An Update in Alport syndrome

By

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An Update in Alport syndrome; Introduction

- Alport syndrome (also referred to as hereditary nephritis) is an inherited progressive form of glomerular disease that is often associated with hearing loss and ocular abnormalities.
- The prevalence of the disease is estimated at approximately 1 in 50,000 live births .
- Alport syndrome reportedly accounts for 0.3 to 2.3 percent of new cases of end-stage renal disease (ESRD).

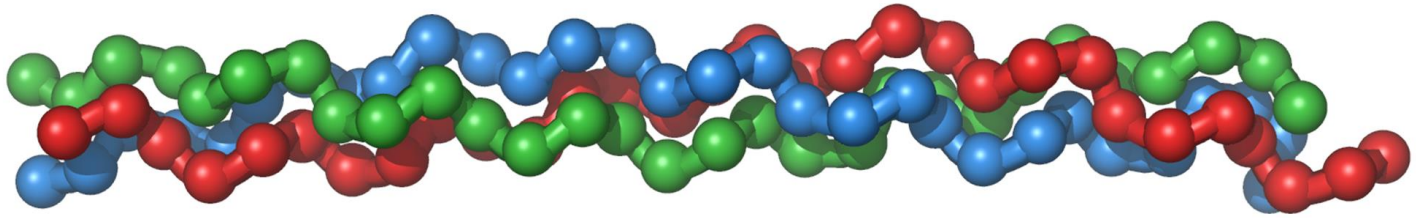
Up to Date 2018

Introduction

- Alport syndrome is a genetically heterogeneous disease that results from mutations in genes encoding the alpha-3, alpha-4, and alpha-5 chains of type IV collagen.
- These type IV collagen alpha chains are normally located in various basement membranes of the kidney, cochlea, and eye. Abnormalities in these chains result in defective basement membranes at these sites, leading to the clinical features of this disorder (ie, progressive glomerular disease, sensorineural hearing loss, and ocular abnormalities).

Pathophysiology and Etiology

- Type IV collagen is the major constituent of the GBM. Each type IV collagen molecule is composed of 3 subunits, called alpha (IV) chains, which are intertwined into a triple helical structure.



- Six isomers of the alpha (IV) chains exist and are designated alpha-1 (IV) to alpha-6 (IV).
- e Medcine; Alport

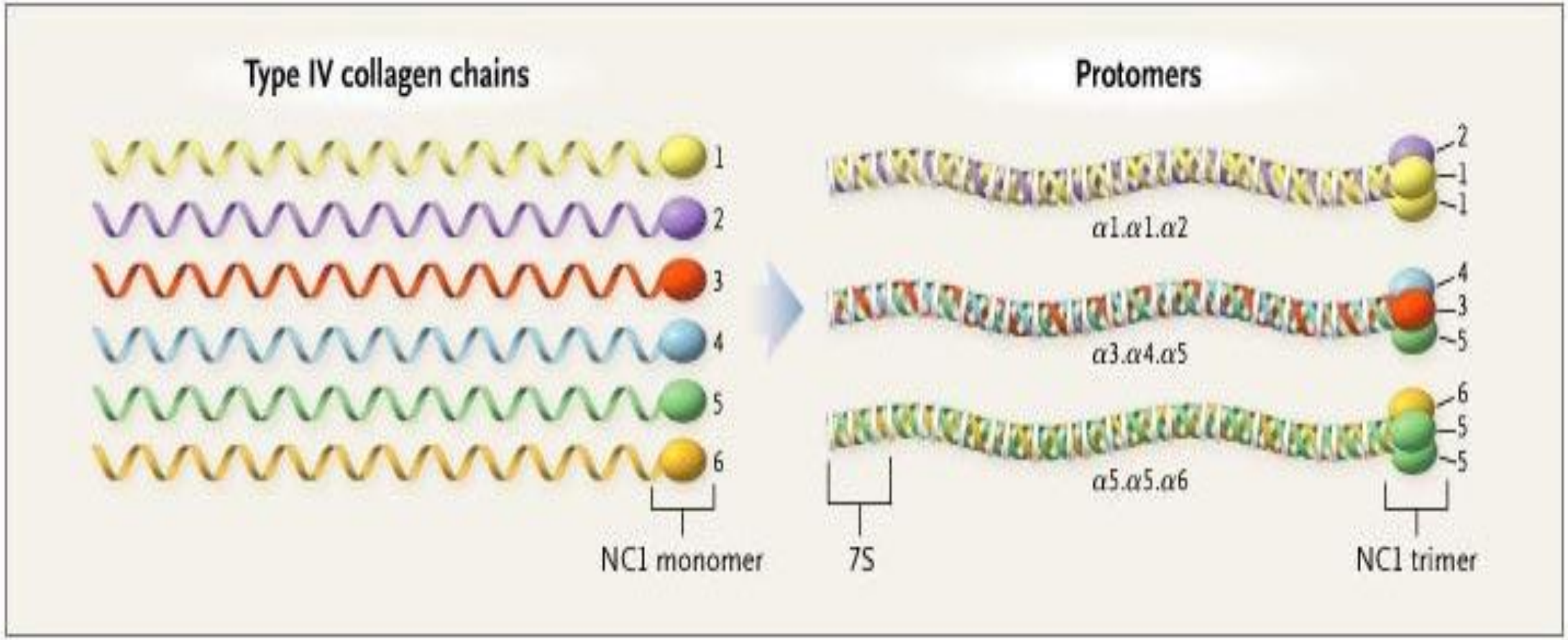
- Only three trimer combinations of Alpha chains are found in tissues:

