Rare Diseases in Nephrology: Challenges in Diagnosis and Treatment

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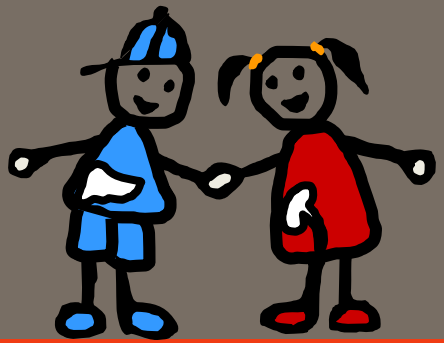
Center for Rare Kidney Diseases



MHH
Medizinische Hochschule Hannover

4th GCC Organ Transplantation & Nephrology Congress
Kuwait, 25 January 2025

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Speaker fees/consultancy

- Advicenne, Biologix, Chiesi, Kyowa Kirin, Medison Pharma, Recordati Rare Diseases, and Ultragenyx

Rare kidney diseases

- In the EU, a rare disease is one that affects no more than 1 person in 2000.
- Over 6000 distinct rare diseasers are known.

- 512 Million people living in the EU including
  - 36 Million with rare diseases
  - 2 Million affected by rare kidney conditions
  - **300.000 children with rare kidney diseases**

  => significant disease burden and risk for kidney failure

https://research-and-innovation.ec.europa.eu/research-area/health/rare-diseases_en

Disease / Mechanism specific drugs

- Biologicals including monoclonal antibodies (mABs)
- Small compounds with novel actions

  e.g. selective complement inhibitors
- Gene therapies
- siRNA*: gene expression ⇩

* Small interfering RNA = silencing RNA

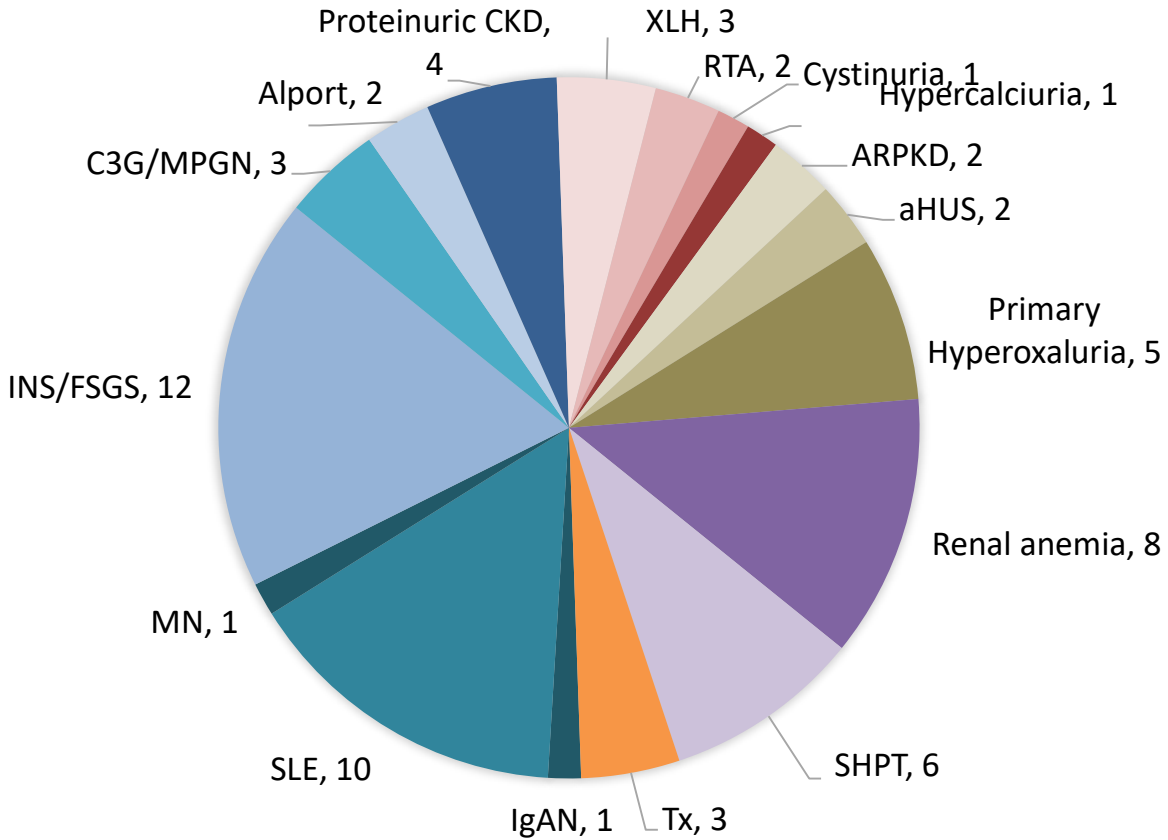
Novel Drug Therapies Under Development

clinicaltrials.gov search 07/2024:
Currently active drug studies on kidney diseases including children

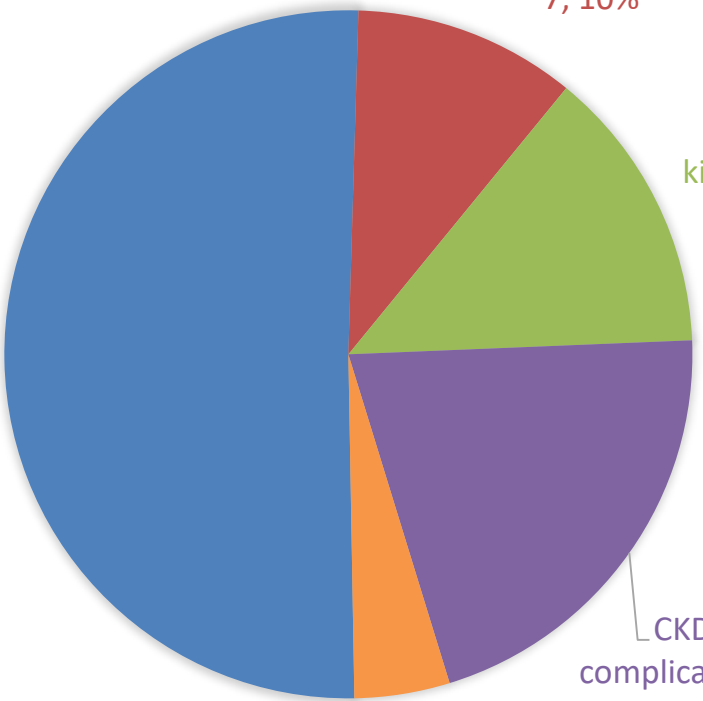
67 trials identified

60% children inclusive

4 Phase 1
16 Phase 2
3 Phase 2/3
39 Phase 3
5 Phase 4



Novel Drug Therapies Under Development



2 **Burosumab**
3 ADV-7103

2 **Lumasiran**
2 **Nedosiran**
2 **Tolvaptan**
2 **Crovalimab**

9 **Rituximab**
4 **Obinutuzumab**
2 **Sparsentan**
2 **Finerenone**
2 **Pegcetacoplan**
1 **Iptacopan**
2 **Voclosporin**

