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Role of B cell-targeted therapies in the management of IgAN

Professor Jonathan Barratt

University of Leicester

&

John Walls Renal Unit, Leicester

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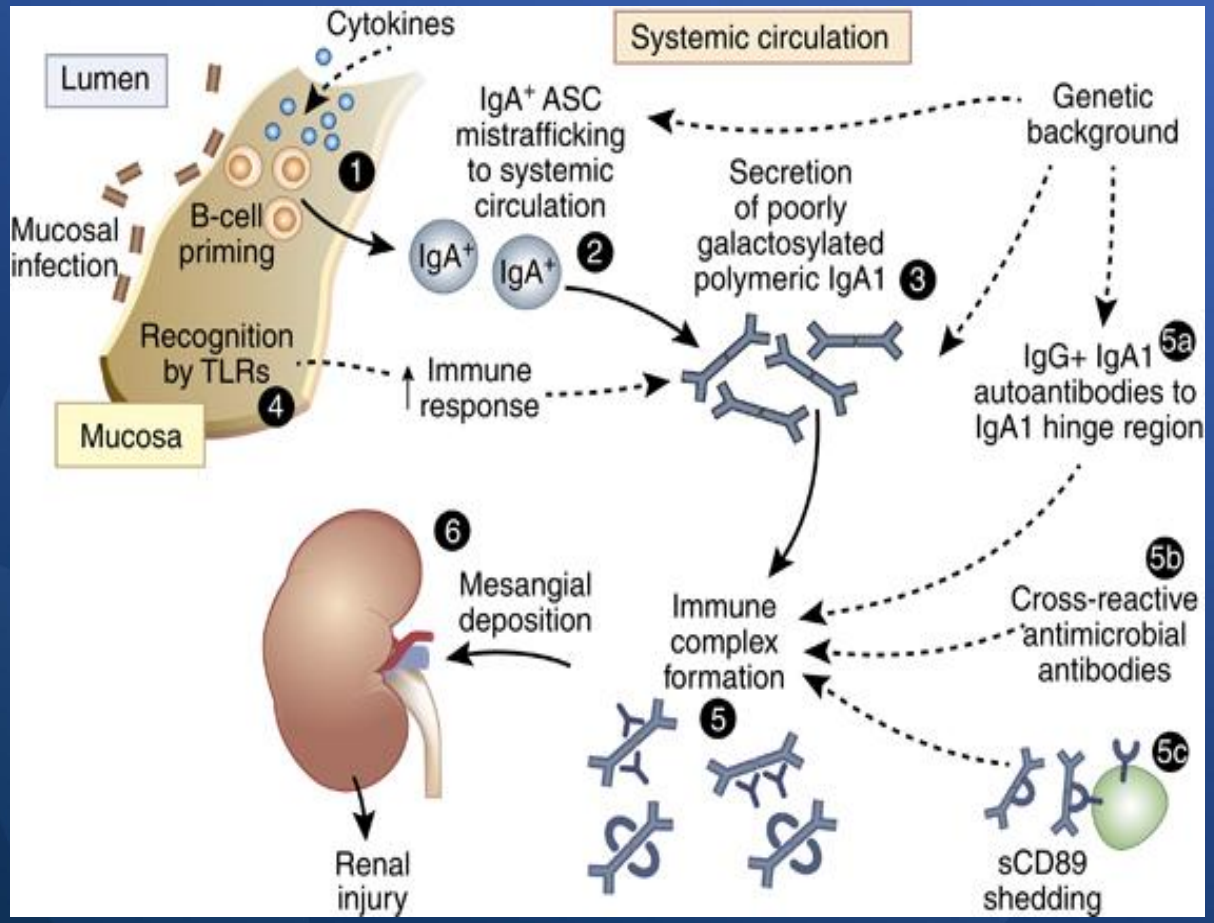
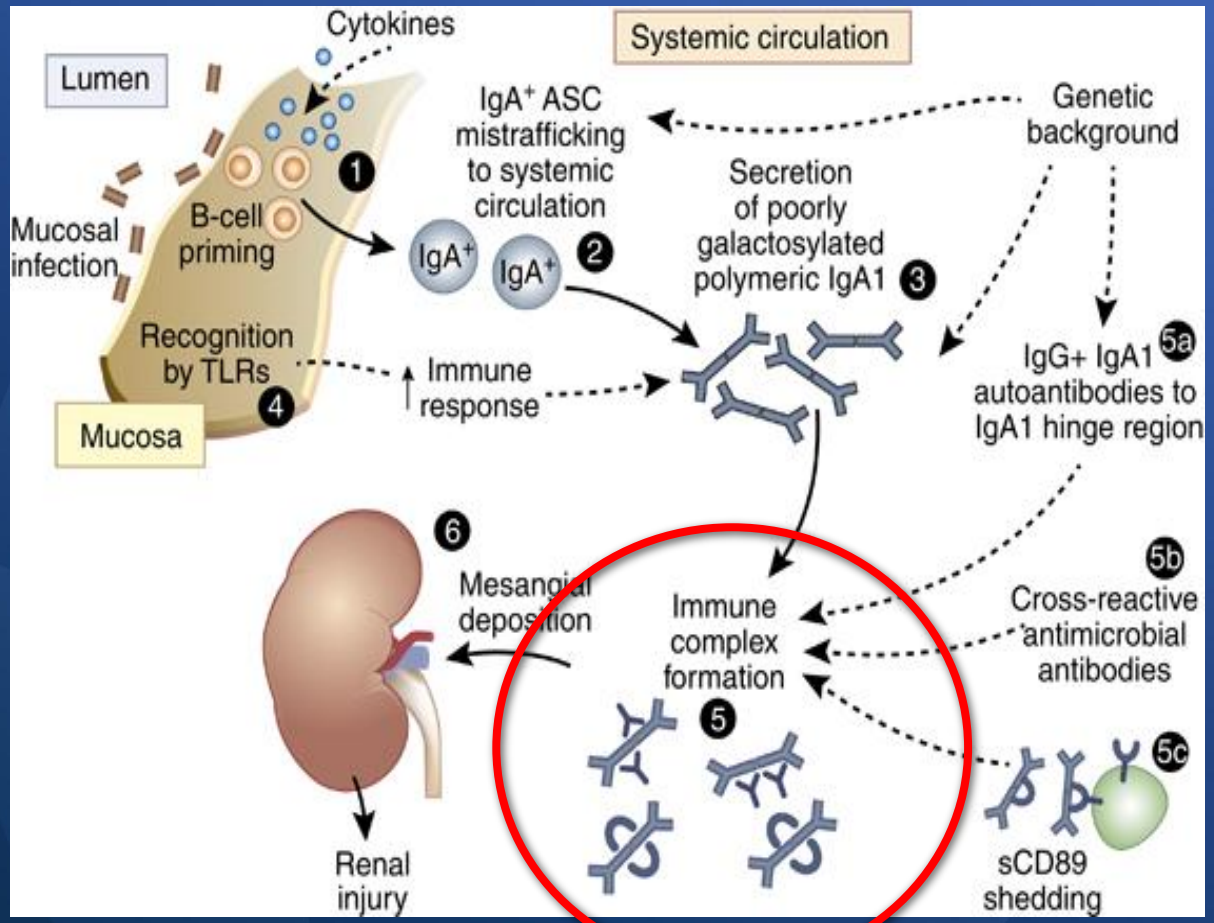
Speaker Declarations

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+
IgA+
2
Secretion of poorly galactosylated polymeric IgA1
3
Recognition by TLRs
4
Immune response
IgG+ IgA1 autoantibodies to IgA1 hinge region
5a
Mucosa
6
Mesangial deposition
5b
Cross-reactive antimicrobial antibodies
Immune complex formation
5
5c
Renal injury
sCD89 shedding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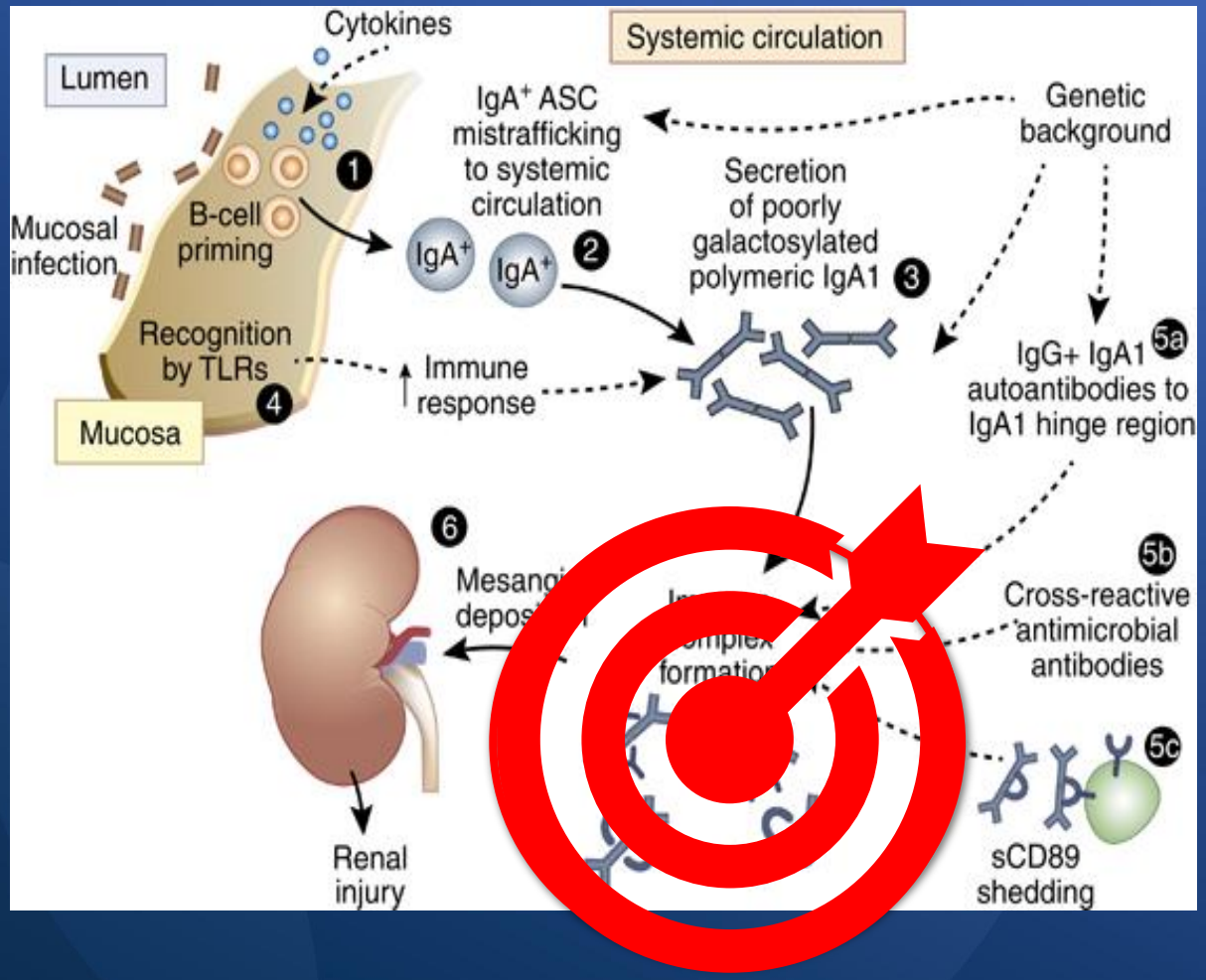

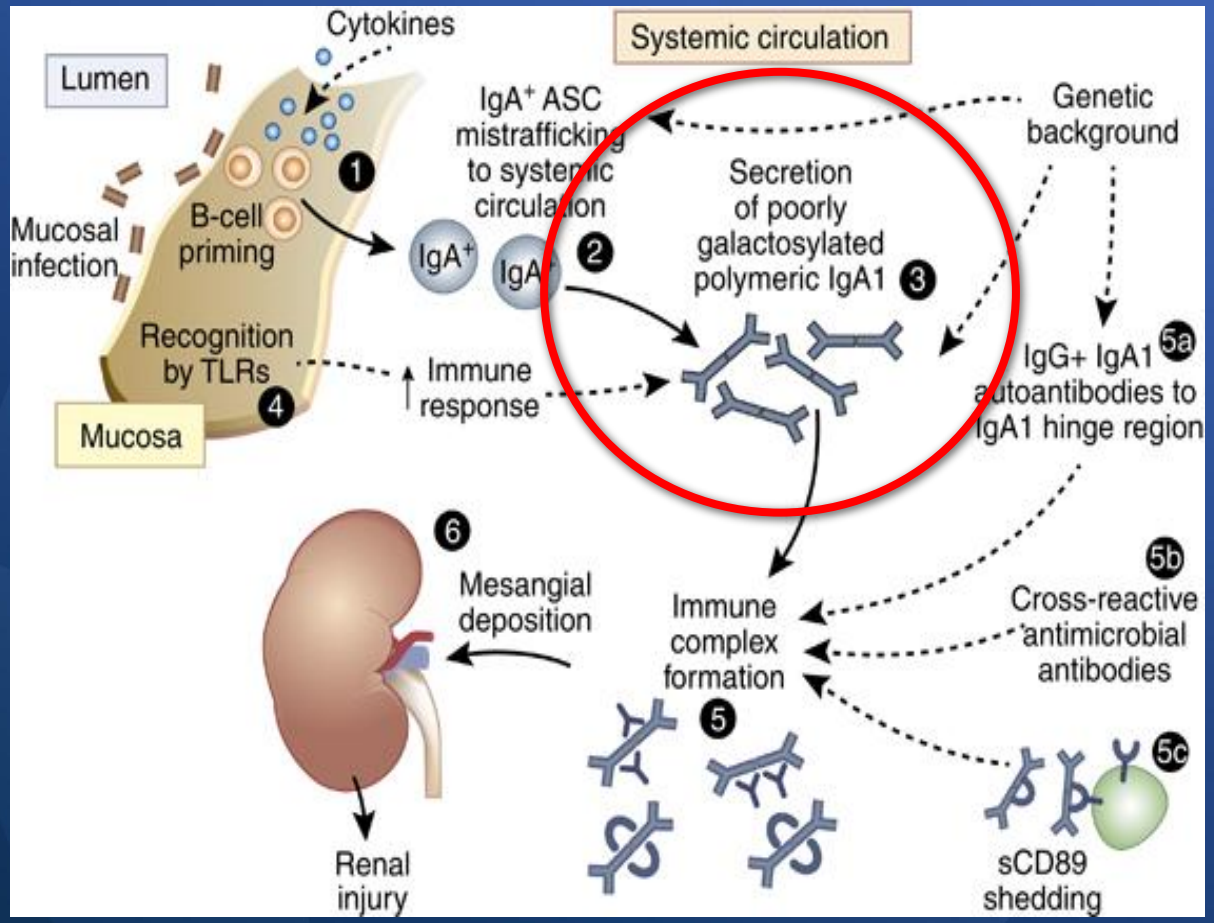
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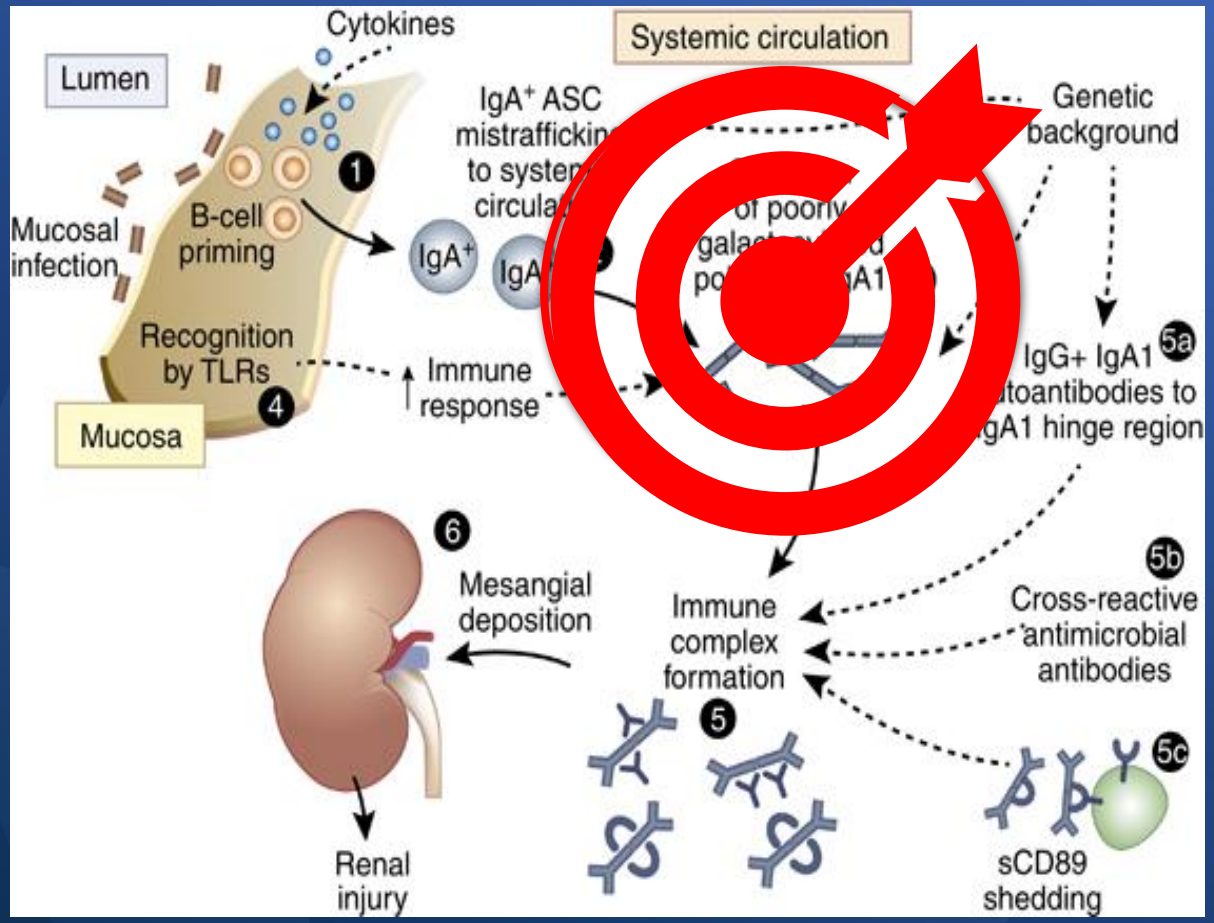

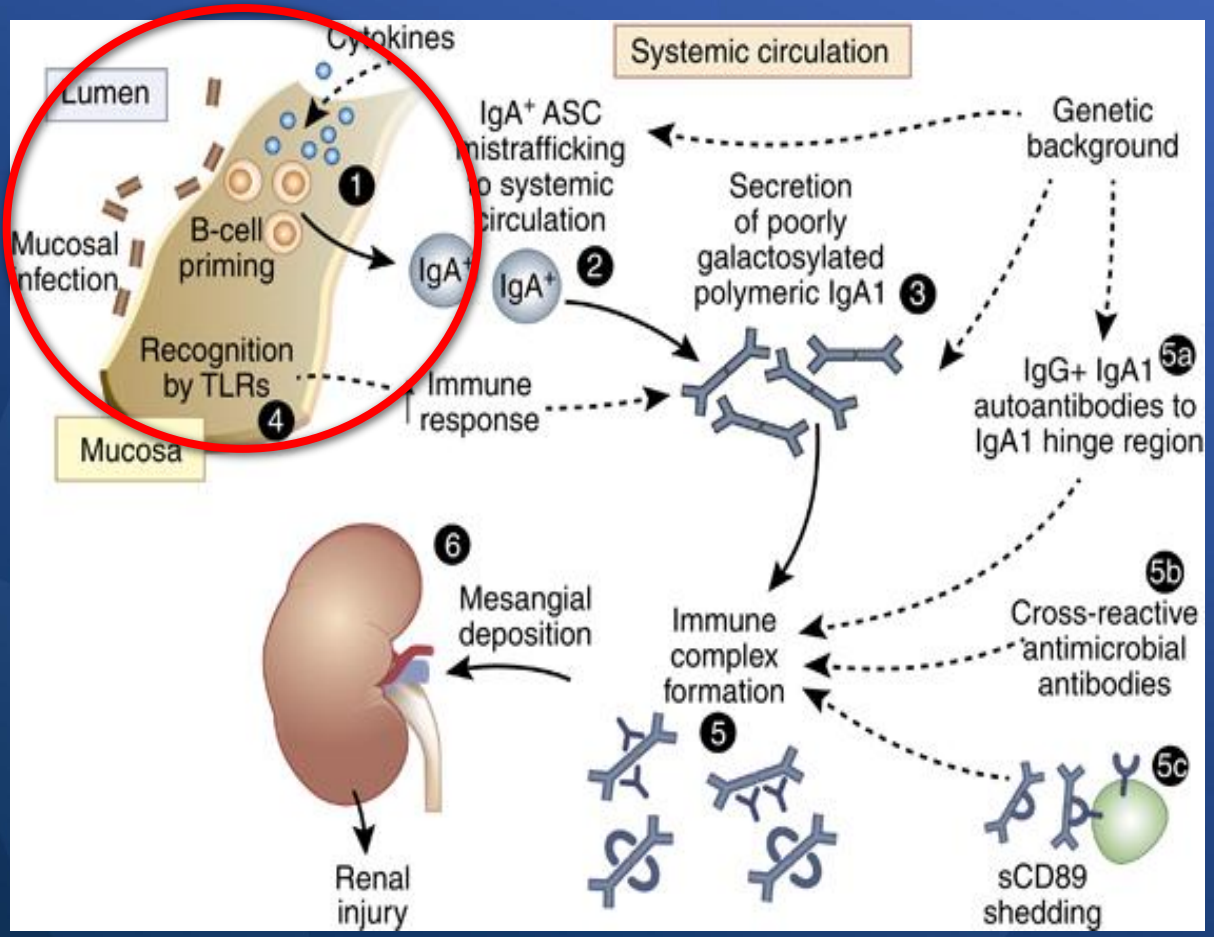
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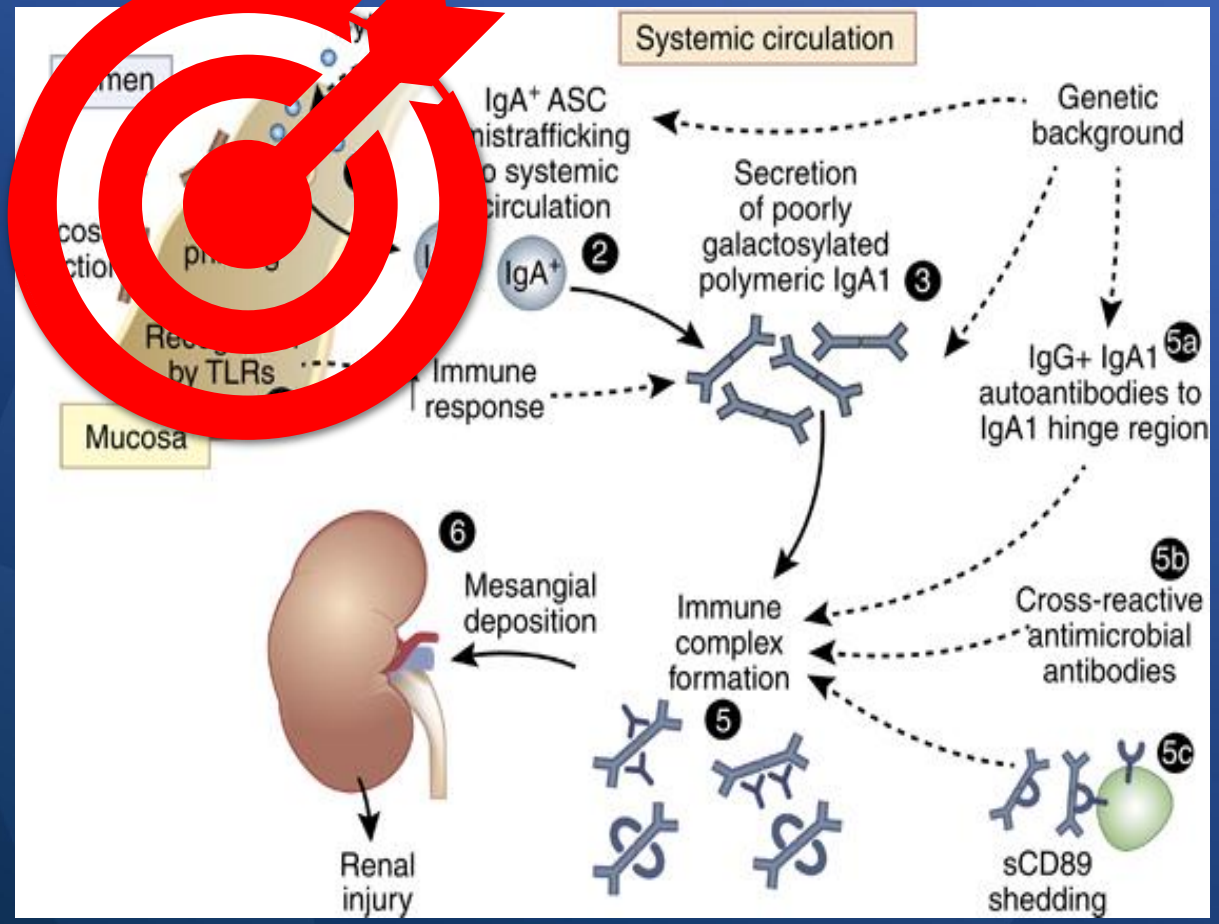

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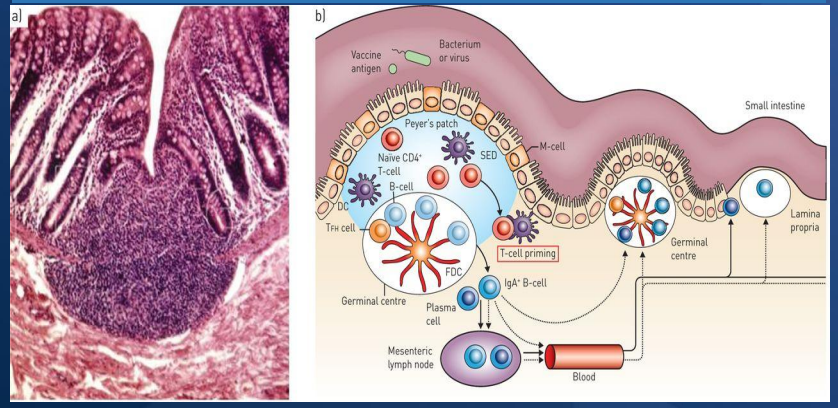
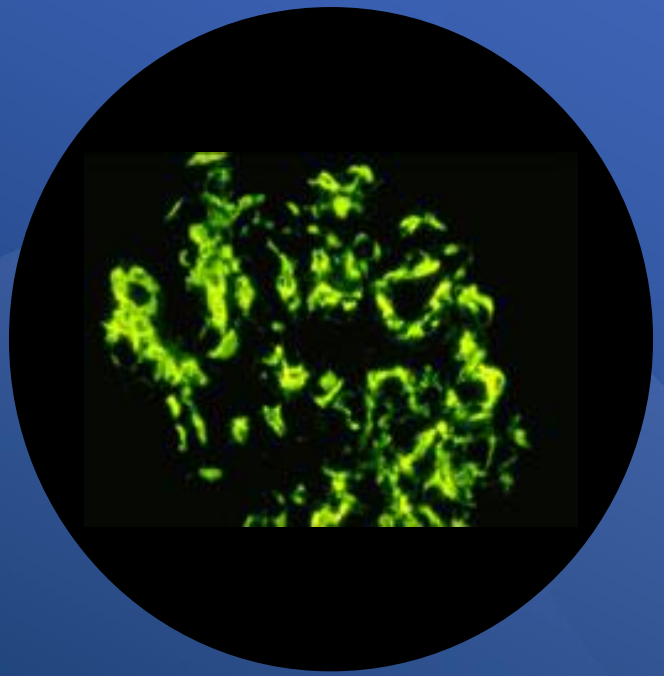
Mucosa Associated Lymphoid Tissue





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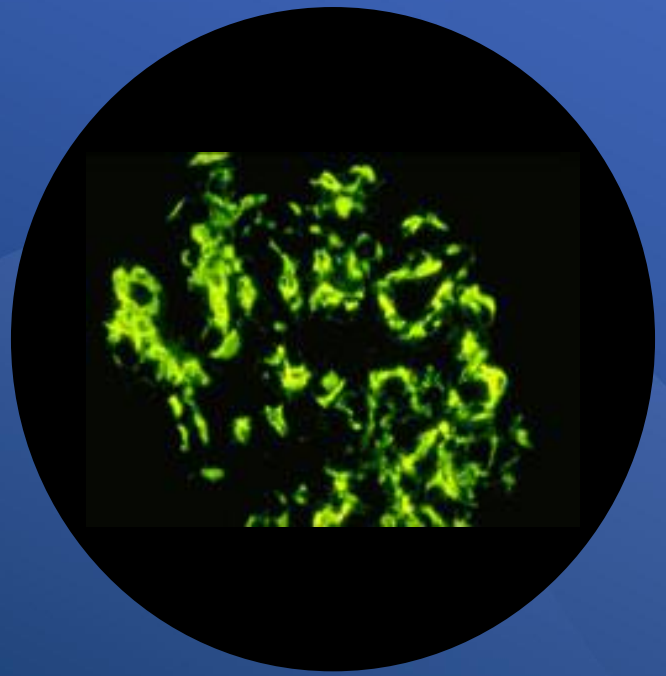

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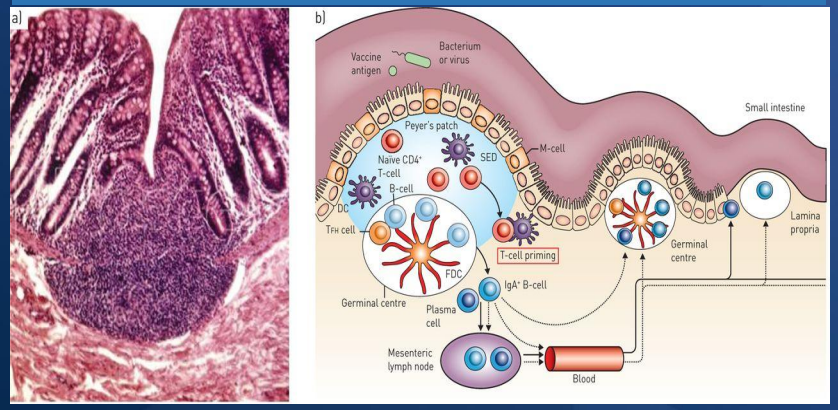

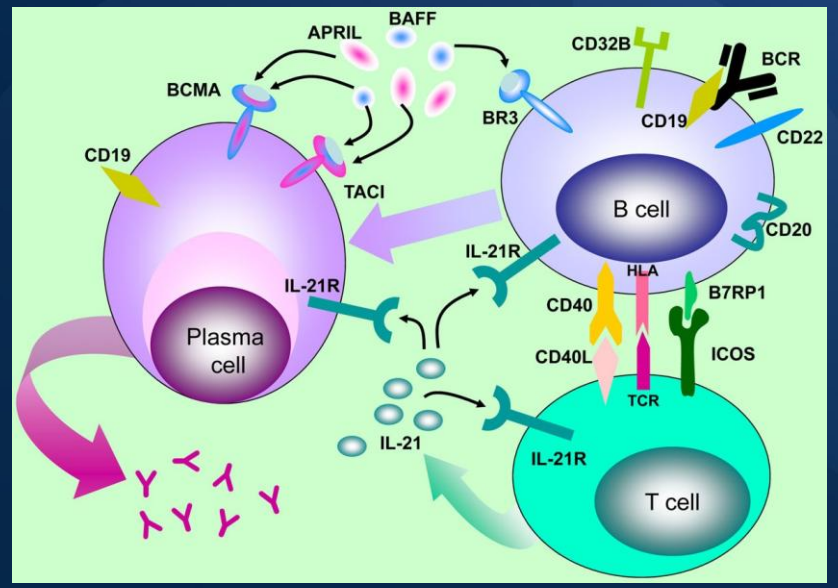

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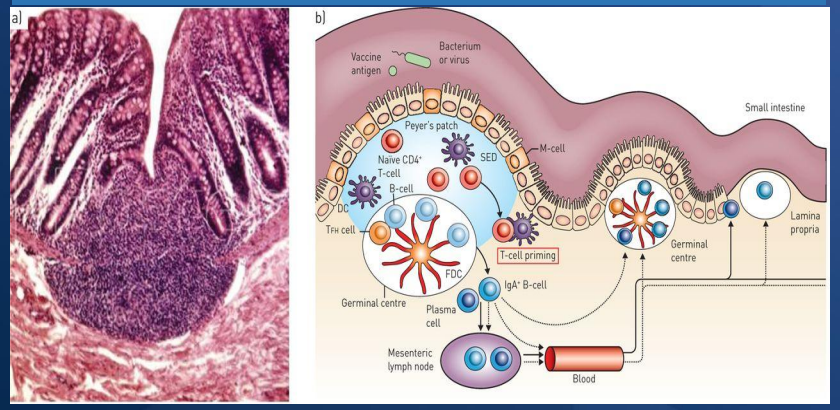

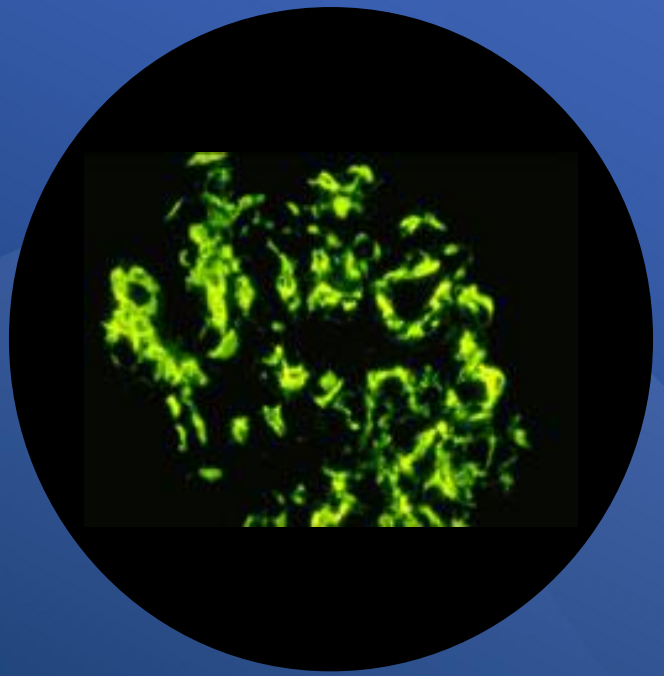

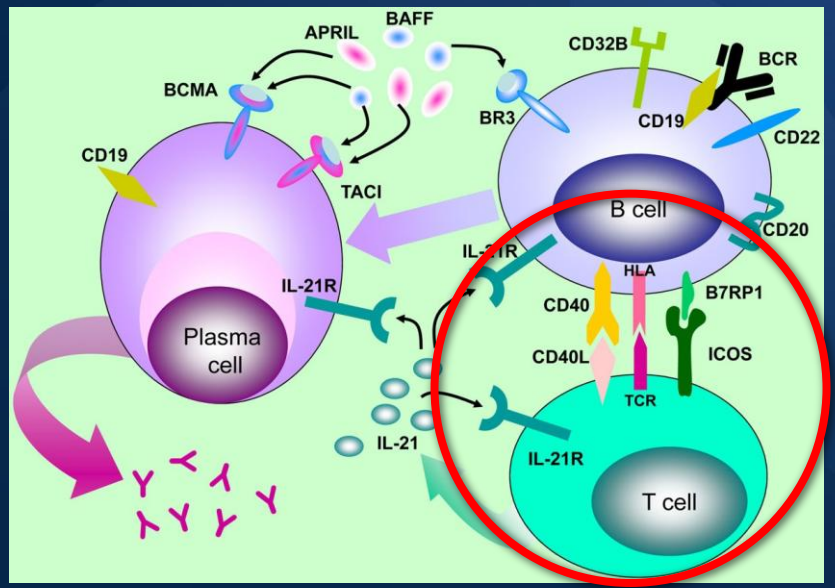

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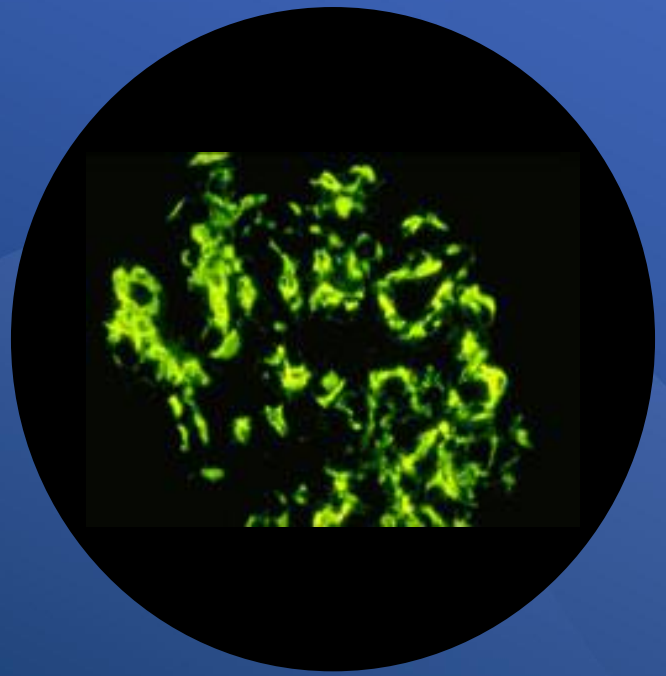

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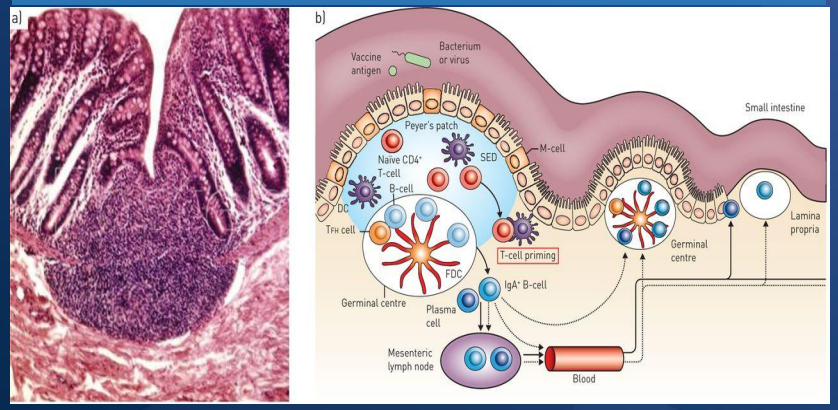