α1-α1-α2

α3-α4-α5

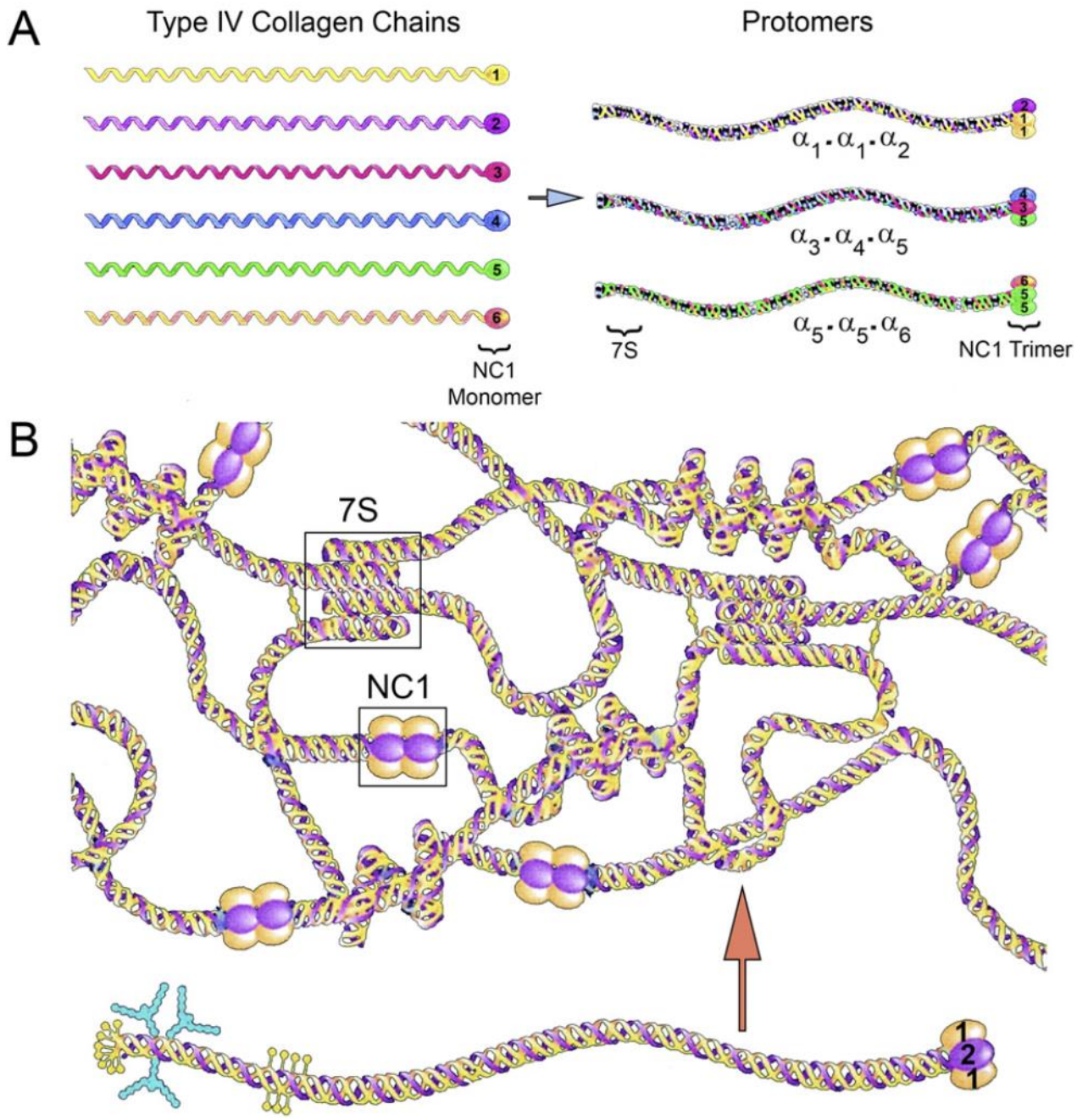
α5-α5-α6

- They form the GBM collagen network.
- In the glomerulus, the initial embryonal α1-α1-α2 network is subsequently replaced by the α3-α4-α5 configuration, during nephron maturation (the so-called developmental switch).
- This switch provides more resistance to physical and chemical effects. When an abnormality occurs in the α-chain, these triple helix structures are broken, causing nephropathy, sensorineural hearing loss, and eye lesions.