1 **Daprodustat**
4 Ferric citrate
1 Ferumoxitol
1 Lactoferrin
1 Etelcalcetide

New Opportunities in Rare Kidney Diseases

Idiopathic nephrotic syndrome,
Glomerulopathies Alport syndrome
IgA nephritis; C3 glomerulopathy

Tubulopathies

Thrombotic microangiopathies
Atypical hemolytic uremic syndrome

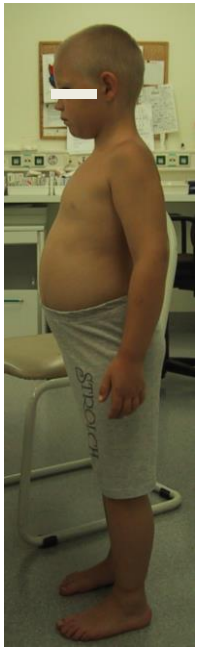
Primary hyperoxaluria
Metabolic nephropathies
(Nephropathic cystinosis)

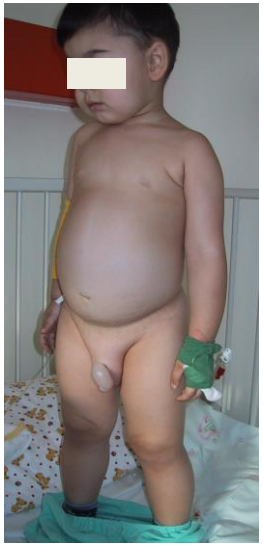
Renal or urinary tract malformations

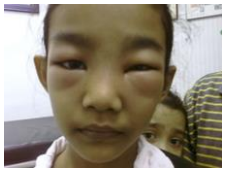
Familial cystic renal diseases

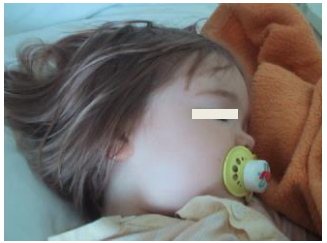
Non-disease-specific measures to slow down the progression of CKD: SGLT2i, Finerone

Idiopathic nephrotic syndrome in children

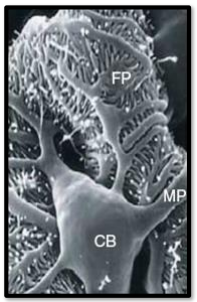


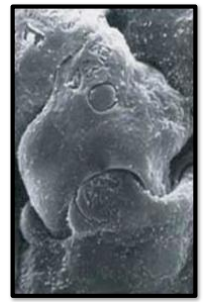




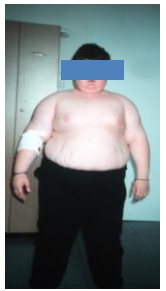


- The most frequent pediatric glomerular disease
- Incidence: 2.92 per 100,000 children per year globally
- 85-90% are steroid-sensitive (SSNS)
  - Minimal change disease
  - Foot process effacement
  - 70-80% at least one relapse
  - 50% show FRNS or SDNS



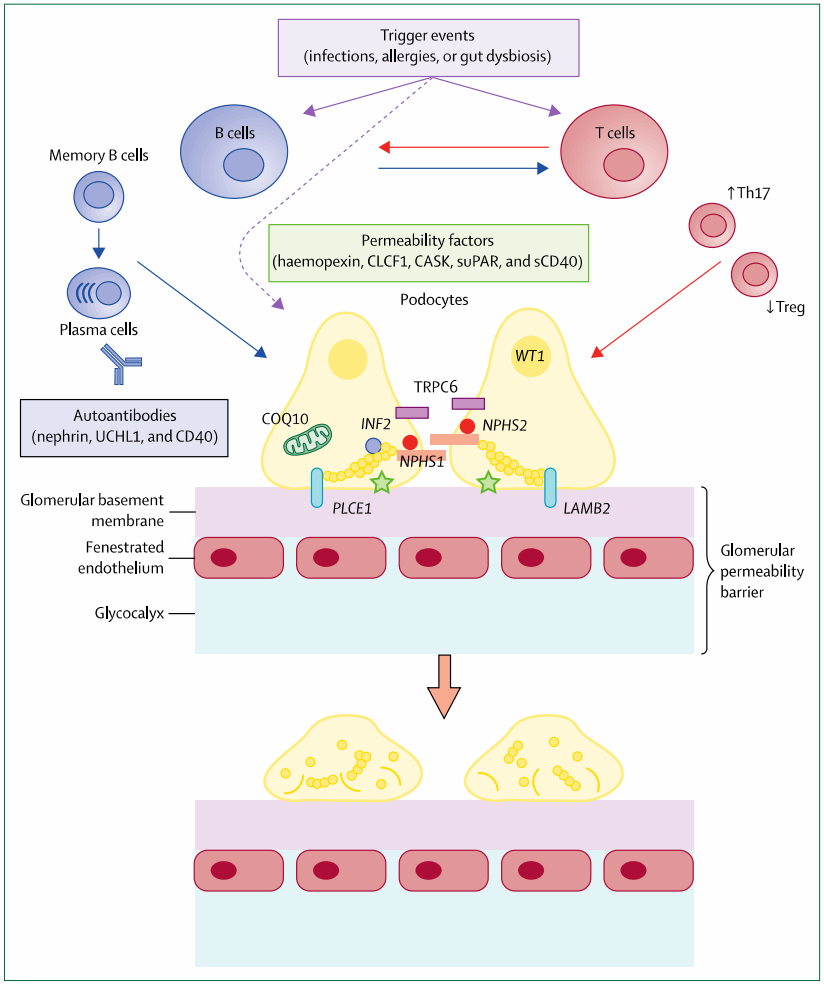


- 5-10% are steroid-resistant (SRNS)
  - FSGS, MCD, DMS, MN…
  - 30% have genetic forms
- Challenging treatment
  High treatment associated morbidity