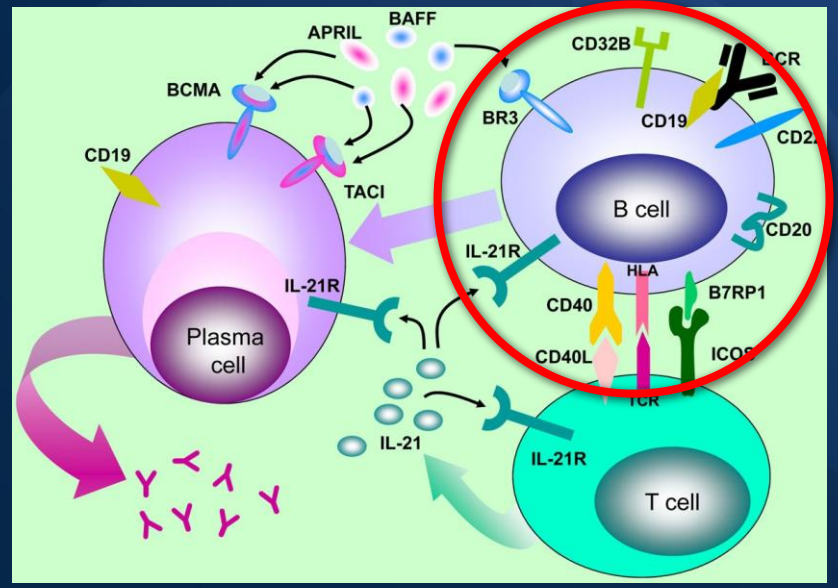

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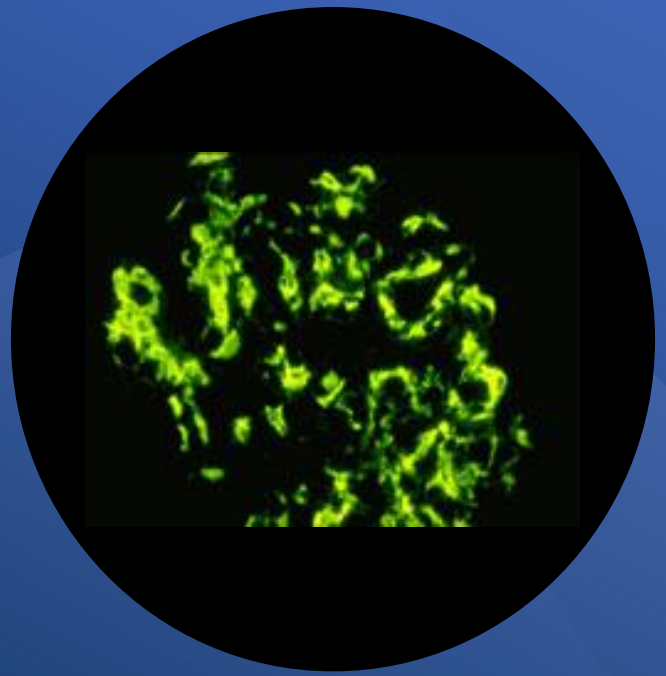

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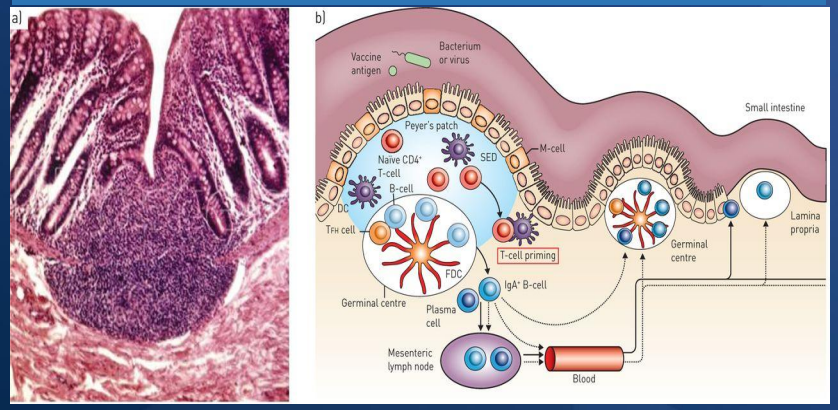

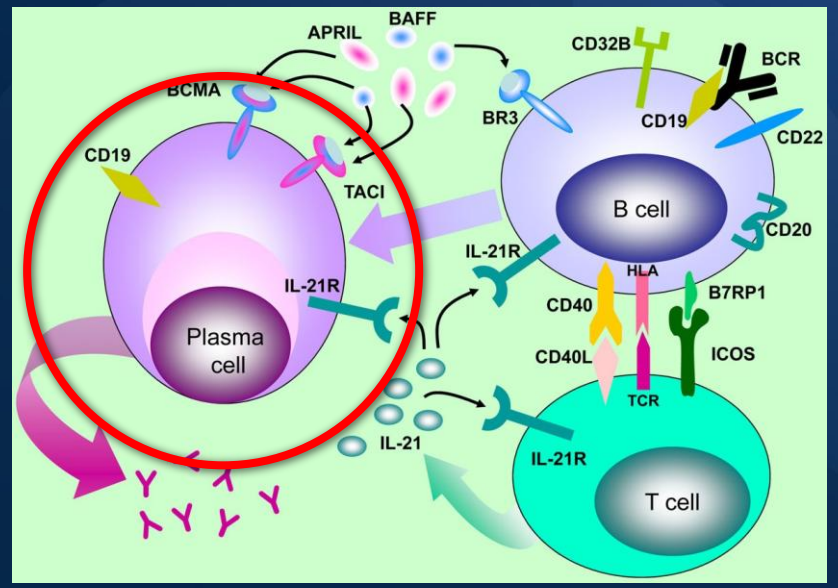

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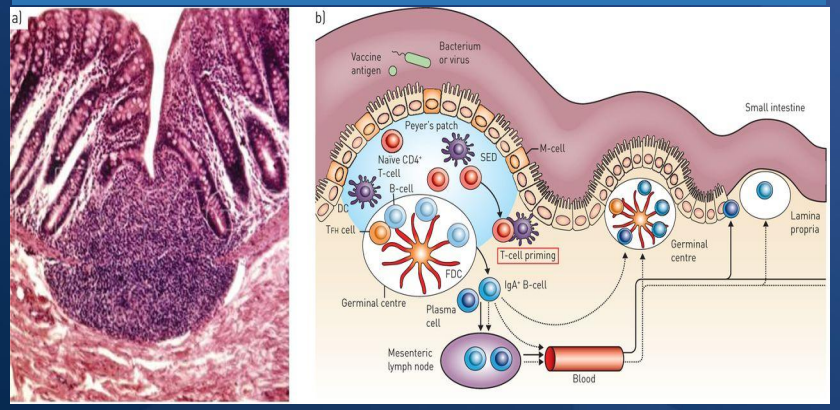

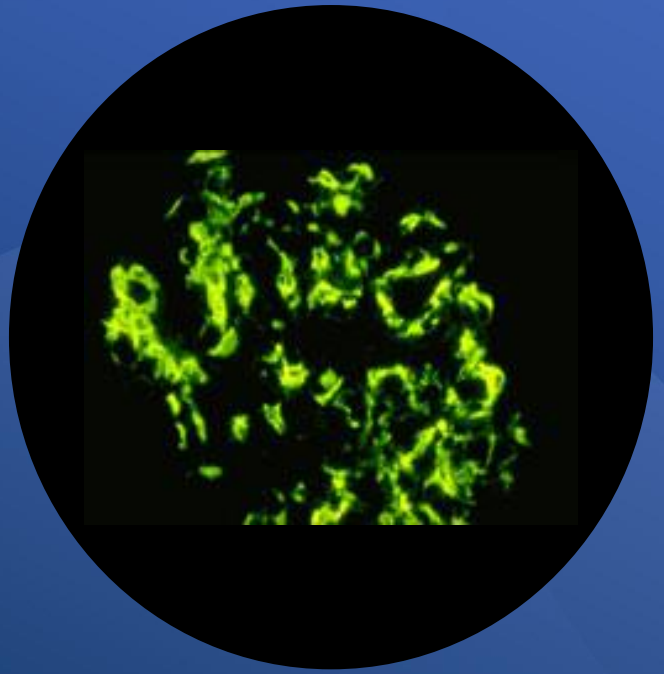

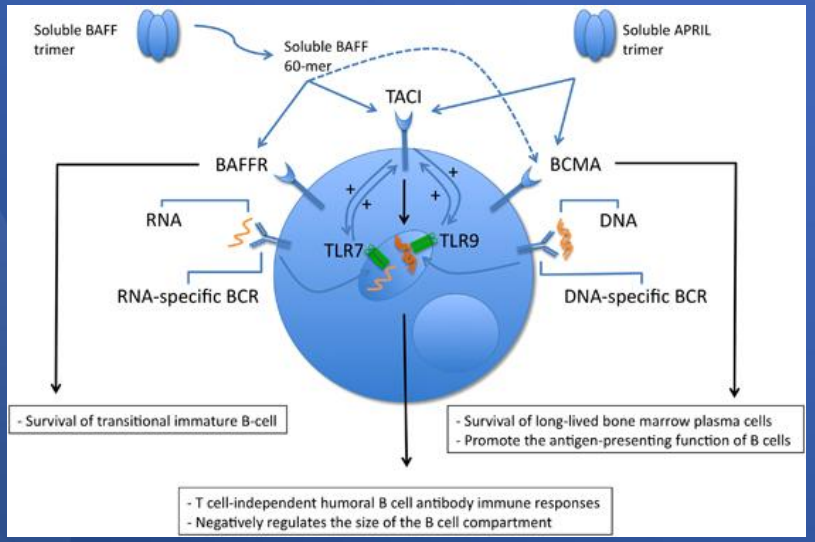

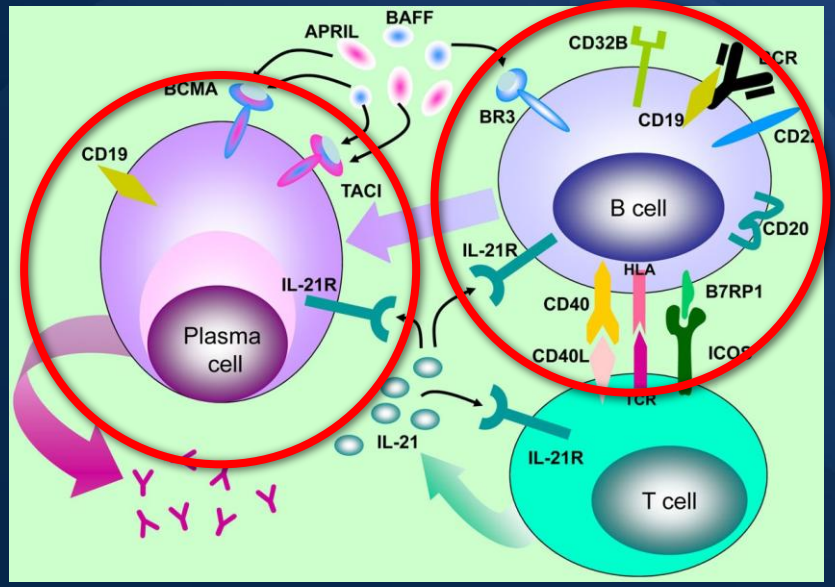

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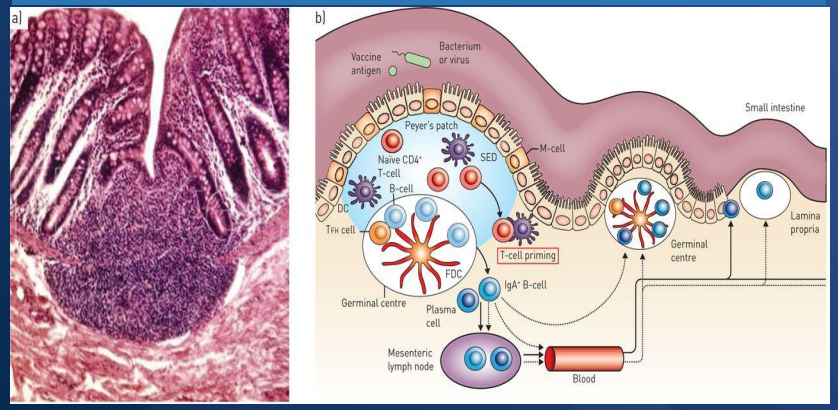

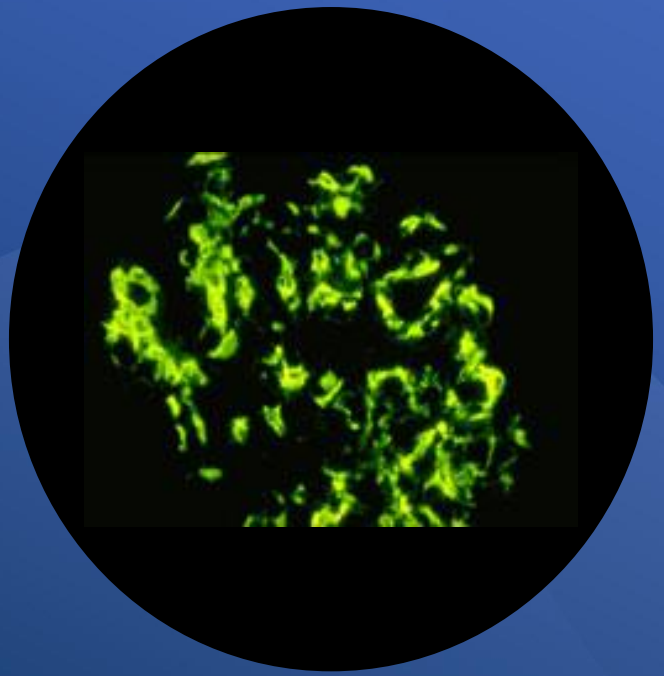

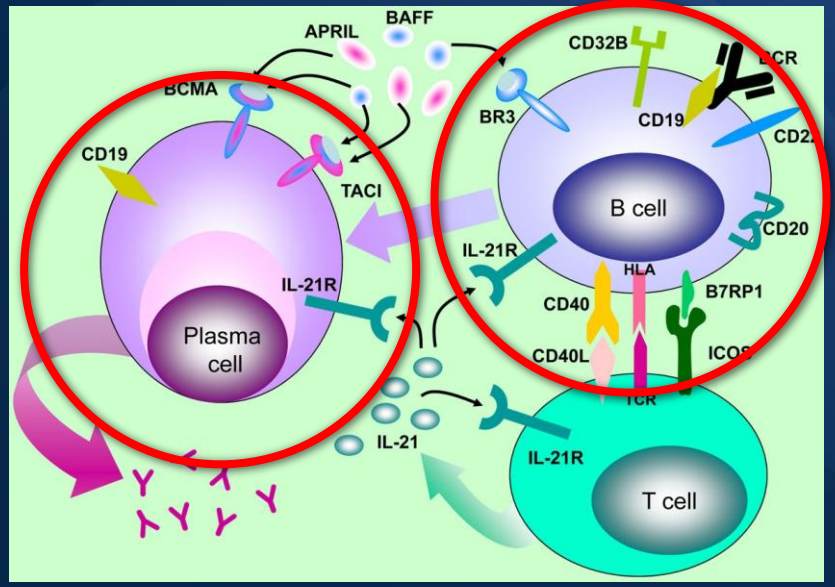

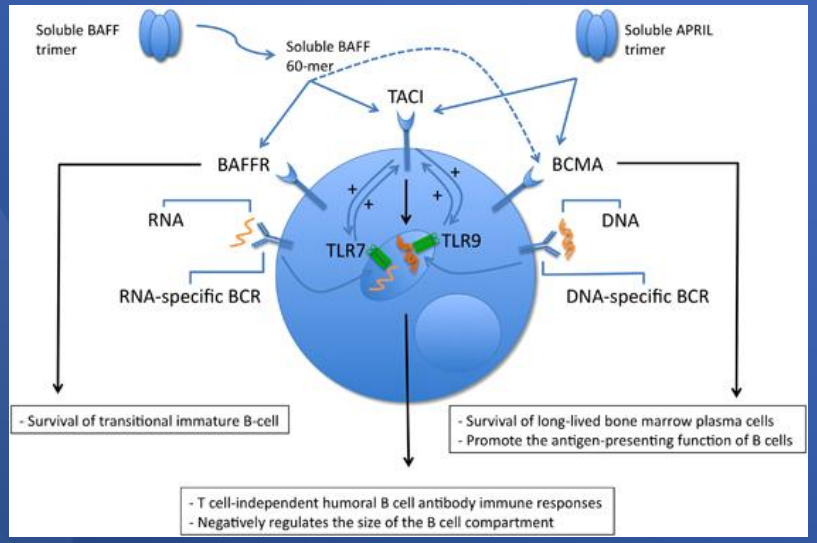

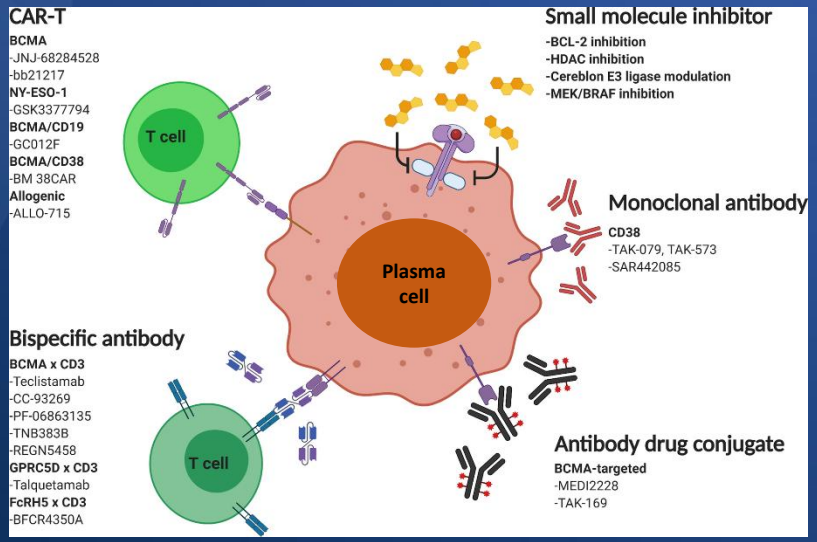

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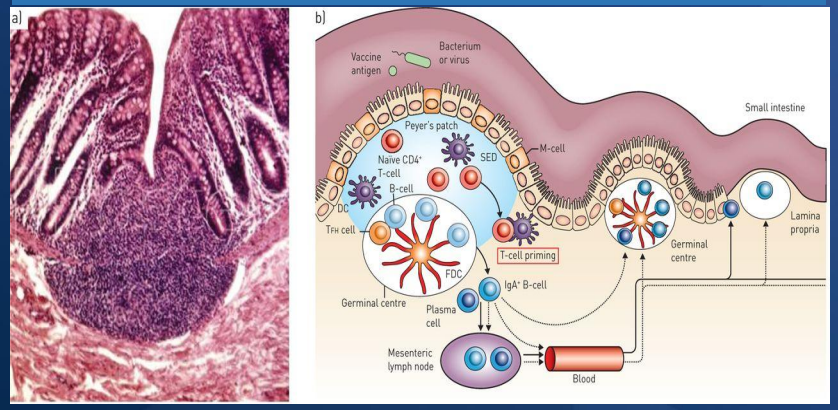

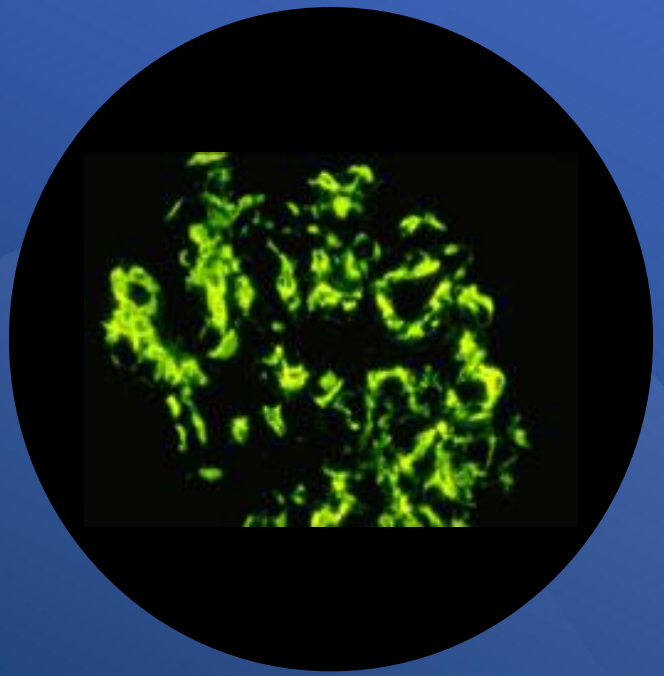

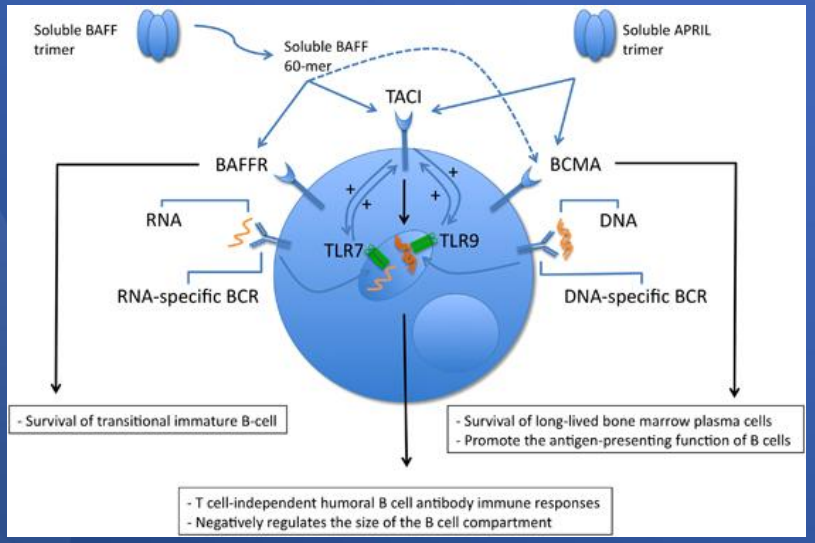

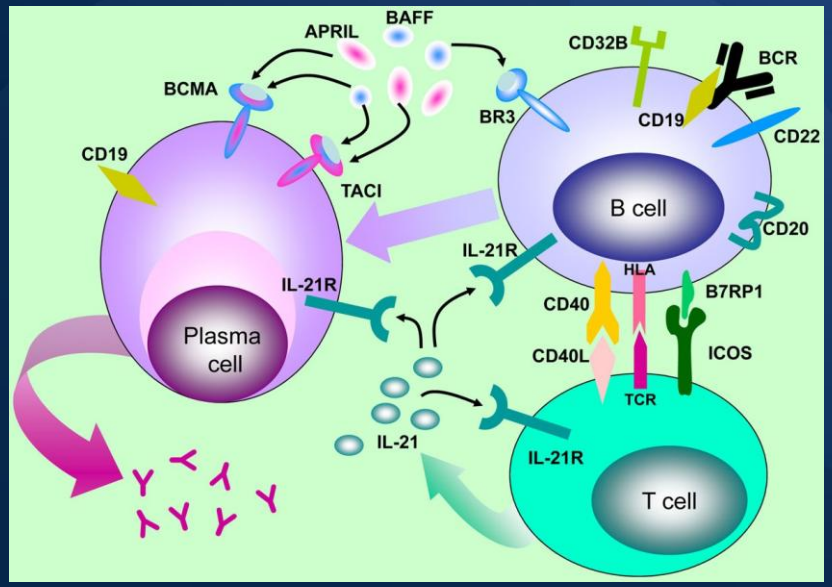

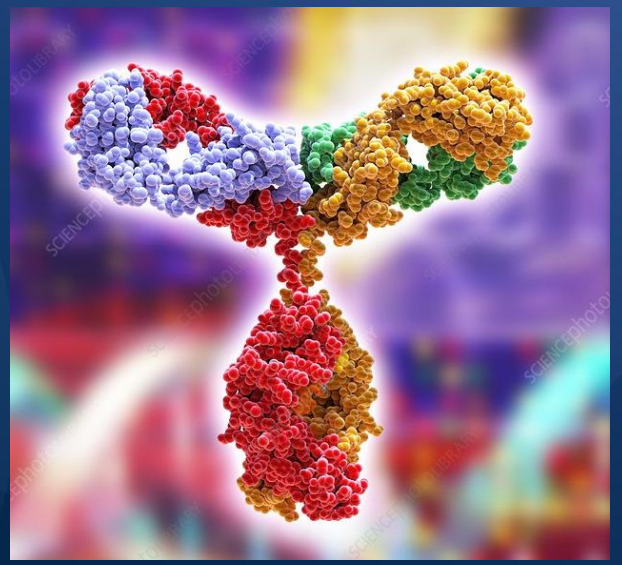

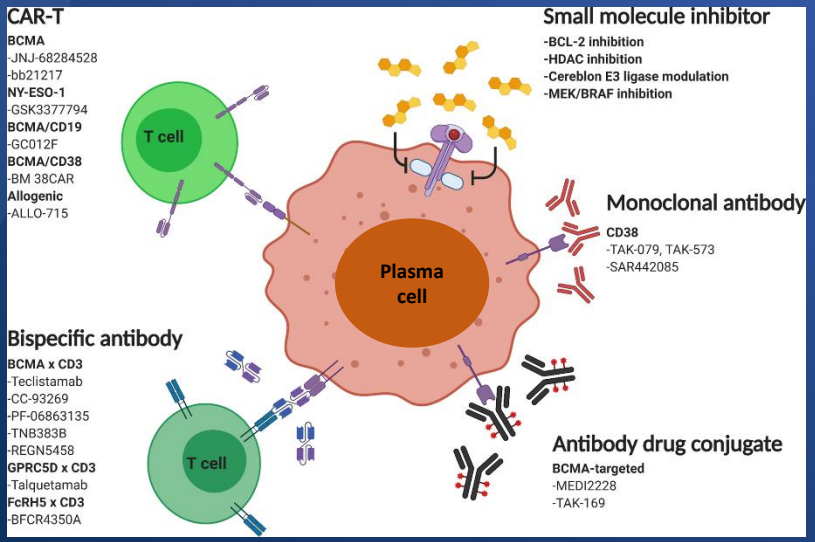

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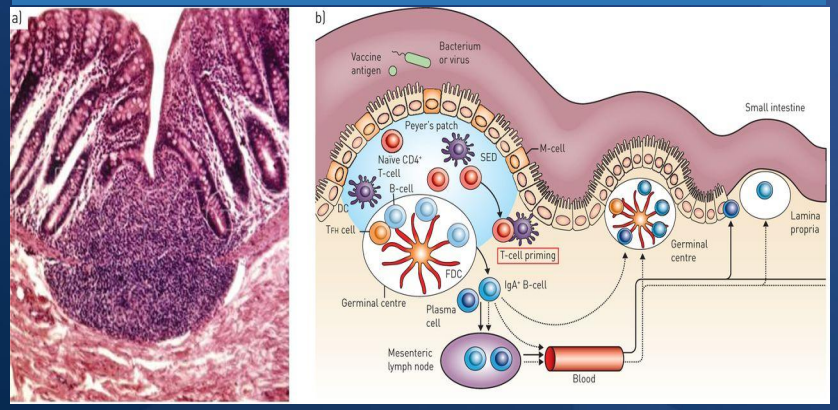

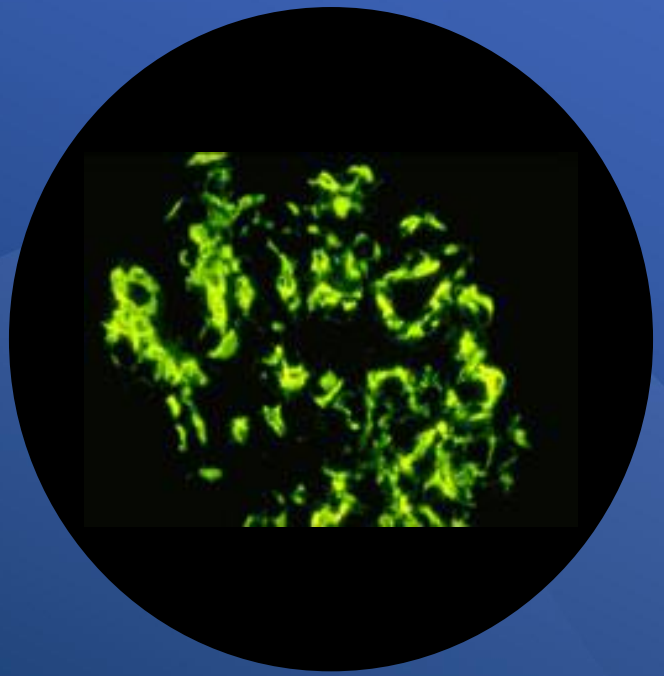

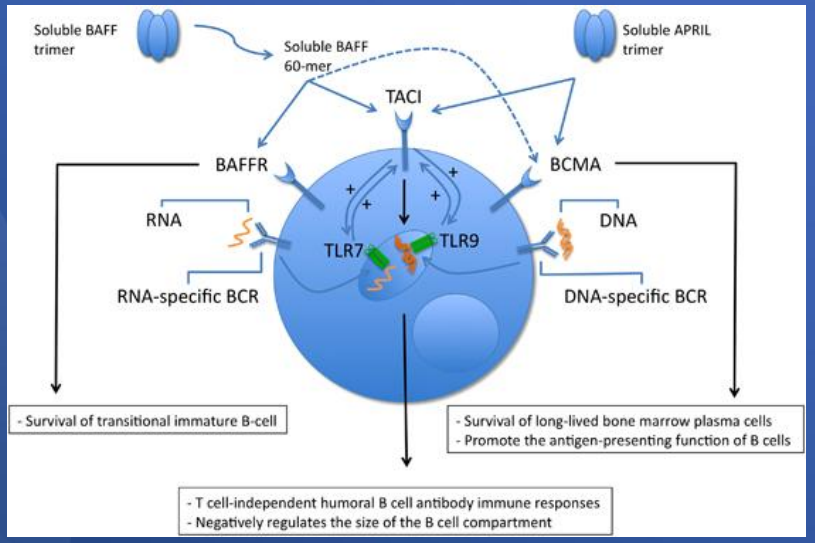

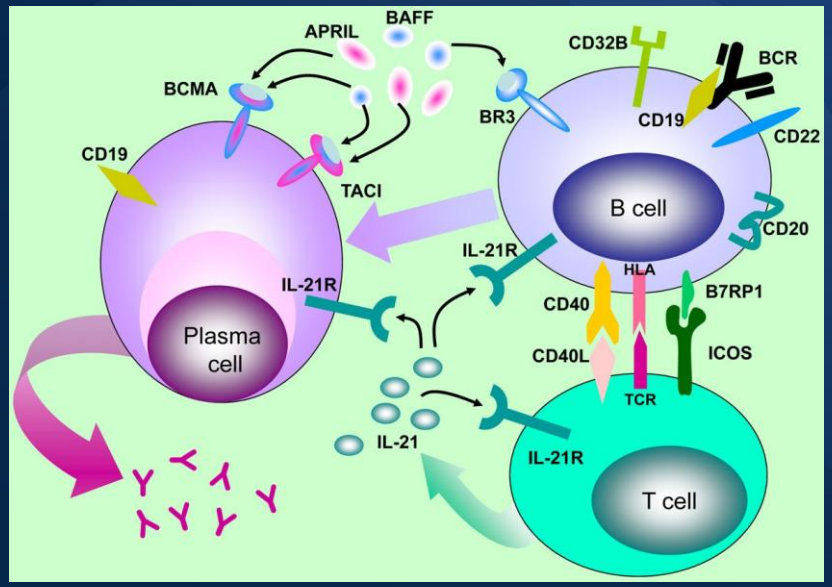

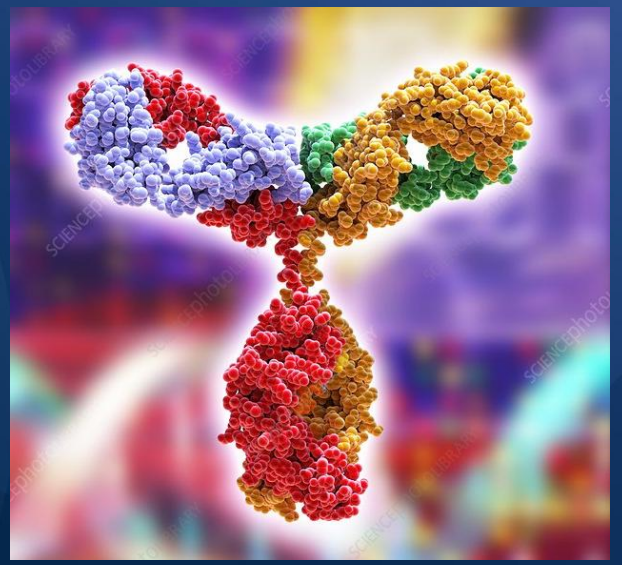

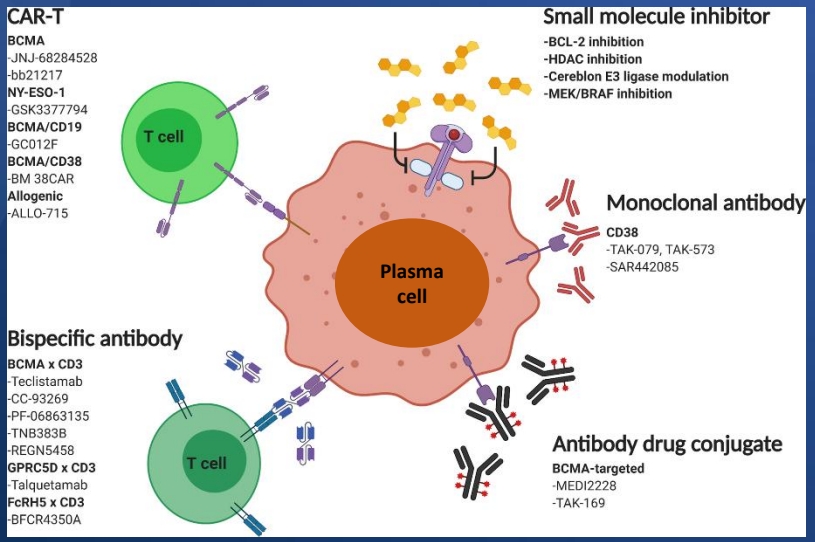

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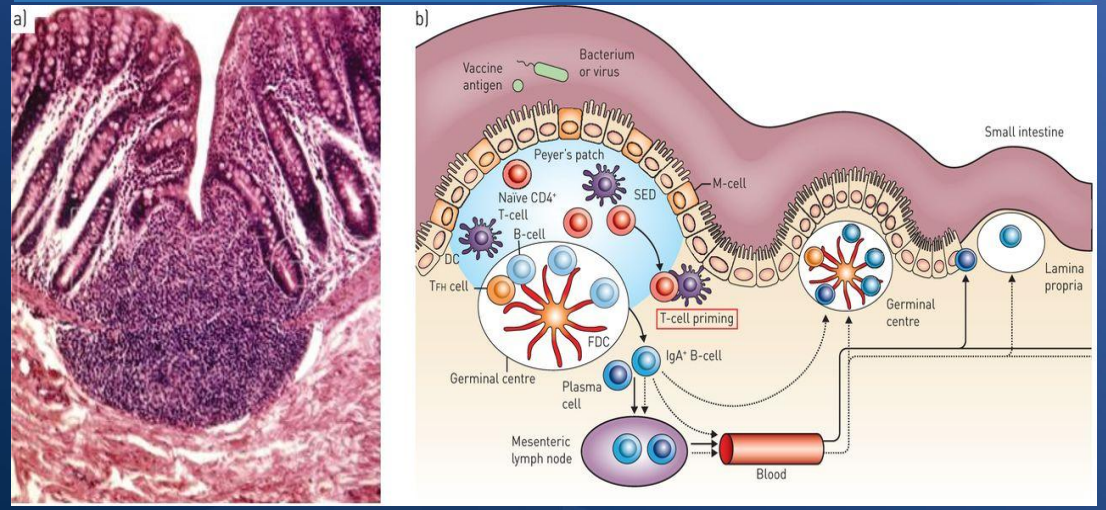
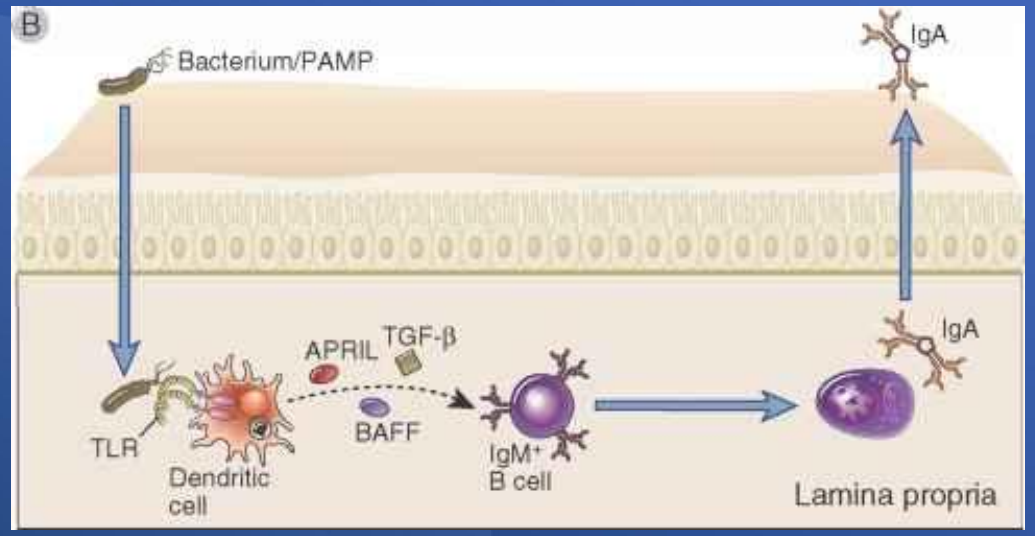
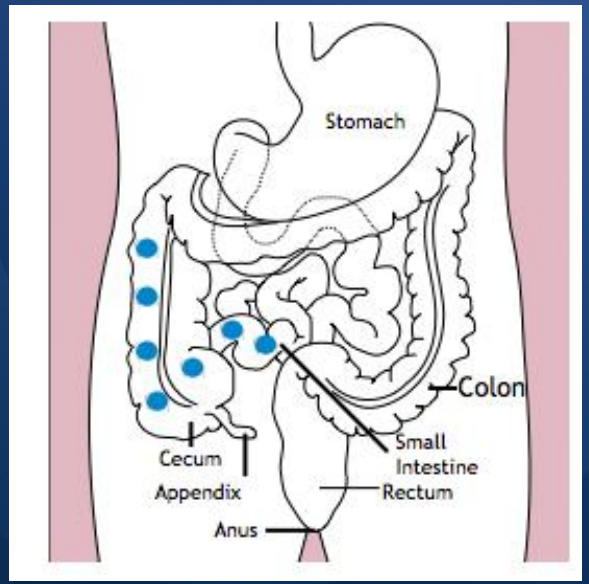
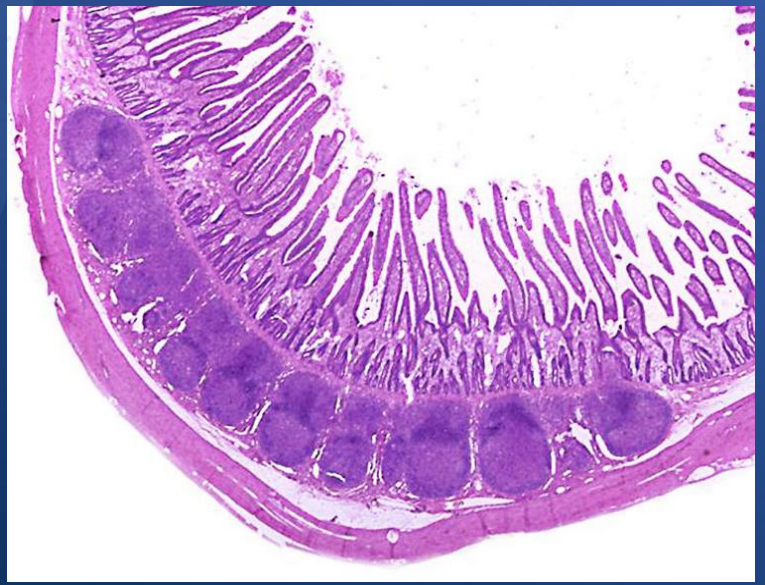




NEFECON - enteric-coated starch capsules filled with budesonide coated spheres.





