Lupus Nephritis or IgA Nephropathy, NCT04564339.

JASN 00: 1–12, 2024. doi: https://doi.org/10.1681/ASN.0000000534

Due to the number of contributing authors, the affiliations are listed at the end of this article.

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*The list of nonauthor contributors is extensive and has been provided in Supplemental Summary 1.

ICAN

CLINICAL STUDY FOR PATIENTS WITH IgAN

RECRUITING

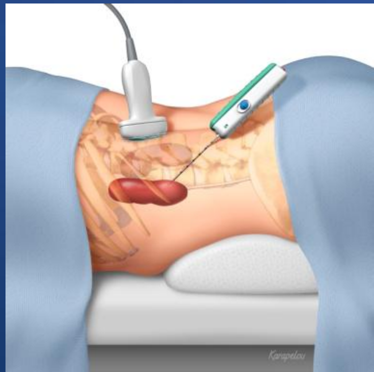
Study of Ravulizumab in Immunoglobulin A Nephropathy (IgAN) (ICAN)

ClinicalTrials.gov ID NCT06291376

Sponsor Alexion Pharmaceuticals, Inc.

Information provided by Alexion Pharmaceuticals, Inc. (Responsible Party)

Last Update Posted 2024-05-03



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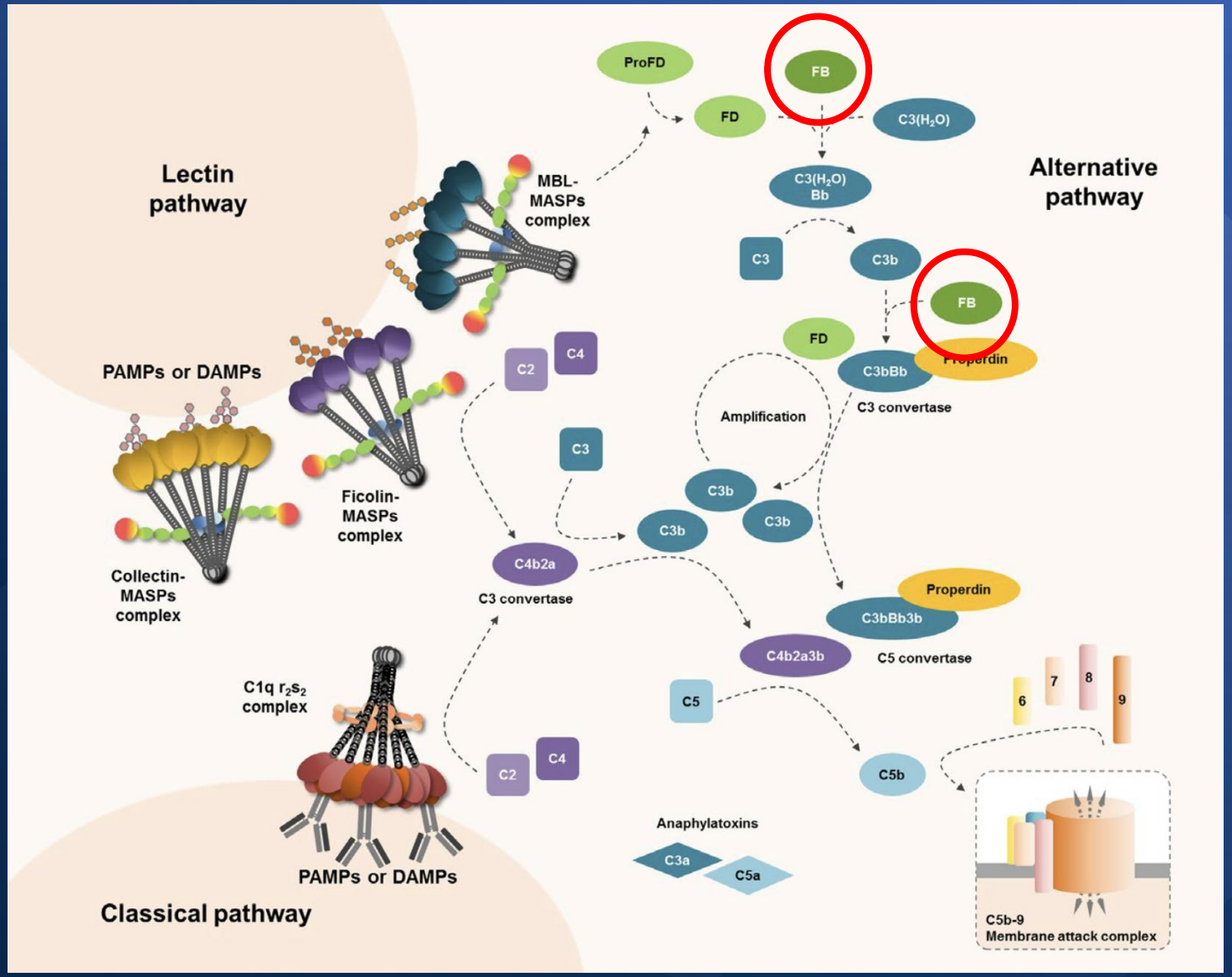

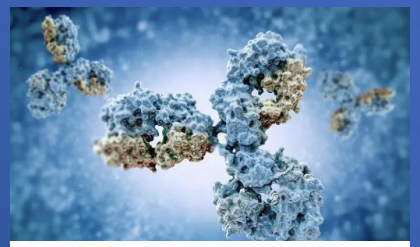

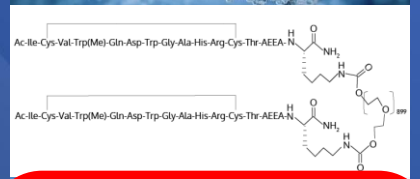

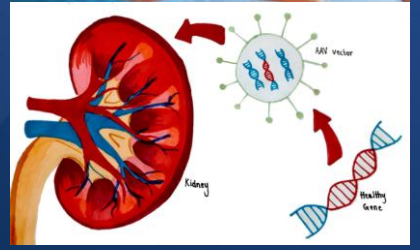

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A mechanistic biopsy study of the effect of iptacopan on immunopathology in patients with IgA nephropathy (IgAN)