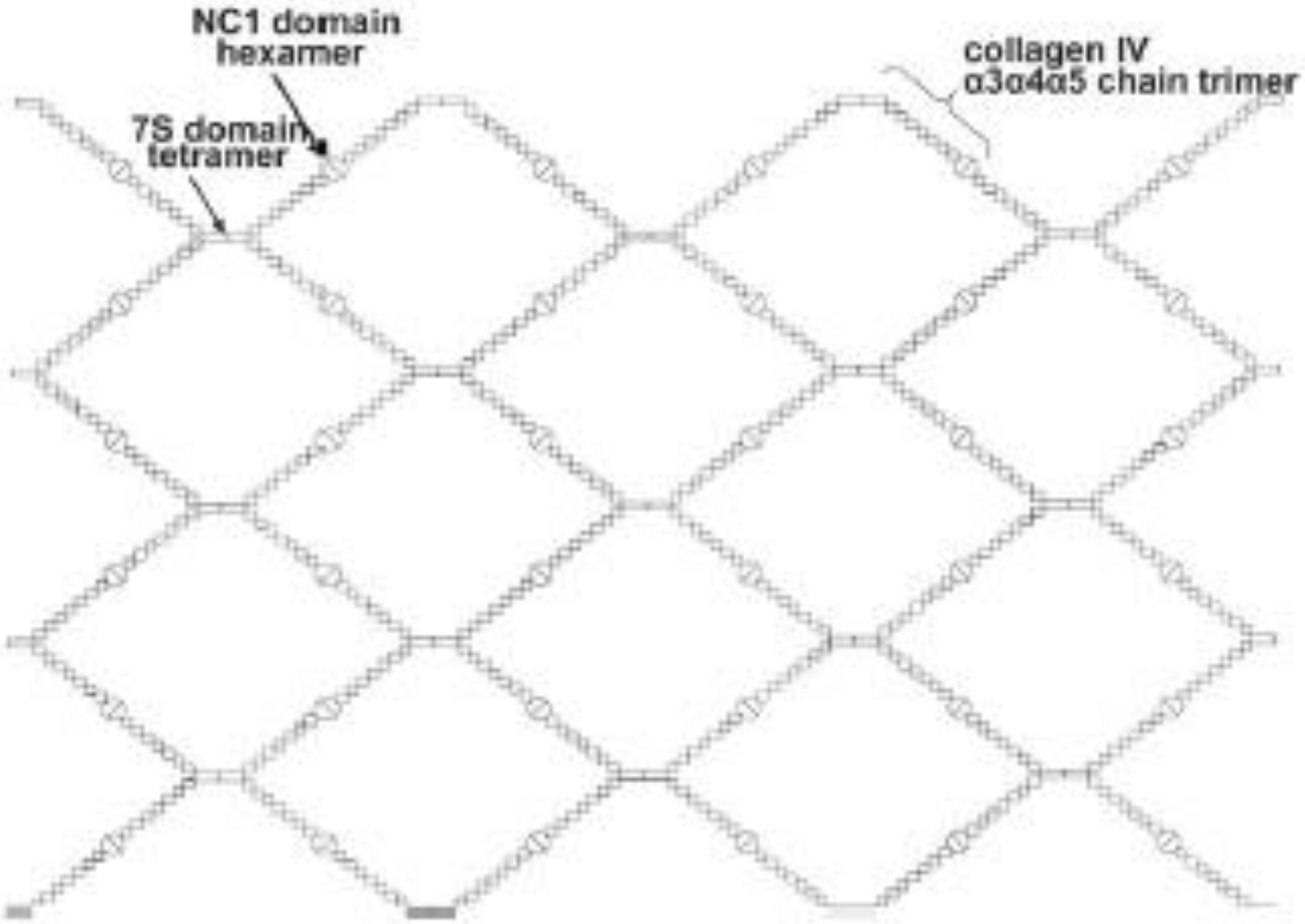

Type IV collagen chains
1
2
3
4
5
6
NC1 monomer
Protomers
2
1
1
α1.α1.α2
4
3
5
α3.α4.α5
6
5
5
α5.α5.α6
7S
NC1 trimer

A: Six isomers of the alpha (IV) chains and trimer combinations of Alpha chains .

B: How they form the GBM collagen network.



Dominic Cosgrove, and Shiguang Liu : Collagen IV diseases: A focus on the glomerular basement membrane in Alport syndrome, Matrix Biol. (2017) 57–58, 45–54



Collagen IV structure in the basement membrane

Pavlína Plevová, et al, Familial hematuria: A review, m e d i c i n a 5 3 (2 0 1 7) 1 – 1 0

Structure of Type 4 collagen

- Due to the fact that all three of the encoded type IV collagen α-chains are required to form the heterotrimeric protomers, debilitating mutations in any of these type IV collagen genes results in the complete absence of the α3(IV)/α4(IV)/α5(IV) network in the GBM.
- The resulting mature GBM in Alport syndrome is thinner and has only α1(IV)/α2(IV) networks. When an abnormality occurs in the α-chain, these triple helix structures are broken, causing nephropathy, sensorineural hearing loss, and eye lesions

Dominic Cosgrove, and Shiguang Liu : Collagen IV diseases: A focus on the glomerular basement membrane in Alport syndrome, Matrix Biol. (2017) 57–58, 45–54

Distribution

- The alpha-1 (IV) and alpha-2 (IV) chains are ubiquitous in all basement membranes , while the other type IV collagen chains have more restricted tissue distribution.
- The basement membranes of the glomerulus, cochlea, lung, lens capsule, and Bruch and Descemet membranes in the eye contain alpha-3 (IV), alpha-4 (IV), and alpha-5 (IV) chains, in addition to alpha-1 (IV) and alpha-2 (IV) chains.
- The alpha-6 (IV) chains are present in epidermal basement membranes.