Trautmann et al. Pediatr Nephrol 2023; Chan et al. Pediatr Nephrol 2024

Pathophysiology of nephrotic syndrome: Immune system vs. genetic



Vivarelli et al. Lancet 2023

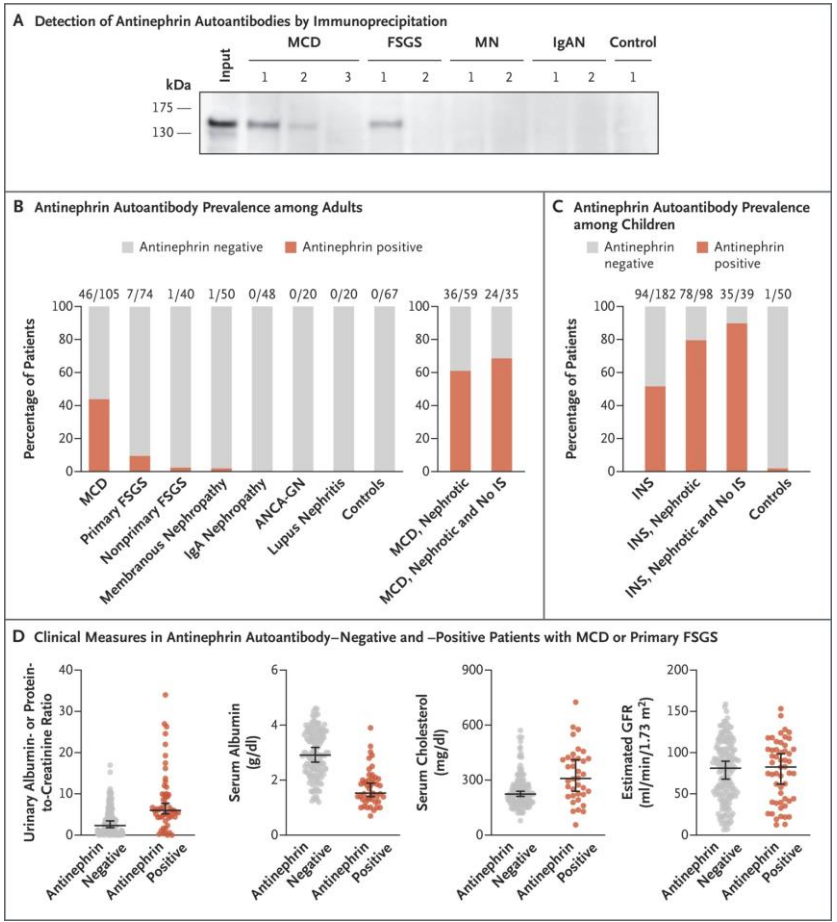
Prevalence of Antinephrin Autoantibodies in Patients with Proteinuric Glomerular Diseases and in Controls

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

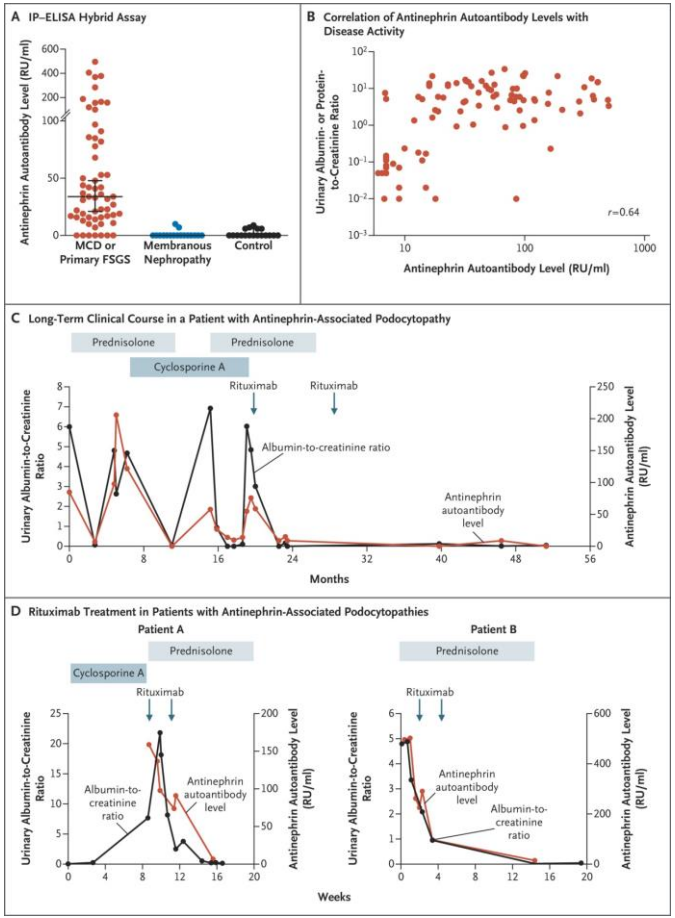
Autoantibodies Targeting Nephrin in Podocytopathies

F.E. Hengel, S. Dehde, M. Lassé, G. Zahner, L. Seifert, A. Schnarre, O. Kretz, F. Demir, H.O. Pinnschmidt, F. Grahammer, R. Lucas, L.M. Mehner, T. Zimmermann, A.M. Billing, J. Oh, A. Mitrotti, P. Pontrelli, H. Debiec, C. Dossier, M. Colucci, F. Emma, W.E. Smoyer, A. Weins, F. Schaefer, N. Alachkar, A. Diemert, J. Hogan, E. Hoxha, T. Wiech, M.M. Rinschen, P. Ronco, M. Vivarelli, L. Gesualdo, N.M. Tomas, and T.B. Huber, for the International Society of Glomerular Disease



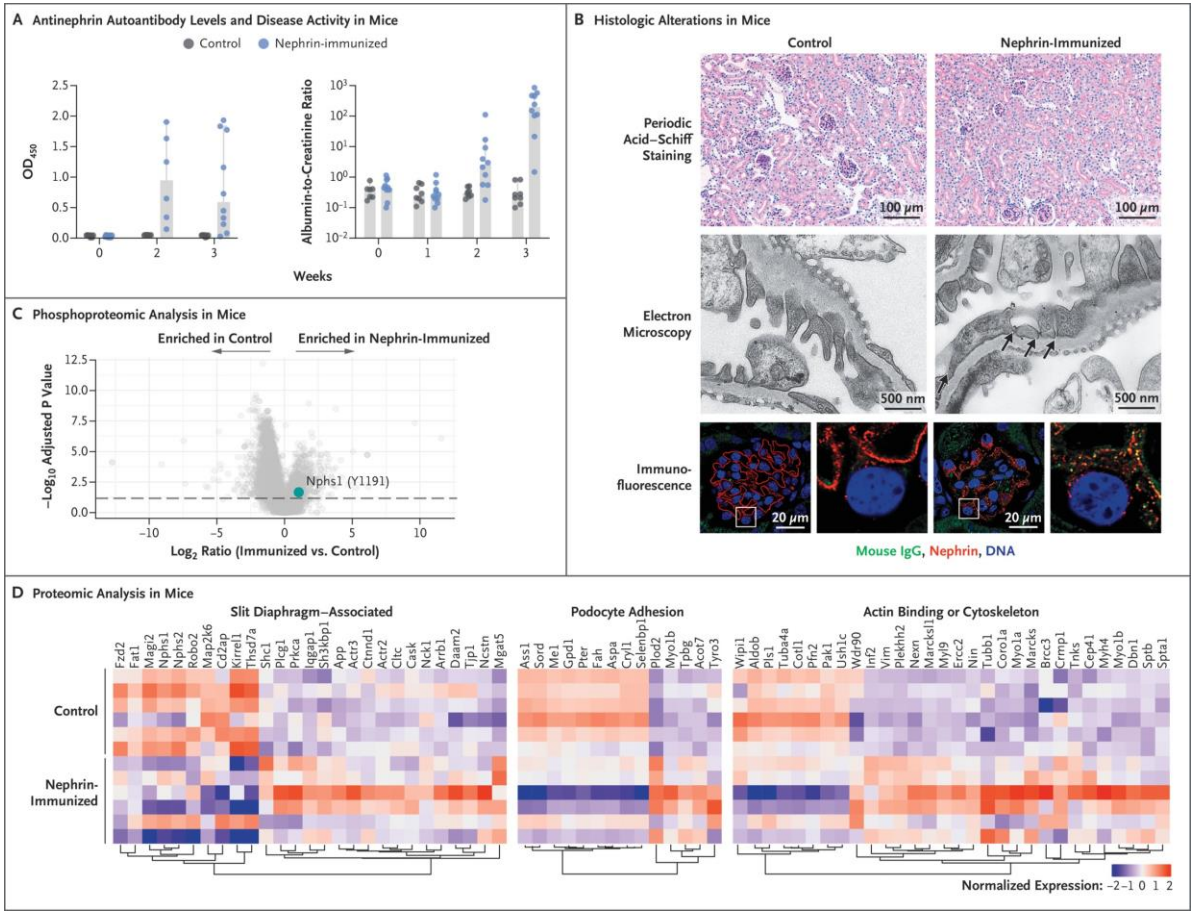
Hengel et al, N Engl J 2024

Quantitative Measurement of Antinephrin Autoantibodies



Hengel et al, N Engl J 2024

Induction of an MCD-like Phenotype and Rapid-Onset Nephrotic Syndrome in Mice



Foot process effacement

→ Mouse IgG at the slit diaphram

Nephrin endocytosis

Hengel et al, N Engl J 2024

Anti-slit diaphragm antibodies on kidney biopsy identify pediatric patients with steroid-resistant nephrotic syndrome responsive to second-line immunosuppressants.