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INTRODUCTION

- Overactivation of the alternative pathway is one of the key drivers of IgAN. Targeting the alternative pathway may address an unmet need for targeted immunomodulation and result in the improvement of kidney function and prevention of disease progression.[1,2]
- Iptacopan is a proximal complement inhibitor that targets factor B to specifically inhibit the alternative complement pathway while leaving signaling from the lectin and classical pathways intact.[1,3,4]

AIM

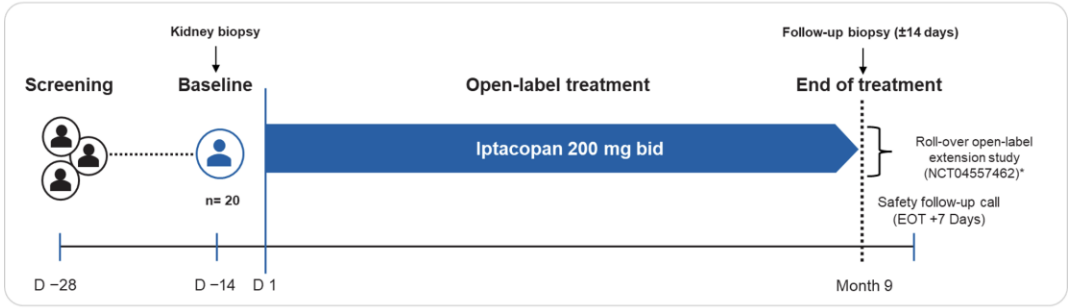
- This repeat-biopsy mechanistic study aims to evaluate the effects of iptacopan on the underlying immunopathology in patients with IgAN and to better understand the role of complement activation in IgAN

ABBREVIATIONS

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; bid, twice a day; C3c, complement 3c; eGFR, estimated glomerular filtration rate; FMV, first morning void; IgAN, IgA nephropathy; RBC/HPF, red blood cell per high power field; SGLT2i, sodium-glucose co-transporter 2 inhibitors; UPCR, urine protein–creatinine ratio.

METHOD

- This Phase IIa multicenter, single-arm, open-label, repeat-biopsy study will enroll up to 20 adult patients with IgAN (**Figure**).
- Key inclusion criteria include biopsy-proven IgAN; eGFR ≥30 mL/min/1.73 m^2; proteinuria ≥0.8 g/g from FMV; receiving a maximally tolerated and/or stable dose of supportive care treatment (ACEi or ARB and/or SGLT2i) for ≥90 days before baseline. Vaccination against *Neisseria meningitidis* and *Streptococcus pneumoniae* must be completed, and—if available and per local regulations—*Haemophilus influenzae* vaccination should be administered, at least 2 weeks before starting study treatment.
- The primary, secondary, exploratory objectives are listed in the **Table**.



bid, twice a day; D, day; EOT, end of treatment; n, number of participants. *Eligible participants may enroll in the roll-over extension study, contingent upon local regulations.

Table: Key Study Objectives

Objective	Endpoint (s)
Primary	
Quantifying the change after treatment with iptacopan in mesangial C3c and C3c-containing fragments	Achievement of a minimum one-grade reduction from baseline at 9 months in mesangial C3c and C3c-containing fragments
Secondary	
Describing the histopathological changes after iptacopan treatment	Change from baseline at 9 months in CD68+ cells and immunoglobulins
Exploratory	
Evaluating the histopathological changes in complement biomarkers after treatment with iptacopan	Change from baseline at 9 months in MEST-C score
Describing changes in UPCR, hematuria, and eGFR after treatment with iptacopan	Log-transformed ratio to baseline of UPCR at 9 months. Change from baseline at 9 months in dipstick and RBC/HPF, and in eGFR
Exploring the correlation of histopathological changes with proteinuria and eGFR changes after treatment with iptacopan	Correlation between changes in histology and eGFR changes

CONCLUSIONS

- This repeat-biopsy study will explore the impact of iptacopan on IgAN immunopathology by assessing glomerular complement activation together with renal histopathology, kidney function, and key biomarkers.
- The findings will enhance understanding of the mechanistic effects of iptacopan on IgAN and potential kidney protective benefits.

REFERENCES

1. Zhang H, et al. *Kidney Int*. 2024;105(1):189-199
2. Rizk DV, et al. *Kidney Int Rep*. 2023. 9;8(5):968-979
3. Schubart A, *et al. Proc Natl Acad Sci USA*. 2019;116(16):7926-7931
4. Novartis Pharmaceuticals Corporation. Fabhalta prescribing information. 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/218276s00[illegible].pdf (accessed May 2025)

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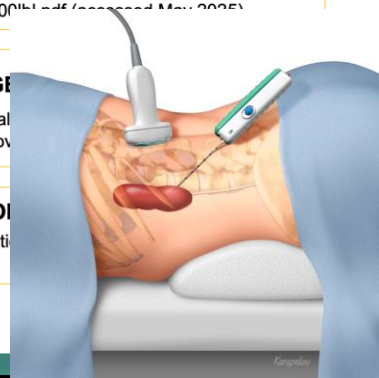