Dominic Cosgrovea and Shiguang Liu; Collagen IV diseases: A focus on the glomerular basement membrane in Alport syndrome, Matrix Biol. (2017) 57–58, 45–54

Mutations

Alport syndrome, which is genetically heterogeneous, is caused by defects in the genes encoding alpha-3, alpha-4, or alpha-5 chains of type IV collagen of the basement membranes.

<u>The following 3 genetic forms of Alport syndrome exist:</u>

- XLAS - Results from mutations in the COL4**A5** gene; accounts for 85% of cases of Alport syndrome
- Autosomal recessive Alport syndrome (ARAS) - Caused by mutations in either the COL4**A3** or COL4**A4** gene; responsible for approximately 10-15% of cases
- Autosomal dominant Alport syndrome (ADAS) - Rare; caused by mutations in either the COL4**A3** or COL4**A4** gene in at least some families and accounts for the remainder of cases.

More than 300 mutations have been reported In the COL4A5 genes from families with XLAS.

Mutation-induced GBM changes

- In the early developmental period of the kidney, alpha-1 (IV) and alpha-2 (IV) chains predominate in the GBM.
- With glomerular maturation, alpha-3 (IV), alpha-4 (IV), and alpha-5 (IV) chains become preponderant through a process called **isotype switching**. Evidence shows that alpha-3 (IV), alpha-4 (IV), and alpha-5 (IV) chains combine to form a unique collagen network.
- Abnormality of any of these chains, as observed in patients with Alport syndrome, limits formation of the collagen network and prevents incorporation of the other collagen chains.

Mutation-induced GBM changes

- Evidence has demonstrated that isoform switching of type IV collagen becomes developmentally arrested in patients with AS. This leads to retention of the fetal distribution of alpha-1 (IV) and alpha-2 (IV) isoforms and the absence of alpha-3 (IV), alpha-4 (IV), and alpha-5 (IV) isoforms.
- The cysteine-rich alpha-3 (IV), alpha-4 (IV), and alpha-5 (IV) chains are thought to enhance the resistance of GBM to proteolytic degradation at the site of glomerular filtration; thus, anomalous persistence of alpha-1 (IV) and alpha-2 (IV) isoforms confers an unexpected increase in the susceptibility of GBM to proteolytic enzymes, leading to basement membrane splitting and damage.

THE ROLE OF A SPONGY ALPORT-GBM FOR THERAPY

The GBM in most AS patients consists of α1/α2 (iv) chains only, making this altered GBM more porous and more susceptible to endoproteolysis. The GBM in AS patients is thought to be more vulnerable by increased (or even normal) filtration pressure. Therefore, thickening and splitting of the GBM in AS in part is a stress response of the podocytes.

Any medication reducing the mechanical stress on the podocyte, such as RAAS blockade, reduces the risk of GBM ruptures and focal segmental glomerulosclerosis, which is a common light microscopical glomerular feature in AS.

MANAGEMENT

- There is no specific treatment for Alport syndrome currently available.
- The use of angiotensin antagonists or cyclosporine has been described in uncontrolled studies on human patients.
- In patients who develop end-stage renal disease, transplantation is the preferred modality for renal replacement therapy.

Kashtan CE, Ding J, Gregory M, et al. Clinical practice recommendations for the treatment of Alport syndrome: a statement of the Alport Syndrome Research Collaborative. Pediatr Nephrol 2013; 28:5.

The Clinical Practice Recommendations for the Treatment of Alport Syndrome

- Annual monitoring for microalbuminuria and proteinuria as soon as the diagnosis of Alport syndrome is made or beginning at one year of age for at-risk children.
- Angiotensin blockade therapy
- Supportive measures are initiated to prevent and treat complications of chronic kidney disease as they develop.
- Renal transplantation is the preferred option over dialysis for patients who develop ESRD. However, there is a small, but not insignificant risk of developing anti-GBM antibody disease.

1- Kashtan CE, Ding J, Gregory M, et al. Clinical practice recommendations for the treatment of Alport syndrome: a statement of the Alport Syndrome Research Collaborative. Pediatr Nephrol 2013; 28:5.

2- Up To Date,2018

Angiotensin blockade

- Angiotensin blockade with an ACE inhibitor (eg, enalapril, lisinopril, ramipril) or an angiotensin receptor blocker (ARB; eg, losartan) is recommended in patients with Alport syndrome.
- It is also reasonable to consider angiotensin blockade therapy in those patients who have microalbuminuria, but who have not yet developed overt proteinuria.