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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

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

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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 1:1:1 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=0·0259); 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).[3,5,6] 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).[7] 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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Results from part A of the multi-center, double-blind, randomized, placebo-controlled NeflgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy

see commentary on page 258

OPEN

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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.

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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

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[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 (NeflgArd): 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 NeflgArd 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 NeflgArd 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 NeflgArd 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 progressive chronic kidney disease should be considered 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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KEYWORDS: chronic kidney disease; complement; cytokines; glomerulus; IgA nephropathy; proteinuria

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).[1,2] 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).[3] 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.[4] Patients (n = 150) were stratified according to the baseline urine protein–creatinine ratio (≤0.8 g/g and >0.8 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.[4] Changes from baseline in multiple biomarkers were observed at 9 months, as described below,

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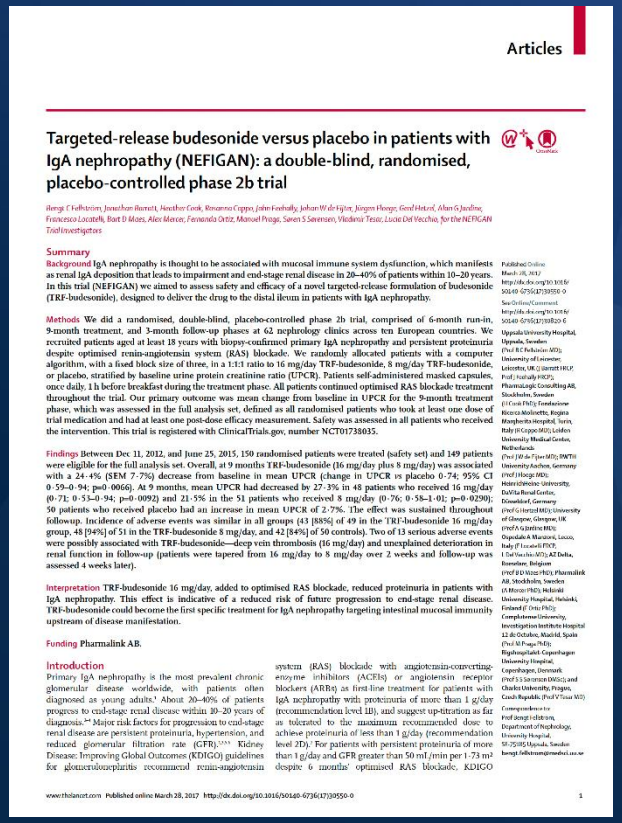

Articles

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

Bengt C Fellström, Jonathan Barratt, Heather Cook, Rosanna Coppo, John Feehally, Johan W de Fijter, Jürgen Floege, Gerd Hetzel, Alan G Jardine, Francesco Locatelli, Bart D Maes, Alex Mercer, Fernanda Ortiz, Manoel 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 1:1:1 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=0·0259); 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.

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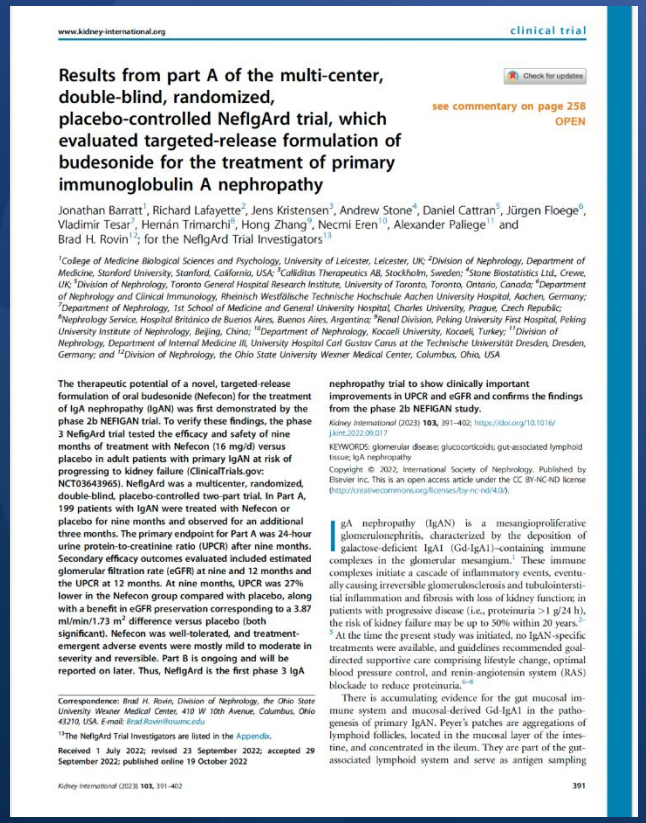
Introduction

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).[3,5,6] 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).[7] 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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Results from part A of the multi-center, double-blind, randomized, placebo-controlled NeflgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy

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see commentary on page 258

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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 NeflgArd Trial Investigators[13]

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Articles

Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NeflgArd): 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 NeflgArd 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 NeflgArd 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 NeflgArd 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.[2–4] 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).[5] After supportive care, patients who remain at high risk for progressive chronic kidney disease should be considered for a clinical trial, or for systemic glucocorticoids (if they

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KEYWORDS: chronic kidney disease; complement; cytokines; glomerulus; IgA nephropathy; proteinuria

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

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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).[1,2] 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).[3] 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.[4] Patients (n = 150) were stratified according to the baseline urine protein-creatinine ratio (≤0.8 g/g and >0.8 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.[4] 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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[1]College of Life Sciences, University of Leicester, Leicester, UK; [2]Calliditas Therapeutics AB, Stockholm, Sweden

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.

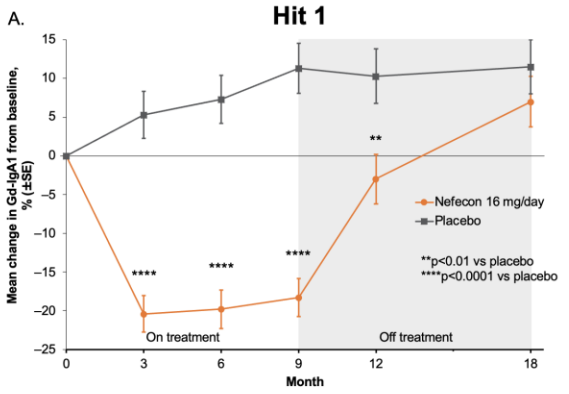
METHOD

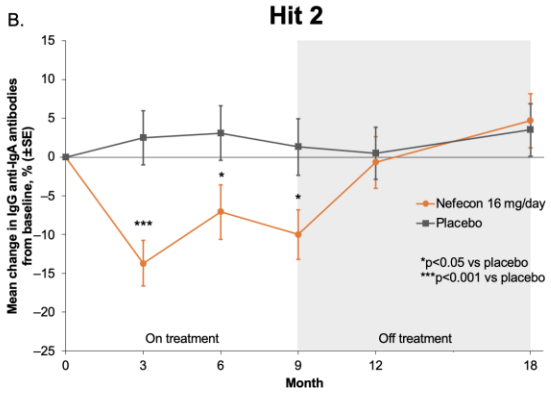
- In the NefIgArd trial (NCT0364396), patients received 9 months of treatment with either placebo or nefecon 16 mg/day, before entering a 15-month off-drug observational period
- Gd-IgA1, IgG anti-IgA autoantibody, and IgA-IC levels in 216 consenting NefIgArd participants (n=108 per group) were measured 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

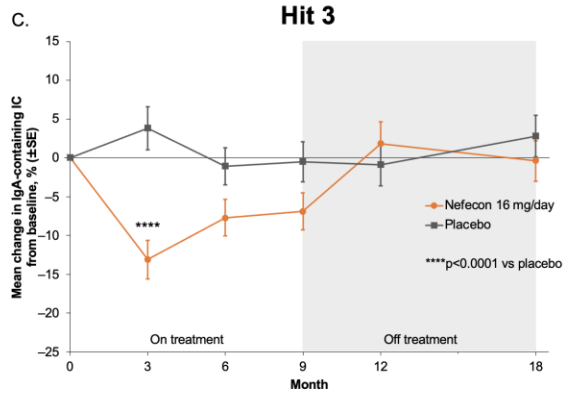
RESULTS

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

We would like to thank the patients and their families, as well as the teams of healthcare professionals and academics involved in this work, without whom none of it would be possible.

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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.

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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.

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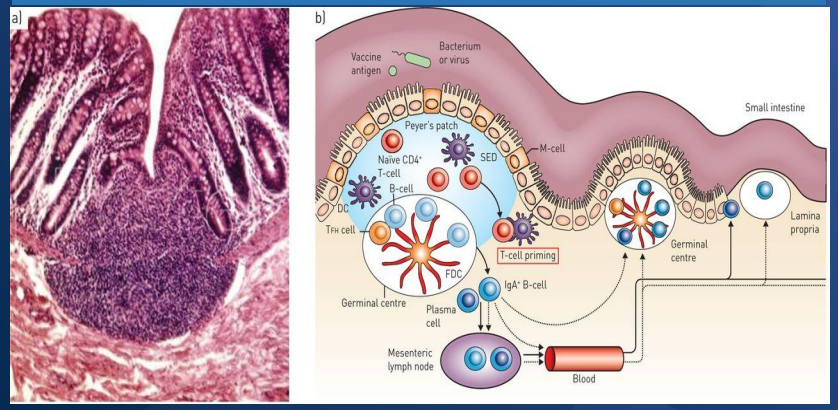
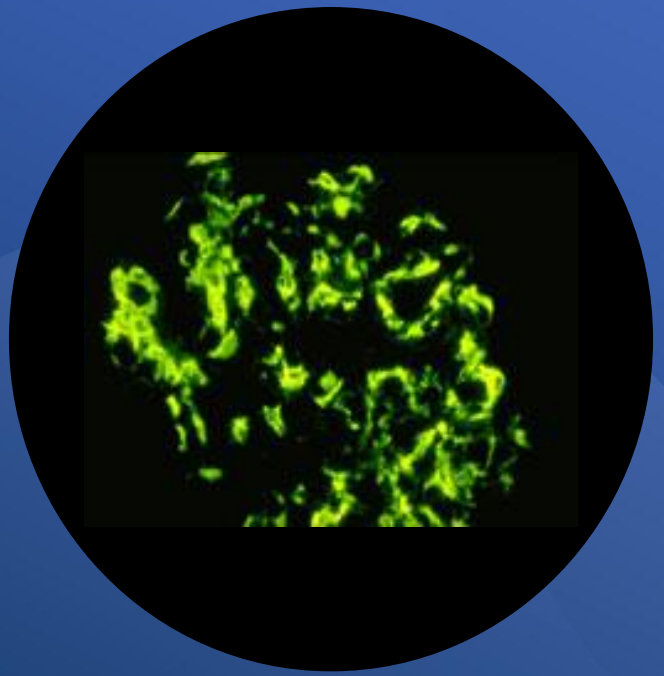
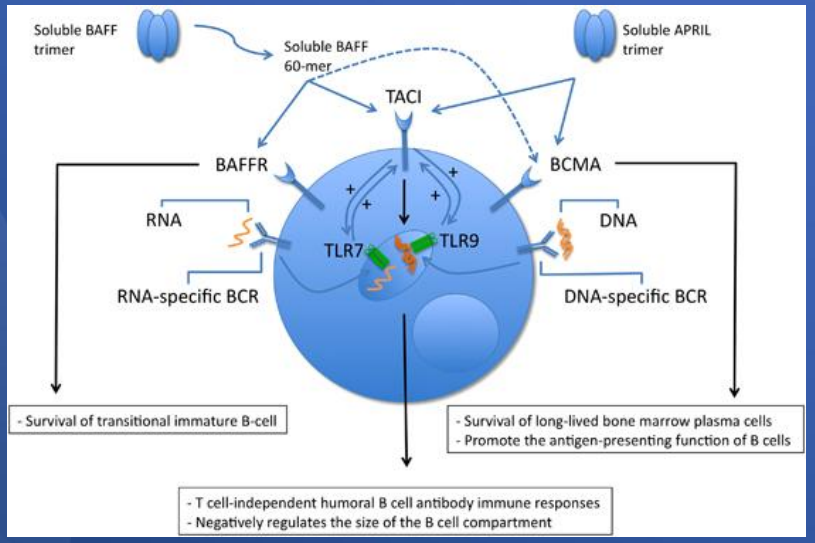
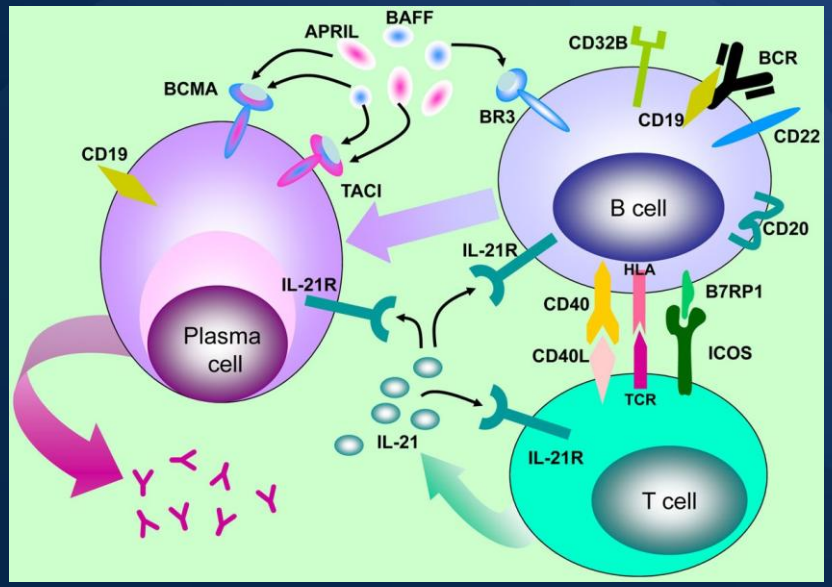
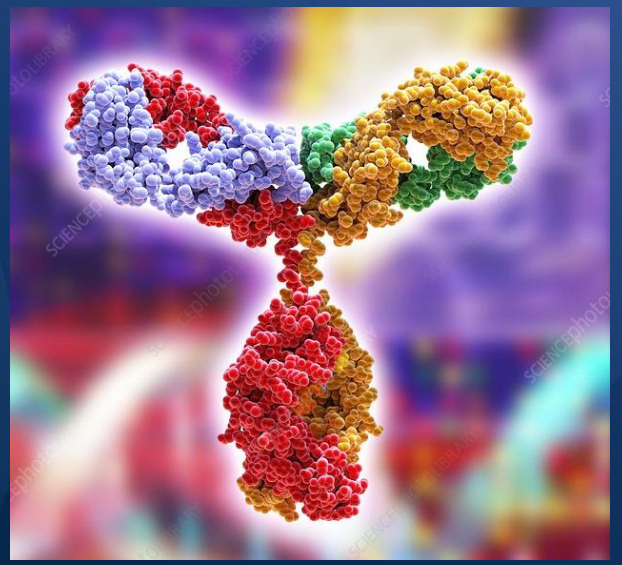
Mucosa Associated Lymphoid Tissue

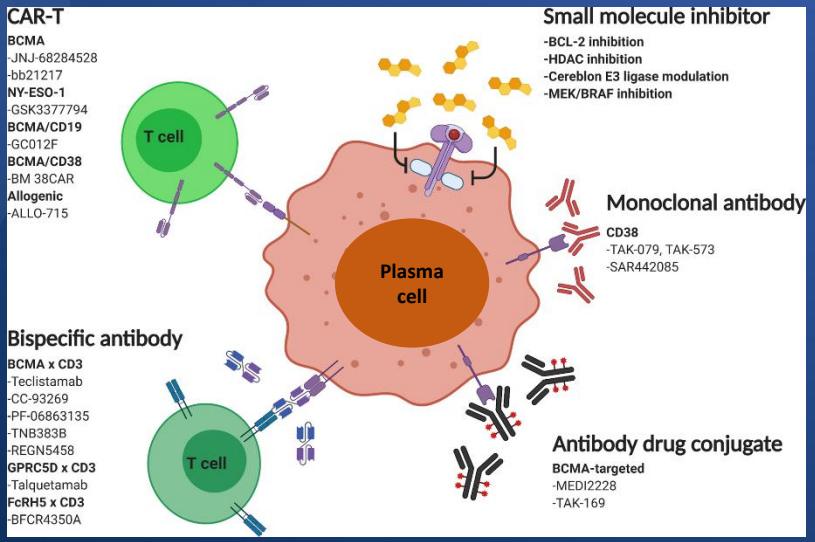












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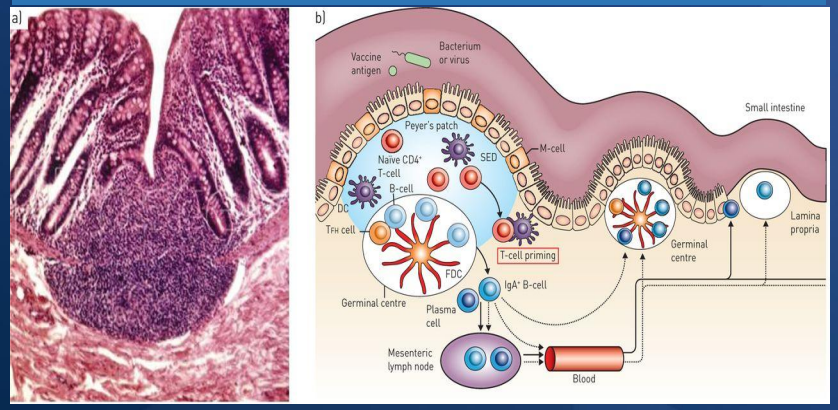

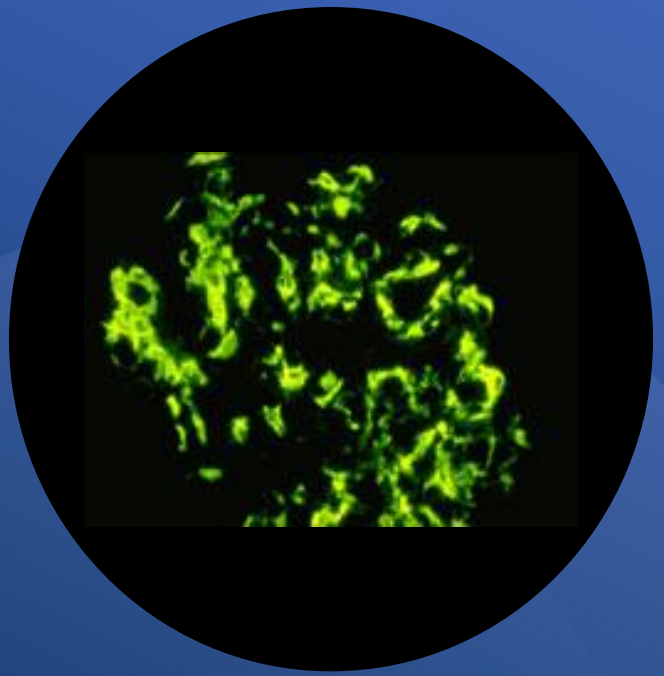

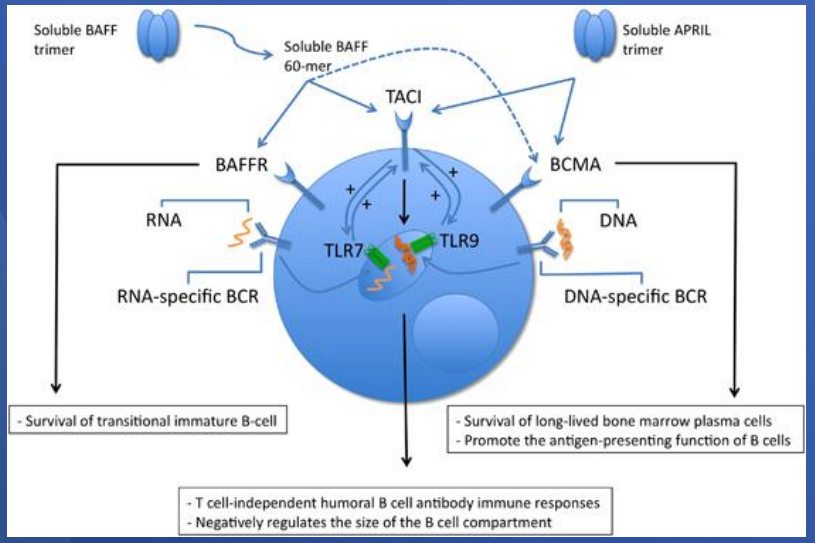

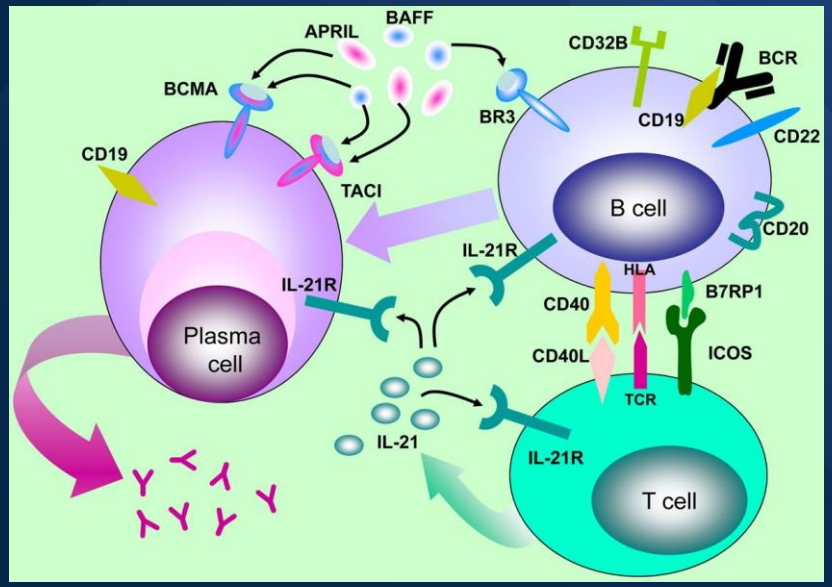

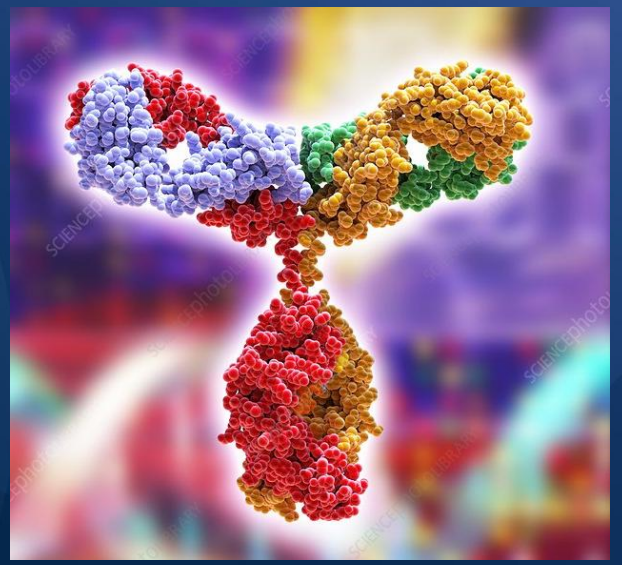

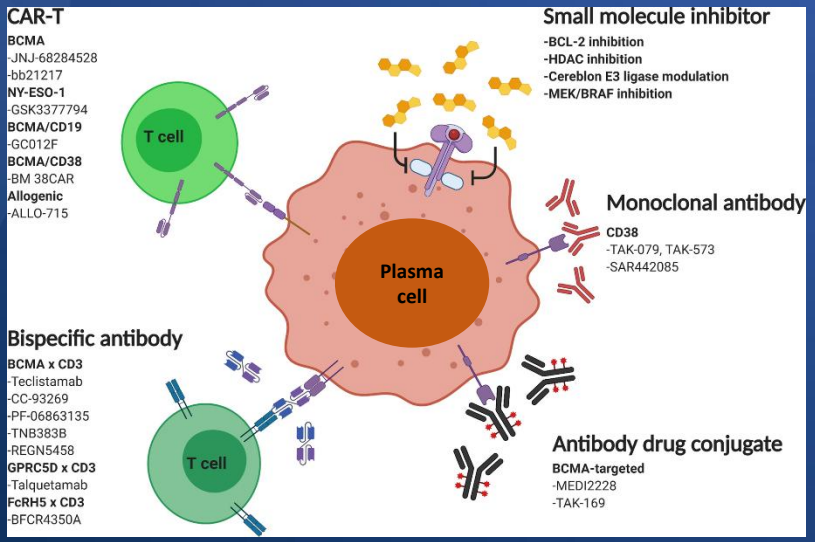

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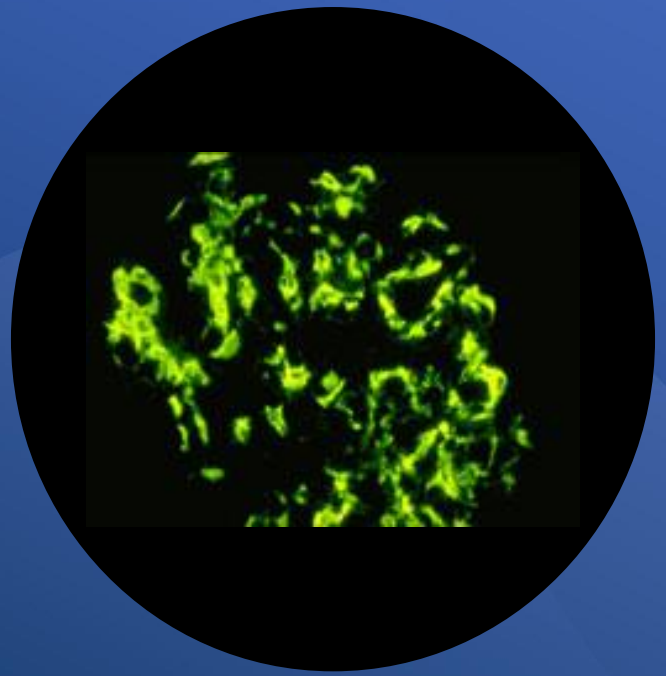

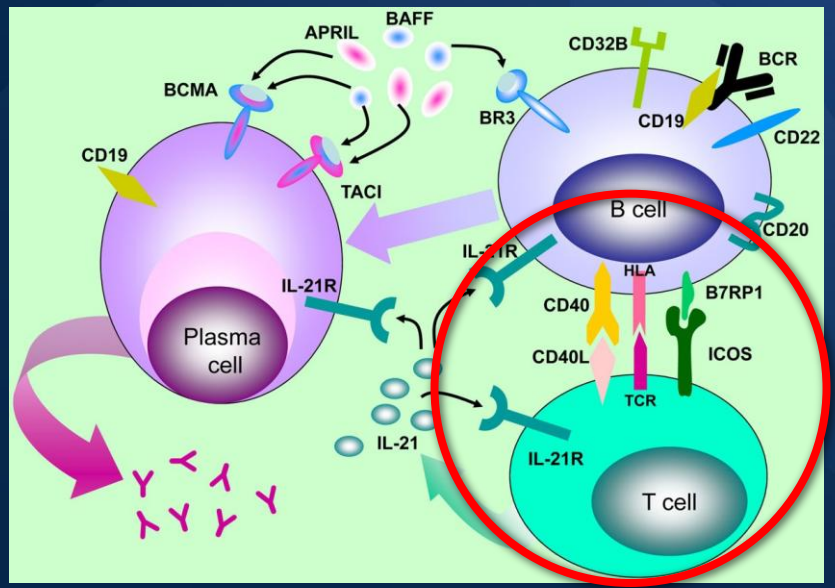

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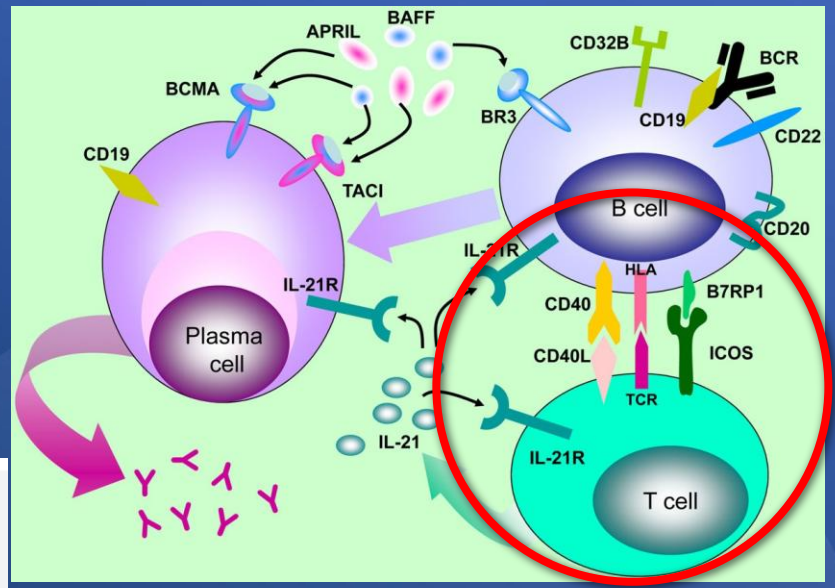

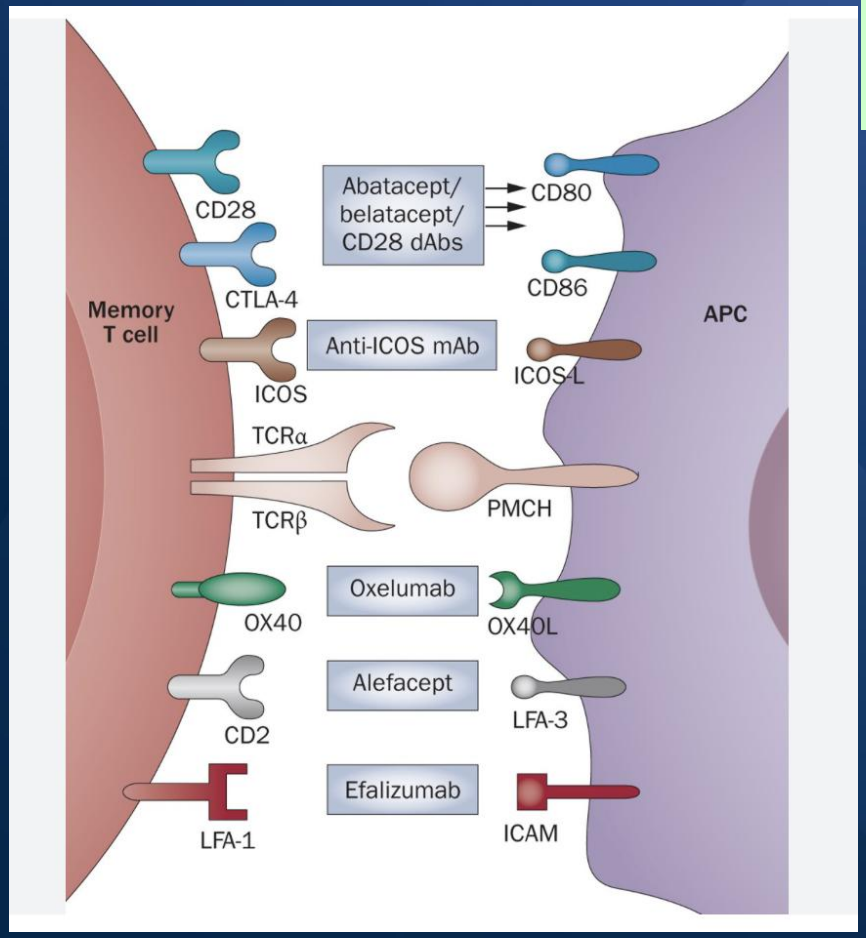

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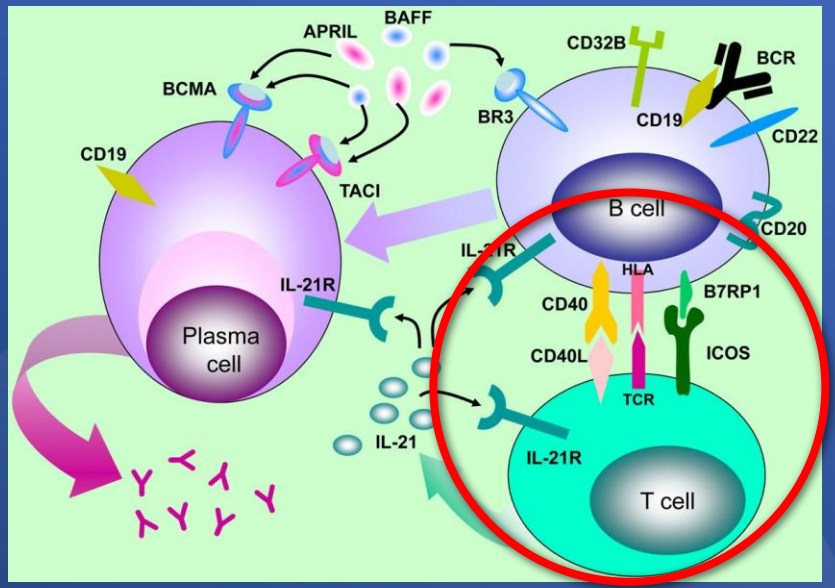
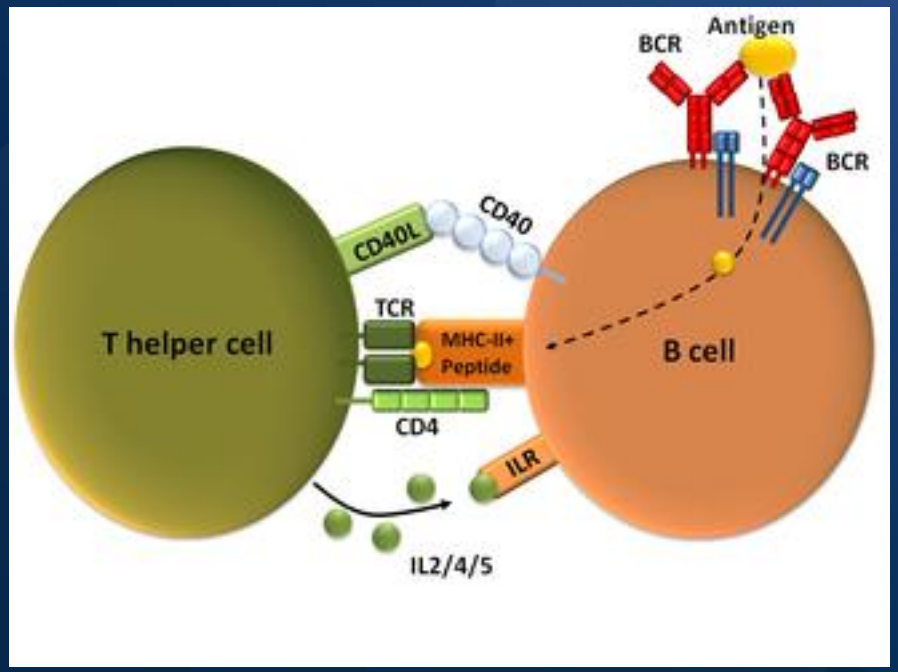




Eledon Pharmaceuticals

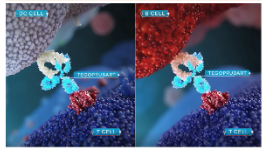
A Phase 2a study to evaluate the safety and efficacy of tegoprubart (AT-1501) in patients with IgA nephropathy (IgAN)

Jonathan Barratt, Adrian Liew, Dana V Rizk, Lisa Willcocks, Richard Lafayette, Muh Geot Wong, Vladimir Tesar, Jeffrey D Bornstein, Heather Reich, Sydney Tang

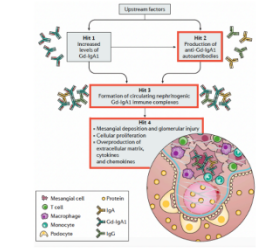
Background

IgAN is the most common autoimmune nephropathy, with a young age of onset and a slow progressive course. ~40% of affected patients progress to kidney failure within 20 years of diagnosis. Therapeutic options that delay progression are limited, and more options are needed. Tegoprubart is a next generation monoclonal antibody directed against CD40 ligand (CD40L; CD154), a target important in both cell and antibody mediated immunity. Inhibiting CD40L is expected to disrupt the pathophysiology of IgAN both upstream, by blocking antibody and immune complex formation, and downstream, by interfering with the cell based inflammatory response in the glomeruli. A Phase 2a dose-finding, open-label study, AT-1501-N205, to evaluate the safety and efficacy of tegoprubart in patients with IgAN is underway.