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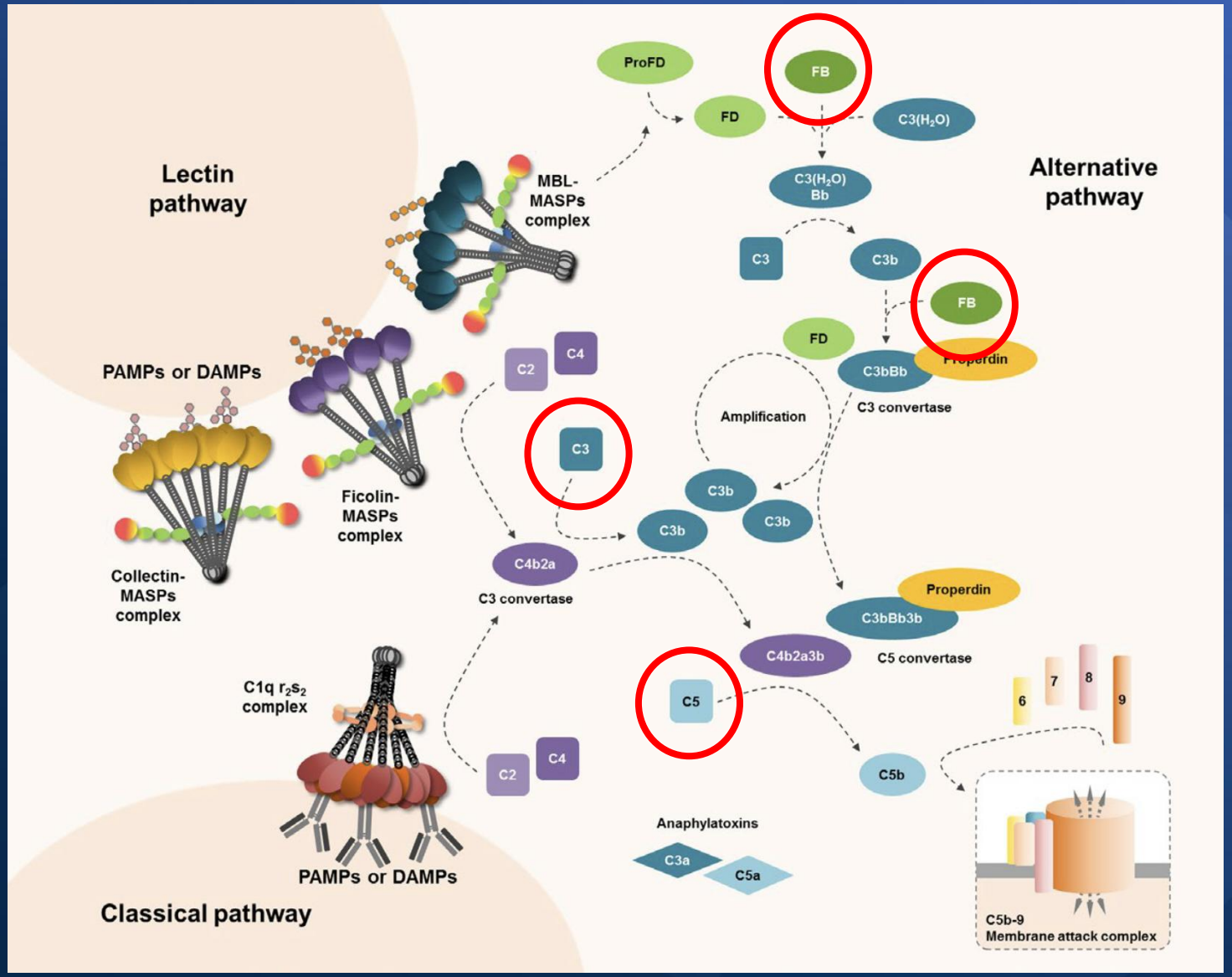

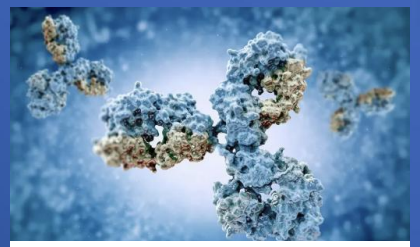

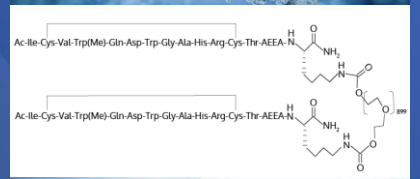

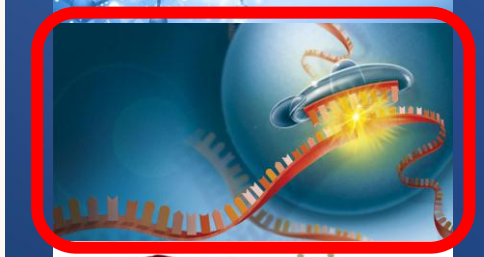

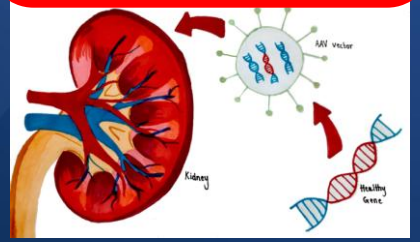

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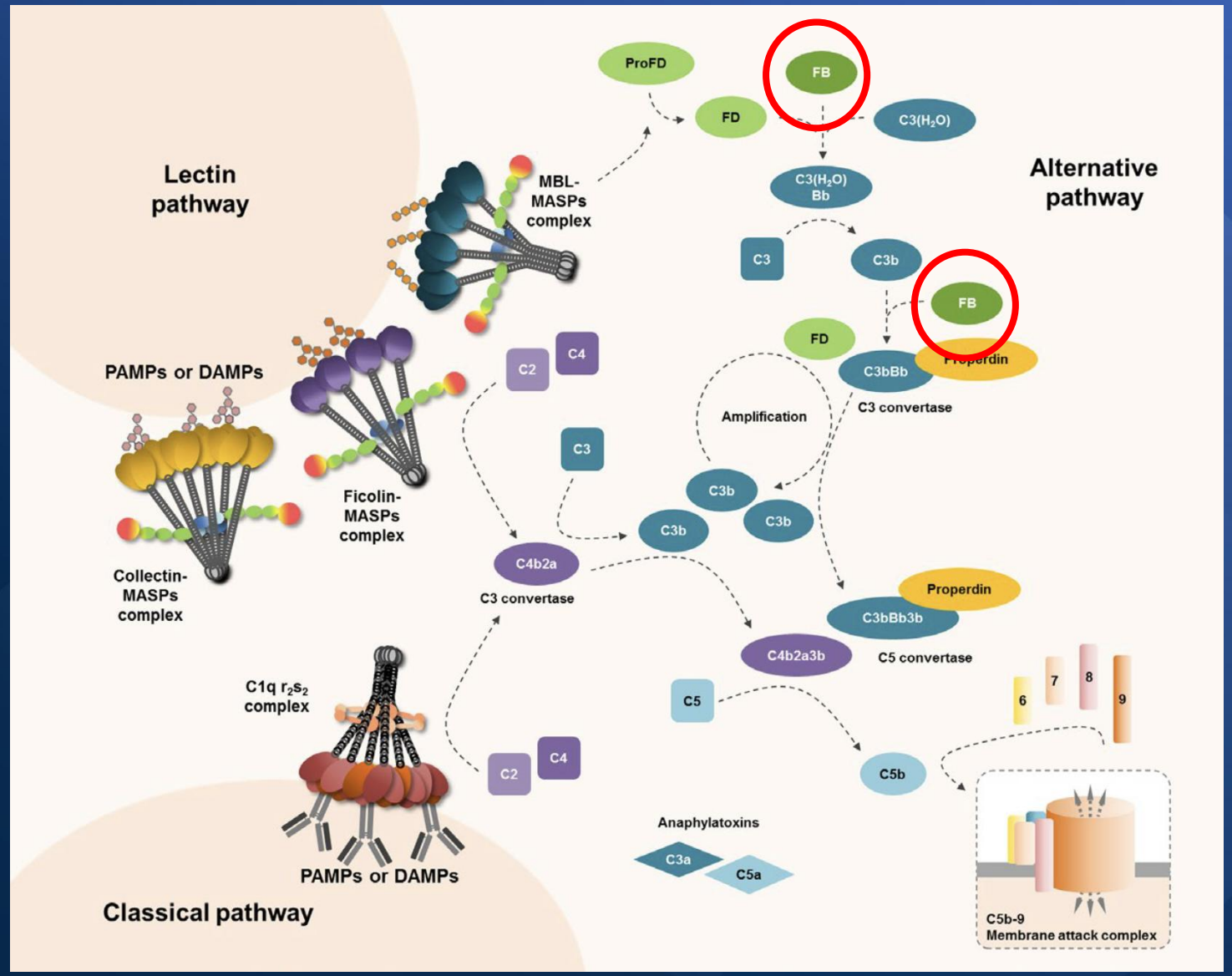