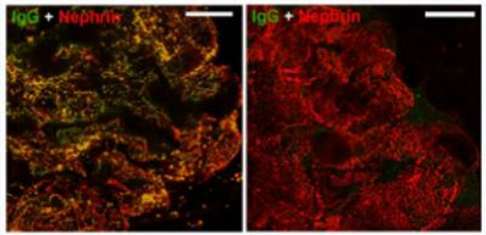
kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

High Resolution microscopy

n=128 Pediatric biopsies
- n=62 MC+FSGS
  - **30%** MC anti-slit +
  - **25%** FSGS anti-slit +
- n=66 Other → **0%** anti-slit +

n=40 Adult biopsies → n=40 MC+FSGS
- **68.4%** MC anti-slit +
- **19%** FSGS anti-slit +

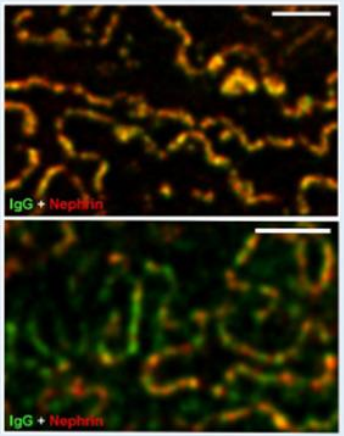


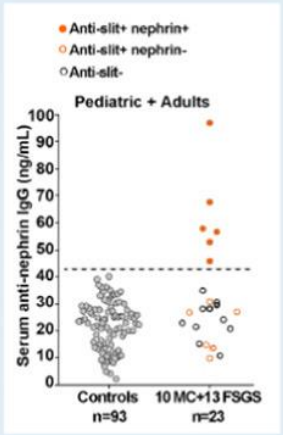
Anti-slit+ Anti-slit-

STED microscopy + ELISA

Pediatric patients
- **78%** anti-slit + anti-nephrin +
- **22%** anti-slit+ anti-nephrin -

Adult patients
- **55%** anti-slit + anti-nephrin +
- **45%** anti-slit+ anti-nephrin -

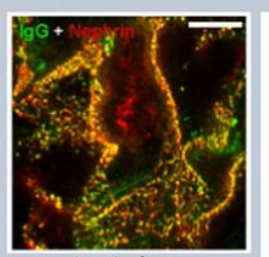




Sub-analysis in pediatric SRNS (n=45)

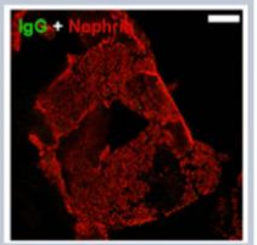
48.5% non-genetic anti-slit +
8.3% genetic anti-slit +

Non-genetic

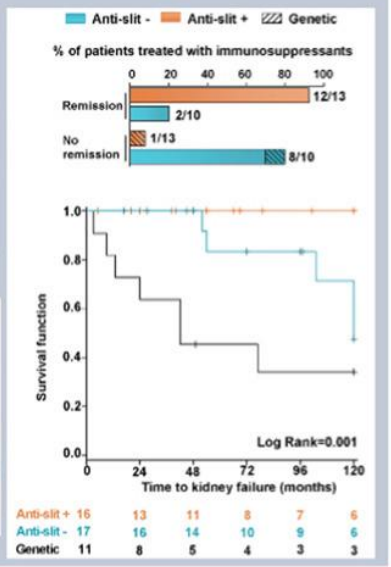


Anti-slit+

Genetic



Anti-slit-



Raglianti V et al, 2024

CONCLUSION

Detection of anti-slit antibodies represents a novel tool for personalized management, by allowing the identification of patients more likely to respond to immunosuppressants and have a better longterm prognosis, i.e. an autoimmune podocytopathy.

Future approach in children with „idiopathic nephrotic syndrome“?

1. IP-ELISA hybrid assay pos. = Nephrin autoantibody mediated NS

   => SSNS (MCD) => steroids; no response => second line therapies

   IP-ELISA hybrid assay neg. => give steroids a try or biopsy
2. SRNS & anti-slit antibody pos. => second line therapies (CNI, RTX)
3. Gene panel: Genetic NS => symptomatic treatment (RAASi)

Based on the results of Hengel et al. 2024 and Rglianti et al. 2024

SGLT2-inhibitors in children with CKD - Offical waivers by the EMA: „likely to be unsafe“ & „no benefit over existing treatments“

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/PDCO/800821/2018
London, 1 February 2019

Opinion of the Paediatric Committee on the granting of a product-specific waiver

EMEA-000828-PIP06-18

Scope of the application

Active substance(s):

Empagliflozin

1. Waiver

1.1. Condition:

Treatment of chronic kidney disease

The waiver applies to:

- all subsets of the paediatric population from birth to less than 18 years of age;
- film-coated tablet, oral use;
- on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments.

EMA/PDCO/529858/2018
London, 19 October 2018

Opinion of the Paediatric Committee on the granting of a product-specific waiver

EMEA-000694-PIP04-18

Scope of the application

Active substance(s):

Dapagliflozin

Invented name:

Forxiga

Condition(s):

Treatment of chronic kidney disease

to grant a product-specific waiver for all subsets of the paediatric population and the above mentioned condition in accordance with Article 11(1)(a) of said Regulation, on the grounds that the specific medicinal product is likely to be unsafe in part or all of the paediatric population and with Article 11(1)(c) of said Regulation, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

Nephrol Dial Transplant, 2024, 0, 1–3
https://doi.org/10.1093/ndt/gfae029
Advance access publication date: 2 February 2024

EDITORIAL

SGLT2 inhibitors: approved for adults and cats but not for children with CKD

Oliver Gross [1], Dieter Haffner [2], Franz Schaefer [3] and Lutz T. Weber [4]