Tegoprubart Mechanism of Action



Rationale for Tegoprubart in the Treatment of IgAN



- The pathophysiology of IgAN is believed to have 4 steps
- Tegoprubart should work both upstream and downstream in IgAN
  - Upstream: By interfering with B cell activation and class switching, tegoprubart should reduce the anti-IgA1 IgG antibodies produced, resulting in less immune complex formation
  - Downstream: By interfering with T cell activation, tegoprubart should reduce cell mediated inflammation in the mesangium

Study Design

AT-1501 10mg/kg in adults with confirmed IgAN & urine protein ≥ 0.75g / day despite optimal therapy

Cohort 1: n = 21

Week 24
Primary endpoints:
- Change from baseline in UPCR
- Safety

Week 96
Secondary endpoints:
- eGFR
- Safety

Exploratory endpoints:
- Biomarkers

Cohort 2 starts at a lower dose once the last subject in Cohort 1 has been enrolled. Cohort 2 has the same sample size, population, interim analysis and endpoints as Cohort 1, but is assessed independently.

AT-1501 5mg/kg

Cohort 2: n = 21

Week 24
Primary endpoint:
- Change from baseline in UPCR
- Safety

Week 96
Secondary endpoints:
- eGFR
- Safety

Exploratory endpoints:
- Biomarkers

Population

- Adults with biopsy confirmed IgAN
- Urine protein ≥ 0.7 g/24 hours despite optimization with ACE inhibitors or angiotensin receptor blockers
- eGFR ≥ 45 mL/min per 1.73 m2 or eGFR < 45 mL/min per 1.73 m2 and ≥ 30 mL/min per 1.73 m2 with a kidney biopsy within 2 years of Screening showing < 50% tubulointerstitial fibrosis
- Any history of kidney transplantation or kidney disease other than IgAN is exclusionary

Rationale for Design

- Sequential cohort design starting at higher dose chosen:
  - The 10 mg/kg dose is well below the NOAEL and less than the dose currently being used in clinical trials of transplant with tegoprubart
  - Starting with the higher dose, allows for decision making to occur on the fewest number of participants possible
    - Only explore a lower dose if high dose appears to be safe and effective
- A placebo arm was not included in this Phase 2a study as the endpoint is a lab value and efficacy can be assessed vs historical comparison data; allows every participant to get tegoprubart

Endpoints

- Primary endpoint: Change from baseline in urine protein to creatinine ratio at week 24
- Secondary endpoints:
  - Safety
  - Change in eGFR slope from baseline to week 96
  - Change from baseline in 24 urine protein at various timepoints
  - Rate of anti-drug antibodies
- Exploratory:
  - Biomarkers
- Each cohort has a futility analysis after 12 participants reach week 24

Conclusions

- Enrollment is ongoing
- For more information or to be considered as a site for our program please contact: jbornstein@eledon.com

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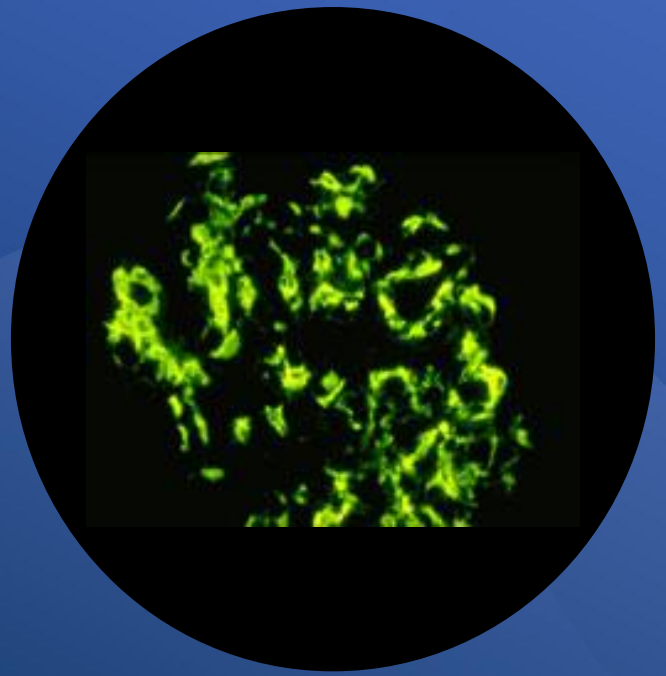

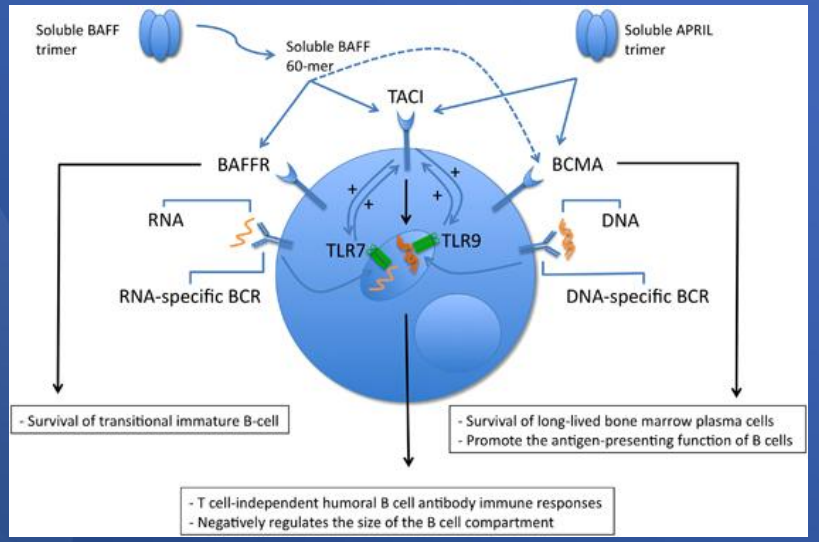

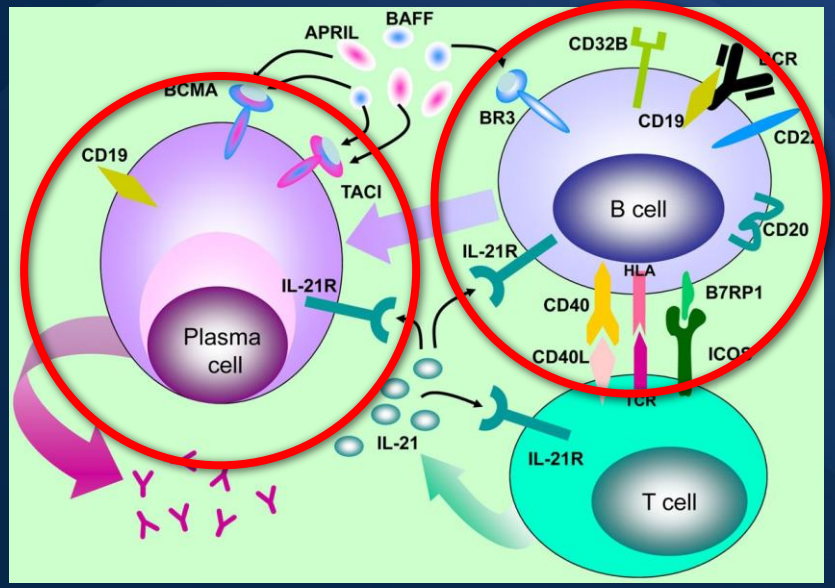

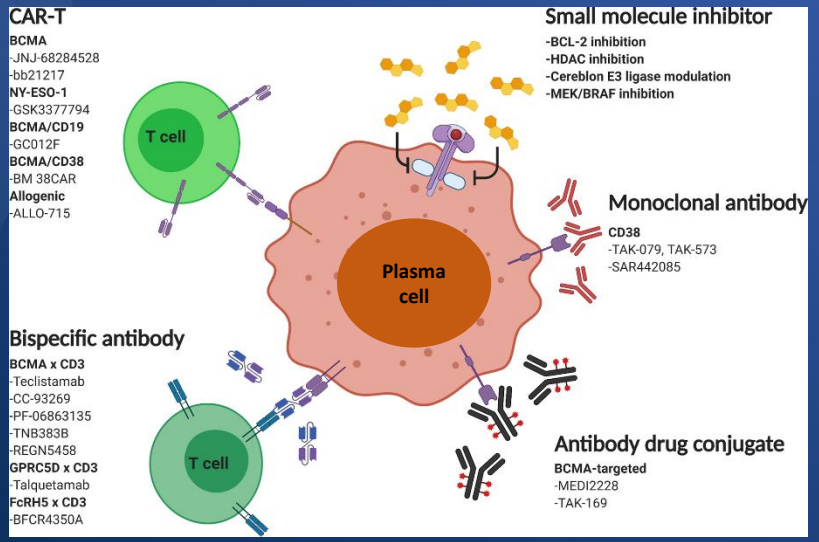

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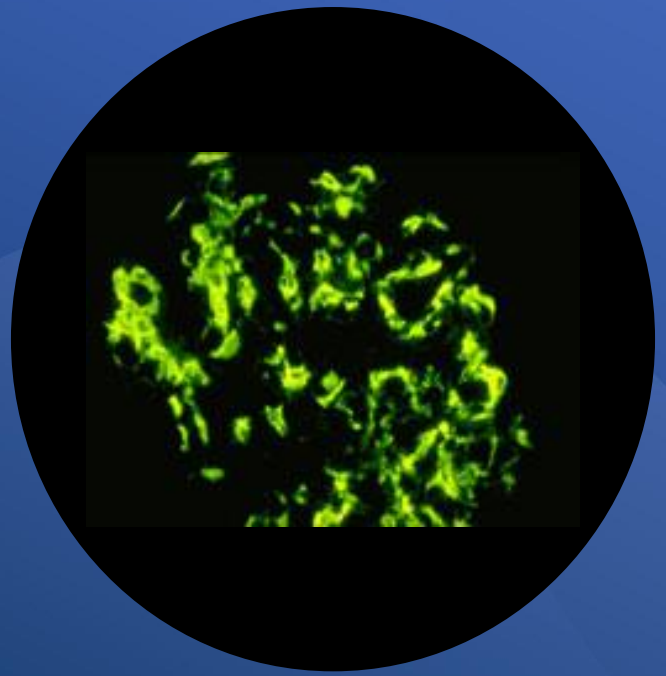

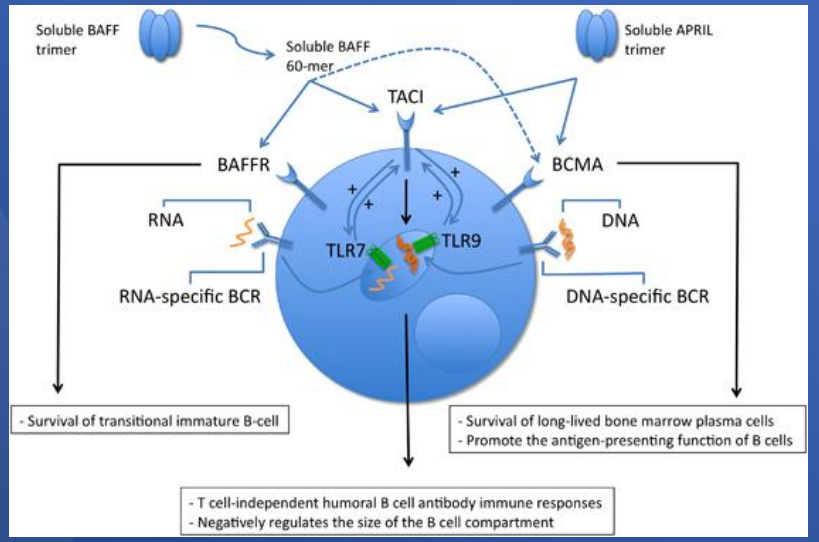

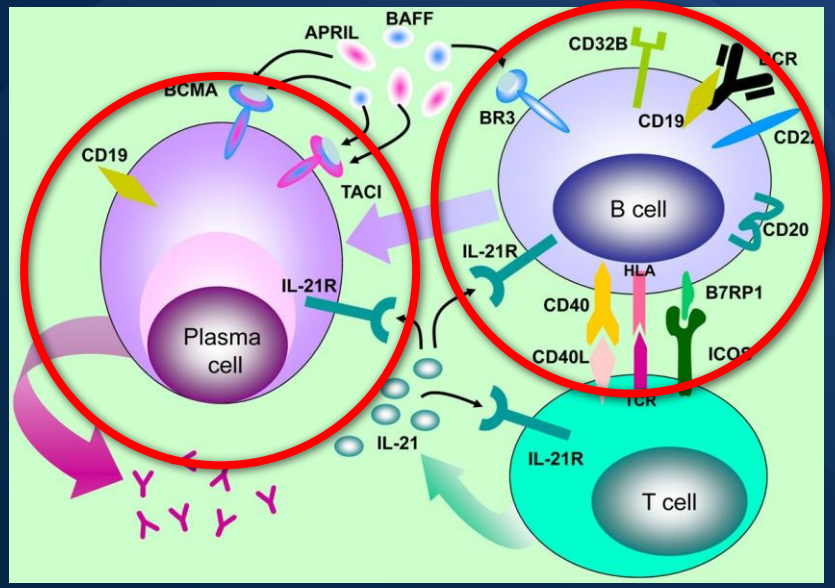

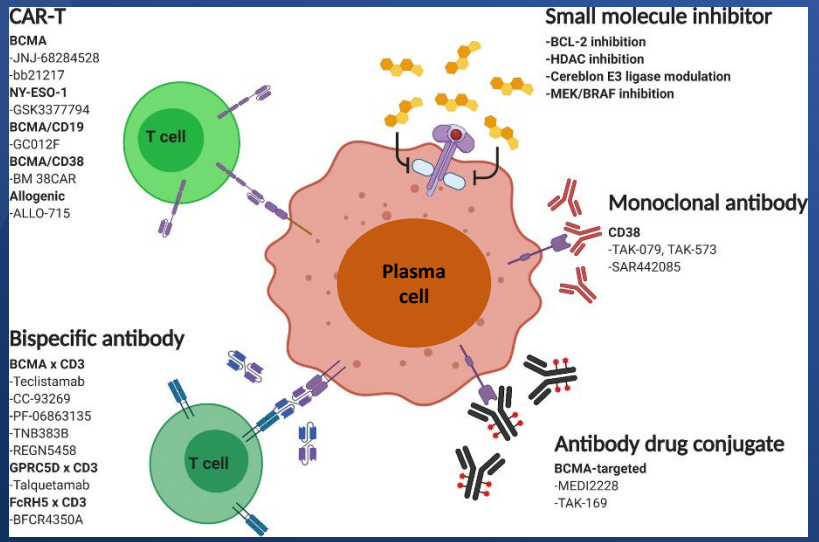

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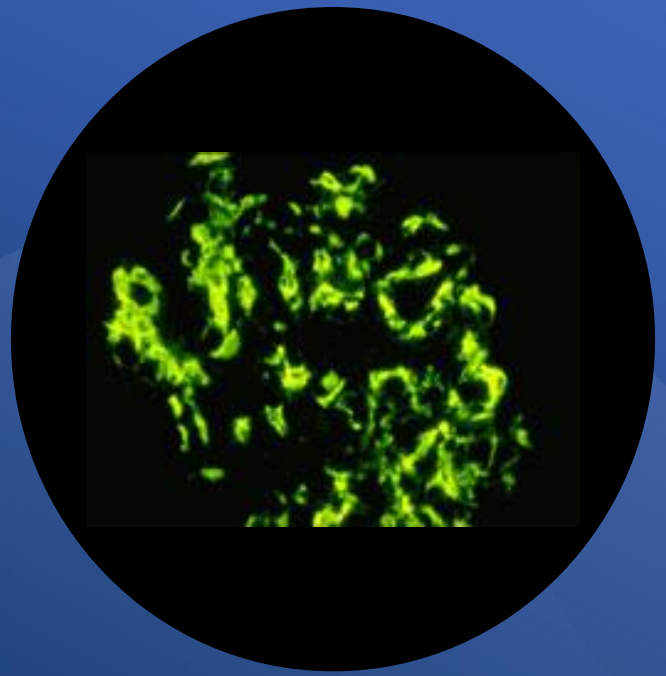

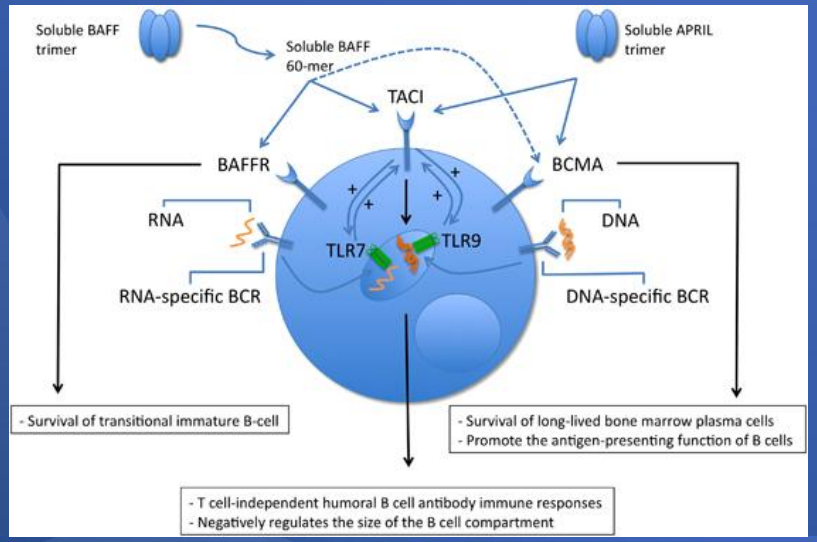

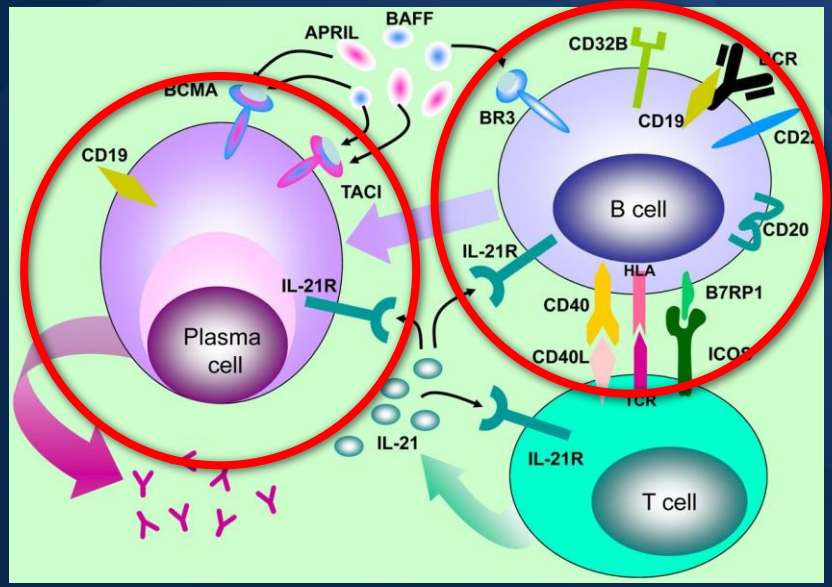

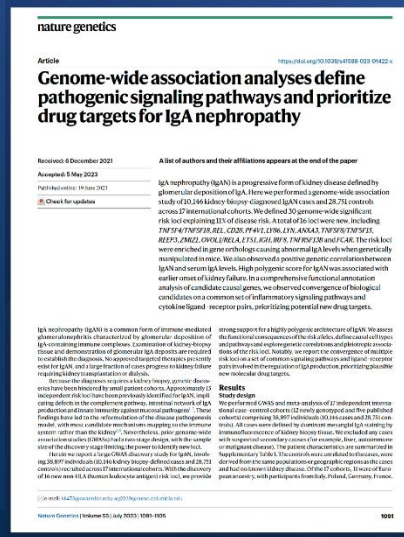
nature genetics

Article

https://doi.org/10.1038/s41588-023-01422-x

Genome-wide association analyses define pathogenic signaling pathways and prioritize drug targets for IgA nephropathy

A list of authors and their affiliations appears at the end of the paper

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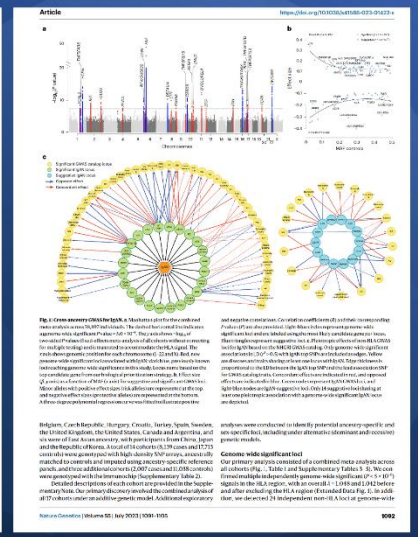
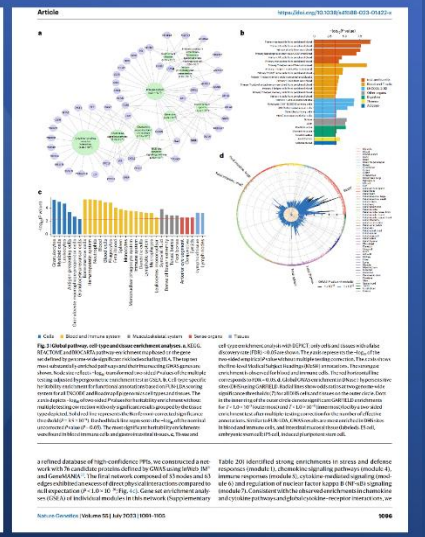
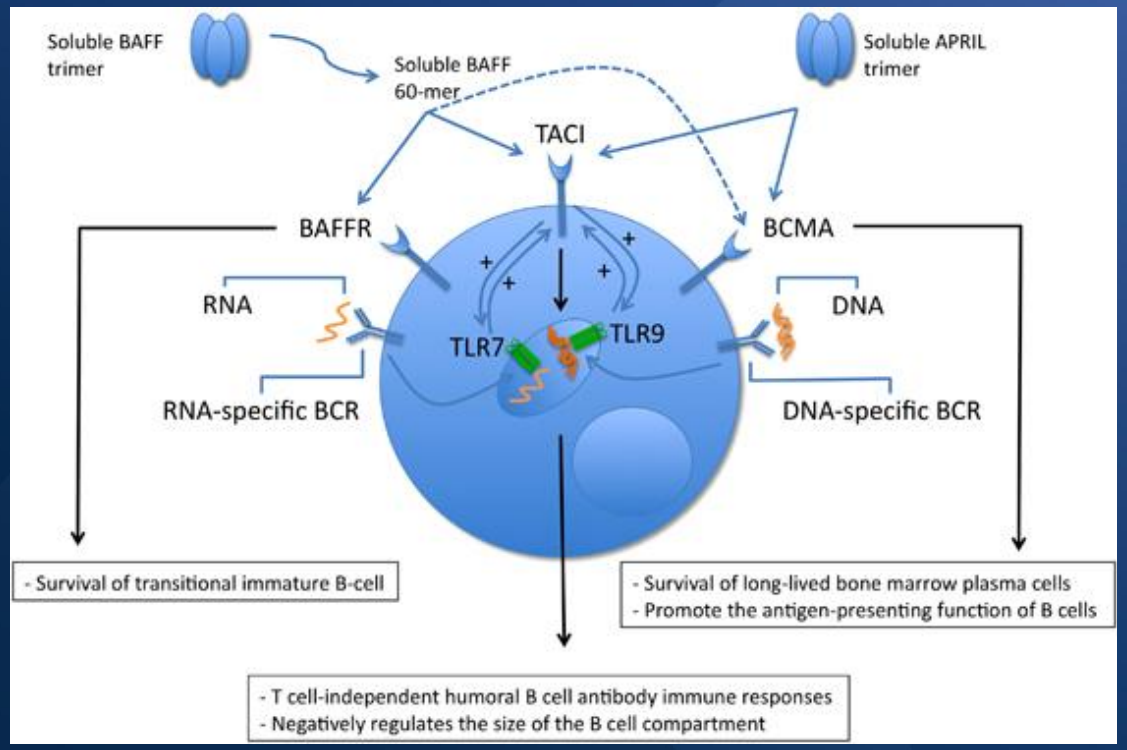
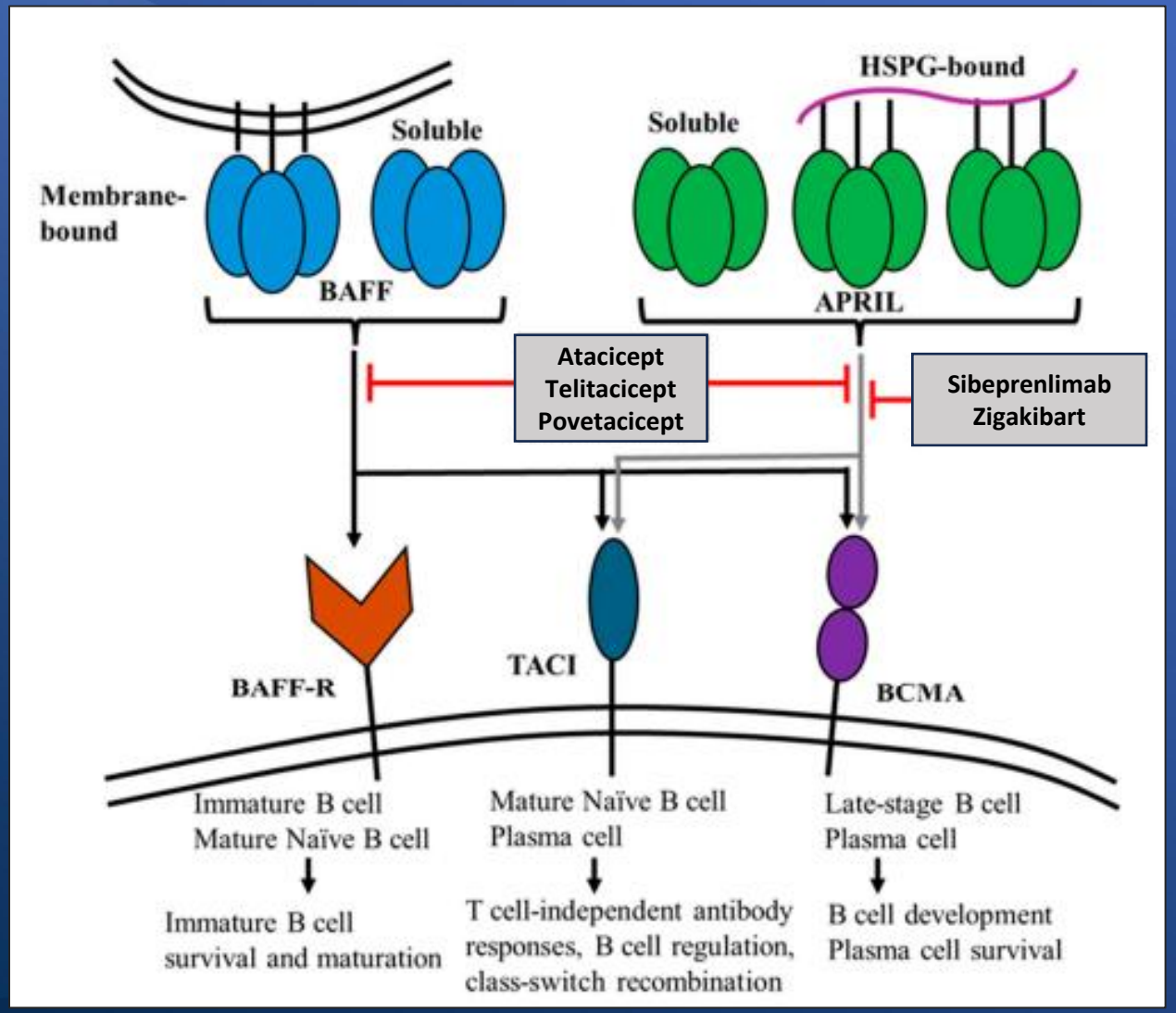
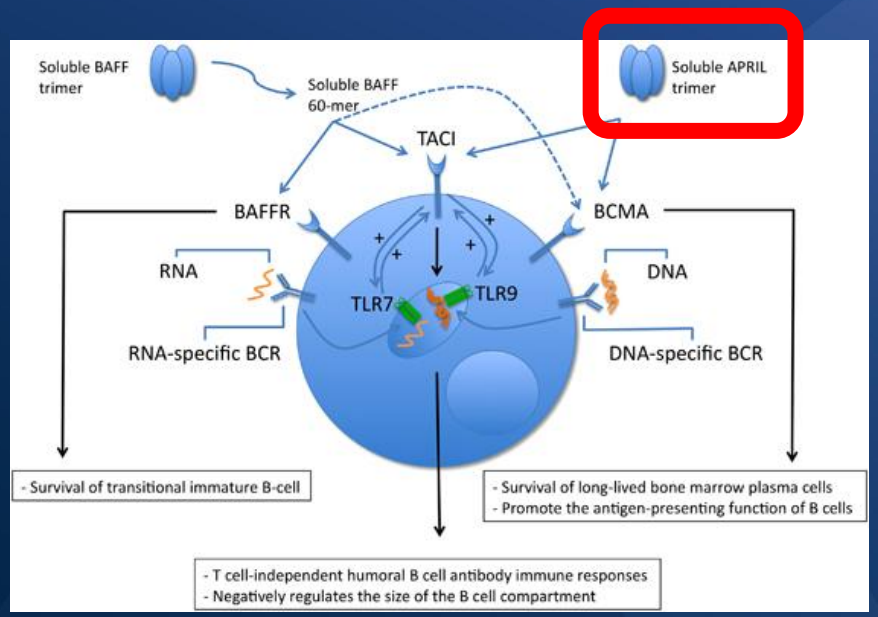





Soluble BAFF trimer
Soluble BAFF 60-mer
Soluble APRIL trimer
TACI
BAFFR
BCMA
RNA
DNA
TLR7
TLR9
RNA-specific BCR
DNA-specific BCR
- Survival of transitional immature B-cell
- Survival of long-lived bone marrow plasma cells
- Promote the antigen-presenting function of B cells
- T cell-independent humoral B cell antibody immune responses
- Negatively regulates the size of the B cell compartment


Membrane-bound
Soluble
HSPG-bound
Soluble
BAFF
APRIL
Atacicept
Telitacicept
Povetacicept
Sibeprenlimab
Zigakibart
BAFF-R
TACI
BCMA
Immature B cell
Mature Naïve B cell
Immature B cell survival and maturation
Mature Naïve B cell
Plasma cell
T cell-independent antibody responses, B cell regulation, class-switch recombination
Late-stage B cell
Plasma cell
B cell development
Plasma cell survival



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.

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

Last Update Posted 2024-03-26

RECRUITING

A Study of BION-1301 in Adults With IgA Nephropathy

ClinicalTrials.gov ID NCT05852938

Sponsor Chinook Therapeutics, Inc.

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

Last Update Posted 2024-04-19

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

A Phase 2 Trial of Sibeprenlimab in Patients with IgA Nephropathy

Mathur M et al. DOI: 10.1056/NEJMoa2305635

CLINICAL PROBLEM

Among patients with IgA nephropathy, kidney failure develops in ≥30% within 20 to 30 years, despite the receipt of optimized standard care. A critical step in the pathogenesis of IgA nephropathy is the production of galactose-deficient IgA1 and resulting autoantibody release. Sibeprenlimab is a humanized IgG2 monoclonal antibody that binds to and neutralizes a proliferation-inducing ligand (APRIL), a member of the tumor necrosis factor α superfamily that regulates IgA production.

CLINICAL TRIAL

Design: A phase 2, multicenter, double-blind, randomized, placebo-controlled, multiple-dose trial examined the efficacy and safety of sibeprenlimab in adults with IgA nephropathy at high risk for disease progression.

Intervention: 155 patients were assigned to receive intravenous sibeprenlimab at a dose of 2, 4, or 8 mg per kilogram of body weight or placebo once monthly for 12 months. The primary end point was the change from baseline to month 12 in the log-transformed 24-hour urinary protein-to-creatinine ratio.

RESULTS

Efficacy: The 24-hour urinary protein-to-creatinine ratio decreased significantly more in the sibeprenlimab groups than in the placebo group. The decreases in the sibeprenlimab groups were dose-dependent.

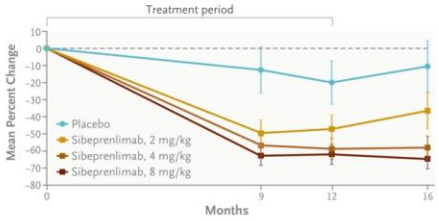
Safety: The incidence of adverse events, including serious adverse events, was similar in the sibeprenlimab groups and the placebo group.

LIMITATIONS AND REMAINING QUESTIONS

- Evidence of a return to baseline levels of APRIL in the 4 months after discontinuation of sibeprenlimab suggests that ongoing treatment will be needed.
- A phase 3 trial has been started to confirm these results in a larger patient population.

Links: Full Article | NEJM Quick Take | Editorial

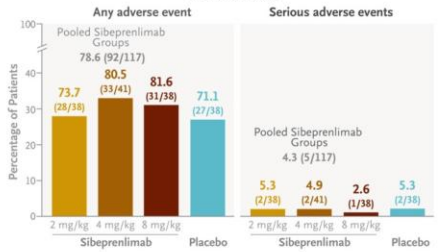
Change in 24-Hr Urinary Protein-to-Creatinine Ratio



Geometric Mean Percent Reduction in 24-Hr Urinary Protein-to-Creatinine Ratio

End Point	Sibeprenlimab 2 mg/kg (N=38)	Sibeprenlimab 4 mg/kg (N=41)	Sibeprenlimab 8 mg/kg (N=38)	Placebo (N=38)
Month 9	49.6±7.7	56.7±6.2	62.8±5.5	12.7±13.4
Month 12	**47.2±8.2**	**58.8±6.1**	**62.0±5.7**	**20.0±12.6**
Month 16	36.5±10.6	58.0±6.6	64.6±5.7	10.6±15.0

Adverse Events



CONCLUSIONS

Among patients with IgA nephropathy at high risk for disease progression, 12 months of treatment with sibeprenlimab resulted in a significantly greater reduction in proteinuria than placebo.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

V. Perkovic,[1] H. Trimarchi,[2] V. Tesar,[3] R. Lafayette,[4] M.G. Wong,[5] J. Barratt,[6] Y. Suzuki,[7] A. Liew,[8] H. Zhang,[9] K. Carroll,[10] V. Jha,[11-13] A. Quevedo,[14] S.H. Han,[15] M. Praga,[16] B. Chacko,[17] M. Sahay,[18] C.K. Cheung,[6] L. Kooienga,[19] M. Walsh,[20,21] J. Xia,[22] C. Fajardo,[22] L. Shah,[22] J. Hafkin,[22] and D.V. Rizk,[23] for the VISIONARY Trial Investigators Group*

ABSTRACT

BACKGROUND

The cytokine A proliferation-inducing ligand (APRIL) is considered a key driver of the pathogenesis of IgA nephropathy. Sibeprenlimab, a humanized IgG2 monoclonal antibody, selectively binds to and inhibits APRIL.

METHODS

In this phase 3, multicenter, double-blind, randomized, placebo-controlled trial, we assigned adults with biopsy-confirmed IgA nephropathy in a 1:1 ratio to receive either subcutaneous sibeprenlimab at a dose of 400 mg or placebo administered every 4 weeks for 100 weeks. The primary end point for this interim analysis was the 24-hour urinary protein-to-creatinine ratio at 9 months as compared with baseline. The key secondary end point, to be reported at trial completion, is the annualized slope of estimated glomerular filtration rate over 24 months. Other secondary end points included the change in the level of serum immunoglobulin and safety. Exploratory end points included the change in galactose-deficient IgA1 and APRIL concentrations, the spot 24-hour urinary protein-to-creatinine ratio, hematuria, and remission of proteinuria.

RESULTS

A total of 510 patients underwent randomization — 259 to the sibeprenlimab group and 251 to the placebo group. The prespecified interim analysis included the first 320 patients (152 who received sibeprenlimab and 168 who received placebo) who had the opportunity to complete the 9-month evaluation of the 24-hour urinary protein-to-creatinine ratio. At 9 months, a significant reduction in 24-hour urinary protein-to-creatinine ratio was observed with sibeprenlimab (–50.2%) as compared with an increase with placebo (2.1%), corresponding to an adjusted geometric least-squares mean 24-hour urinary protein-to-creatinine ratio that was 51.2% (96.5% confidence interval [CI], 42.9 to 58.2) lower with sibeprenlimab than with placebo (P<0.001). The levels of APRIL and pathogenic galactose-deficient IgA1 at week 48 were reduced from baseline by 95.8% and 67.1%, respectively, with sibeprenlimab. The safety profile appeared to be similar with sibeprenlimab and placebo. No deaths were reported, and the incidence of serious adverse events that occurred during the treatment period was 3.5% with sibeprenlimab and 4.4% with placebo.

CONCLUSIONS

Sibeprenlimab resulted in a significant reduction in proteinuria as compared with placebo in patients with IgA nephropathy. (Funded by Otsuka Pharmaceutical Development and Commercialization. VISIONARY ClinicalTrials.gov number, NCT05248646.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Vlado Perkovic can be contacted at vlado.perkovic@unsw.edu.au or at University of New South Wales, Sydney, NSW 2052, Australia.