RECRUITING

A Study to Evaluate the Efficacy and Safety of RO7434656 in Participants With Primary Immunoglobulin A (IgA) Nephropathy at High Risk of Progression (IMAGINATION)

ClinicalTrials.gov ID NCT05797610

Sponsor Hoffmann-La Roche

Information provided by Hoffmann-La Roche (Responsible Party)

Last Update Posted 2024-05-10

RECRUITING

Study of ARO-CFB in Adult Healthy Volunteers and Patients With Complement-Mediated Kidney Disease

ClinicalTrials.gov ID NCT06209177

Sponsor Arrowhead Pharmaceuticals

Information provided by Arrowhead Pharmaceuticals (Responsible Party)

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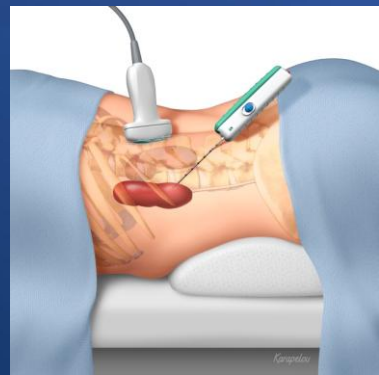

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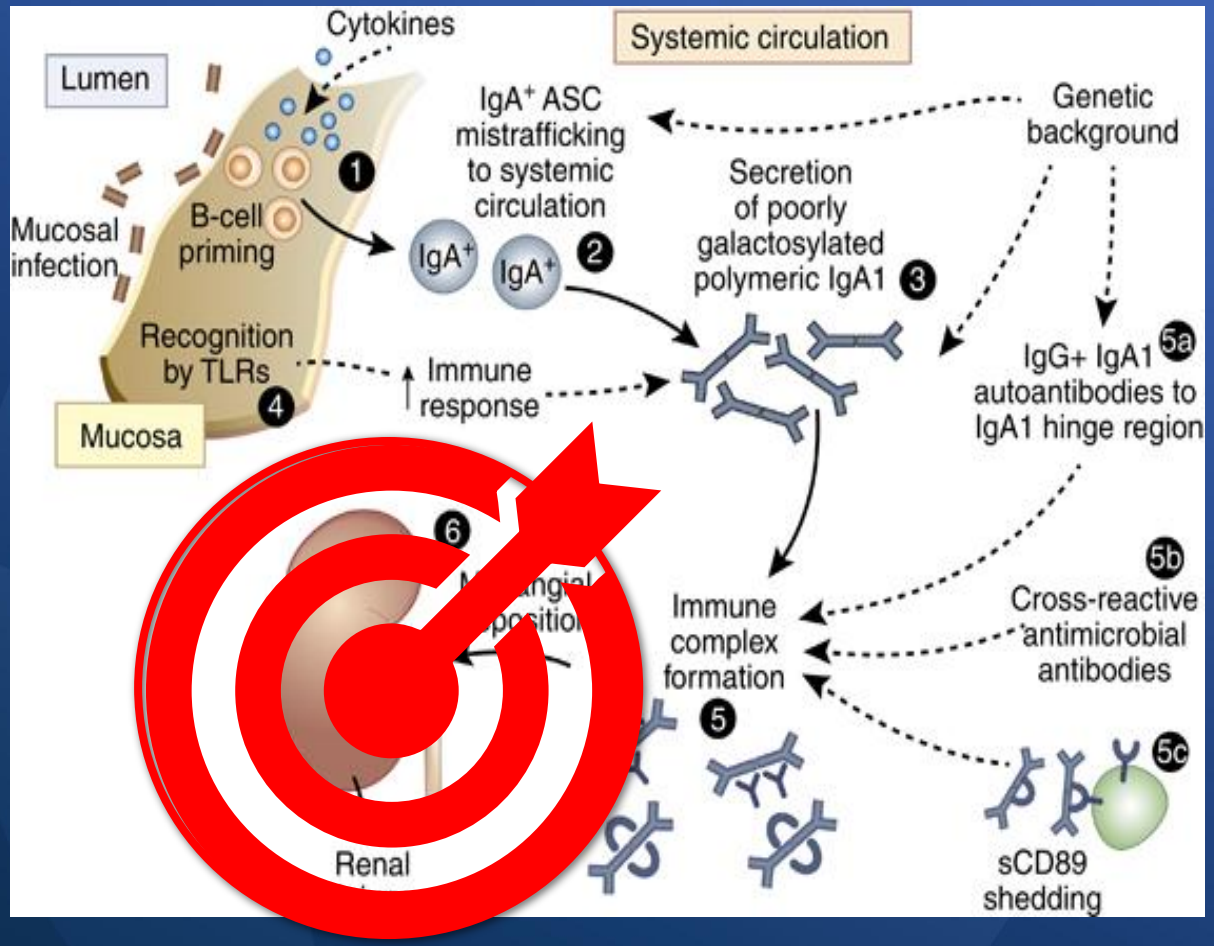