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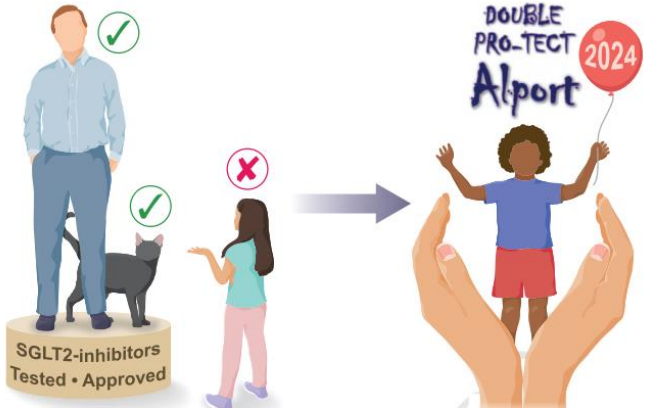
[2]Department of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany
[3]Division of Pediatric Nephrology, Center for Pediatrics and Adolescent Medicine, University of Heidelberg, Heidelberg, Germany
[4]Pediatric Nephrology, Children's and Adolescents' Hospital, University Hospital of Cologne, Faculty of Medicine, University of Cologne, Cologne, Germany
Correspondence to: Oliver Gross; E-mail: gross.oliver@med.uni-goettingen.de



GPN Gesellschaft für Pädiatrische Nephrologie

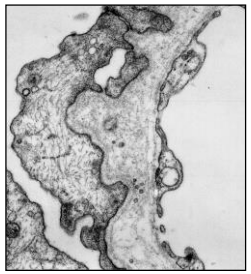
UNIVERSITÄTSMEDIZIN GÖTTINGEN UMG

DOUBLE PRO-TECT Alport

A confirmatory, multicenter, randomized, double-blind, placebo-controlled clinical trial to assess the effect of Dapagliflozin on the progression of CKD in adolescent and young adult patients with Alport syndrome

ClinicalTrials.gov Identifier: NCT05944016
EU Trial No. 2023-508502-18-00

recruiting



Funded by DFG Deutsche Forschungsgemeinschaft German Research Foundation

alport selbsthilfe

ALPORT SYNDROME FOUNDATION Hope | Action | Support

AIRG France Association pour l'Information et la Recherche sur les maladies Rénales Génétiques

alport uk

FEDERG

Prof. Dr. Oliver Gross
Nephrologie und Rheumatologie
Universitätsmedizin Göttingen
gross.oliver@med.uni-goettingen.de

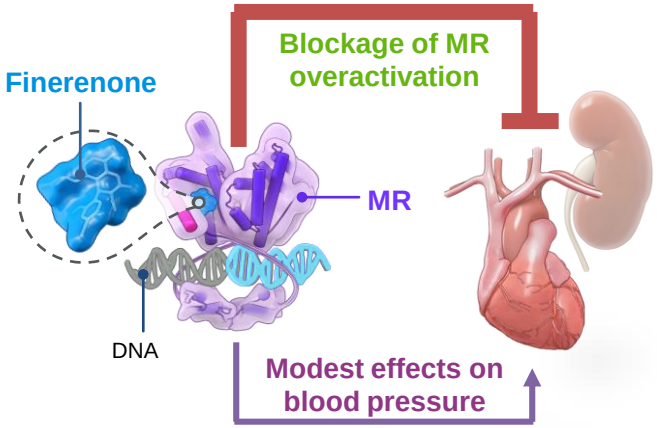
Finerenone: Selective Nonsteroidal Mineralcorticoid Receptor (MR) Antagonist

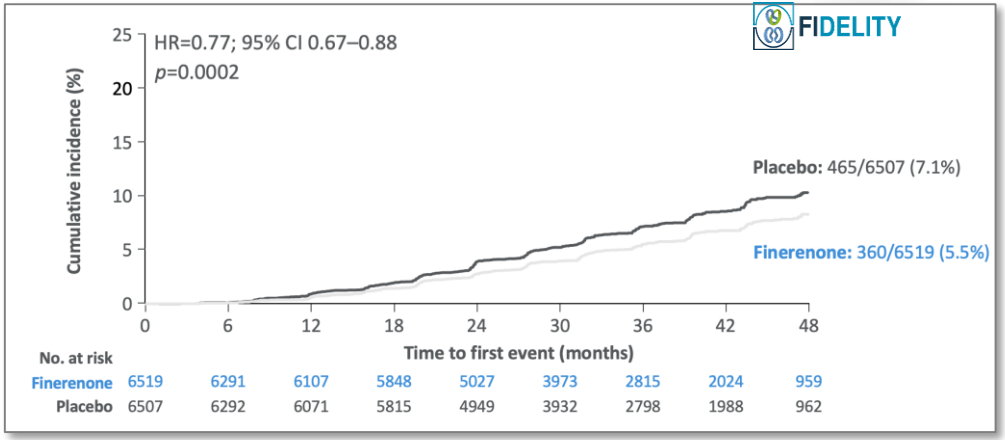
- Finerenone blocks mineralcorticoid receptor (MR) overactivation, which contributes to inflammation and fibrosis, leading to kidney and CV damage

✓ Unique binding mechanism and distribution *vs* steroidal MRAs => high potency and selectivity

✓ Trials in <u>adults</u> with diabetic nephropathy:
- eGFR Loss Endpoint reduced by 23%
- minimal effect on serum potassium

- Trials in adults with non-diabetic CKD underway





FIONA: Global RCT on Finerenone in children

- ✓ Age: 6 months - 18 years
- ✓ CKD stage 1-3
- ✓ uPCR > 0.5 g/g under maximum tolerable RASi, e.g. pts. with Alport syndrome

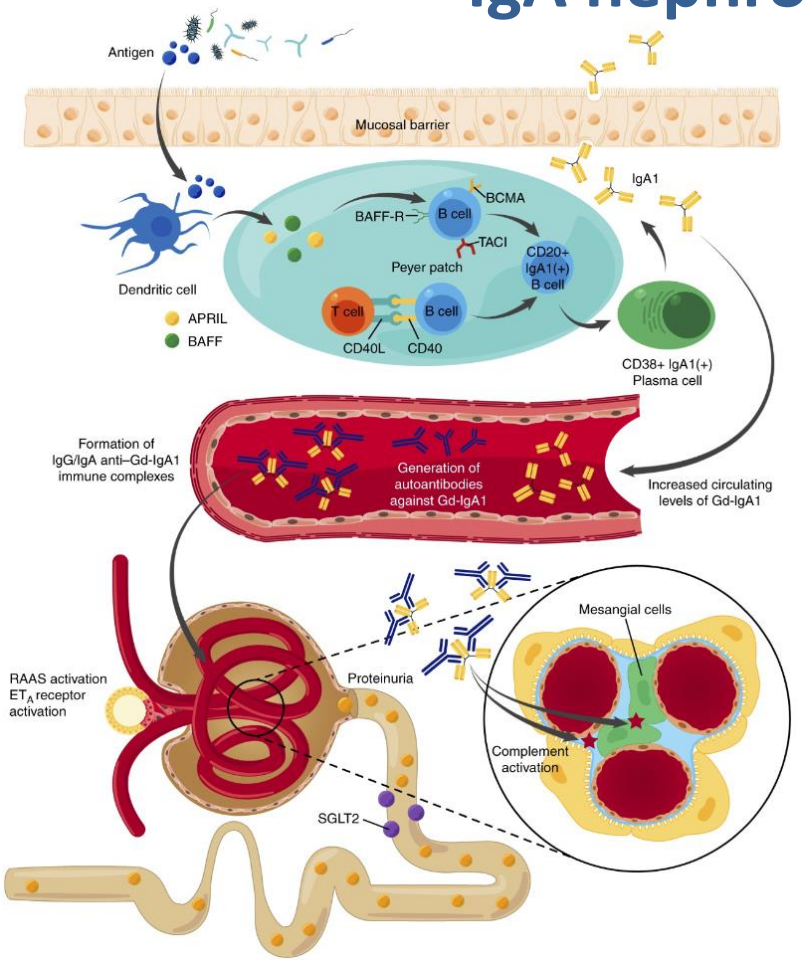
6 months Finerenone vs. Placebo (2:1 randomization)
Primary endpoint: proteinuria reduction after 6 months
18 months open-label extension