*A list of the VISIONARY trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on November 8, 2025, at NEJM.org.

DOI: 10.1056/NEJMoa2512133

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Novel Drug Approvals for 2025

What are "Novel" Drugs?

"Novel" drugs are new drugs never before approved or marketed in the U.S. See Drugs@FDA for information about all of CDER's approved drugs and biological products.

FDA Novel Drug Therapy Approvals for 2025

Search:

Export Excel

No.	Drug Name	Active Ingredient	Approval Date	FDA-approved use on approval date*
39.	Voyxact	sibeprenlimab-szsi	11/25/2025	To reduce proteinuria in primary immunoglobulin A nephropathy in adults at risk for disease progression
38.	Hyrnuo	sevabertinib	11/19/2025	To treat locally advanced or metastatic non-squamous non-small cell lung cancer with tumors that have activating HER2 tyrosine kinase domain activating mutations in patients who received a systemic therapy
37.	Redemplo	plozasiran	11/18/2025	To reduce triglycerides in adults with familial chylomicronemia syndrome
36.	Komzifti	ziftomenib	11/13/2025	To treat adults with relapsed or refractory acute myeloid leukemia with a susceptible nucleophosmin 1 mutation who have no satisfactory alternative treatment options
35.	Kygevvi	doxecitine and doxribtimine	11/3/2025	To treat thymidine kinase 2 deficiency in patients who start to show symptoms when they are 12 years old or younger
34.	Lynkuet	elinzanetant	10/24/2025	To treat moderate-to-severe vasomotor symptoms due to menopause
33.	Jascayd	nerandomilast	10/7/2025	To treat idiopathic pulmonary fibrosis
32.	Rhapsido	remibrutinib	9/30/2025	To treat chronic spontaneous urticaria in adults who remain symptomatic despite H1 antihistamine treatment
31.	Palsonify	paltusotine	9/25/2025	To treat acromegaly in adults who had an inadequate response to surgery and/or for whom surgery is not an option
30.	Inluriyo	imlunestrant	9/25/2025	To treat estrogen receptor-positive, human epidermal growth factor receptor 2-negative, estrogen receptor-1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy

Zigakibart demonstrates clinical safety and efficacy in a Phase 1/2 trial of healthy volunteers and patients with IgA nephropathy

OPEN

Laura Kooienga[1,13], Jeannette Lo[2,3,13], Eun Young Lee[4], Sung Gyun Kim[5], Hannah Thomas[6], Biruh Workeneh[7], Irfan Agha[8,9], Yuanbo Song[10], William Smith[10], Hans van Eenennaam[11], Andrea Van Elsas[11], John Dulos[11] and Jonathan Barratt[12]

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Abstract

Introduction: Zigakibart is a humanized IgG4 monoclonal antibody that binds the cytokine A Proliferation-Inducing Ligand (APRIL, also known as TNFSF13). APRIL is a critical factor in immunoglobulin (Ig) A nephropathy (IgAN) pathogenesis.

Methods: Here, we report healthy volunteers (63 overall) and 100-week data from an ongoing Phase 1/2 clinical trial in 40 patients with IgAN (NCT03945318) treated with zigakibart.

Results: In healthy volunteers, zigakibart was well tolerated following intravenous administration of single doses ranging from 10–1350 mg or multiple doses ranging from 50–450 mg every two weeks. Zigakibart exposure increased in a dose-proportional manner, with corresponding durable reductions in levels of free APRIL, IgA and IgM, and to a lesser extent, IgG. In patients with IgAN, zigakibart 600 mg, administered subcutaneously every two weeks, was well tolerated with no treatment-emergent adverse events leading to study drug discontinuation or death. A 60% reduction in proteinuria and sustained estimated glomerular filtration rate stabilization were observed at week 100. There was a notable decrease in hematuria, as well as rapid and durable reductions in IgA, galactose-deficient IgA (Gd-IgA1), and IgM levels, with a modest reduction in IgG.

Conclusions: Overall, zigakibart demonstrated robust pharmacological activity, and clinical evidence shows an acceptable safety profile with clinically meaningful proteinuria reduction and sustained estimated glomerular filtration rate stabilization in patients with IgAN, providing a potentially disease-modifying approach for the treatment of IgAN. The effects of zigakibart on proteinuria and long-term kidney function in adults with IgAN are being evaluated in the ongoing phase 3 BEYOND study (NCT05852938).

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[13]LK and JL are co–first authors.

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Kidney International (2025) **108,** 445–454; https://doi.org/10.1016/j.kint.2025.05.006

KEYWORDS: anti-APRIL; glomerulonephritis; IgA nephropathy; phase 1/2; TNFSF13; zigakibart

Editor's Note

The online publication of this article coincided with the Game Changers in Nephrology session at the 62nd ERA Congress, Vienna, June 2025. This article provides cutting-edge insight into a recent clinical trial and the implications for kidney care.

IgA nephropathy (IgAN) is the leading cause of primary glomerulonephritis and contributes significantly to the global patient burden of chronic kidney disease and kidney failure.[1–3] Historically, options for IgAN management focused primarily on supportive care, yet despite this approach, a significant proportion of patients remained at high risk of progressive chronic kidney disease advancing to kidney failure,[3,4] highlighting the widespread need for novel treatments targeting the pathogenic mechanisms underlying IgAN. Recently, treatment options for IgAN have been expanded to include budesonide (delayed-release) and sparsentan, both of which received full approval in the United States.[5–8] In addition, iptacopan, a first-in-class complement inhibitor, and atrasentan, a potent and selective endothelin A receptor antagonist, were granted accelerated approval in the United States.[9,10] There are also several novel targeted therapies being investigated in late-stage clinical trials.

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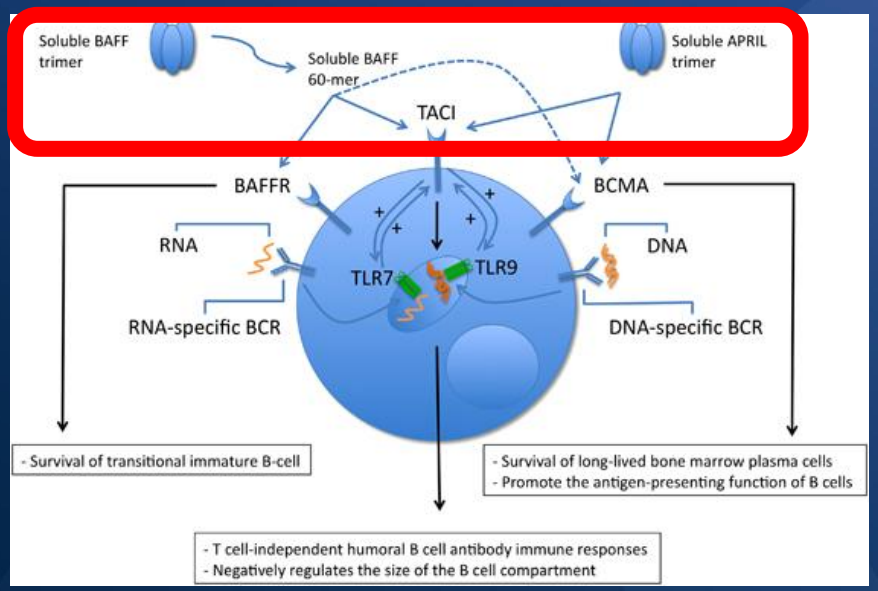

RECRUITING

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

UNIVERSITY OF LEICESTER

Leicester IgA Nephropathy Research Group

A phase 2b, randomized, double-blind, placebo-controlled, clinical trial of atacicept for treatment of IgA nephropathy

Check for updates

OPEN

Richard Lafayette[1], Sean Barbour[2], Rubeen Israni[3], Xuelian Wei[4], Necmi Eren[5], Jürgen Floege[6], Vivekanand Jha[7,8,9], Sung Gyun Kim[10], Bart Maes[11], Richard K.S. Phoon[12], Harmeet Singh[13], Vladimír Tesař[14], Celia J.F. Lin[15] and Jonathan Barratt[16]

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Atacicept is a first-in-class, dual anti-B-cell Activation Factor–A Proliferation-Inducing Ligand fusion protein in clinical evaluation for treatment of IgA nephropathy. To compare efficacy and safety of atacicept versus placebo in patients with IgAN, this randomized, double-blind, placebo-controlled phase 2b clinical trial ORIGIN enrolled 116 individuals with biopsy-proven IgA nephropathy. Participants were randomized to atacicept 150, 75, or 25 mg versus placebo once weekly for up to 36 weeks. Primary and key secondary endpoints were changes in urine protein creatinine ratio based on 24-hour urine collection at weeks 24 and 36, respectively, in the combined atacicept 150 mg and 75 mg group versus placebo. The primary endpoint was met at week 24 as the mean urine protein creatinine ratio was reduced from baseline by 31% in the combined atacicept group versus 8% with placebo, resulting in a significant 25% reduction with atacicept versus placebo. At week 36, the key secondary endpoint was met as the mean urine protein creatinine ratio reduced from baseline by 34% in the combined atacicept group versus a 2% increase with placebo, resulting in a significant 35% reduction with atacicept versus placebo. The reduction in proteinuria was accompanied by stabilization in endpoint eGFR with atacicept compared to a decline with placebo at week 36, resulting in significant between-group geometric mean difference of 11%, approximating an absolute difference of 5.7 mL/min/1.73m^2. Endpoint galactose deficient IgA1 levels significantly decreased from baseline by 60% versus placebo. The safety profile of atacicept was like placebo. Thus, our results provide evidence to support a pivotal, phase 3 study of atacicept in IgA nephropathy.

Kidney International (2024) **105,** 1306–1315; https://doi.org/10.1016/j.kint.2024.03.012

KEYWORDS: B-cell modulator; glomerular disease; IgA nephropathy

Lay Summary

IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide and a significant contributor to the global burden of kidney failure, requiring dialysis or transplant. IgAN is an autoimmune disease where antibodies are produced against an aberrant, galactose-deficient IgA1 (Gd-IgA1). Current treatment of IgAN, which includes renin-angiotensin system inhibition, does not target the early steps underlying the pathology of IgAN. Atacicept is a fusion protein that is able to bind and neutralize both B-cell Activating Factor and A PRoliferation-Inducing Ligand *in vitro*. These ligands play an important role in the maturation, function, and survival of B cells and plasma cells. In the ORIGIN phase 2b study in patients with IgAN, atacicept improved kidney endpoints with a reduction of proteinuria and stabilization of estimated glomerular filtration rate while reducing serum Gd-IgA1, providing evidence that atacicept has the potential to target and improve the underlying process of IgAN.

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OPEN

Long-Term Results from an Open-Label Extension Study of Atacicept for the Treatment of IgA Nephropathy

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Key Points

- Participants who completed a 36-week double-blind study of atacicept were eligible for a 60-week, open-label extension study.
- Atacicept 96-week treatment resulted in sustained reductions in galactose-deficient IgA1, hematuria, and urine protein-creatinine ratio.
- The slope of the eGFR was similar to that observed in the general population without kidney disease.

Abstract

Background B-cell activating factor (BAFF) and A proliferation-inducing ligand (APRIL) play key roles in the pathogenesis of IgA nephropathy. Atacicept is a novel fully humanized fusion protein, self-administered at home by subcutaneous injection, that binds and inhibits BAFF and APRIL. By inhibiting BAFF and APRIL, atacicept targets the underlying B-cell–mediated pathogenesis driving disease progression. This study evaluated the long-term efficacy and safety of atacicept in patients with IgA nephropathy over 96 weeks.

Methods Participants with IgA nephropathy who received atacicept (25, 75, or 150 mg) or placebo in a 36-week phase 2b, randomized, blinded trial were enrolled in an open-label extension study and received atacicept 150 mg for an additional 60 weeks. Key efficacy outcomes were changes in galactose-deficient IgA1 (Gd-IgA1), percentage of participants with hematuria, urine protein-creatinine ratio (UPCR), and eGFR over 96 weeks. Long-term safety data were also evaluated.

Results There were 113 participants (67 [59%] male; 46 [41%] female) who ranged in age from 18 to 67 years who received ≥1 atacicept dose. Over 96 weeks, safety data demonstrated that atacicept was generally well tolerated. There were also sustained reductions (mean±SEM) in Gd-IgA1 (−66%±2%), percentage of participants with hematuria (−75%; 95% confidence intervals, −87 to −59; in participants with baseline hematuria), and UPCR (−52%±5%). The mean annualized slope of eGFR was −0.6±0.5 ml/min per 1.73 m^2 through 96 weeks.

Conclusions Atacicept was well tolerated over the duration of the study. Atacicept treatment reduced Gd-IgA1, hematuria, and UPCR with stabilization of eGFR through 96 weeks.

Clinical Trial registry name and registration number: Atacicept in Subjects with IgA Nephropathy (ORIGIN 2), NCT04716231.

JASN 00: 1–9, 2024. doi: https://doi.org/10.1681/ASN.0000000541

Introduction

IgA nephropathy, predominantly diagnosed in young adults, represents a critical challenge in nephrology because of its progressive nature and significant effect on life expectancy and quality.[1–3] At least 50% of patients with IgA nephropathy develop kidney failure within 10–20 years of initial diagnosis.[4–6] Although currently available therapies provide benefit, they fail to stop an unrelenting decline in kidney function.[7–9] Unless the rate of eGFR decline can be minimized, most patients are likely to experience kidney

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

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*A list of investigators and collaborators for the ORIGIN phase 2b study is provided in the Supplemental Material.

ORIGINAL ARTICLE

A Phase 3 Trial of Atacicept in Patients with IgA Nephropathy

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ABSTRACT

BACKGROUND

IgA nephropathy, the most common primary glomerulopathy worldwide, is a kidney disorder of B-cell origin characterized by mesangial accumulation of IgA-containing immune complexes. In at least 50% of patients, IgA nephropathy leads to kidney failure or death within 10 to 20 years after diagnosis. Atacicept is a native human transmembrane activator and calcium-modulator and cyclophilin-ligand interactor (TACI)–Fc fusion protein that inhibits two key immunoregulatory cytokines — B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) — that are thought to be central to the pathophysiology of IgA nephropathy.

METHODS

In this ongoing, phase 3, multicenter, double-blind, randomized, placebo-controlled trial, we assigned patients with IgA nephropathy in a 1:1 ratio to receive atacicept at a dose of 150 mg once weekly, administered subcutaneously by patients at home, or matching placebo. The primary end point was the percentage change from baseline in the 24-hour urinary protein-to-creatinine ratio at week 36. Safety was also evaluated.

RESULTS

A total of 203 patients were included in the prespecified interim analysis: 106 patients in the atacicept group and 97 in the placebo group. At week 36, the percentage reduction from baseline in the urinary protein-to-creatinine ratio was 45.7% in the atacicept group and 6.8% in the placebo group, with a geometric mean between-group difference of 41.8 percentage points (95% confidence interval, 28.9 to 52.3; P<0.001). Adverse events were observed in 59.3% of the patients in the atacicept group and in 50.0% in the placebo group; most were mild or moderate in severity.

CONCLUSIONS

In this prespecified interim analysis, treatment with atacicept resulted in a significantly greater reduction in proteinuria than placebo at week 36 in patients with IgA nephropathy. (Funded by Vera Therapeutics; ORIGIN 3 ClinicalTrials.gov number, NCT04716231.)

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*A list of investigators and collaborators for the ORIGIN 3 trial is provided in the Supplementary Appendix.

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CLINICAL RESEARCH

Randomized Phase 2 Trial of Telitacicept in Patients With IgA Nephropathy With Persistent Proteinuria

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Introduction: To date, no specific therapies have been approved for immunoglobulin A nephropathy (IgAN) treatment. Telitacicept is a fusion protein composed of transmembrane activator and calcium-modulating cyclophilin ligand interactor and fragment crystallizable portion of immunoglobulin G (IgG), which neutralizes the B lymphocyte stimulator and a proliferation-inducing ligand.

Methods: This phase 2 randomized placebo-controlled trial aimed to evaluate the efficacy and safety of telitacicept in patients with IgAN. Participants with an estimated glomerular filtration rate (eGFR) >35 ml/min per 1.73 m^2 and proteinuria ≥0.75 g/d despite optimal supportive therapy, were randomized 1:1:1 to receive subcutaneous telitacicept 160 mg, telitacicept 240 mg, or placebo weekly for 24 weeks. The primary end point was the change in 24-hour proteinuria at week 24 from baseline.

Results: Forty-four participants were randomized into placebo ($n = 14$), telitacicept 160 mg ($n = 16$), and telitacicept 240 mg ($n = 14$) groups. Continuous reductions in serum IgA, IgG, and IgM levels were observed in the telitacicept group. Telitacicept 240 mg therapy reduced mean proteinuria by 49% from baseline (change in proteinuria vs. placebo, 0.88; 95% confidence interval, −1.57 to −0.20; $P = 0.013$), whereas telitacicept 160 mg reduced it by 25% (−0.29; 95% confidence interval, −0.95 to 0.37; $P = 0.389$). The eGFR remained stable over time. Adverse events (AEs) were similar in all groups. Treatment-emergent AEs were mild or moderate, and no severe AEs were reported.

Conclusion: Telitacicept treatment led to a clinically meaningful reduction in proteinuria in patients with IgAN in the present phase 2 clinical trial. This effect is indicative of a reduced risk for future kidney disease progression.

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KEYWORDS: BLyS/APRIL inhibitors; IgA Nephropathy; proteinuria; TACI-Fc fusion protein; telitacicept

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IgAN is the most common form of primary glomerulonephritis worldwide. Persistent proteinuria, hypertension, impaired kidney function, and pathologic lesions are its strongest risk factors.[1] Supportive therapy, including blood pressure management, maximally

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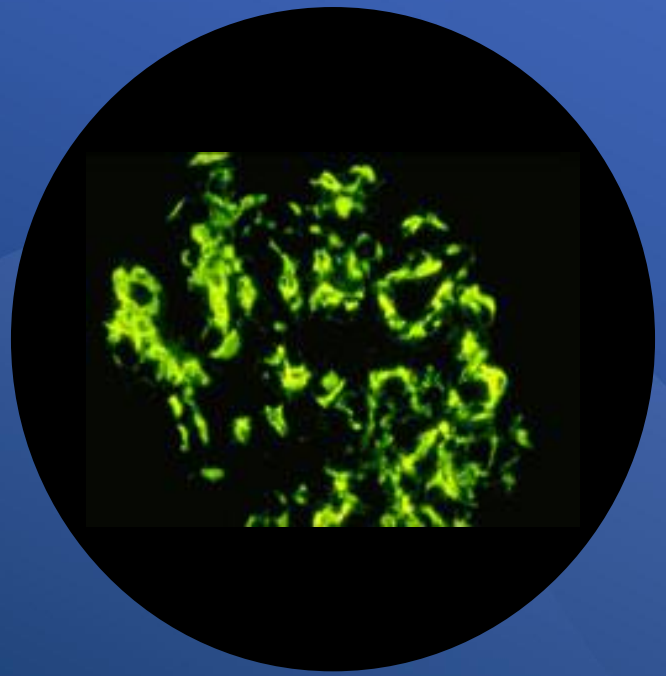

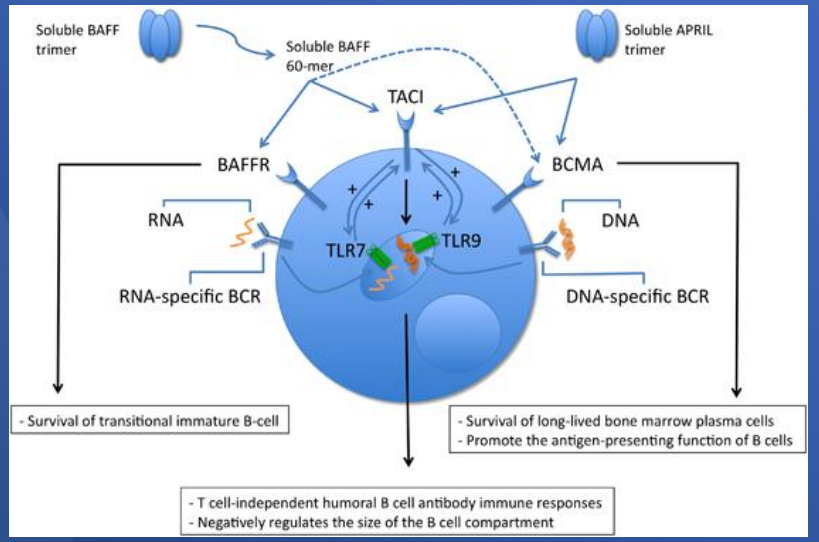

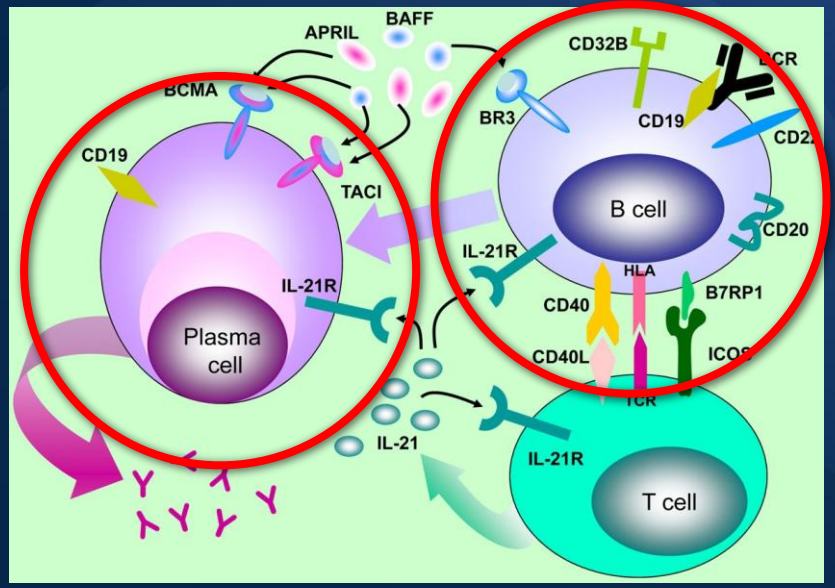

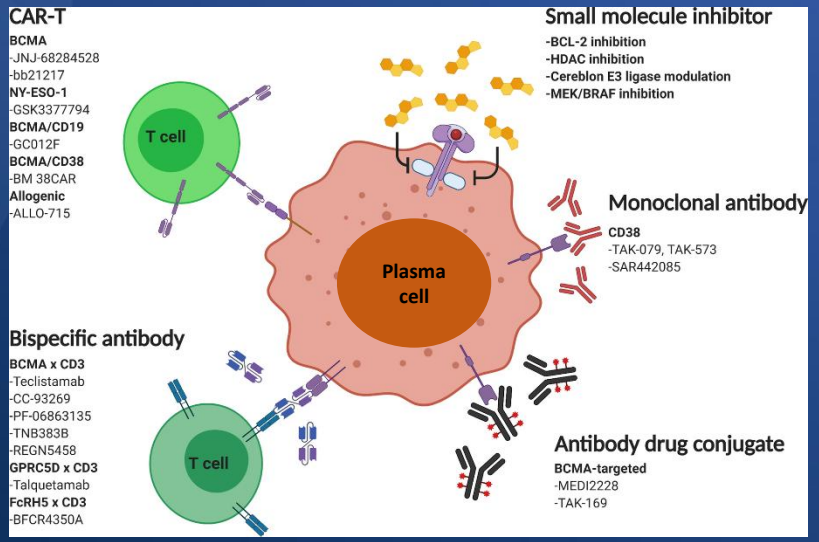

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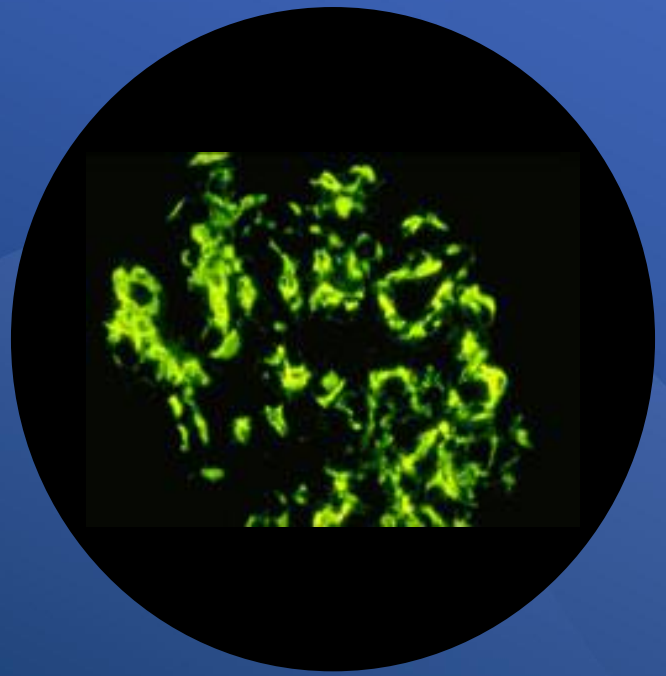