Angiotensin blockade

- In a study of patients followed by the European Alport Registry for a mean duration of over 20 years, retrospective analysis found that initiation of angiotensin-converting enzyme inhibitors delayed dialysis in patients with proteinuria and normal renal function compared with those who never received such therapy or who received treatment only when they developed impaired renal function .

Gross O, et al. Early angiotensin-converting enzyme inhibition in Alport syndrome delays renal failure and improves life expectancy. Kidney Int 2012; 81:494.

Stock J, et al. Prospective study on the potential of RAAS blockade to halt renal disease in Alport syndrome patients with heterozygous mutations. Pediatr Nephrol 2017; 32:131.

Cyclosporine

- Data are inconclusive regarding the benefit of cyclosporine to improve renal survival, and cyclosporin is associated with nephrotoxicity.
- Cyclosporin A (CsA) can reduce massive proteinuria in patients with Alport syndrome. However, recent data do not support the use of CsA therapy for proteinuric patients
- As a result until further data demonstrate benefit from cyclosporine therapy, we do not suggest that this agent be used in patients with Alport syndrome to slow the progression of renal disease.

Massella L,et al (2010) Cyclosporine a treatment in patients with Alport syndrome: a single-center experience.

Pediatr Nephrol 25:1269–1275

Callís L, et al,(1999) Long-term effects of cyclosporine A in Alport's syndrome. Kidney Int 55:1051–1056

Renal transplantation

- Patients with Alport syndrome typically have excellent renal transplant outcomes.
- Recurrent disease does not occur in the transplanted graft because the donor kidney has a normal glomerular basement membrane (GBM).
- However, anti-glomerular basement membrane antibody disease (anti-GBM antibody disease) occurs in approximately 3 percent of affected males who receive transplants.

Future treatments

- There is no specific treatment for Alport syndrome currently available.
- Progress in basic research is raising hopes of defining new targets for the treatment of Alport syndrome.
- Many potential treatment approaches in Alport syndrome have been revealed by animal models.

Future treatment approaches in Alport syndrome

1-Stem cell therapy:

Bone marrow stem cells

Amniotic fluid stem cells

Mesenchymal stem cells

2-Gene therapy

3-Anti-inflammatory therapy:

- DDR1 inhibitors
- EGFR inhibitors
- Integrin inhibitors
- Endothelin receptor antagonists
- Anti-miR-21

ZhangY, Ding J, Renal, auricular, and ocular outcomes of Alport syndrome and their current management, Pediatr Nephrol (2018) 33:1309–1316

Promising New Therapeutics –Ready for Prime-Time Players

- There are at least three companies with publicized interests in pursuing clinical trials in AS patients using different approaches.
- Although this is welcome news for the AS patient community, this could lead to concerns about whether there are enough well-characterized patients to fill the cohorts that will be needed for large-scale studies and whether participation in one trial prohibits participation in another trial.

Omachi K, and Miner JH, Alport Syndrome Therapeutics: Ready for Prime-Time Players, Trends in Pharmacological Sciences, Month 2019, Vol. xx, No. xx

Promising New Therapeutics –Ready for Prime Time Players

- The involvement of patient-founded organizations, such as the Alport Syndrome Foundation, Alport UK, and others, that advocate for patient education, will be critical for successfully carrying out clinical trials.
- There is agreement among clinicians that patients already receiving standard of care therapy (taking an ACEi or an ARB) should continue to do so upon enrollment in a trial due to the demonstrated benefits.

1-Anti–micro RNA-21(RG-012®)

By

Anti–micro RNA-21 Oligonucleotides

Introduction:

- MicroRNAs (miRNAs) represent distinct small noncoding RNAs that function as important posttranscriptional regulators of gene expression.
- A single miRNA can silence the expression of a number of functionally related genes, and therefore, miRNA can function in an analogous but reciprocal way to transcription factors.
- Several independent studies in human and animal models of kidney disease suggest a number of miRNAs are regulated in response to acute injury and remain dysregulated in chronic disease settings, contributing to the pathogenesis of kidney disease.

Guo J et Al: Dysregulated Expression of microRNA-21 and Disease-Related Genes in Human Patients and in a Mouse Model of Alport Syndrome, Hum Gene Ther. 2019 Jul;30(7):865-881

micro RNA-21

One such miRNA is miR-21, which is thought to be involved in regulating tissue repair responses after injury.

- Investigations have shown that miR-21 is widely expressed in multiple cell types in the kidney and is upregulated in multiple acute and chronic kidney diseases (CKDs).
- MicroRNA-21 (miR-21) contributes to the pathogenesis of fibrogenic diseases in multiple organs, including the kidneys, potentially by silencing metabolic pathways that are critical for cellular ATP generation, ROS(reactive chemical species containing oxygen) production, and inflammatory signaling.