Objective: 219 randomized patients

>100 pediatric nephrology centers worldwide
Participation of many european centers
Recruiting started

FIONA

IgA nephropathy - 4 HIT model



- ✓ Antigens
- ✓ B cell priming to mucosa associated lymphoid tissues

HIT 1: Production of Galactose-deficient IgA1 from mucosal surfaces

HIT 2: Formation of autoantibodies against IgA1

HIT 3: Formation of circulating IgG-Gd-IgA1 immune complexes

HIT 4: RAAS activation
Endothelin A receptor activation
Deposition of immune complexes in the kidneys
=> multiple therapeutic options

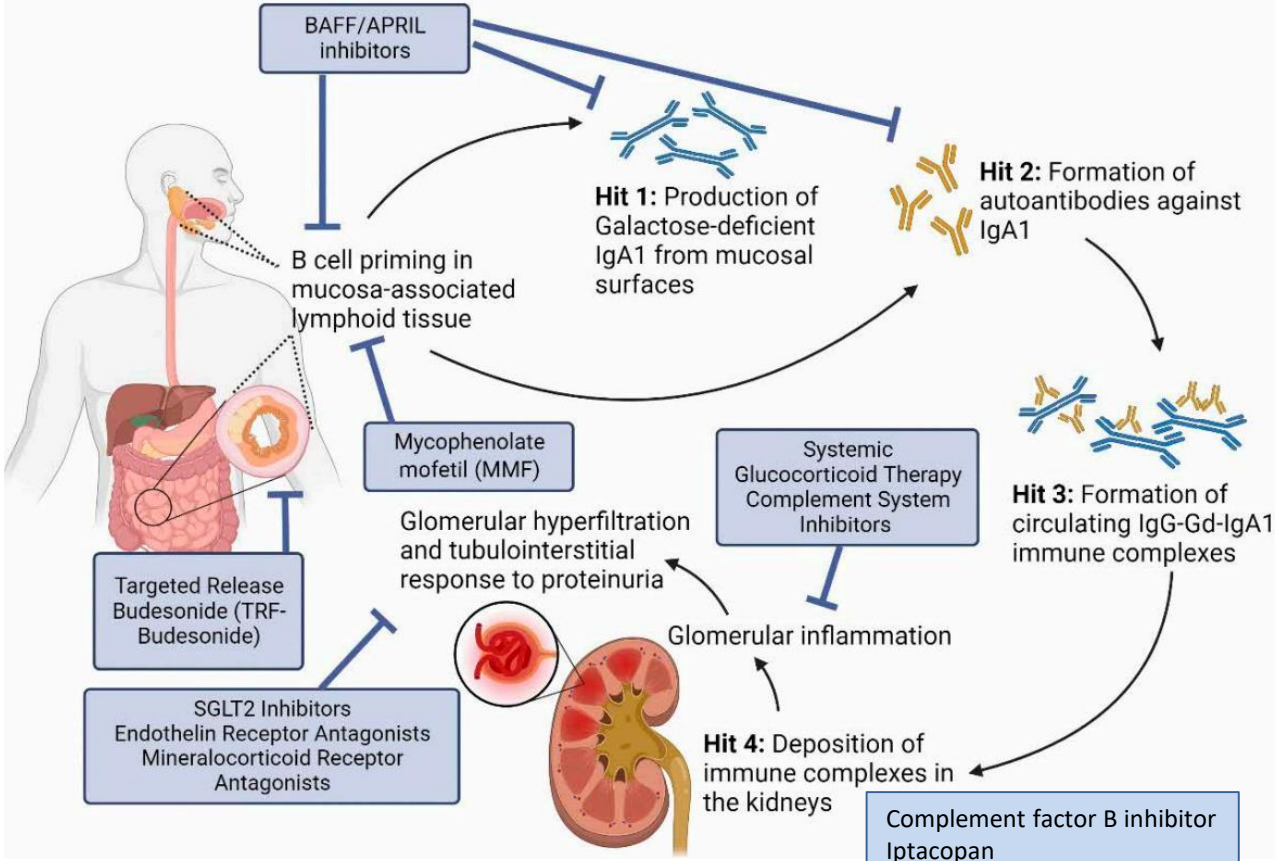
El Karoui K et al. J Am Soc Nephrol. 2024 Jan 1;35(1):103-116.
Huang X, et al. Front Pharmacol. 2021 Aug 23;12:715253.
Gesualdo L et al. Semin Immunopathol. 2021 Oct;43(5):657-66

Annual eGFR-loss in recent IgAN trials in adults

	Trial	Control Arm	Annual eGFR loss [ml/min]	Reference
	STOP-IgAN (Steroids)	Supportive therapy	-1.5	Rauen, NEJM 2015
	TESTING (Steroids)	Placebo	-5.0	Lv, JAMA 2022
✓EMA	PROTECT (Sparsentan - ETAR-B + ARB)	Irbesartan 300 mg	-3.8	Rovin, Lancet 2023
✓EMA	NEFIGARD (Nefecon - Budenosid)	Placebo	-6.0	Lafayette, Lancet 2023
✓EMA	DAPA-CKD (Dapagliflozin - SGLT2i)	Placebo	-4.7	Wheeler, Kidney Int 2021
✓FDA EMA	Iptacopan Phase II (complement Factor B inhibitor)	Placebo	-38% Proteinuria at 9 months	Perkovic, NEJM 2024
✓FDA SLE	Telitacicept Phase II (BAFF + APRIL inhibitor)	Placebo	-10.0 (extrapolated from -5 at 6 Mo)	Lv, Kidney Int Rep 2023
	MMF	Losartan	-3.8	Hou, JAMA Netw Open 2023