Sparsentan in patients with IgA nephropathy: a prespecified interim analysis from a randomised, double-blind, active-controlled clinical trial

Hiddo J L Heerspink, Jai Radhakrishnan, Charles E Alpers, Jonathan Barratt, Stewart Bieler, Ulysses Diva, Jula Inrig, Radko Komers, Alex Mercer, Irene L Noronha, Michelle N Rheault, William Rote, Brad Rovin, Howard Trachtman, Hernán Trimarchi, Muh Geot Wong, Vlado Perkovic, for the PROTECT Investigators*

Summary

Background Sparsentan is a novel, non-immunosuppressive, single-molecule, dual endothelin and angiotensin receptor antagonist being examined in an ongoing phase 3 trial in adults with IgA nephropathy. We report the prespecified interim analysis of the primary proteinuria efficacy endpoint, and safety.

Methods PROTECT is an international, randomised, double-blind, active-controlled study, being conducted in 134 clinical practice sites in 18 countries. The study examines sparsentan versus irbesartan in adults (aged ≥18 years) with biopsy-proven IgA nephropathy and proteinuria of 1·0 g/day or higher despite maximised renin-angiotensin system inhibitor treatment for at least 12 weeks. Participants were randomly assigned in a 1:1 ratio to receive sparsentan 400 mg once daily or irbesartan 300 mg once daily, stratified by estimated glomerular filtration rate at screening (30 to <60 mL/min per 1·73 m² and ≥60 mL/min per 1·73 m²) and urine protein excretion at screening (≤1·75 g/day and >1·75 g/day). The primary efficacy endpoint was change from baseline to week 36 in urine protein–creatinine ratio based on a 24-h urine sample, assessed using mixed model repeated measures. Treatment-emergent adverse events (TEAEs) were safety endpoints. All endpoints were examined in all participants who received at least one dose of randomised treatment. The study is ongoing and is registered with ClinicalTrials.gov, NCT03762850.

Findings Between Dec 20, 2018, and May 26, 2021, 404 participants were randomly assigned to sparsentan (n=202) or irbesartan (n=202) and received treatment. At week 36, the geometric least squares mean percent change from baseline in urine protein–creatinine ratio was statistically significantly greater in the sparsentan group (–49·8%) than the irbesartan group (–15·1%), resulting in a between-group relative reduction of 41% (least squares mean ratio=0·59; 95% CI 0·51–0·69; p<0·0001). TEAEs with sparsentan were similar to irbesartan. There were no cases of severe oedema, heart failure, hepatotoxicity, or oedema-related discontinuations. Bodyweight changes from baseline were not different between the sparsentan and irbesartan groups.

Interpretation Once-daily treatment with sparsentan produced meaningful reduction in proteinuria compared with irbesartan in adults with IgA nephropathy. Safety of sparsentan was similar to irbesartan. Future analyses after completion of the 2-year double-blind period will show whether these beneficial effects translate into a long-term nephroprotective potential of sparsentan.

Funding Travere Therapeutics.

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*PROTECT Investigators are listed in the appendix (pp 2–5)

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Introduction

Immunoglobulin A (IgA) nephropathy is the most common primary glomerulonephritis and an important cause of kidney failure.[1,2] Proteinuria has been consistently shown to be a risk factor for progressive kidney function loss in patients with IgA nephropathy,[3] and remission of proteinuria is associated with improved kidney outcomes.[4] Despite the risk of progressive kidney disease and kidney failure, few therapeutic options are available. The Kidney Disease Improving Global Outcomes (KDIGO) guideline recommends the use of renin-angiotensin system (RAS) inhibitors in patients with proteinuria more than 0·5 g/day.[4] Following 3 months of RAS inhibitor treatment, patients with proteinuria of 1 g/day or higher have a greater risk of disease progression, and additional treatment is recommended.

The use of RAS inhibitors as standard of care in IgA nephropathy is based on their well established pleiotropic nephroprotective actions in a variety of kidney diseases and indicates a contribution of its main effector, angiotensin II, in the pathophysiology of IgA nephropathy.[5] More recently, advances in our understanding of the pathogenesis of IgA nephropathy show that endothelin-1 (ET-1) contributes to the pathophysiology of IgA nephropathy via activation of ET_A receptors, leading to a variety of effects including vasoconstriction, podocyte dysfunction, tubular injury, inflammation, and fibrosis.[6]

Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active-controlled, phase 3 trial

Brad H Rovin*, Jonathan Barratt*, Hiddo J L Heerspink, Charles E Alpers, Stewart Bieler, Dong-Wan Chae, Ulysses A Diva, Jürgen Floege, Loreto Gesualdo, Jula K Inrig, Donald E Kohan, Radko Komers, Laura Ann Kooienga, Richard J Lafayette, Bart Maes, Robert Maiecki, Alex Mercer, Irene L Noronha, Se Won Oh, Chen Au Peh, Manuel Praga, Priscila Preciado, Jai Radhakrishnan, Michelle N Rheault, William E Rote, Sydney C W Tang, Vladimir Tesar, Howard Trachtman, Hernán Trimarchi, James A Tumlin, Muh Geot Wong, Vlado Perkovic, on behalf of the DUPRO steering committee and PROTECT Investigators†

Summary

Background Sparsentan, a novel, non-immunosuppressive, single-molecule, dual endothelin angiotensin receptor antagonist, significantly reduced proteinuria versus irbesartan, an angiotensin II receptor blocker, at 36 weeks (primary endpoint) in patients with immunoglobulin A nephropathy in the phase 3 PROTECT trial's previously reported interim analysis. Here, we report kidney function and outcomes over 110 weeks from the double-blind final analysis.