Anti-micro RNA-21

- Advances in the development of oligonucleotide chemistry have allowed for development of engineered oligonucleotides directed against specific miRNAs that can be administered s.c., taken up freely into cells, bind specifically to individual miRNAs by sequence complementarity, and block the specific miRNA function . Therefore, unlike transcription factors, individual miRNAs are readily targetable with oligonucleotides in both animals and humans.

The Journal of Clinical Investigation RESEARCH ARTICLE

Anti–microRNA-21 oligonucleotides prevent Alport nephropathy progression by stimulating metabolic pathways

Ivan G. Gomez,[1] Deidre A. MacKenna,[2] Bryce G. Johnson,[1] Vivek Kaimal,[2] Allie M. Roach,[1] Shuyu Ren,[1] Naoki Nakagawa,[1] Cuiyan Xin,[1] Rick Newitt,[1] Shweta Pandya,[2] Tai-He Xia,[3] Xueqing Liu,[2] Dorin-Bogdan Borza,[4] Monica Grafals,[5] Stuart J. Shankland,[1] Jonathan Himmelfarb,[1] Didier Portilla,[6] Shiguang Liu,[3] B. Nelson Chau,[2] and Jeremy S. Duffield[1]

[1]Division of Nephrology and Institute for Stem Cell and Regenerative Medicine, Departments of Medicine and Pathology, University of Washington, Seattle, Washington, USA. [2]Regulus Therapeutics Inc., San Diego, California, USA. [3]Genzyme R&D, a Sanofi company, Cambridge, Massachusetts, USA. [4]Meharry Medical College, Nashville, Tennessee, USA. [5]Georgetown University, Washington, DC, USA. [6]University of Virginia, Charlottesville, Virginia, USA.

Dr Gomez and his Co-workers developed highly specific oligonucleotides that distribute to the kidney and inhibit miR-21 function when administered subcutaneously and evaluated the therapeutic potential of these anti–miR-21 oligonucleotides in chronic kidney disease. In a murine model of Alport nephropathy, miR-21 silencing did not produce any adverse effects and resulted in substantially milder kidney disease, with minimal albuminuria and dysfunction, compared with vehicle-treated mice. miR-21 silencing dramatically improved survival of Alport mice and reduced histological end points, including glomerulosclerosis, interstitial fibrosis, tubular injury, and inflammation.

- The studies described herein show clearly that inhibition of miR- 21 by anti–miR-21 oligonucleotides administered s.c. improved kidney function, improved disease pathology, and increased the median life span of mice that had a relentlessly progressive kidney disease by more than 40 percent.
- As markers of this improved function, anti–miR-21 reduces blood BUN and albuminuria and preserves the secretion of uremic toxins, including IS, by the kidney tubule.
- **As such, anti–miR-21 represents an approach for new therapeutics to treat human Alport nephropathy patients** and potentially to treat patients with other forms of CKD. The mouse model of Alport nephropathy has been used successfully for the preclinical development of other therapies in clinical practice or currently in clinical trials.

Gomez, I.G. et al. (2015) Anti-microRNA-21 oligonucleotides prevent Alport nephropathy progression by stimulating metabolic pathways. J. Clin. Invest. 125, 141–156

- Regulus Therapeutics Inc. is a biopharmaceutical company leading the discovery and development of innovative medicines targeting microRNAs.
- Regulus Initiated Phase I Clinical Study of RG-012, a microRNA for the Treatment of Alport Syndrome.
- RG-012 is being developed by Regulus in a strategic alliance with Genzyme, and Sanofi company, for the treatment of Alport syndrome.
- The Phase I clinical study is being conducted in the United States as a randomized, double-blind, placebo-controlled, to evaluate the safety, tolerability and pharmacokinetics of subcutaneous dosing of RG-012 in healthy volunteers.

REGULUS
THERAPEUTICS™

Anti-miR-21

Based on promising studies in a mouse model of AS showing that antibodies to the profibrotic miR-21 slows kidney disease progression and extends lifespan by stimulating metabolic pathways , Regulus Therapeutics began recruiting AS patients for a clinical trial of its anti-miR-21 therapeutic RG-012 by performing an observational natural history study of AS (ATHENA; clinical trial number: NCT02136862).

Regulus had planned to complete a Phase II, randomized, double-blind, placebo-controlled study in 40 patients over a 48-week period, (clinical trial number: NCT02855268).

The company has since transitioned

development responsibilities of

RG-012 to Genzyme, a Sanofi company.

Omachi K, et al, Alport Syndrome Therapeutics: Ready for Prime-Time Players; Trends in Pharmacological Sciences, Month 2019, Vol. xx, No. xx

2-Bardoxolone Methyl

By

Bardoxolone Methyl

- Bardoxolone methyl is an experimental and orally-bioavailable semi-synthetic triterpenoid.
- Triterpenoids are a large family of compounds synthesized in some plants, such as the chrysanthemum flower(گل داودی) , that have been used in traditional Asian medicine for disease management.
- Naturally occurring triterpenoids like oleanolic acid (OA) have only weak anti-inflammatory and anticarcinogenic activities.
- To increase their usefulness, a series of novel derivatives of oleanolic acid have been synthesized.