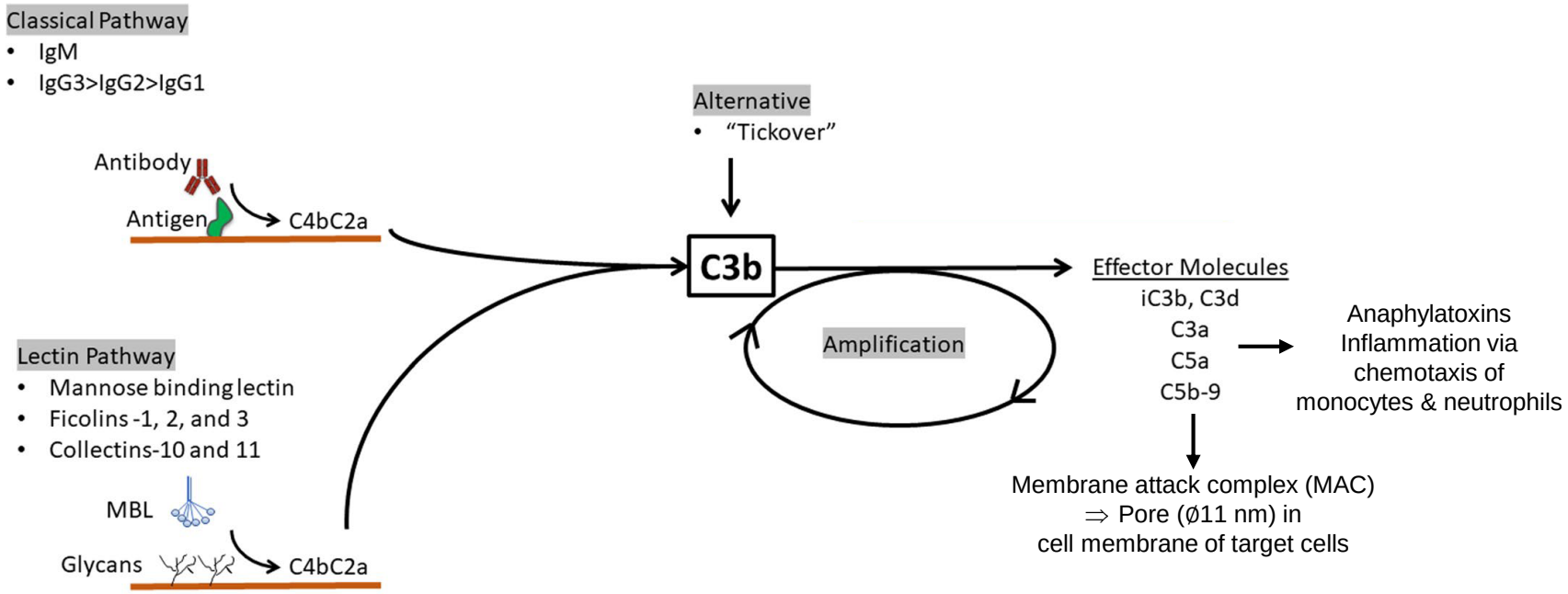
BAFF (also termed BLyS) and APRIL are B lymphocyte survival factors

New approaches for IgAN- 4-Hit Model



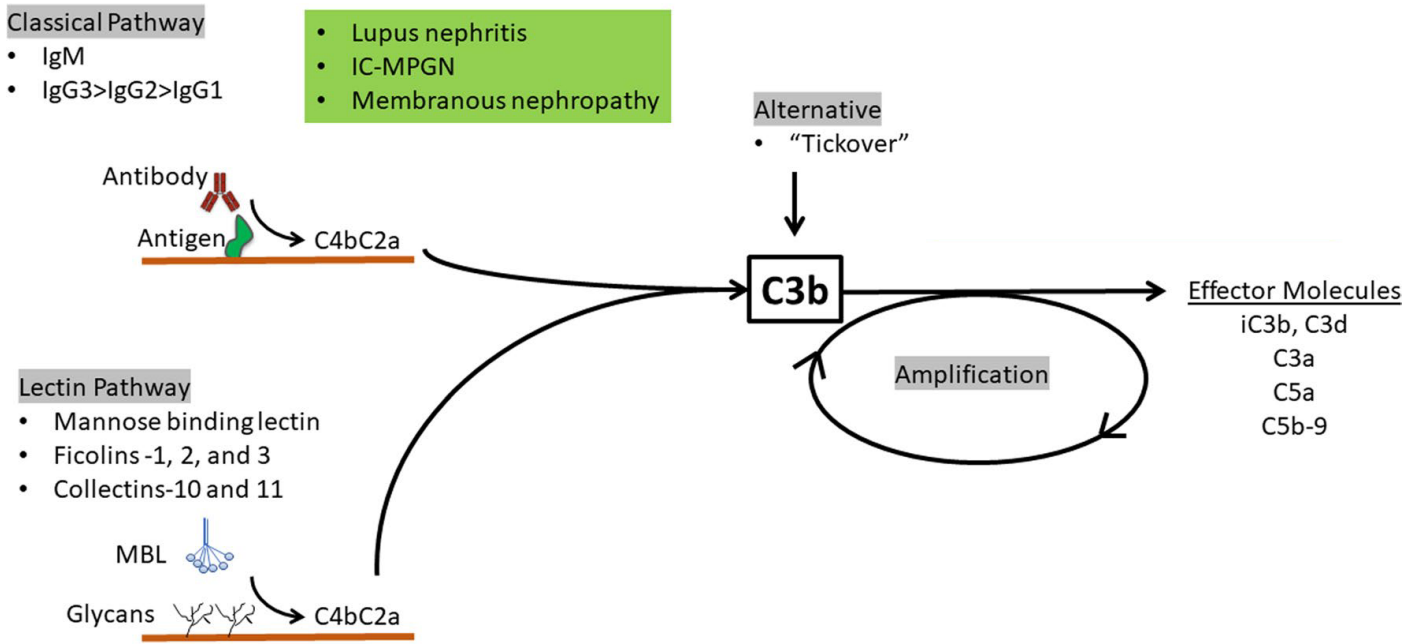
Adapted from Lim RS et al. J Clin Med. 2024 Feb 7;13(4):947.