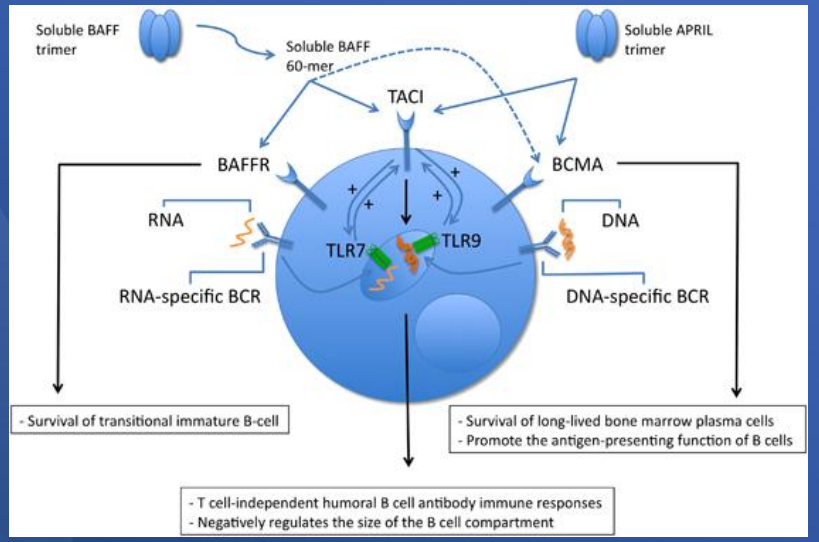

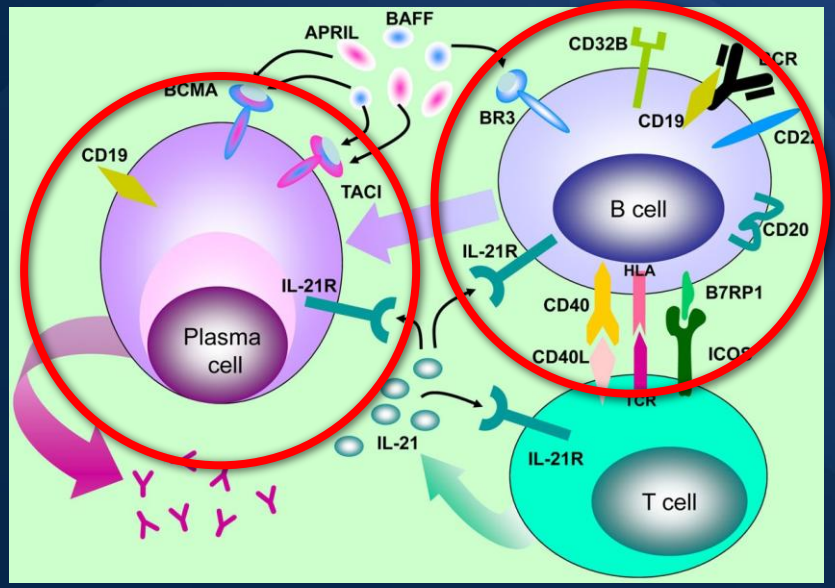

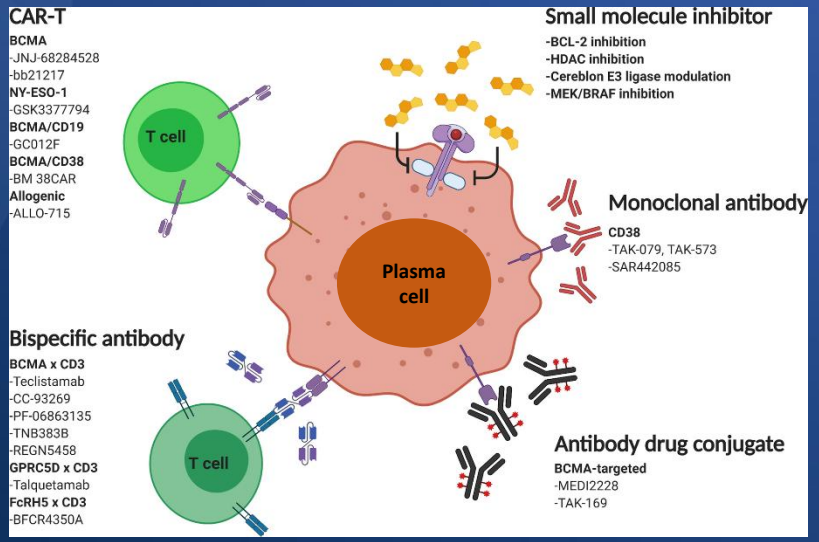

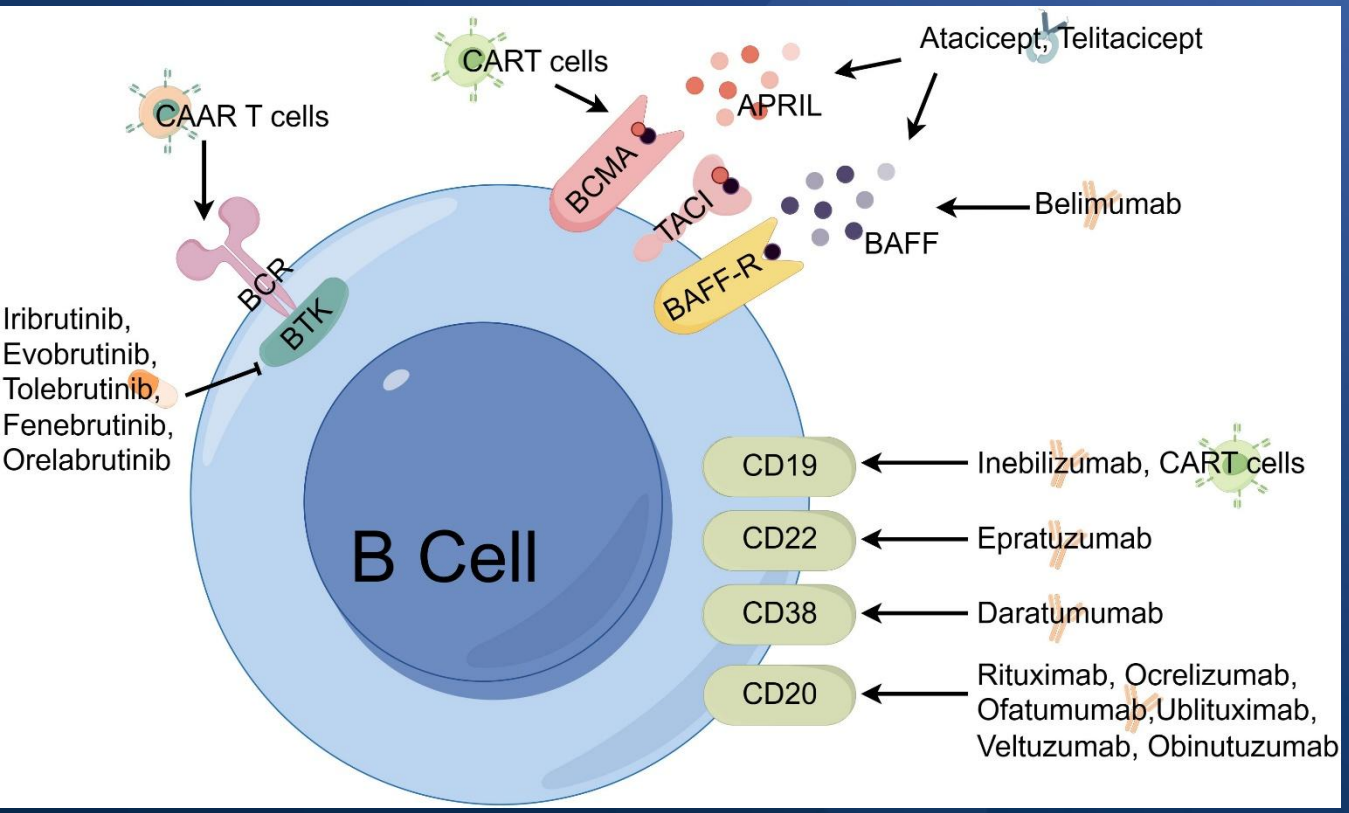
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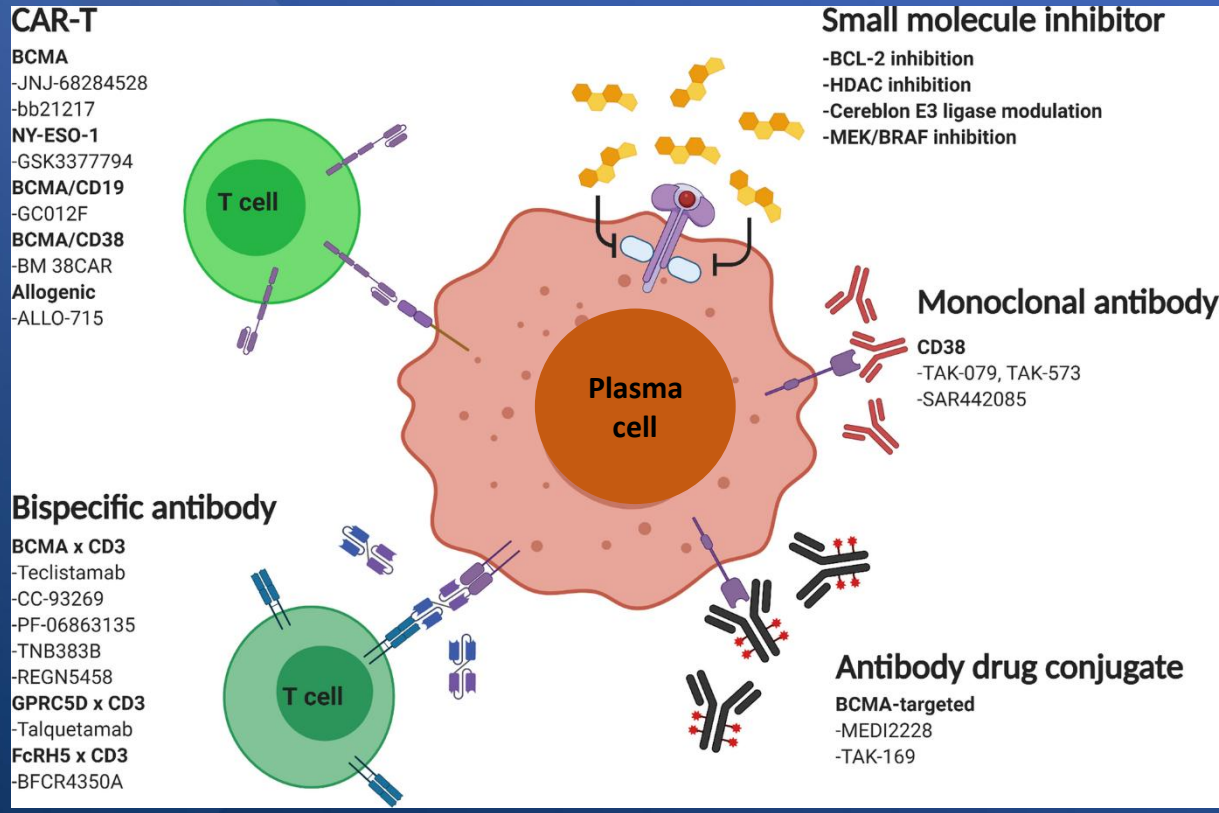
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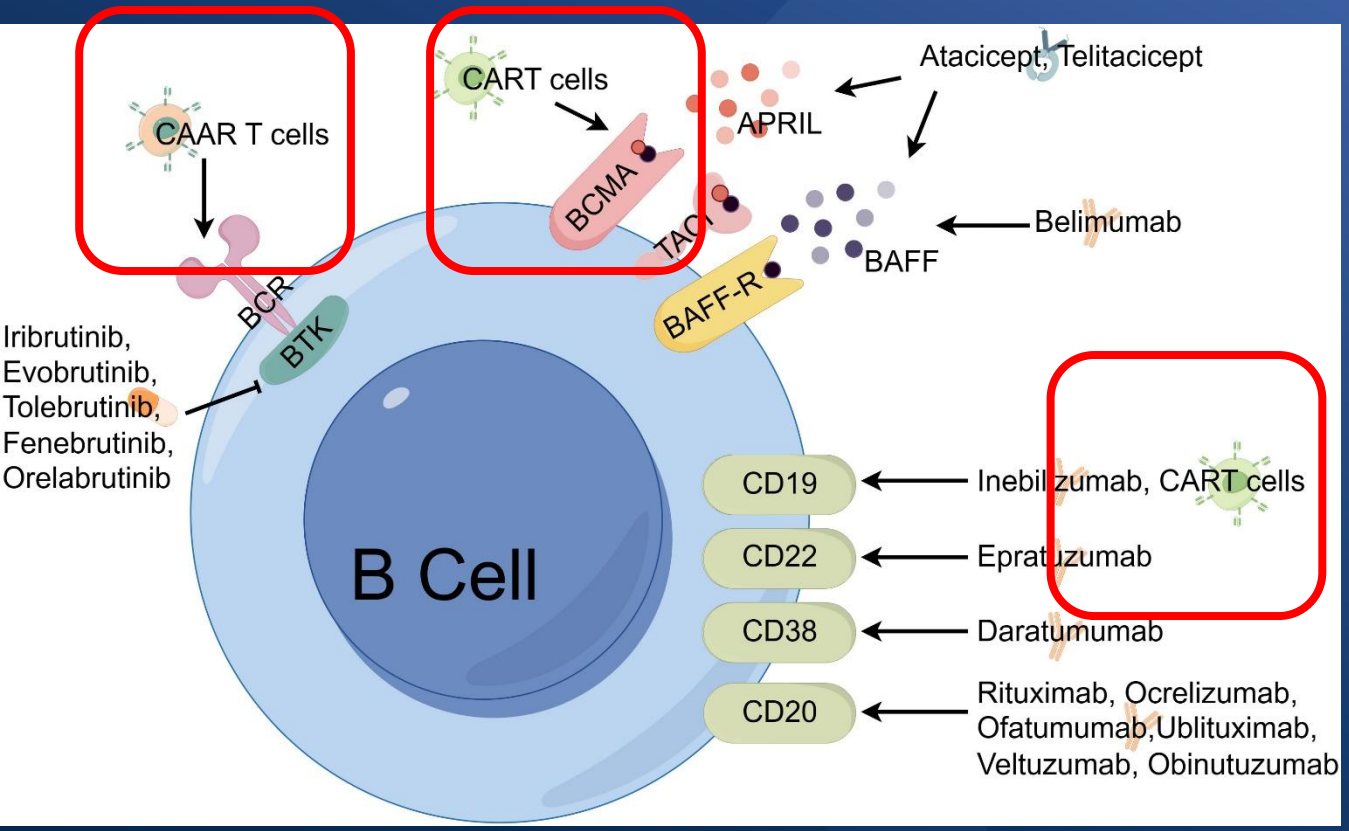
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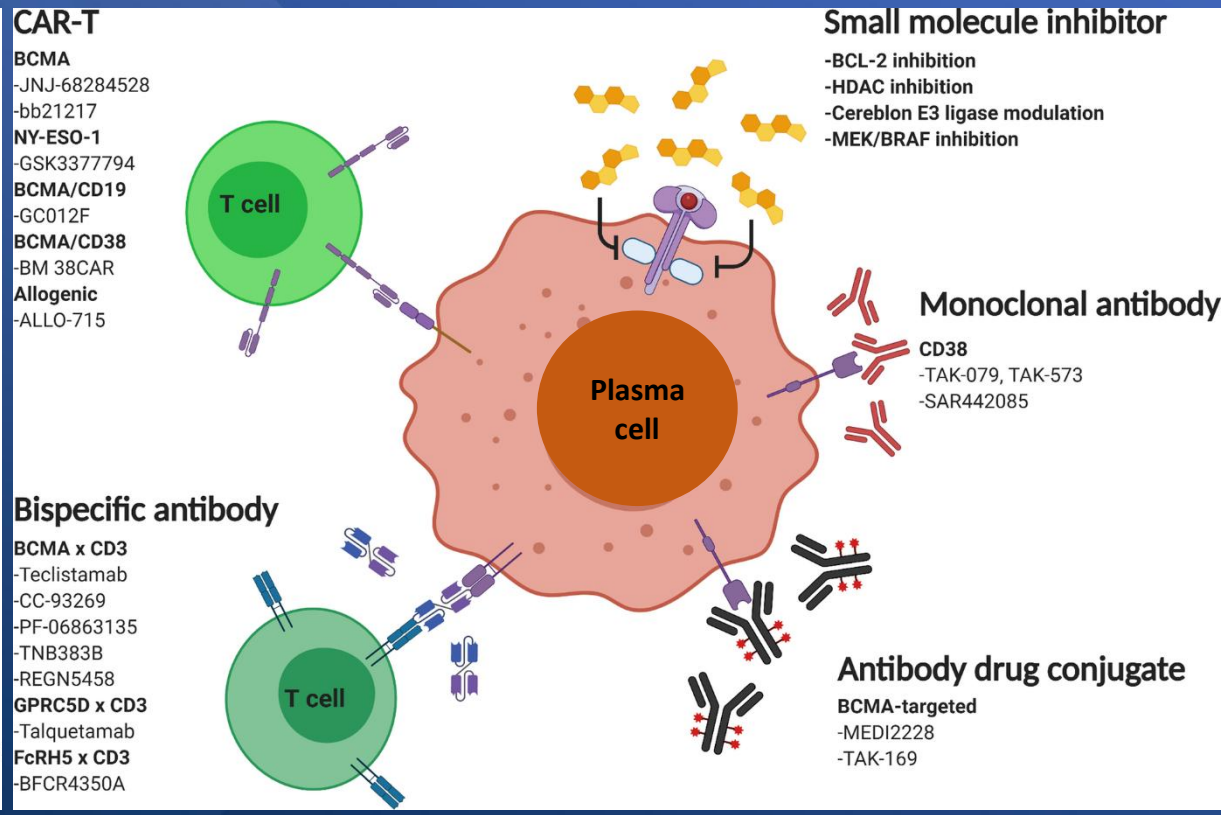
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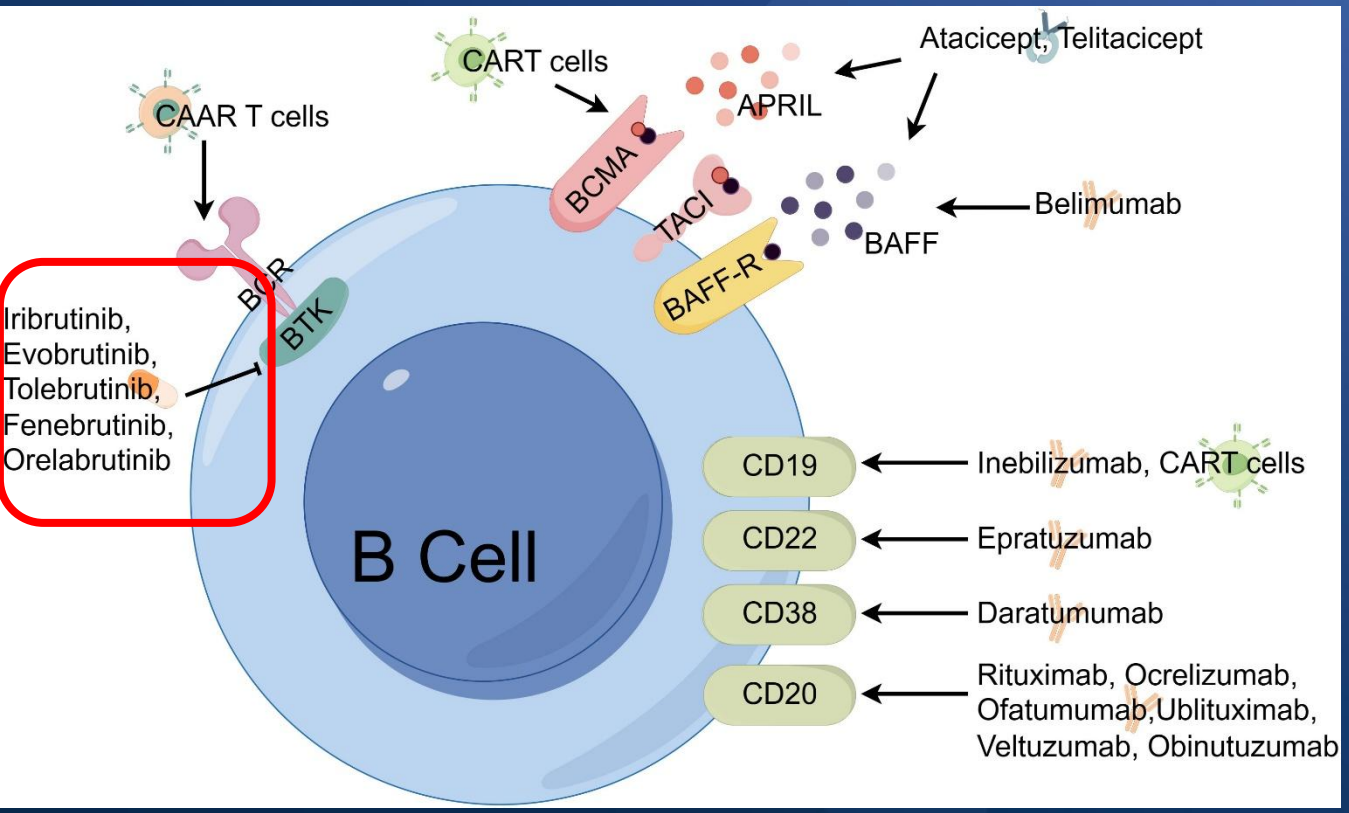
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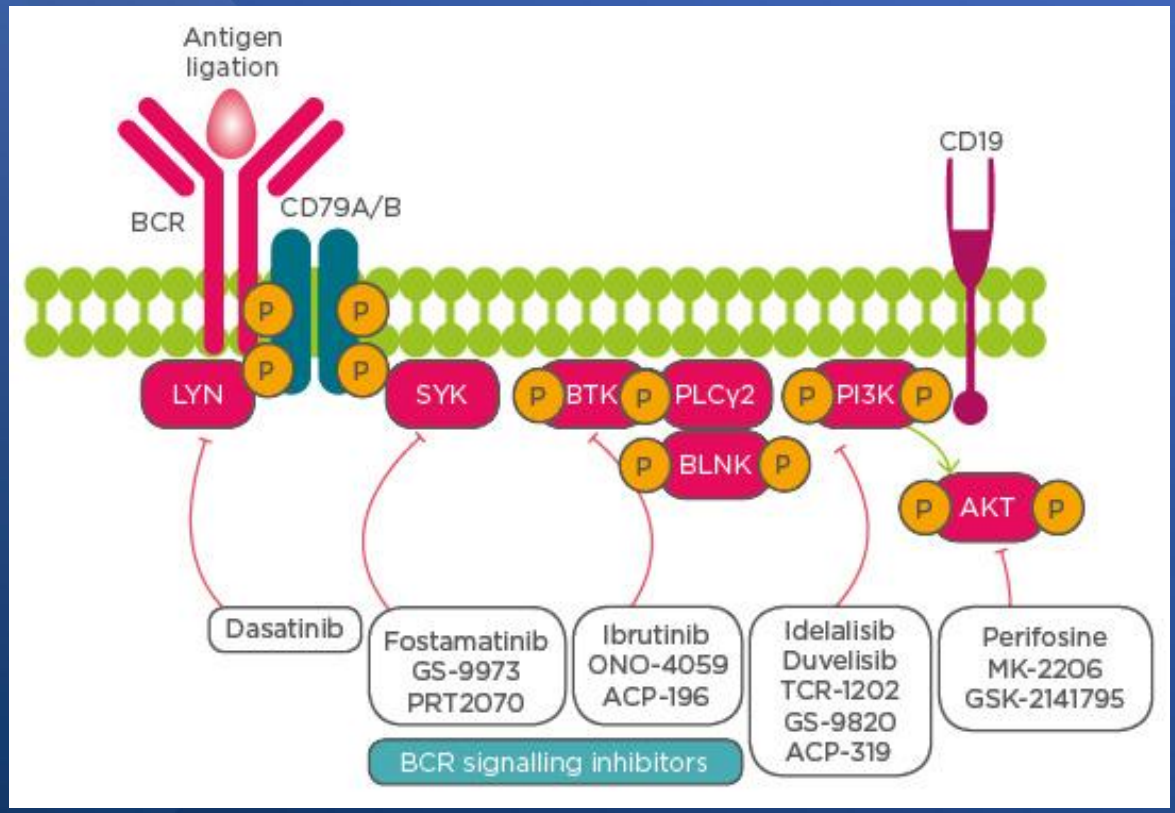
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BCR signalling inhibitors

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CLINICAL RESEARCH

Randomized Trial on the Effect of an Oral Spleen Tyrosine Kinase Inhibitor in the Treatment of IgA Nephropathy

Frederick W.K. Tam[1], James Tumlin[2], Jonathan Barratt[3], Brad H. Rovin[4], Ian S.D. Roberts[5], Candice Roufosse[1], H. Terence Cook[1], Gurjeet Bhangal[1], Alison L. Brown[6], Martin Busch[7], Fayaz Dudhiya[1], Anne-Marie Duliege[8], Donald J. Fraser[9], Daniel P. Gale[10], Chiu-Ching Huang[11], Ping-Chin Lai[11,12], Meng Lee[8], Esteban S. Masuda[8], Stephen P. McAdoo[1], Alexander R. Rosenkranz[13], Claudia Sommerer[14], Gere Sunder-Plassmann[15], Cheuk-Chun Szeto[16], Sydney C.W. Tang[17], Don E. Williamson[18], Lisa Willcocks[19], Volker Vielhauer[20], Min Jeong Kim[21], Leslie Todd[8], Hany Zayed[8], Sandra Tong-Starksen[8] and Richard Lafayette[22]

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Introduction: We reported increased spleen tyrosine kinase (SYK) expression in kidney biopsies of patients with IgA nephropathy (IgAN) and that inhibition of SYK reduces inflammatory cytokines production from IgA stimulated mesangial cells.

Methods: This study was a double-blind, randomized, placebo-controlled phase 2 trial of fostamatinib (an oral SYK inhibitor) in 76 patients with IgAN. Patients were randomized to receive placebo, fostamatinib at 100 mg or 150 mg twice daily for 24 weeks on top of maximum tolerated dose of renin-angiotensin system inhibitors. The primary end point was reduction of proteinuria. Secondary end points included change from baseline in estimated glomerular filtration rate (eGFR) and kidney histology.

Results: Although we could not detect significant reduction in proteinuria with fostamatinib overall, in a predetermined subgroup analysis, there was a trend for dose-dependent reduction in median proteinuria (from baseline to 24 weeks by 14%, 27%, and 36% in the placebo, fostamatinib 100 mg, and 150 mg groups, respectively) in patients with baseline urinary protein-to-creatinine ratios (UPCR) more than 1000 mg/g. Kidney function (eGFR) remained stable in all groups. Fostamatinib was well-tolerated. Side effects included diarrhea, hypertension, and increased liver enzymes. Thirty-nine patients underwent repeat biopsy showing reductions in SYK staining associated with therapy at low dose (−1.5 vs. 1.7 SYK+ cells/glomerulus in the placebo group, $P < 0.05$).

Conclusions: There was a trend toward reduction in proteinuria with fostamatinib in a predefined analysis of high risk patients with IgAN despite maximal care, as defined by baseline UPCR greater than 1000 mg/g. Further study may be warranted.

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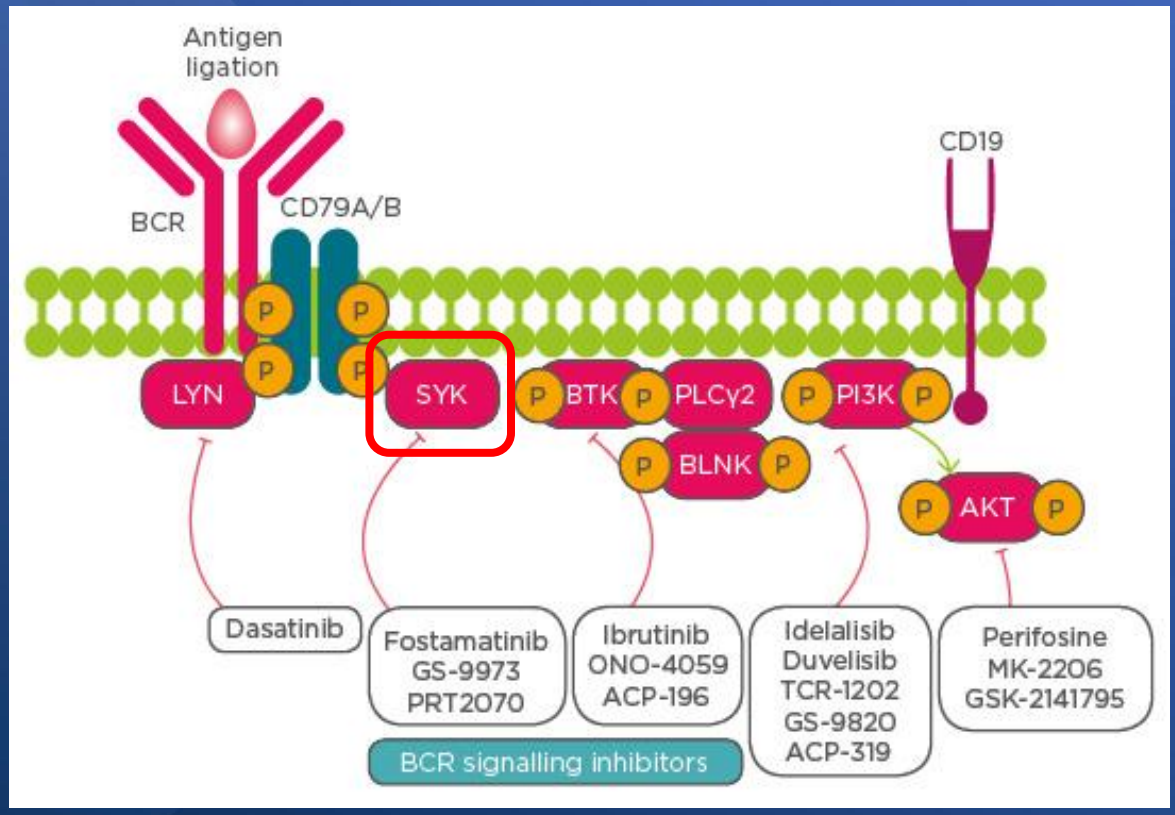

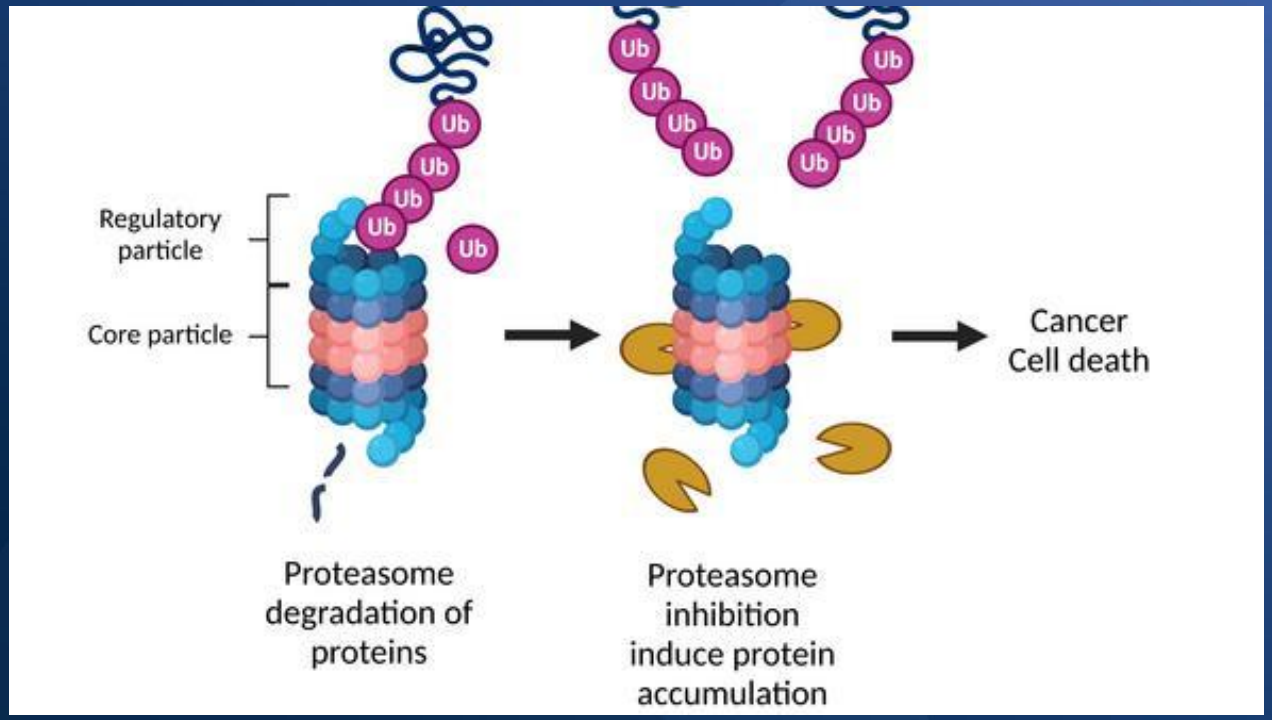
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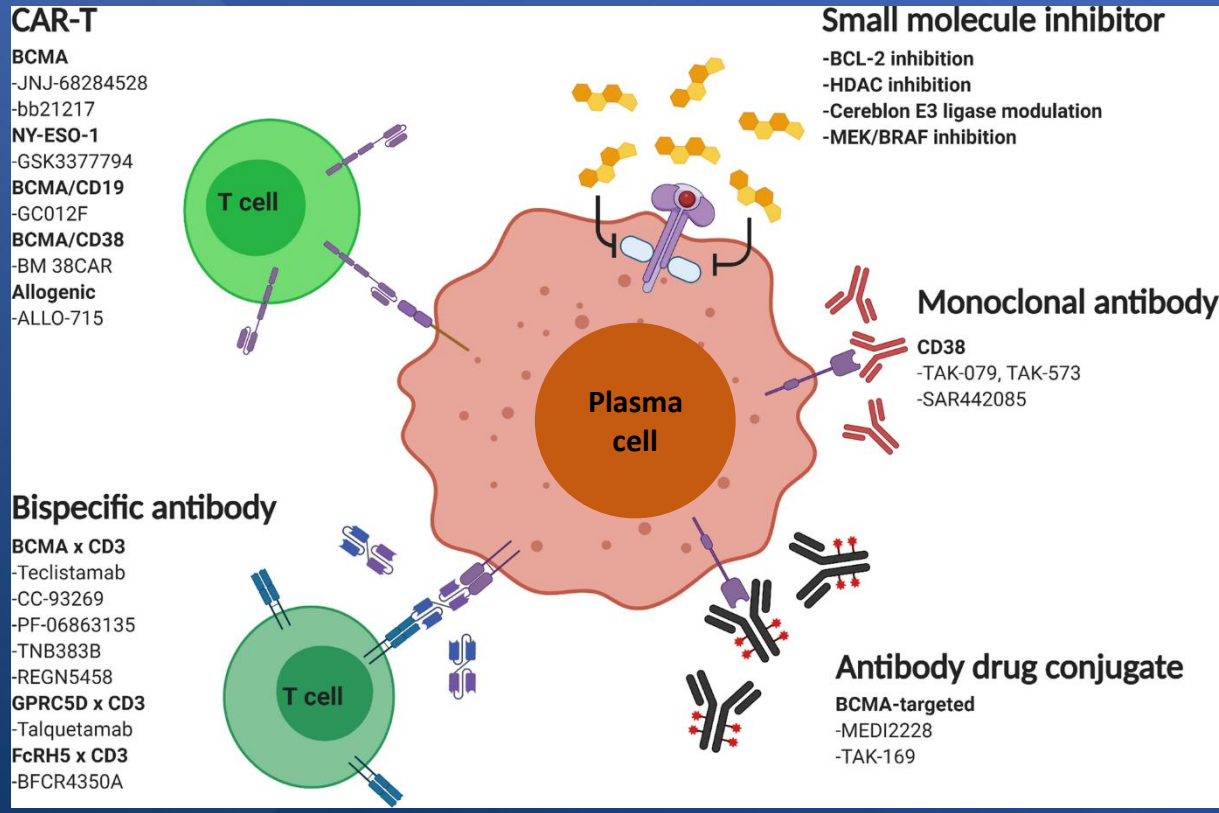
Core particle
Proteasome degradation of proteins
Proteasome inhibition induce protein accumulation
Cancer Cell death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-MEK/BRAF inhibition
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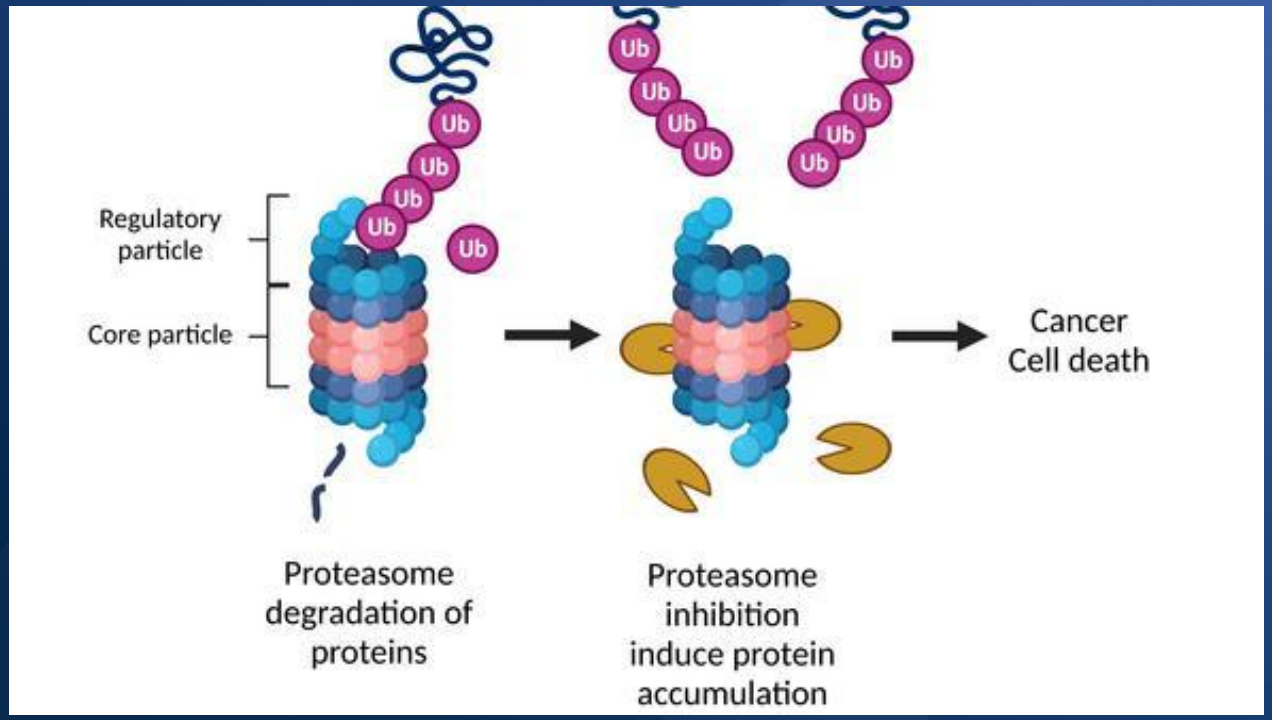

KI REPORTS
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CLINICAL RESEARCH

Bortezomib for Reduction of Proteinuria in IgA Nephropathy

Choli Hartono[1,2], Miriam Chung[3], Alan S. Perlman[1,2], James M. Chevalier[1,2], David Serur[1,2], Surya V. Seshan[4] and Thangamani Muthukumar[1]

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Introduction: IgA nephropathy is the most common glomerulonephritis in the world. We conducted a pilot trial (NCT01103778) to test the effect of bortezomib in patients with IgA nephropathy and significant proteinuria.

Methods: We treated 8 consecutive subjects from July 2011 until March 2016 with 4 doses of bortezomib. All subjects had biopsy-proven IgA nephropathy and proteinuria of greater than 1 g per day. They were given 4 doses of bortezomib i.v. at 1.3 mg/m^2 of body surface area per dose. Changes in proteinuria and renal function were followed for 1 year after enrollment. The primary endpoint was full remission defined as proteinuria of less than 300 mg per day.

Results: All 8 subjects received and tolerated 4 doses of bortezomib over a 2-week period during enrollment. The median baseline daily proteinuria was 2.46 g (interquartile range: 2.29–3.16 g). At 1-year follow-up, 3 subjects (38%) had achieved the primary endpoint. The 3 subjects who had complete remission had Oxford classification T scores of 0 before enrollment. Of the remaining 5 subjects, 1 was lost to follow-up within 1 month of enrollment and 4 (50%) did not have any response or had progression of disease.

Conclusion: Proteasome inhibition by bortezomib may reduce significant proteinuria in select cases of IgA nephropathy. Subjects who responded to bortezomib had Oxford classification T score of 0 and normal renal function.

Kidney Int Rep (2018) **3**, 861–866; https://doi.org/10.1016/j.ekir.2018.03.001
KEYWORDS: bortezomib; IgA nephropathy; proteinuria

IgA nephropathy is the most common glomerulonephritis in the world.[1] Renin-angiotensin-aldosterone system blockade is accepted as first-line therapy.[2] However, select patients treated with renin-angiotensin-aldosterone system blockade remain at risk for worsening of renal function.[1] For severe disease, existing treatment options, such as corticosteroids, cyclophosphamide, and azathioprine, potentially confer more risk without significant benefit.[2,3] IgA nephropathy is an autoimmune disease whereby the pathogenesis involves autoantibodies directed against galactose-deficient IgA1 (Gd-IgA1) or other endogenous proteins that act as autoantigens.[6,7] Immortalization of cell lines from peripheral blood of patients with IgA nephropathy demonstrated production of the aberrant glycosylation of IgA1 antibodies from B cells.[8] In a murine model, an increase in the number of intestinal IgA-producing plasma cells and decreased excretion of IgA into the intestinal lumen also could contribute to elevated serum IgA level and deposition in the kidney.[9] Abrogating the production of Gd-IgA1 by antibody-producing cells could be a promising strategy to treat IgA nephropathy.

Bortezomib is a proteasome inhibitor that targets plasma cells, which are professional antibody-producing cells and is approved by the Food and Drug Administration for the treatment of multiple myeloma by inhibiting transcriptional factor nuclear factor kappa B and inducing apoptosis of myeloma cells via misfolded protein response.[10,11] Bortezomib, in off-label use, was shown to deplete A Disintegrin and Metalloproteinase with Thrombospondin motifs-13 antibodies in thrombotic thrombocytopenic purpura, as well as depleting alloantibodies in the setting of antibody-mediated kidney transplant rejection.[12,13] Extended bortezomib therapy was reported to be associated with the

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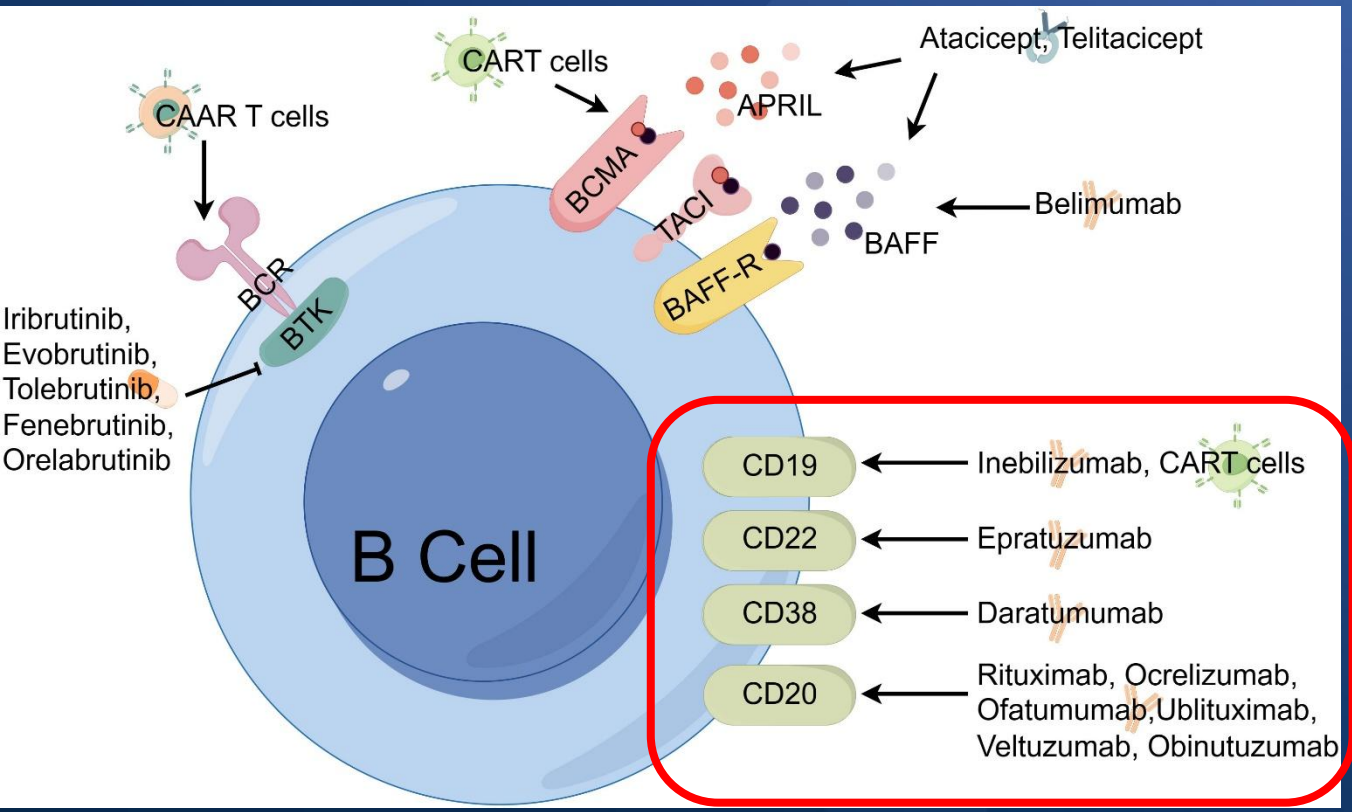
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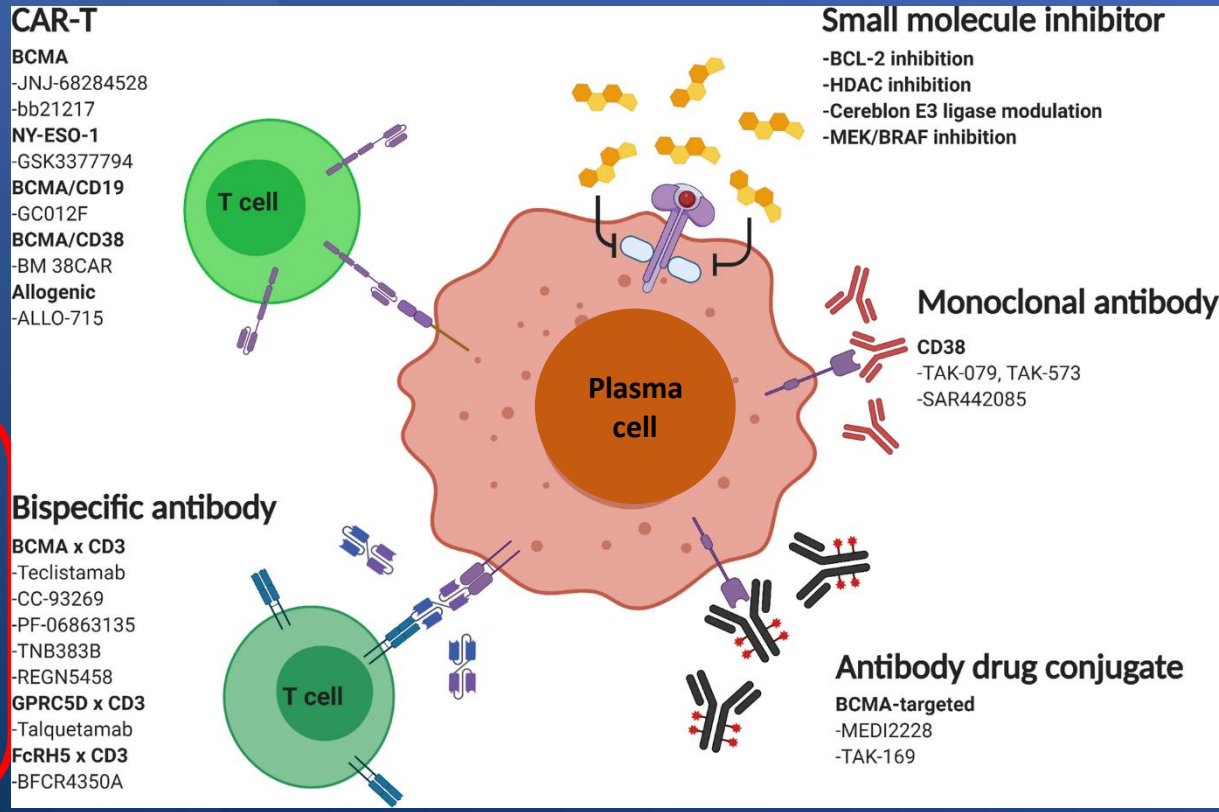
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Small molecule inhibitor
-BCL-2 inhibition
-HDAC inhibition
-Cereblon E3 ligase modulation
-MEK/BRAF inhibition
T cell
Plasma cell
Monoclonal antibody
CD38
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-SAR442085
Bispecific antibody
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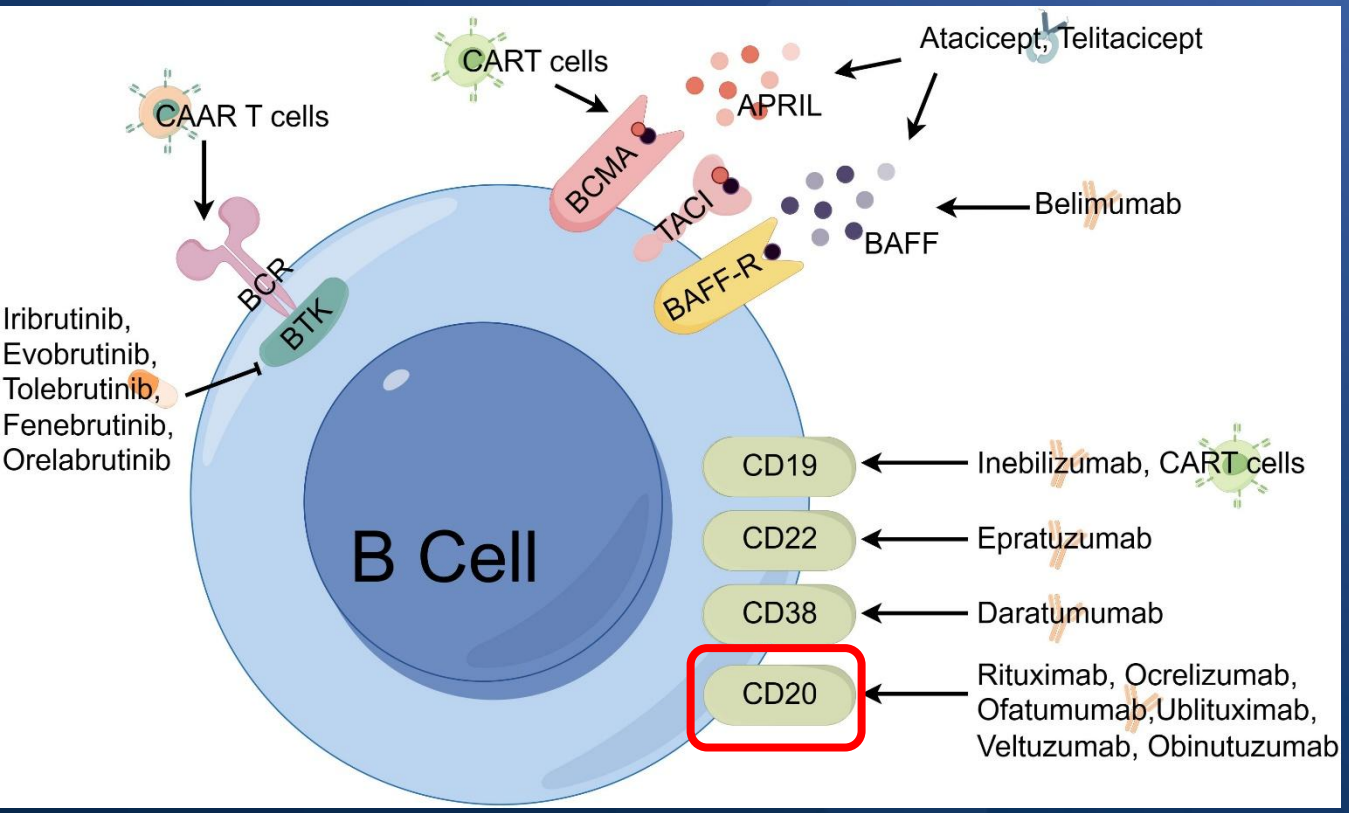