Bardoxolone Methyl

- The synthetic triterpenoids, such as CDDO methyl (Bardoxolone methyl) ester are compounds originally developed for the prevention and treatment of inflammation and cancer.
- These synthetic triterpenoids are potent inhibitors of synthesis of inflammatory enzymes. As a noncytotoxic and multifunctional drug, CDDO-Me has applications for the prevention and treatment of not only cancer, but also of many other diseases with an inflammatory component.

Wang YY et al, Bardoxolone methyl (CDDO-Me) as a therapeutic agent, Drug Design, Development and Therapy 2014:8 2075–2088

Bardoxolone

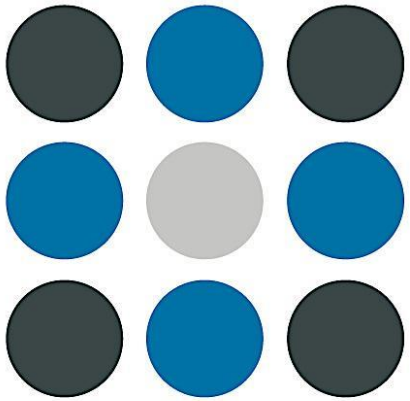
- Bardoxolone is an experimental, oral, once-daily activator of Nrf2, a transcription factor that induces molecular pathways that promote restoration of mitochondrial function, reduction of oxidative stress, and inhibition of pro-inflammatory signaling. In addition, bardoxolone methyl has been proven to increase estimated GFR (eGFR) in patients with type II diabetes and CKD*.
- **The FDA has granted orphan drug designation to bardoxolone for the treatment of Alport syndrome**, ADPKD, and pulmonary arterial hypertension.
- **The European Commission has granted orphan drug designation to bardoxolone for the treatment of Alport syndrome**. Bardoxolone is currently being studied in CARDINAL, a Phase 3 study for the treatment of Alport syndrome.

Wang YY et al, Bardoxolone methyl (CDDO-Me) as a therapeutic agent, Drug Design, Development and Therapy 2014:8 2075–2088

Bardoxolone Methyl

- Reata Pharmaceuticals is investigating bardoxolone methyl for the treatment of AS. This drug inhibits nuclear factor (NF)- κB, which promotes inflammation, and induces nuclear factor erythroid 2-related factor 2 (Nrf2), which activates expression of antioxidants and helps restore mitochondrial function; both of these activities could theoretically be beneficial for AS patients.
- In addition, bardoxolone methyl has been proven to increase estimated GFR (eGFR) in patients with type II diabetes and CKD.

Pergola, P.E. et al. (2011) Bardoxolone methyl and kidney function in CKD with type 2 diabetes. N. Engl. J. Med. 365, 327–336



REATA™

PHARMACEUTICALS

Reata has initiated the CARDINAL trial, a multicenter Phase II/III study (clinical trial number: NCT03019185); **Phase II** is open-label treatment of 30 patients for 12 weeks to look for changes in baseline eGFR. **Phase III** is double-blind, randomized, placebo-controlled for up to 180 patients for 48 weeks, followed by withdrawal for 4 weeks and restart of treatment at week 52, continuing through week 100.

Bardoxolone Methyl

- Despite good reasons for treating AS patients with bardoxolone methyl, the idea has generated controversy among some nephrologists because of safety concerns.
- Although bardoxolone methyl did increase eGFR, this could be accompanied by hyperfiltration and glomerular hypertension, which would likely be injurious to the potentially fragile GBMs.
- Treatment also increased urinary albumin: creatinine ratios, something unwanted in patients with kidney disease due to toxicity of filtered albumin (demonstrated in an AS mouse model) and associated with accelerated decline of GFR.
- In addition, there were cardiovascular complications in a follow up study.
- The results of the CARDINAL trial are eagerly awaited.

Baigent C et al: Should We Increase GFR with Bardoxolone in Alport Syndrome?, J Am Soc Nephrol 29: 357–359, 2018

3- Sparsentan (RE-021®)

By

Retrophin®

Sparsentan

- Sparsentan is a dual acting drug that is being investigated by Retrophin for treating several kidney diseases.
- Sparsentan blocks endothelin-1 activation of the endothelin receptor type A .
- Endothelin A receptor activation on mesangial cells initiates Alport glomerular disease
- Sparsentan is also an ARB, so it inhibits both endothelin-1 signaling and the RAS.

Dufek, B. et al. (2016) Endothelin A receptor activation on mesangial cells initiates Alport glomerular disease. Kidney Int. 90, 300–310

Endothelin A receptor antagonists for treatment of AS

- Like angiotensin II, endothelin-1 is a bioactive peptide that increases blood pressure.
- In a mouse model of AS showed that blocking the ETRA (endothelin A receptor antagonist) with sitaxentan delays the onset of proteinuria and reduces GBM abnormalities, but without impacting blood pressure .
- Thus endothelin A receptor activation on mesangial cells is a key event in initiation of Alport glomerular disease in this model.
- This study showed that the source of increased endothelin-1 is the glomerular endothelial cell, and its receptor was increased in the neighboring mesangial cells, which are smooth muscle-like cells that maintain the structure of the glomerular tuft and can change the diameter of glomerular capillaries by contraction and relaxation.