Methods PROTECT, a double-blind, randomised, active-controlled, phase 3 study, was done across 134 clinical practice sites in 18 countries throughout the Americas, Asia, and Europe. Patients aged 18 years or older with biopsy-proven primary IgA nephropathy and proteinuria of at least 1·0 g per day despite maximised renin–angiotensin system inhibition for at least 12 weeks were randomly assigned (1:1) to receive sparsentan (target dose 400 mg oral sparsentan once daily) or irbesartan (target dose 300 mg oral irbesartan once daily) based on a permuted-block randomisation method. The primary endpoint was proteinuria change between treatment groups at 36 weeks. Secondary endpoints included rate of change (slope) of the estimated glomerular filtration rate (eGFR), changes in proteinuria, a composite of kidney failure (confirmed 40% eGFR reduction, end-stage kidney disease, or all-cause mortality), and safety and tolerability up to 110 weeks from randomisation. Secondary efficacy outcomes were assessed in the full analysis set and safety was assessed in the safety set, both of which were defined as all patients who were randomly assigned and received at least one dose of randomly assigned study drug. This trial is registered with ClinicalTrials.gov, NCT03762850.

Findings Between Dec 20, 2018, and May 26, 2021, 203 patients were randomly assigned to the sparsentan group and 203 to the irbesartan group. One patient from each group did not receive the study drug and was excluded from the efficacy and safety analyses (282 [70%] of 404 included patients were male and 272 [67%] were White) . Patients in the sparsentan group had a slower rate of eGFR decline than those in the irbesartan group. eGFR chronic 2-year slope (weeks 6–110) was −2·7 mL/min per 1·73 m² per year versus −3·8 mL/min per 1·73 m² per year (difference 1·1 mL/min per 1·73 m² per year, 95% CI 0·1 to 2·1; p=0·037); total 2-year slope (day 1–week 110) was −2·9 mL/min per 1·73 m² per year versus −3·9 mL/min per 1·73 m² per year (difference 1·0 mL/min per 1·73 m² per year, 95% CI −0·03 to 1·94; p=0·058). The significant reduction in proteinuria at 36 weeks with sparsentan was maintained throughout the study period; at 110 weeks, proteinuria, as determined by the change from baseline in urine protein-to-creatinine ratio, was 40% lower in the sparsentan group than in the irbesartan group (−42·8%, 95% CI −49·8 to −35·0, with sparsentan versus −4·4%, −15·8 to 8·7, with irbesartan; geometric least-squares mean ratio 0·60, 95% CI 0·50 to 0·72). The composite kidney failure endpoint was reached by 18 (9%) of 202 patients in the sparsentan group versus 26 (13%) of 202 patients in the irbesartan group (relative risk 0·7, 95% CI 0·4 to 1·2). Treatment-emergent adverse events were well balanced between sparsentan and irbesartan, with no new safety signals.

Interpretation Over 110 weeks, treatment with sparsentan versus maximally titrated irbesartan in patients with IgA nephropathy resulted in significant reductions in proteinuria and preservation of kidney function.

Funding Travere Therapeutics.

Introduction

Immunoglobulin A nephropathy is the most common primary glomerular disease worldwide[1] and is associated with significant lifetime risk of kidney failure.[2] Current treatment options are limited,[3] and it is only since December, 2021, that a small number of approved treatments have become available in Europe and the USA.[3,5] IgA nephropathy is usually found in

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*Contributed equally

†PROTECT Investigators are listed in the appendix (pp 2–4)

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ACTIVE, NOT RECRUITING

A Study of the Safety and Activity of Sparsentan for the Treatment of Incident Patients With Immunoglobulin A Nephropathy (SPARTAN)

ClinicalTrials.gov ID NCT04663204

Sponsor University of Leicester

Information provided by University of Leicester (Responsible Party)

Last Update Posted 2023-10-24

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SPARTAN (NCT0466320) Study Design

SPARTAN

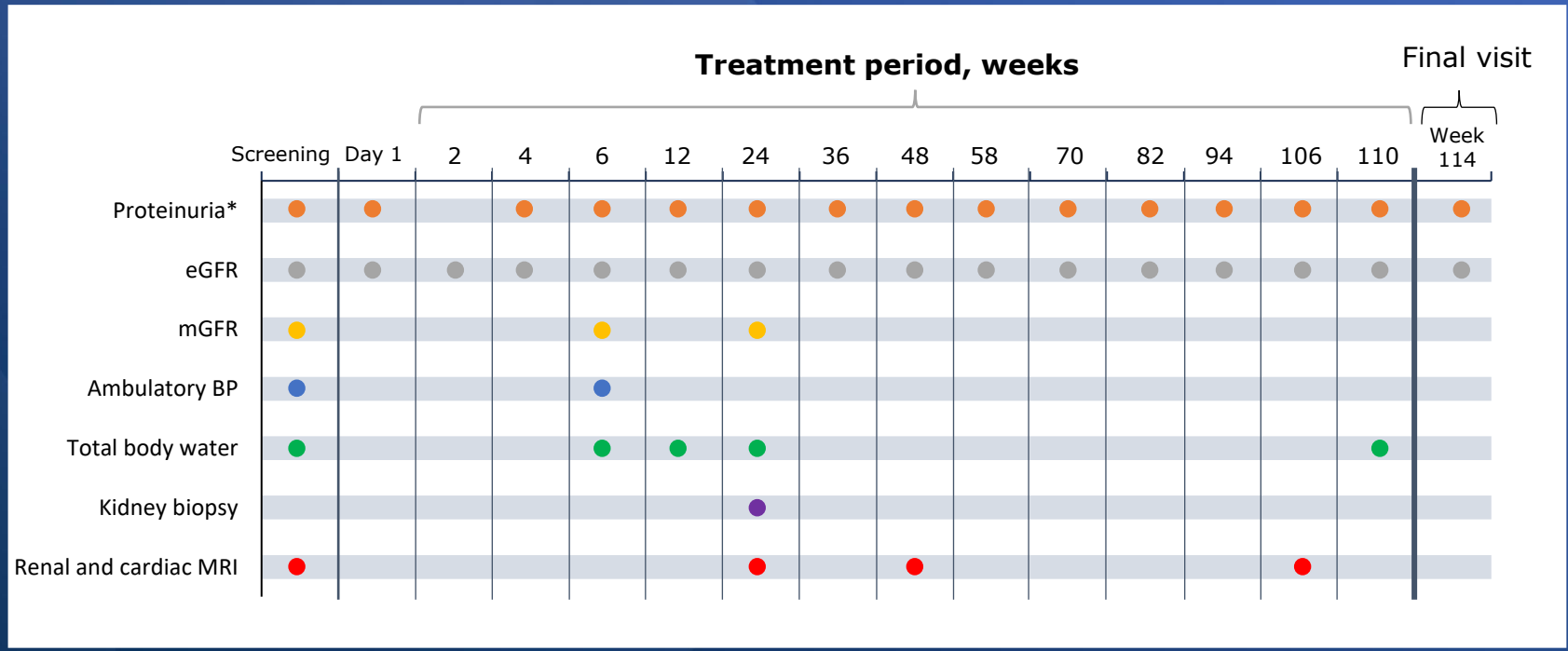
Screening	Day 1 to Week 2	Weeks 3 to 110	Weeks 110 to 114
	SPARSENTAN 200 mg	SPARSENTAN 400 mg	Follow-up
N=12			Start SOC RASB therapy