CLINICAL RESEARCH www.jasn.org

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‖

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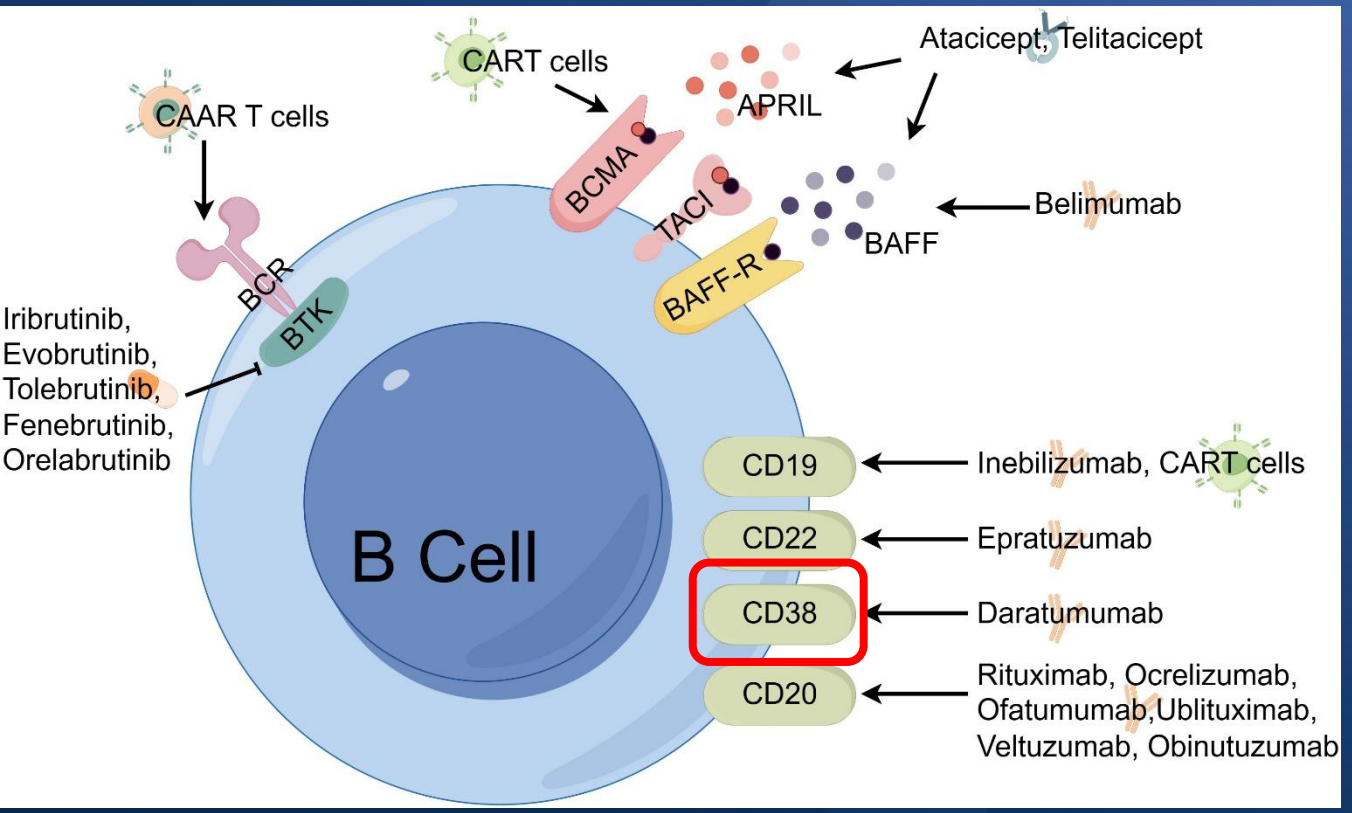

NCT06935357 Recruiting

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

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

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ARTICLE IN PRESS

www.kidney-international.org clinical trial

Randomized, double-blind, placebo-controlled phase 2a study assessing the efficacy and safety of felzartamab for IgA nephropathy

OPEN

Jürgen Floege[1], Richard Lafayette[2], Jonathan Barratt[3], Brian Schwartz[4], Paul T. Manser[4], Uptal D. Patel[4], Millie Shah[4], Lisa Kivman[4], Nicola Faulhaber[5], Tabea Kräft[5], Anjali Thakur[5], Stefan Härtle[5] and Sean J. Barbour[6]

[1]Division of Nephrology and Cardiology, University Hospital, Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen, Aachen, Germany; [2]Division of Nephrology, Department of Medicine, Stanford University, Stanford, California, USA; [3]Department of Cardiovascular Sciences, University of Leicester, Leicester, UK; [4]Biogen, South San Francisco, California, USA; [5]MorphoSys GmbH, a Novartis Company, Planegg, Germany; and [6]Division of Nephrology, University of British Columbia, Vancouver, British Columbia, Canada

Abstract

Introduction: Felzartamab is a fully human anti-CD38 monoclonal antibody under investigation for treatment of IgA nephropathy (IgAN). IGNAZ (NCT05065970) is a randomized, double blind, placebo-controlled Phase 2a study that assessed the efficacy and safety of felzartamab in 54 patients with biopsy-confirmed IgAN despite maximal renin angiotensin system blockade.

Methods: In part 1, patients were randomized in the 6-month treatment period to receive intravenous placebo (12 patients) or felzartamab in three arms: two doses in 15 days (2-dose, 12 patients), five doses in 2 months (5-dose, 11 patients), or nine doses in five months (9-dose, 13 patients). In part 2, six Japanese patients received the felzartamab 9-dose schedule open-label. Follow-up in parts 1 and 2 was 24 and 12 months, respectively, after the first dose. The primary endpoint was change in proteinuria (urine protein to creatinine ratio [UPCR]) at nine months.

Results: Treatment with felzartamab versus placebo led to rapid (within 3–6 months) reduction in least-squares mean UPCR sustained at nine months (placebo, −5.7%; 2-dose, −12.5%; 5-dose, −12.8%; 9-dose, −29.5%; part 2, −44.8%) and at 18 months after ending treatment (24 months), particularly in the 9-dose arm (−44.5%). Mean decreases in estimated glomerular filtration rate were lower with felzartamab than with placebo through 24 months in part 1 and 12 months in part 2. Felzartamab safety was consistent with prior observations; adverse events were predominantly grade 1 or 2.

Conclusions: Treatment with felzartamab results in sustained reduction of proteinuria, suggesting disease improvement. Further evidence is needed to understand the impact of felzartamab on preservation of kidney function in high-risk patients with IgAN.

Kidney International (2025) ■, ■–■; https://doi.org/10.1016/j.kint.2025.05.028

KEYWORDS: clinical trial; felzartamab; Gd-IgA1; IgA nephropathy; IgAN; phase 2

Lay Summary

IgA nephropathy is the most common primary glomerular disease worldwide, leading to kidney failure in a large proportion of patients. Despite the standard of care that includes renin-angiotensin blockade, many patients with IgA nephropathy (IgAN) will experience persistent proteinuria and progressive loss of kidney function, ultimately resulting in poor outcomes. Targeting the underlying pathogenic events in IgAN is an essential component of an optimal treatment strategy. Thus, a potential therapeutic approach is to deplete CD38$^+$ plasma cells, which are responsible for the production of galactose-deficient IgA1 (Gd-IgA1) and autoantibodies against Gd-IgA1 that contribute to the development of IgAN. In the IGNAZ phase 2a study, treatment with felzartamab, which specifically depletes CD38$^+$ plasma cells, was generally well tolerated and led to improvements in proteinuria and decreases in relevant serum immunoglobulins, suggesting that felzartamab may modulate the underlying pathogenesis of IgAN.

Primary IgA nephropathy (IgAN) is the most common primary glomerular disease worldwide, and up to 50% of patients will develop kidney failure within 10–20 years.[1–3] The pathogenesis of IgAN is thought to be a "four-hit" process consisting of the generation of galactose-deficient IgA1 (Gd-IgA1), the development of anti–Gd-IgA1

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

in collaboration with Österreichische Gesellschaft für Nephrologie

Safety, tolerability, and efficacy of mezagitamab (TAK-079) as add-on to standard-of-care therapy in primary IgA nephropathy: results from a phase 1b Study

Jonathan Barratt,[1] Yusuke Suzuki,[2] Van Anh Nguyen,[3] Iwona Dobler,[3] Cheryl Li,[3] Parth Patwari,[3] MK Farmer[3]

[1]Department of Cardiovascular Sciences, University of Leicester, Leicester, UK; [2]Department of Nephrology, Juntendo University Faculty of Medicine, Tokyo, Japan; [3]Takeda Development Center Americas, Inc., Cambridge, MA, USA

INTRODUCTION

- Immunoglobulin (Ig) A nephropathy (IgAN) is the most prevalent form of primary glomerulonephritis worldwide.[1]
  - IgAN is associated with a poor prognosis and can progress to kidney failure, lead to reduced quality of life, or cause premature death.[2]
- Despite recent approvals of medications for IgAN, an unmet need remains for safe and effective medications.
- Mezagitamab is a fully human, anti-CD38 IgG1 monoclonal antibody that depletes plasma cells, plasmablasts, and natural killer cells expressing CD38.[3,4]
  - Mezagitamab depletes cells responsible for producing galactose-deficient IgA1 (Gd-IgA1) and autoantibodies against Gd-IgA1.
  - Depletion of these cells is predicted to decrease formation of pathogenic Gd-IgA1 and IgA immune complexes, potentially reducing proteinuria and thus promoting stabilization of renal function over time.

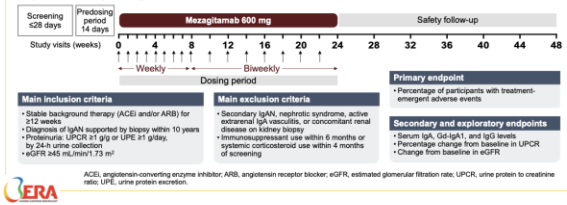
OBJECTIVE

- To report week 48 results from a phase 1b study evaluating the safety, tolerability, and efficacy of mezagitamab in combination with stable background therapy in participants with primary IgAN.

METHODS

- Open-label, single-arm, phase 1b, multicenter study (NCT05174221) (**Figure 1**).
- 17 participants enrolled and received subcutaneous mezagitamab 600 mg once weekly for 8 weeks, then 600 mg every 2 weeks for 16 weeks (for a total of 16 doses), followed by a 24-week safety follow-up period.
- Data are reported up to the week 48 visit.

Figure 1. Study design



ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; UPCR, urine protein to creatinine ratio; UPE, urine protein excretion.

RESULTS

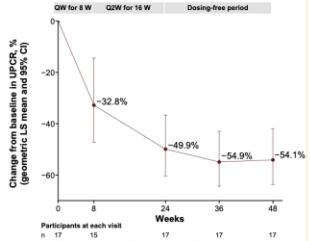
- This analysis was performed when all 17 participants had completed the week 48 visit.
- A summary of safety is shown in **Table 1**. There were no reported grade ≥3 infections or opportunistic infections.
- Rapid and sustained reductions in serum IgA, Gd-IgA1, and IgG were observed, with mean reductions from baseline of 52.4%, 57.8%, and 18.9%, respectively, at week 48. Serum IgA and IgG levels trended toward baseline by week 48.
- At week 48, there was a 54.1% mean reduction in proteinuria as measured by UPCR from a 24-h urine collection (**Figure 2**).
- Renal function, as measured by eGFR, remained stable through week 48 (**Figure 3**).

Table 1. Summary of safety

	Total (N=17)
Any AE, n (%)*	16 (94.1)
AE related to study drug, n (%)	11 (64.7)
Grade ≥3 severity AE, n (%)	3 (17.6)
Grade ≥3 severity AE related to study drug, n (%)	2 (11.8)
Infectious AEs, n (%)	13 (76.5)
Serious AE, n (%)	0
Study discontinuations due to AE, n (%)	0

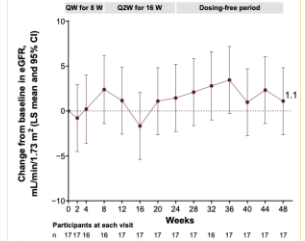
AE, adverse event; n, number of participants experiencing the event.
*The most frequently occurring AEs were upper respiratory tract infection (n=6; 35.3%), pyrexia (n=4; 23.5%), and oropharyngeal pain (n=4; 23.5%).

Figure 2. Rapid and sustained reduction in proteinuria through week 48



LS, least squares; Q2W, every 2 weeks; QW, once weekly; UPCR, urine protein to creatinine ratio; W, week.
Data are presented as model-based geometric mean with 95% CI. From a mixed-effects model for repeated measurement analysis with visit as a factor, and adjusted baseline value and baseline-by-visit interaction.

Figure 3. Renal function remained stable through week 48



LS, least squares; Q2W, every 2 weeks; QW, once weekly; W, week.
Data presented as model-based mean and 95% CI. From a mixed-effects model for repeated measures analysis over all postbaseline visits, with change from baseline in eGFR as the outcome and visit as the factor.

CONCLUSIONS

- Mezagitamab was generally well tolerated as an add-on to standard-of-care therapy in participants with primary IgAN.
- No opportunistic infections or grade ≥3 infections were observed.
- Rapid and sustained reductions in serum IgA, Gd-IgA1, IgG, and proteinuria were observed. Serum IgA and IgG levels trended toward baseline by week 48.
- Renal function, as measured by eGFR, remained stable during the first year of this study.

ACKNOWLEDGEMENTS

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Disclaimer: This presentation is intended for health care professionals only.

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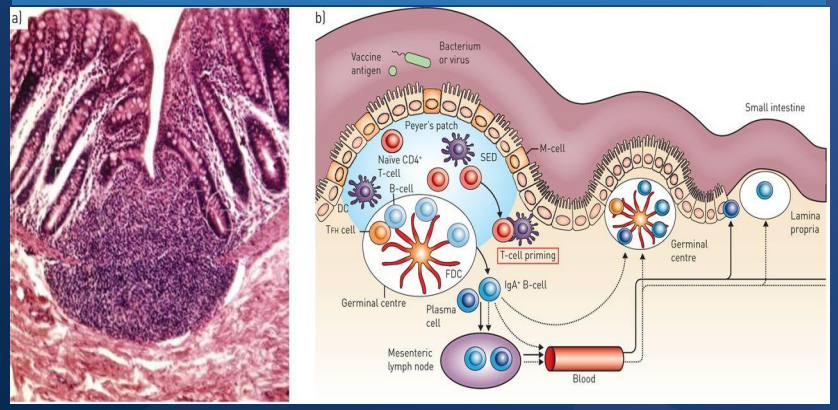
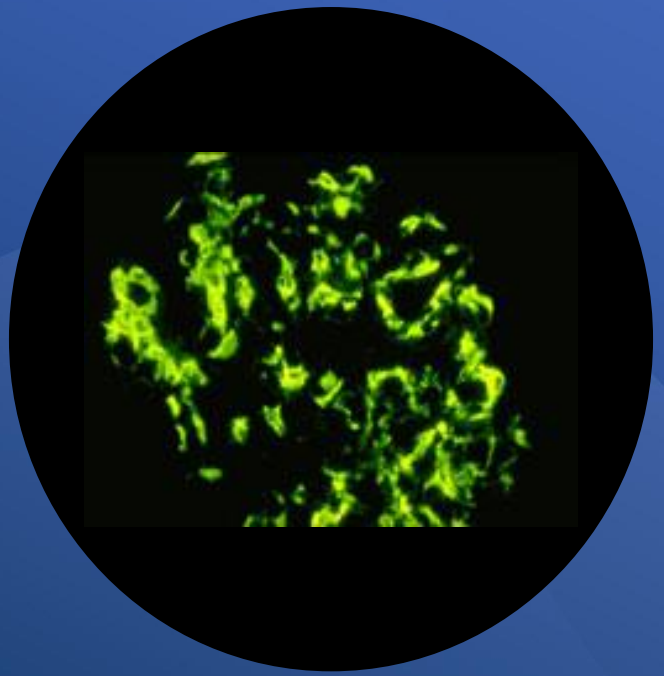
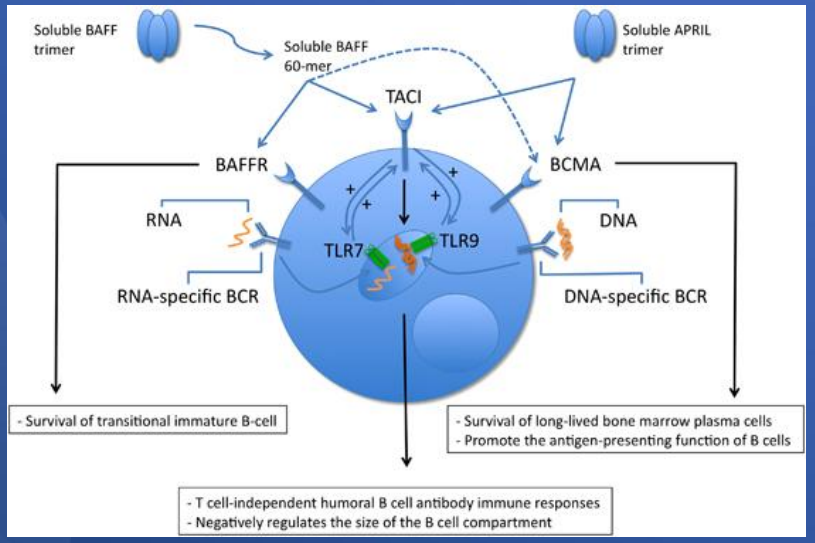
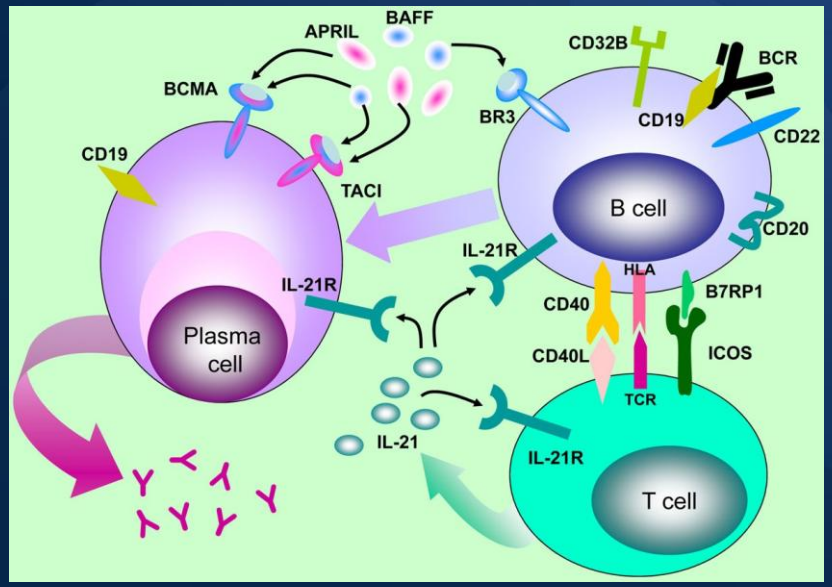
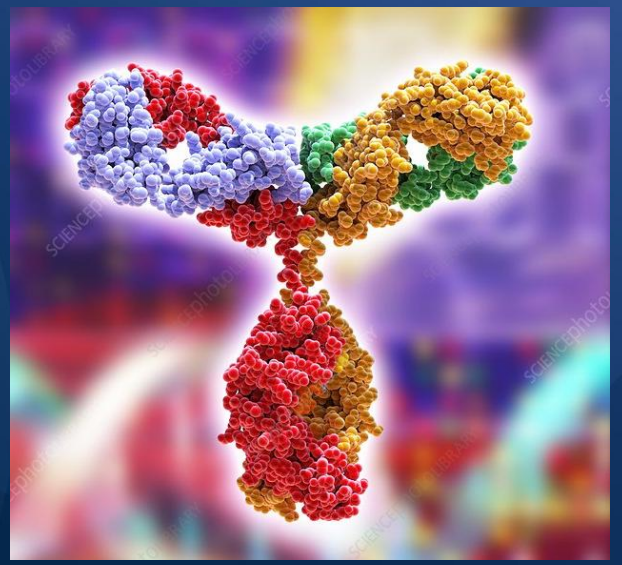
Mucosa Associated Lymphoid Tissue

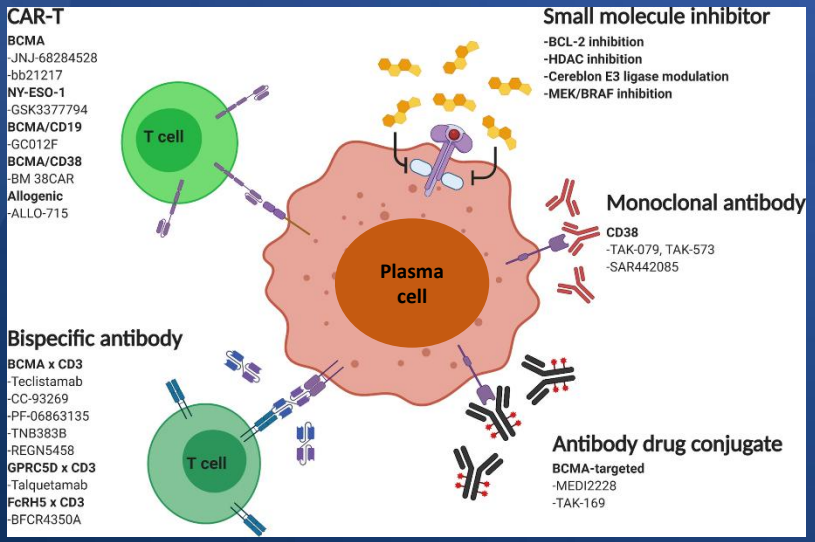












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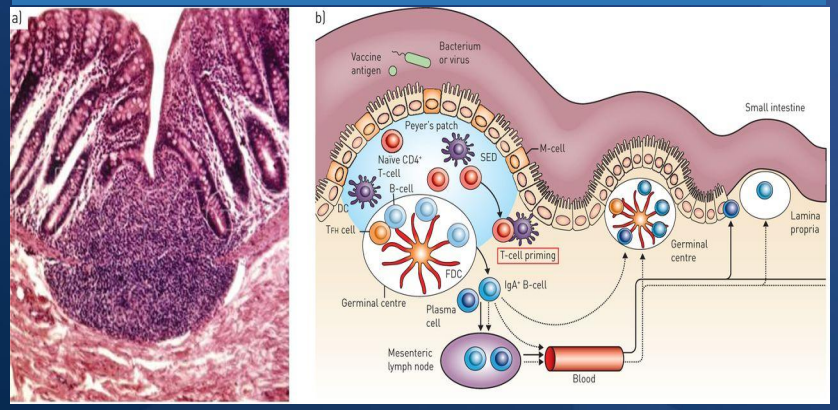
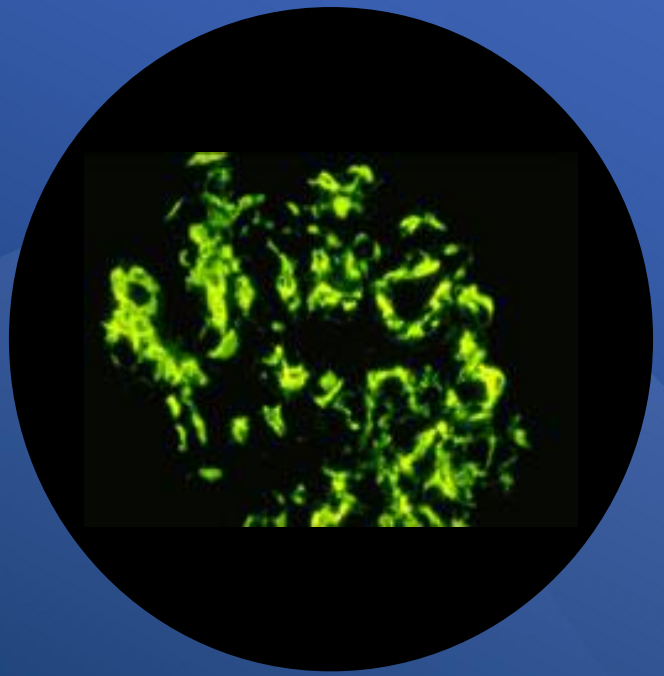
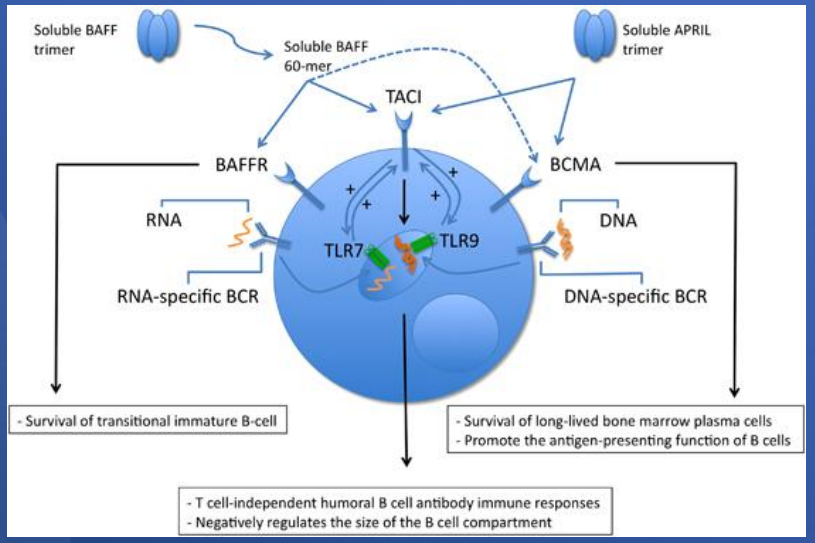
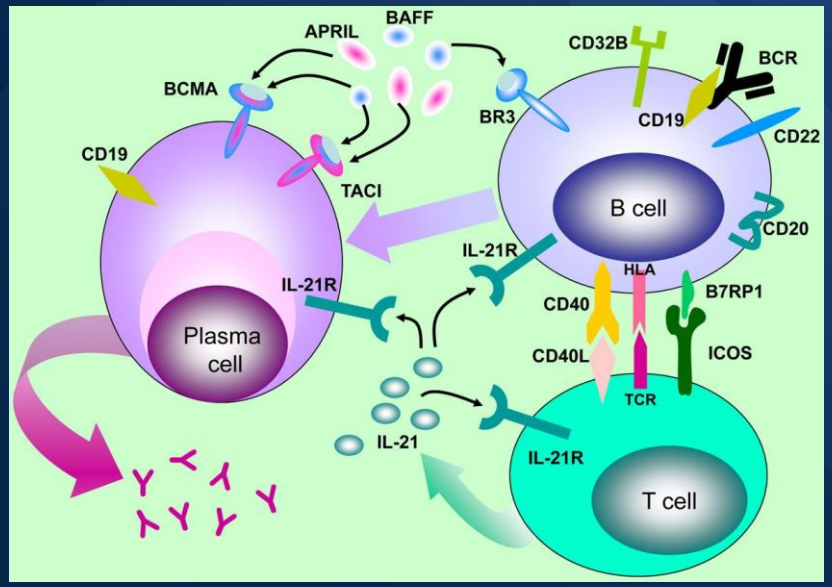
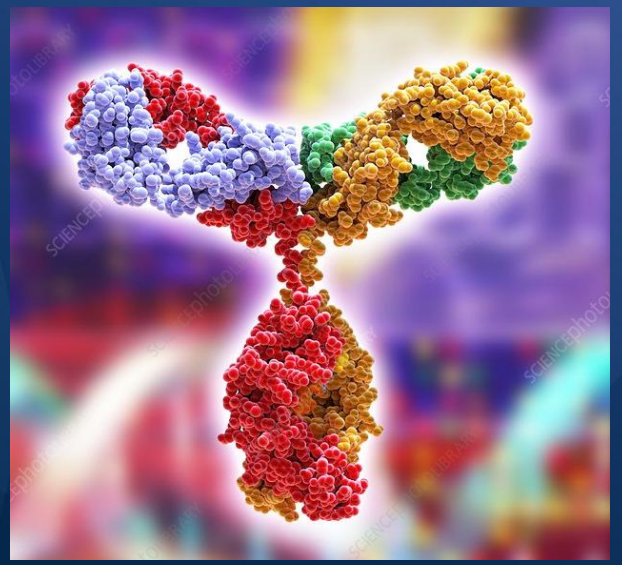
Mucosa Associated Lymphoid Tissue

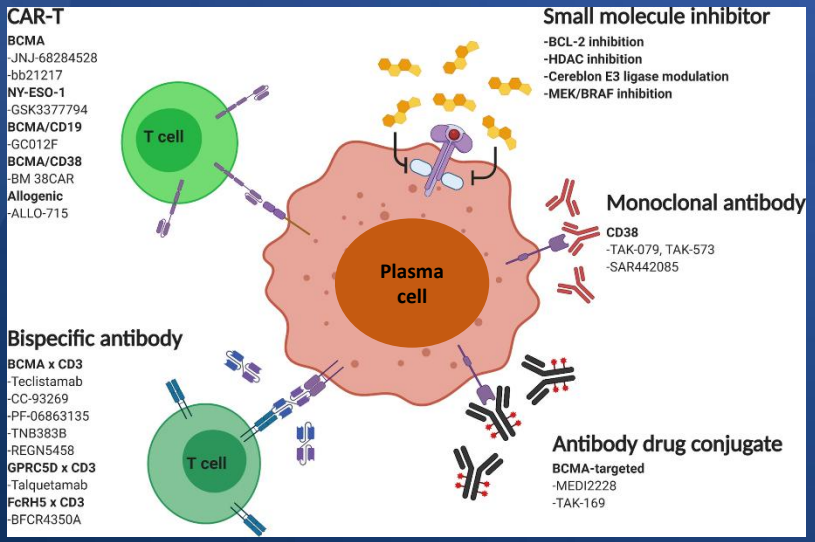












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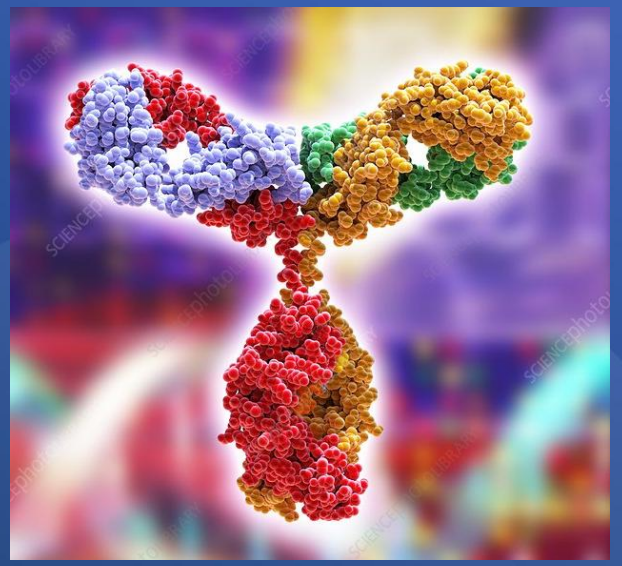
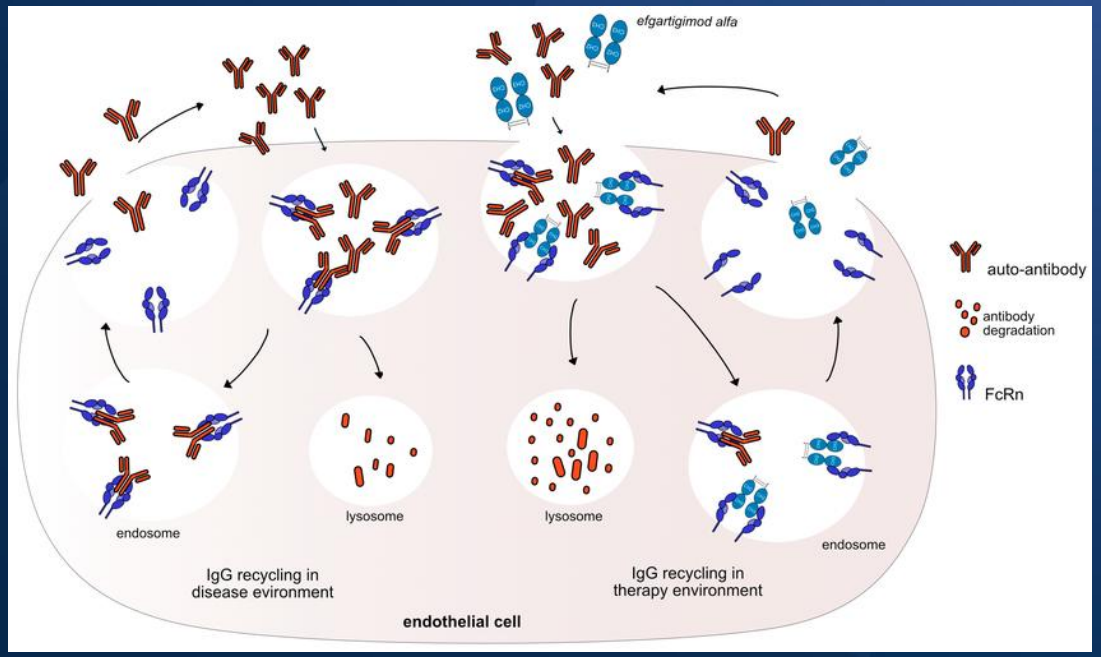
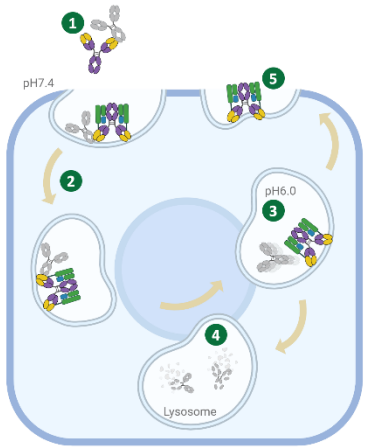
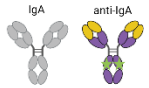




Development of a sweeping and blocking anti-IgA antibody

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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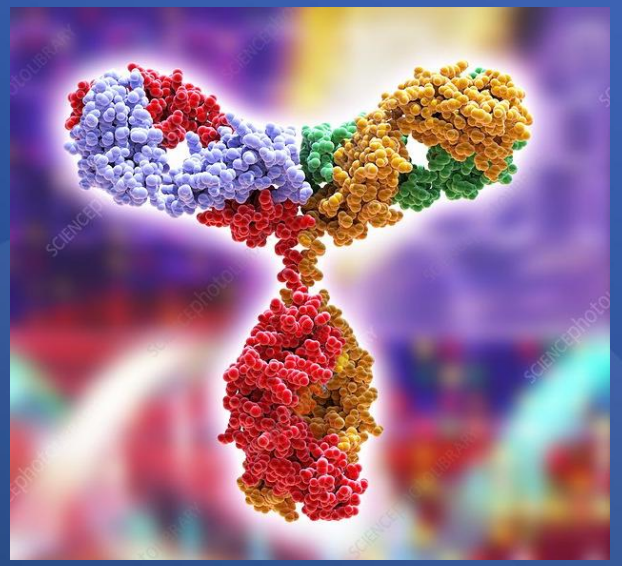

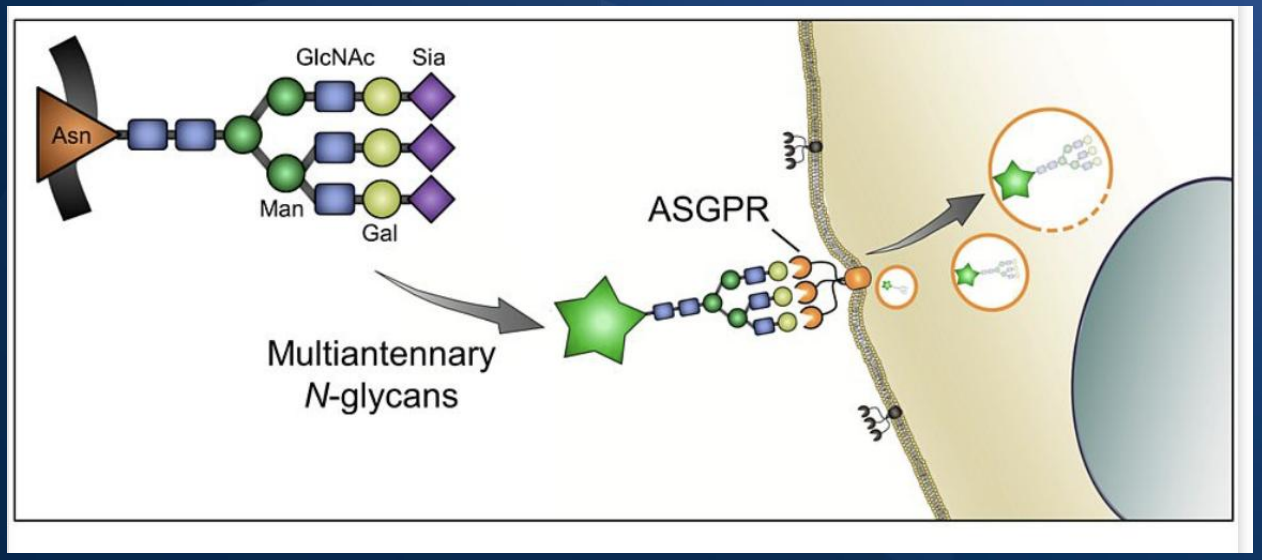

biohaven

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

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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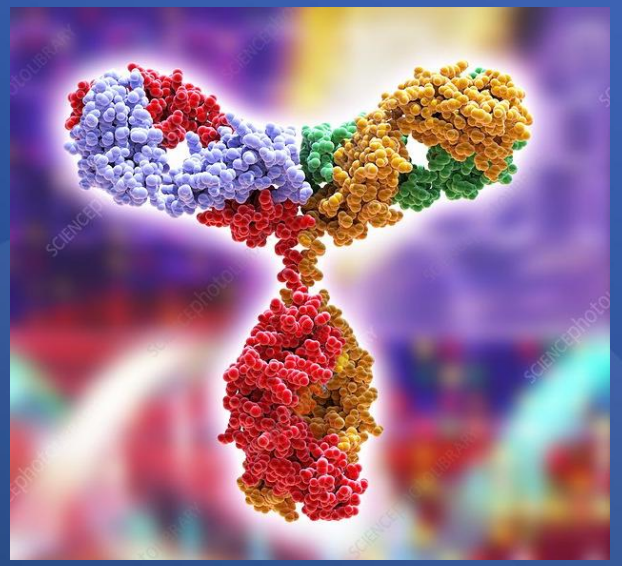

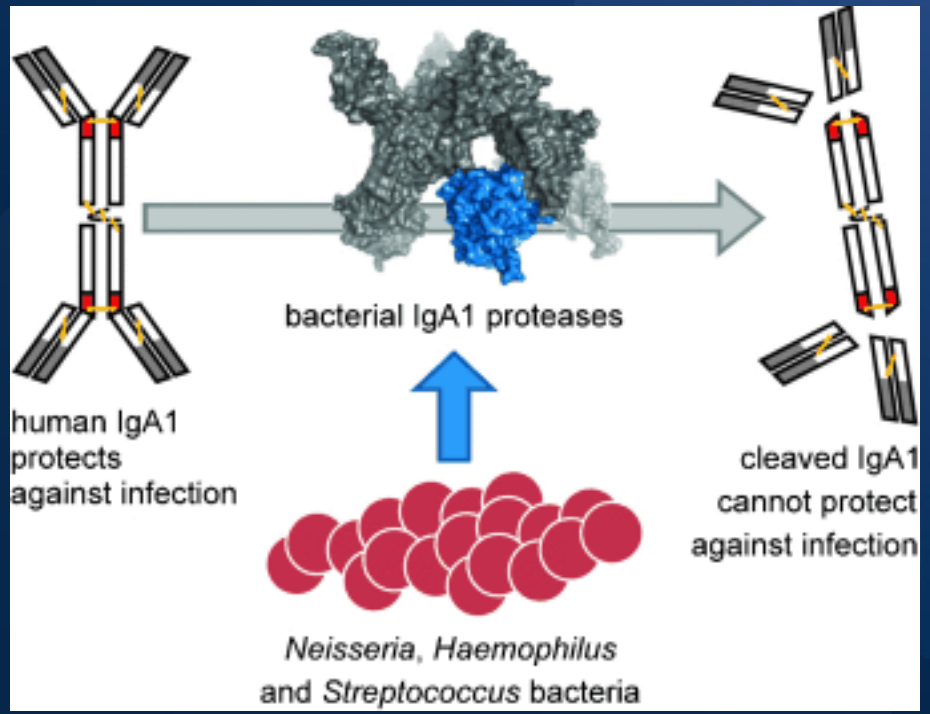

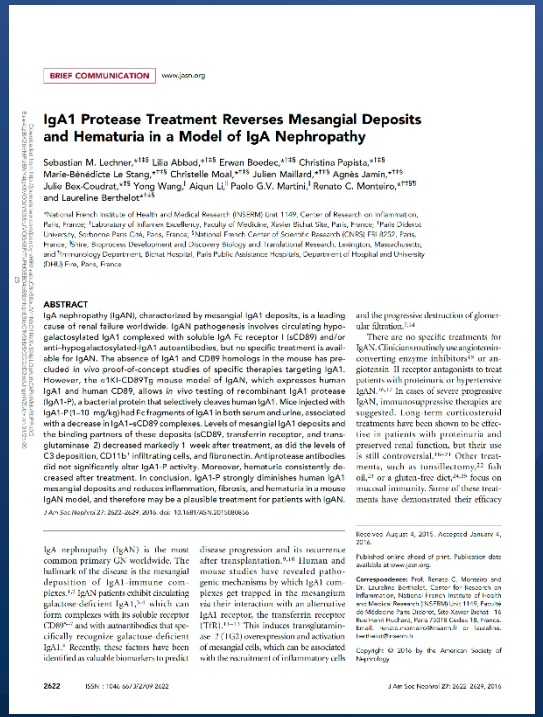

BRIEF COMMUNICATION www.jasn.org

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*†‡§

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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,[3–5] which can form complexes with its soluble receptor CD89[6–8] and with autoantibodies that specifically recognize galactose-deficient IgA1.[9] 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.[9,14]

There are no specific treatments for IgAN. Clinicians routinely use angiotensin-converting enzyme inhibitors[15] or angiotensin II receptor antagonists to treat patients with proteinuria 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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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.)