Dufek B, et al, Endothelin A receptor activation on mesangial cells initiates Alport glomerular disease, Kidney Int. 2016; 90(2): 300–310

Endothelin A receptor antagonists for treatment of AS

These findings reinforce the importance of intercellular crosstalk among resident glomerular cells in driving the progression of AS and support proceeding with studies of sparsentan in AS to block both the ETRA and RAS, which could be more efficacious than RAS inhibition alone.

Dufek B, et al,Endothelin A receptor activation on mesangial cells initiates Alport glomerular disease, Kidney Int. 2016; 90(2): 300–310

Mechanism of Action

- Sparsentan, which possesses two clinically validated mechanisms of action in a single molecule, works by selectively blocking the action of two potent vasoconstrictor and mitogenic agents, angiotensin II (AII) and endothelin 1 (ET1), at their respective receptors.
- As such, Sparsentan combines the properties of an angiotensin receptor blocker (ARB) and an endothelin receptor antagonist (ERA) in the same molecule.

Sparsentan

- In a preclinical study of a mouse model of AS, sparsentan was reported by Cosgrove and colleagues in a 2018 meeting abstracts (FR-PO995) to slow the progression of glomerular and tubulointerstitial disease without affecting blood pressure.
- It is hoped that sparsentan will be a therapeutic option for AS and perhaps for other kidney diseases.
- In this regard, Retrophin sponsored the Phase II DUET study (clinical trial number: NCT01613118) of sparsentan (RE-021) versus irbesartan (an ARB only) for treatment of FSGS in 96 patients.

Trachtman, H. et al. (2018) DUET: a phase 2 study evaluating the efficacy and safety of sparsentan in patients with FSGS. J. Am. Soc. Nephrol. 29, 2745–2754

Retrophin®

- Retrophin is a biopharmaceutical company focused on developing on sparsentan.
- Sparsentan is an investigational product candidate in **Phase 3** clinical development that has a dual mechanism of action combining angiotensin receptor blockade with endothelin receptor type A blockade.
- Retrophin is developing sparsentan for the treatment of FSGS, as well as for IgA nephropathy (IgAN), kidney disorders that also often lead to ESRD. In several forms of chronic kidney disease, such as FSGS and IgAN, endothelin receptor blockade has been shown to have an additive beneficial effect on proteinuria in combination with renin-angiotensin blockade via angiotensin receptor blockade or angiotensin converting enzyme inhibitors.
- Sparsentan has been granted orphan drug designation for the treatment of FSGS by the FDA and European Commission.

- The Phase 2 DUET Study of sparsentan in FSGS met its primary efficacy endpoint for the combined treatment group, demonstrating a greater than two-fold reduction in proteinuria compared to irbesartan after the eight-week, double-blind treatment period.
- Irbesartan (Angiotensin II Receptor Blocker) is part of a class of drugs used to manage FSGS and IgAN in the absence of an approved pharmacologic treatment.
- Retrophin is currently enrolling the pivotal Phase 3 DUPLEX Study of sparsentan for the treatment of FSGS , as well as the pivotal Phase 3 PROTECT Study of sparsentan for the treatment of IgAN . Both studies contain 36-week proteinuria-based endpoints.

Sparsentan

Sparsentan reduced proteinuria more than irbesartan during the 8-week treatment period, showing the efficacy of ETRA antagonism over and above ARB.

Recruitment for a Phase III randomized, double-blind study of sparsentan versus irbesartan in 300 FSGS patients (DUPLEX; clinical trial number: NCT03493685) is in progress. Furthermore, a similar trial of sparsentan versus irbesartan in patients with immunoglobulin A nephropathy is also in the recruiting phase (clinical trial number: NCT03762850).

PERSPECTIVE CURRENT AND FUTURE THERAPY

Yesterday, in the textbooks the course of AS was described as ‘inevitable’ for the past 90 years after the first description by Alport.

PERSPECTIVE CURRENT AND FUTURE THERAPY

Today, RAAS blockade has changed the ‘inevitable’ course of AS to a treatable disease and led to treatment recommendations .

Additional therapies that are currently used in humans and that might influence the course of AS. There is preliminary scientific evidence for effectiveness in animal models.

However, the long-term effects of these therapies still need to be evaluated in humans with AS. These therapies might well be additive to RAAS blockade and might further delay renal failure by years.

Some medications are already board-approved for other indications; therefore, international Alport registries hopefully will generate the evidence for patients with AS

PERSPECTIVE CURRENT AND FUTURE THERAPY

Tomorrow, several promising new therapies, all with different targets additive to existing therapies. This revives hope that AS has not only become a treatable disease, but end-stage renal failure can be prevented in most patients by multimodal therapy.

Gross O, et al, Nephrol Dial Transplant (2014) 29: iv124–iv130


Thank You