Key Eligibility Criteria

- Age ≥18 years
- Biopsy-proven IgAN within ≤6 months
- Proteinuria ≥0.5 g/day
- eGFR ≥30 mL/min/1.73 m^2
- No ACEIs/ARBs within ≤12 months

Key Endpoints

- Safety
- Change in proteinuria from baseline
- Complete remission of proteinuria (<0.3 g/day)
- Change in GFR and BP from baseline



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SPARTAN

Kidney Transplantation

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Figure 1. Study Design

Screen
≤8 weeks

- Standard of care
- Confirm eligibility
- Informed consent
- Week -2: 2-week washout period (no RAAS inhibitors)

Study Cohorts

Population 1 (n=30)
(FSGS and/or MCD)

Cohort 1	≥8 to <18 years	n = 6
Cohort 2	≥3 to <8 years	n = 18
Cohort 3	≥1 to <3 years	n = 6

Population 2 (n=27)
(IgAN, IgAV, or AS)

Cohort 1	≥8 to <18 years	n = 9
Cohort 2	≥5 to <8 years	n = 12
Cohort 3	≥2 to <5 years	n = 6

Week 1 to Week 108

- Dosing: Once-daily dosing of Sparsentan
- Assessments:
  - Safety, tolerability and clinical response
  - PK (Day 1, Day 2, and Week 12)

RAAS, renin-angiotensin-aldosterone system.

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Recruiting

Trial of the Impact of Sibeprenlimab on Immunoglobulin A Nephropathy Kidney Tissue

ClinicalTrials.gov ID NCT06740526

Sponsor Otsuka Pharmaceutical Development & Commercialization, Inc.

Information provided by Otsuka Pharmaceutical Development & Commercialization, Inc. (Responsible Party)

Last Update Posted 2025-04-06

62nd ERA CONGRESS VIENNA & VIRTUAL JUNE 4-7, 2025 Beyond Nephrology

In collaboration with ÖGN Österreichische Gesellschaft für Nephrologie

A mechanistic biopsy study of the effect of iptacopan on immunopathology in patients with IgA nephropathy (IgAN)

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INTRODUCTION

- Overactivation of the alternative pathway is one of the key drivers of IgAN. Targeting the alternative pathway may address an unmet need for targeted immunomodulation and result in the improvement of kidney function and prevention of disease progression.[1,2]
- Iptacopan is a proximal complement inhibitor that targets factor B to specifically inhibit the alternative complement pathway while leaving signaling from the lectin and classical pathways intact.[1,3,4]

AIM

- This repeat-biopsy mechanistic study aims to evaluate the effects of iptacopan on the underlying immunopathology in patients with IgAN and to better understand the role of complement activation in IgAN

ABBREVIATIONS

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; bid, twice a day; C3c, complement 3c; eGFR, estimated glomerular filtration rate; FMV, first morning void; IgAN, IgA nephropathy; RBC/HPF, red blood cell per high power field; SGLT2i, sodium-glucose co-transporter 2 inhibitors; UPCR, urine protein–creatinine ratio.

METHOD

- This Phase IIa multicenter, single-arm, open-label, repeat-biopsy study will enroll up to 20 adult patients with IgAN (**Figure**).
- Key inclusion criteria include biopsy-proven IgAN; eGFR ≥30 mL/min/1.73 m^2; proteinuria ≥0.8 g/g from FMV; receiving a maximally tolerated and/or stable dose of supportive care treatment (ACEi or ARB and/or SGLT2i) for ≥90 days before baseline. Vaccination against *Neisseria meningitidis* and *Streptococcus pneumoniae* must be completed, and—if available and per local regulations—*Haemophilus influenzae* vaccination should be administered, at least 2 weeks before starting study treatment.
- The primary, secondary, exploratory objectives are listed in the **Table**.

bid, twice a day; D, day; EOT, end of treatment; n, number of participants. *Eligible participants may enroll in the roll-over extension study, contingent upon local regulations.

Table: Key Study Objectives

Objective	Endpoint (s)
Primary	
Quantifying the change after treatment with iptacopan in mesangial C3c and C3c-containing fragments	Achievement of a minimum one-grade reduction from baseline at 9 months in mesangial C3c and C3c-containing fragments
Secondary	
Describing the histopathological changes after iptacopan treatment	Change from baseline at 9 months in CD68+ cells and immunoglobulins
Exploratory	
Evaluating the histopathological changes in complement biomarkers after treatment with iptacopan	Change from baseline at 9 months in MEST-C score
Describing changes in UPCR, hematuria, and eGFR after treatment with iptacopan	Log-transformed ratio to baseline of UPCR at 9 months. Change from baseline at 9 months in dipstick and RBC/HPF, and in eGFR
Exploring the correlation of histopathological changes with proteinuria and eGFR changes after treatment with iptacopan	Correlation between changes in histology and eGFR changes

CONCLUSIONS

- This repeat-biopsy study will explore the impact of iptacopan on IgAN immunopathology by assessing glomerular complement activation together with renal histopathology, kidney function, and key biomarkers.
- The findings will enhance understanding of the mechanistic effects of iptacopan on IgAN and potential kidney protective benefits.