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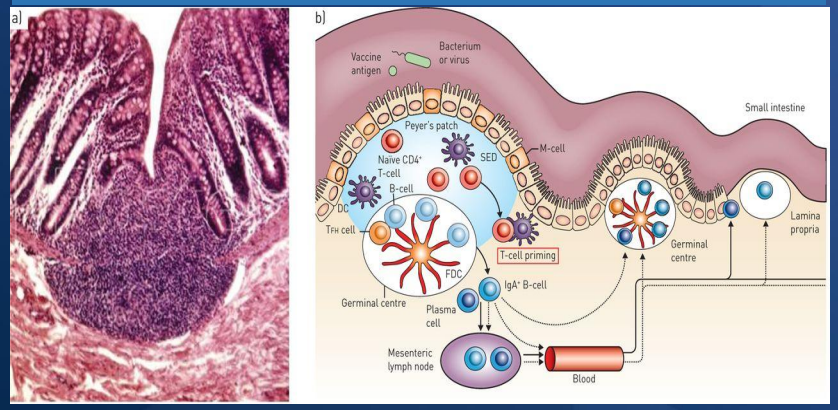
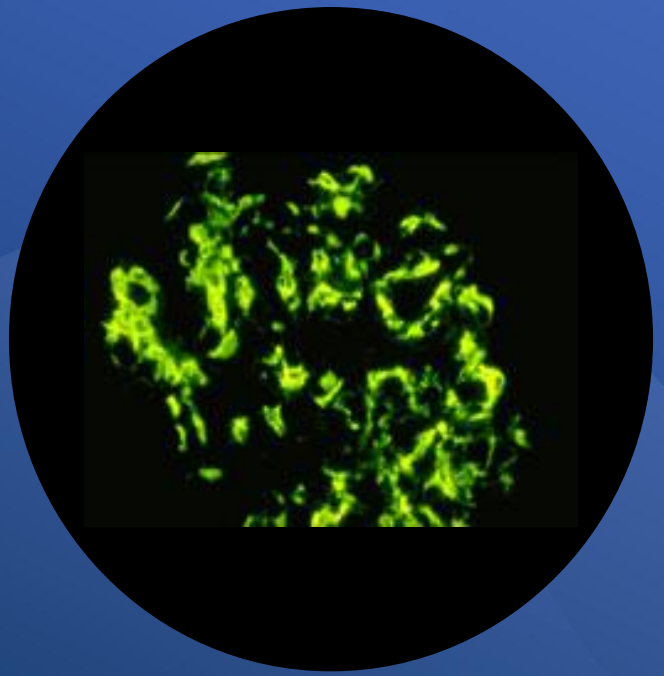
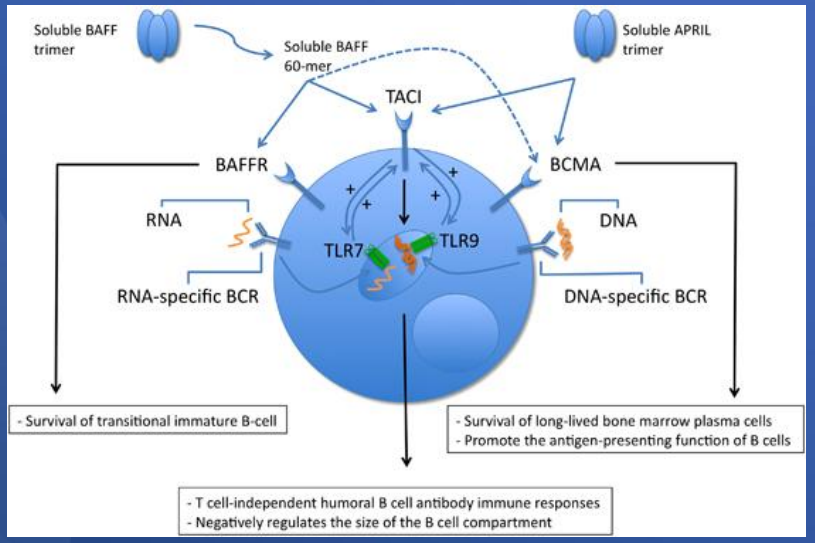
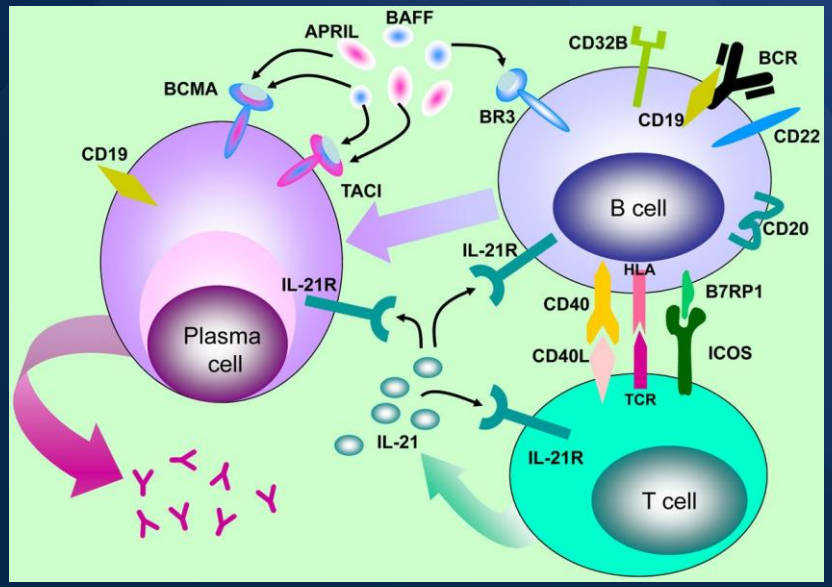
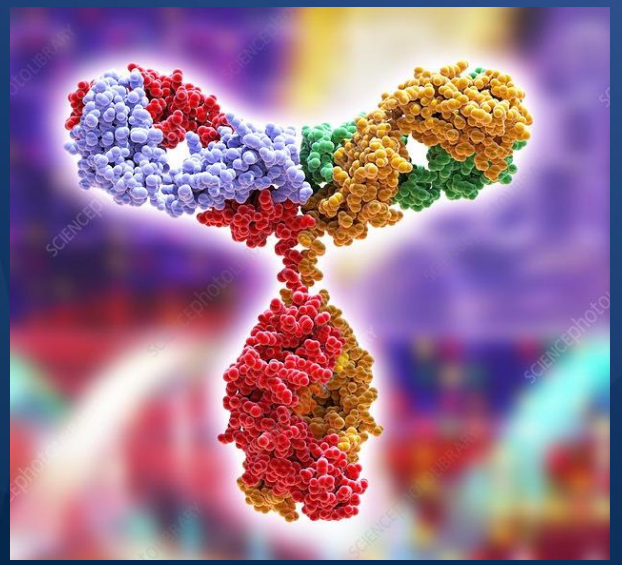
Mucosa Associated Lymphoid Tissue

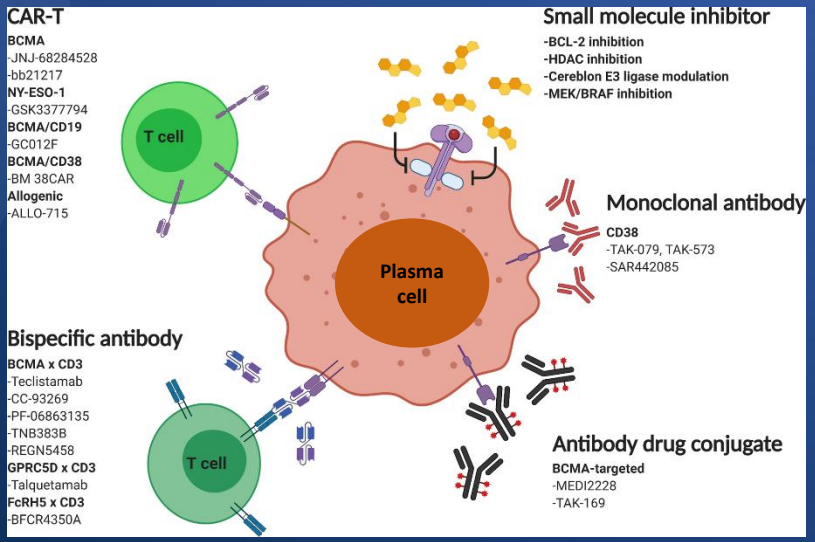












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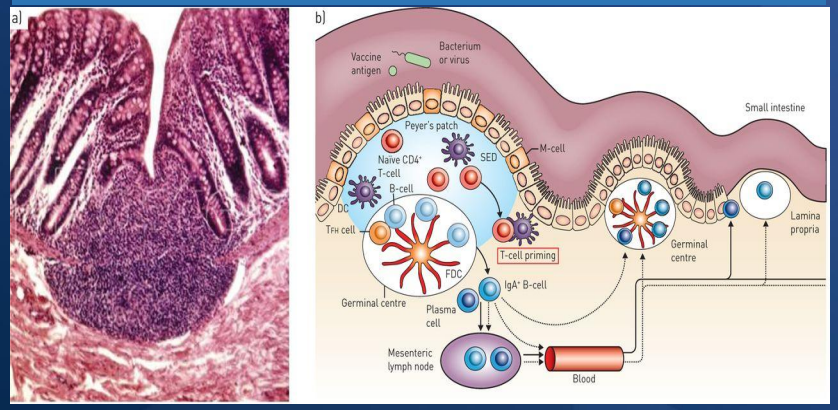
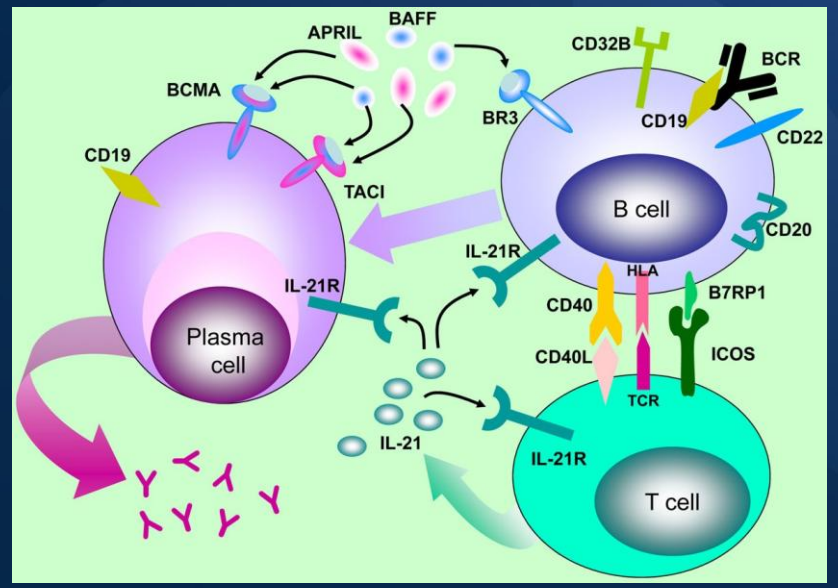
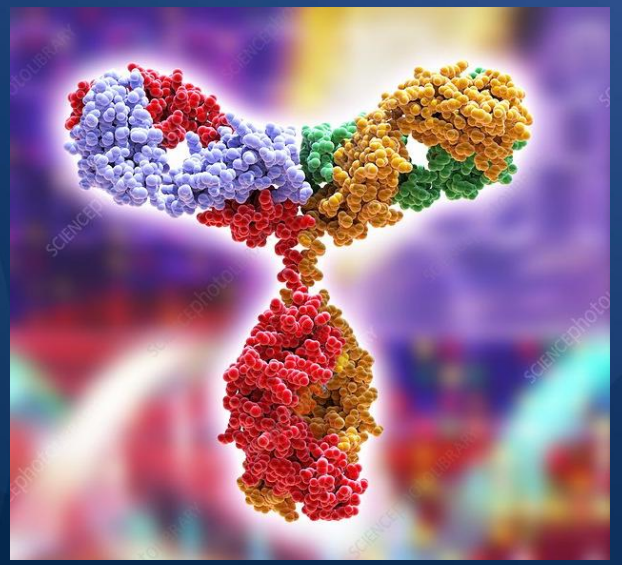
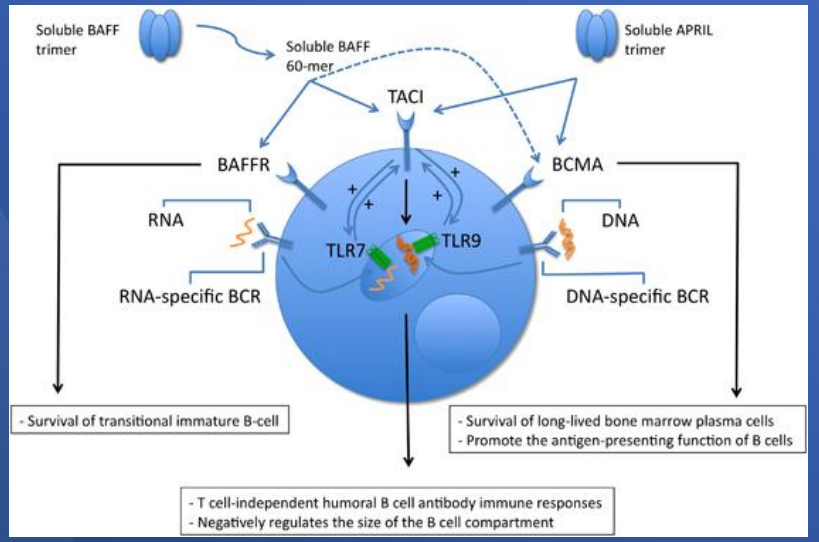
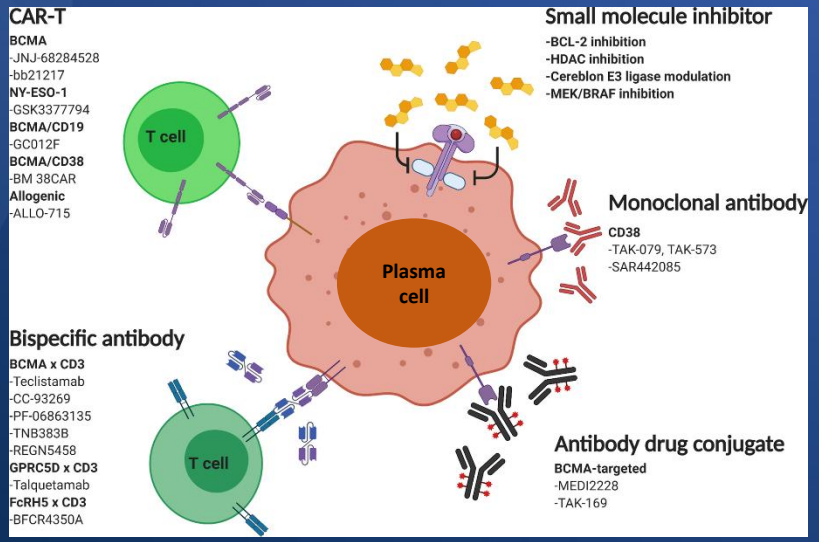
Mucosa Associated Lymphoid Tissue











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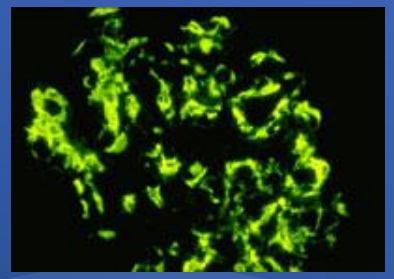

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Address immune & inflammatory drivers of continued nephron loss

Stop mesangial IgA-IC accumulation

Reduce formation of circulating IgA-IC

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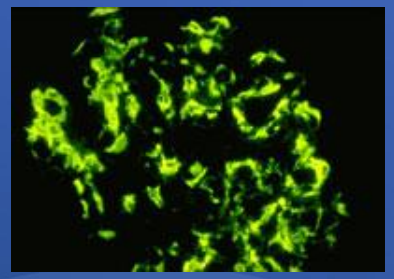

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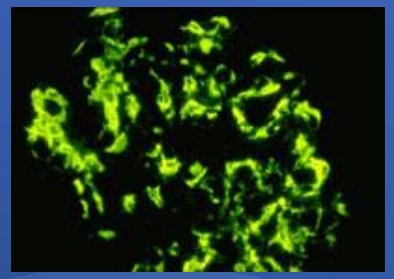

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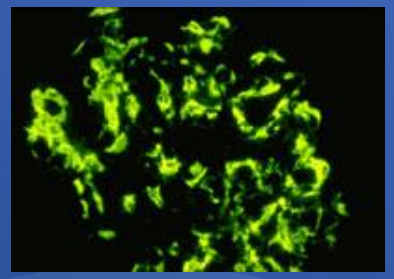

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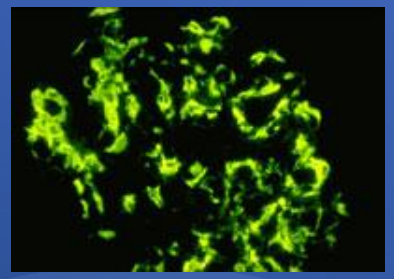

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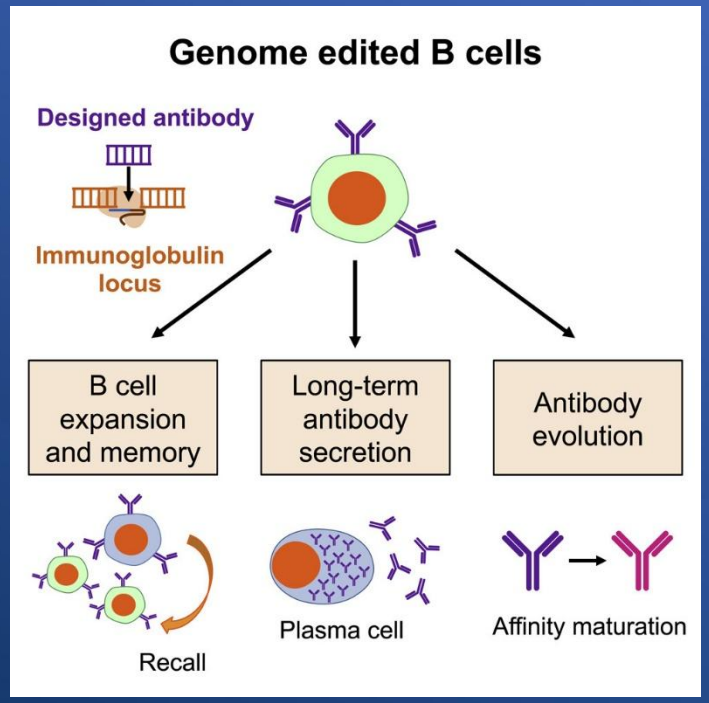

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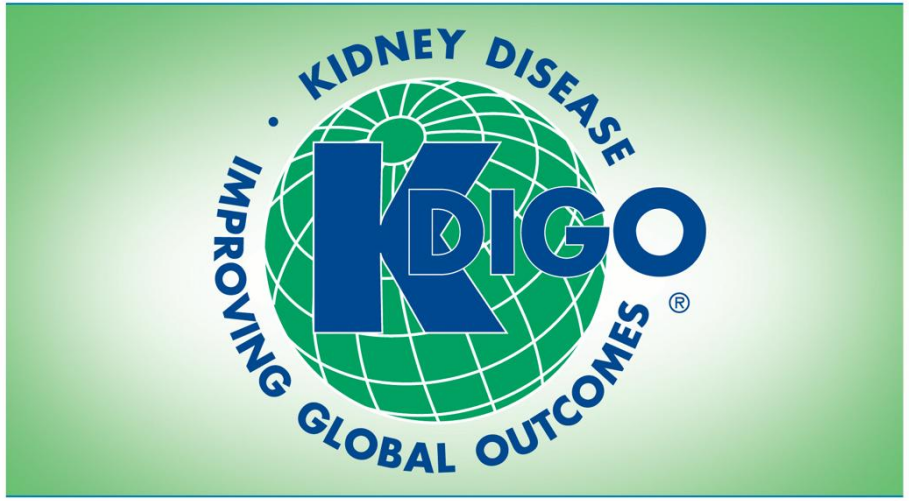

KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV)

VOLUME 108 | ISSUE 5S | NOVEMBER 2025

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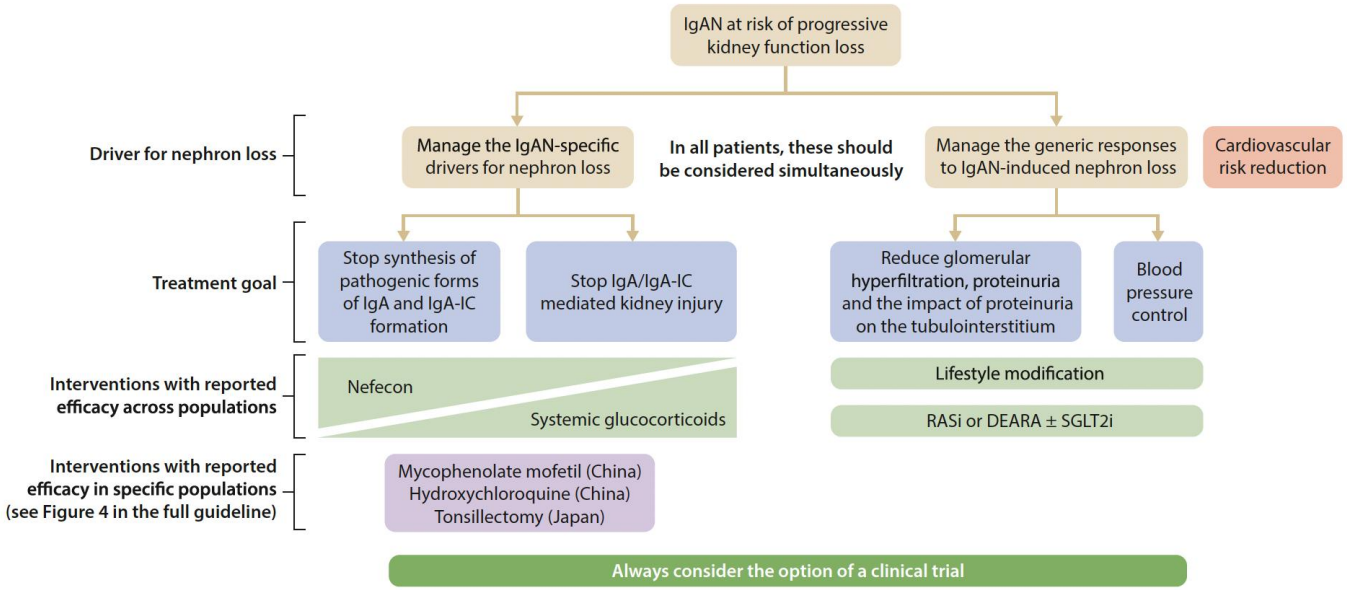

Figure 2 | Treatment targets in immunoglobulin A nephropathy (IgAN) and the positioning of drugs included in this guideline. Reflecting current understanding, Nefecon is shown as having a predominant effect on the production of pathogenic forms of IgA and IgA-containing immune complexes (IgA-ICs), with an undetermined direct effect of systemically absorbed budesonide on the kidneys. Systemic glucocorticoids have a well-documented anti-inflammatory effect within the kidneys and an undetermined direct effect on the production of pathogenic forms of IgA and IgA-ICs. Strategies to manage the generic response to IgAN-induced nephron loss may also include the use of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors in selected patients. DEARA, dual endothelin angiotensin receptor antagonist; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

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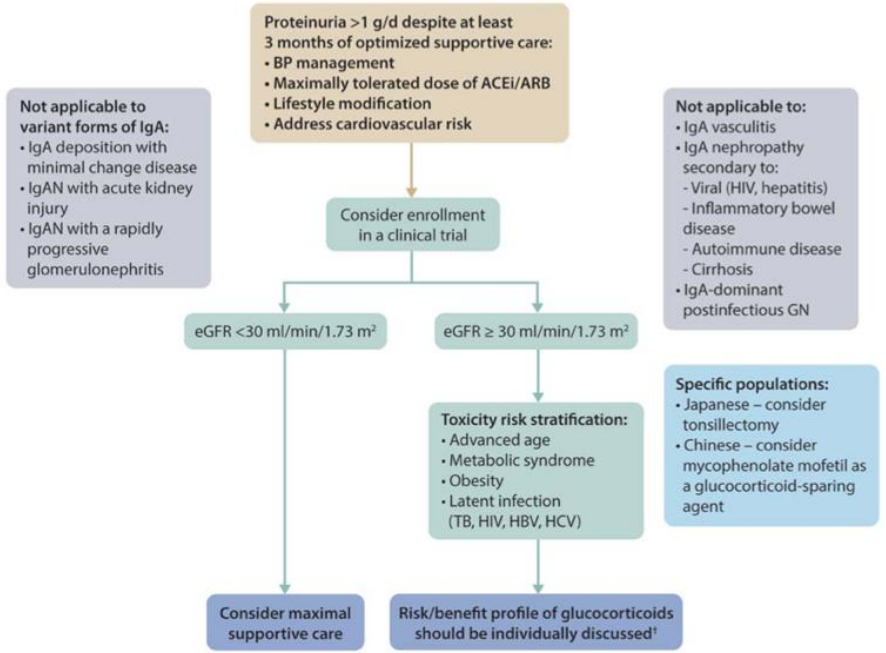

Figure 24 | Management of patients with IgAN who remain at high risk for progression after maximal supportive care. *IgAN with rapidly progressive glomerulonephritis is covered in Practice Point 2.4.3. †The TESTING study[109] shows early evidence of efficacy in patients who had marked proteinuria (2.4 g/d average) at the expense of treatment-associated morbidity and mortality. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure, eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgAN, immunoglobulin A nephropathy; TB, tuberculosis.

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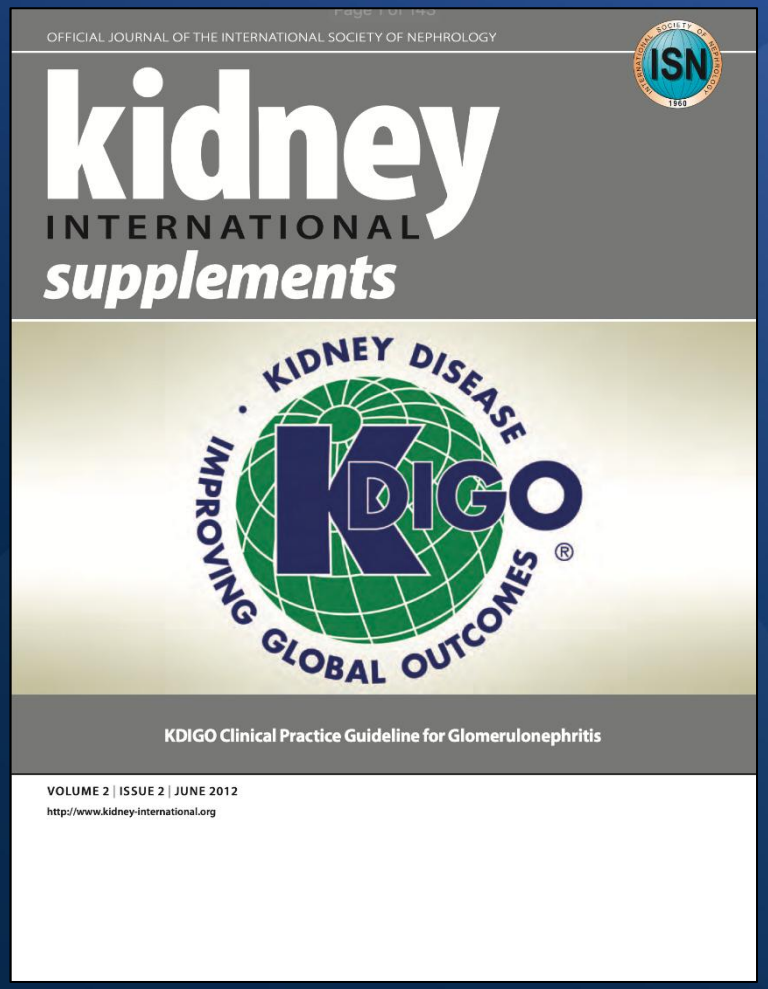

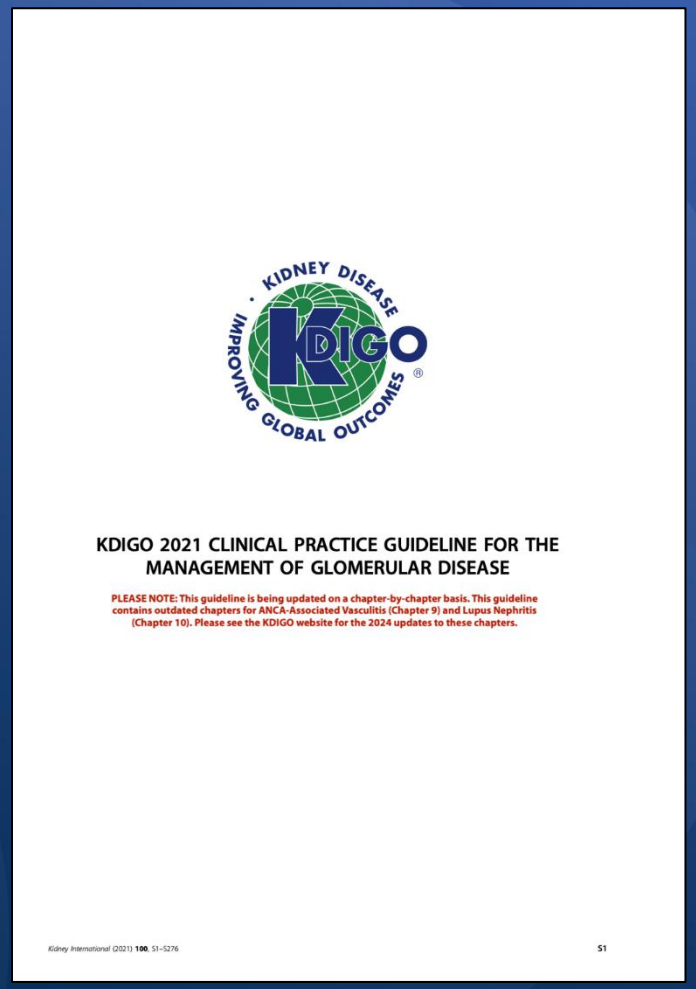

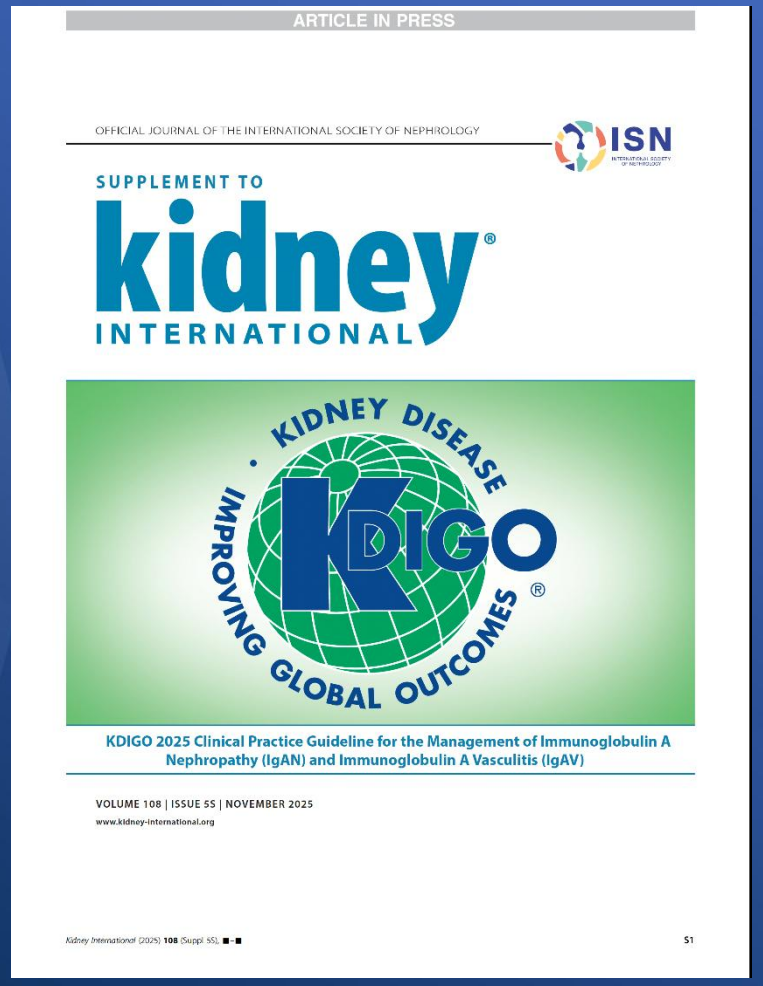

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