REFERENCES

1. Zhang H, et al. *Kidney Int.* 2024;105(1):189-199
2. Rizk DV, et al. *Kidney Int Rep.* 2023. 9;8(5):968-979
3. Schubart A, *et al. Proc Natl Acad Sci USA.* 2019;116(16):7926-7931
4. Novartis Pharmaceuticals Corporation. Fabhalta prescribing information. 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/218276s000lbl.pdf (accessed May 2025).

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ERA

SPARTAN

RECRUITING

A Study to Evaluate the Efficacy and Safety of RO7434656 in Participants With Primary Immunoglobulin A (IgA) Nephropathy at High Risk of Progression (IMAGINATION)

ClinicalTrials.gov ID NCT05797610

Sponsor Hoffmann-La Roche

Information provided by Hoffmann-La Roche (Responsible Party)

Last Update Posted 2024-05-10

RECRUITING

Study of Ravulizumab in Immunoglobulin A Nephropathy (IgAN) (ICAN)

ClinicalTrials.gov ID NCT06291376

Sponsor Alexion Pharmaceuticals, Inc.

Information provided by Alexion Pharmaceuticals, Inc. (Responsible Party)

Last Update Posted 2024-05-03

Recruiting

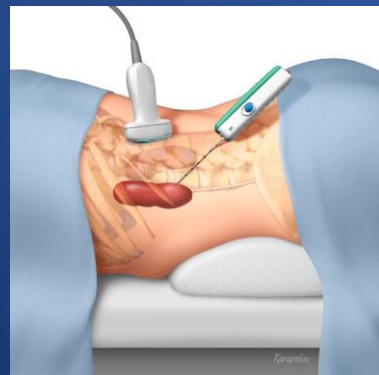
Evaluation of Efficacy of Povetacicept in Adults With Immunoglobulin A Nephropathy (IgAN)

ClinicalTrials.gov ID NCT06564142

Sponsor Alpine Immune Sciences Inc, A Subsidiary of Vertex

Information provided by Alpine Immune Sciences, Inc. (Alpine Immune Sciences Inc, A Subsidiary of Vertex) (Responsible Party)

Last Update Posted 2024-12-05



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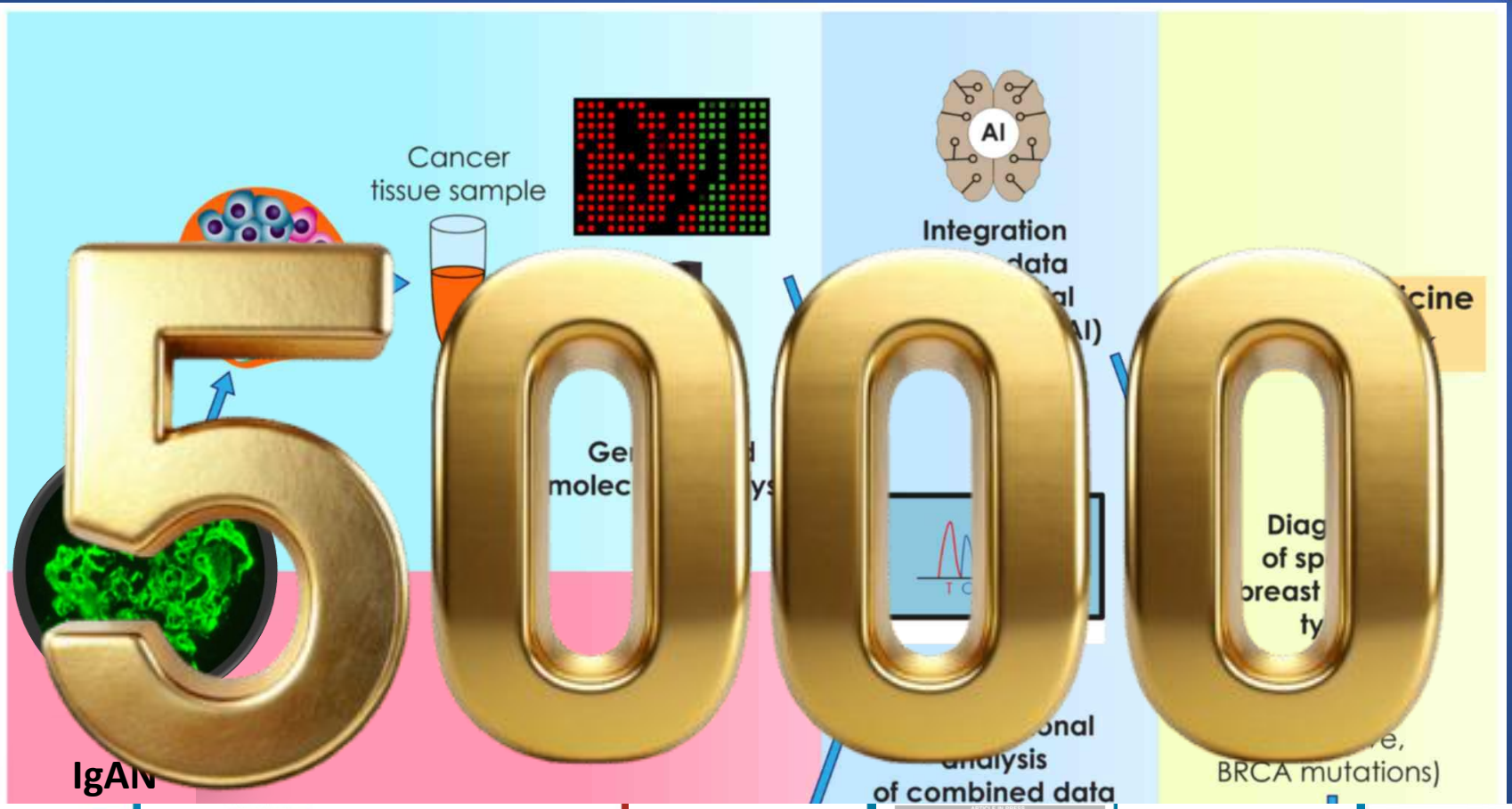

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