The complement system and ist role in different kidney diseases



Antonucci et al., Pediatr Nephrol. 2024 May;39(5):1387-1404

The complement system and ist role in different kidney diseases



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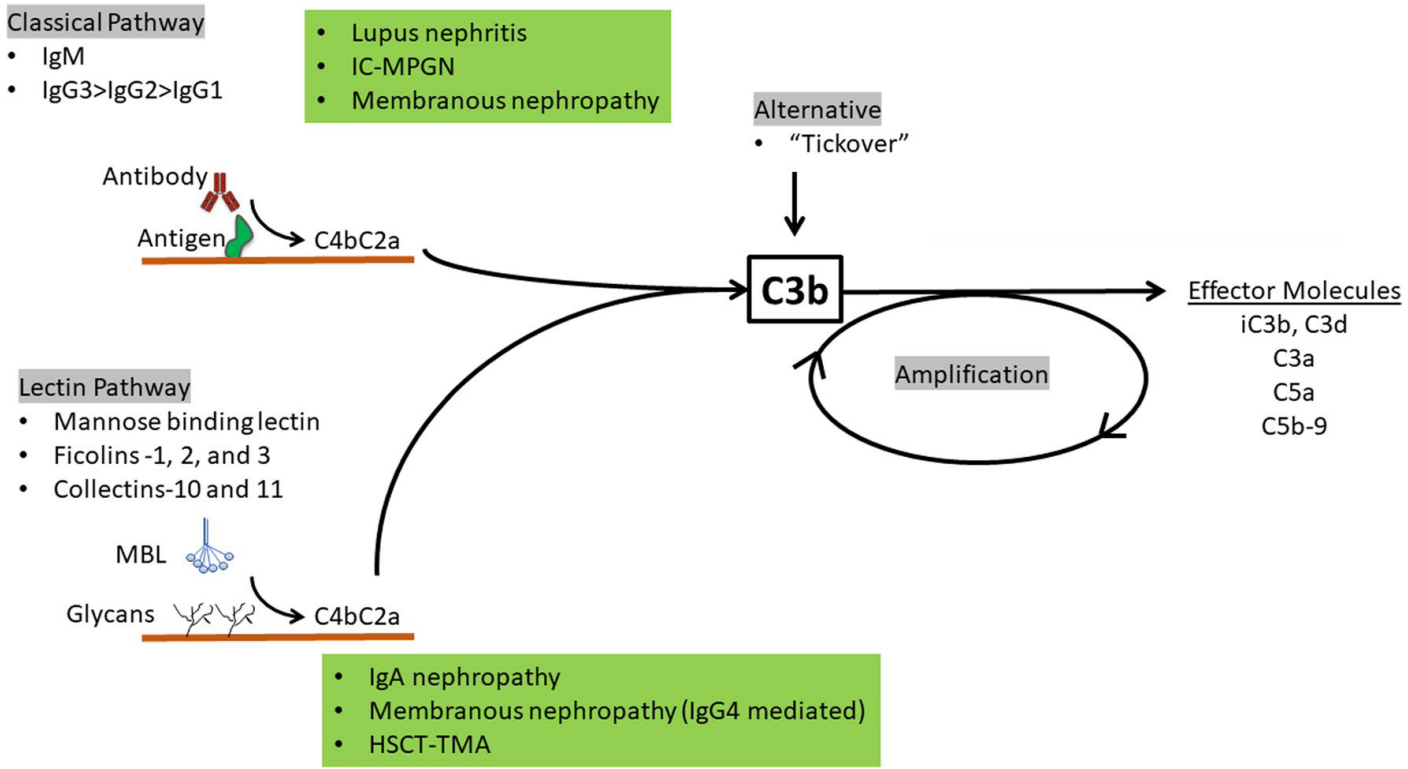
The complement system and ist role in different kidney diseases



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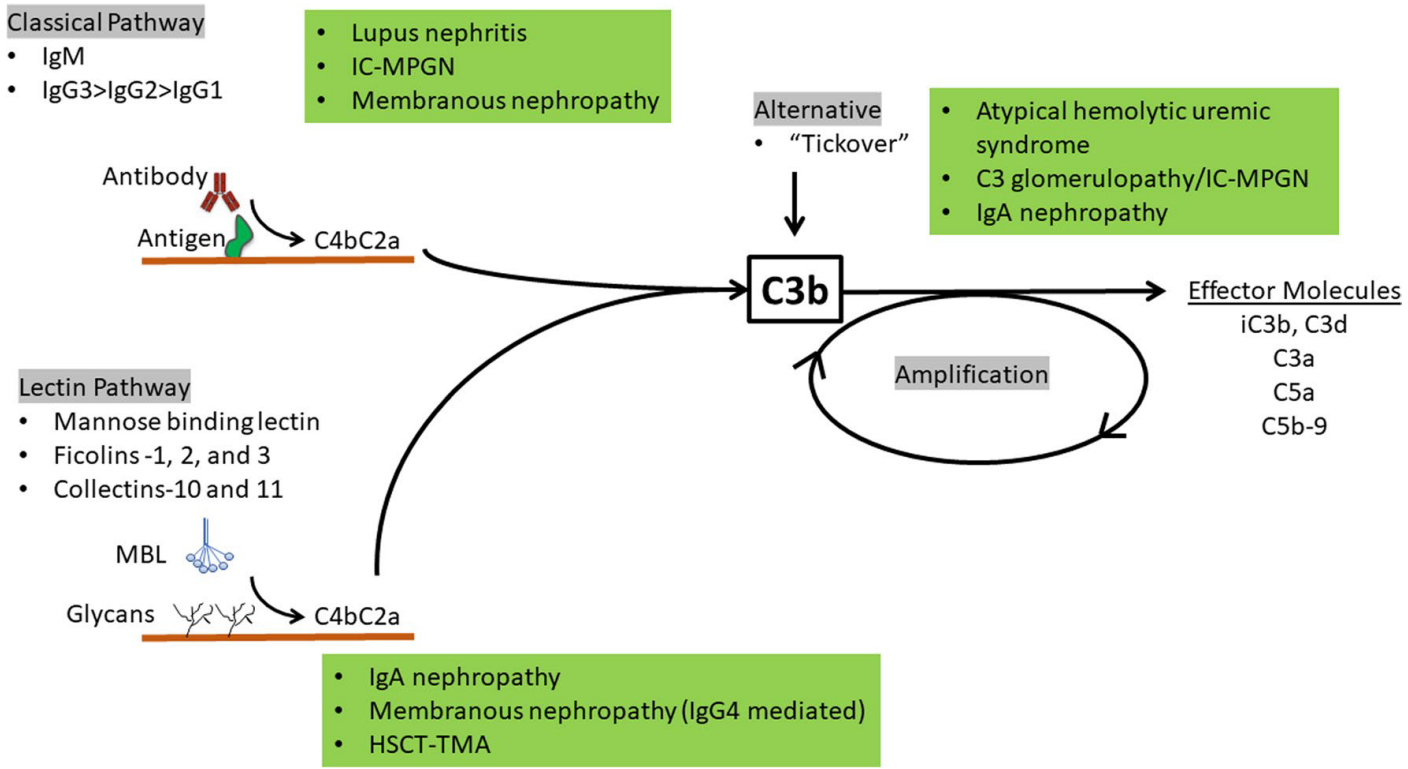
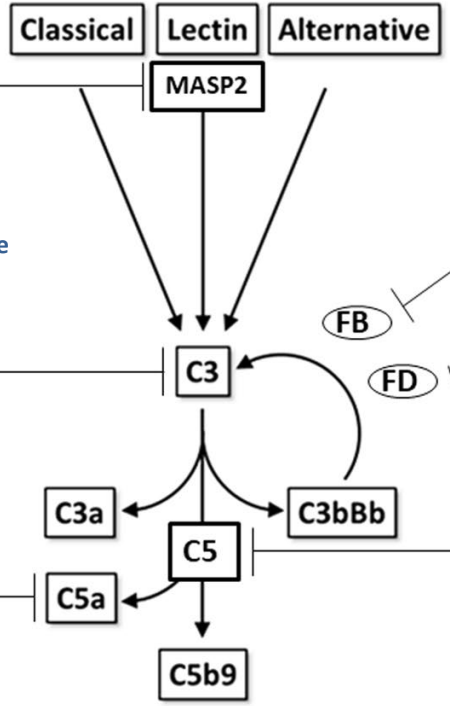
The complement system and ist role in different kidney diseases



Antonucci et al. , Pediatr Nephrol. 2024 May;39(5):1387-1404

The complement pathway and different inhibitors at different points in the cascade



Inhibitor of Lectin Pathway
RCTs: IgAN, aHUS, post-HSCT-TMA

Narsoplimab

Inhibitor of C3, blocks formation of C3 and C5 convertase
On-label (FDA): PNH, superior to Eculizumab
RCTs: C3GN & IC-MPGN, post-HSCT-TMA

Pegcetacoplan
AMY101

C5aR blocker, small molecule
⇩ anaphylatoxin formation
⇩ neutrophil chemotaxis
Steroid-sparing agent
AAV: ⇧ sustained remission
On-label: severe AAV

Trials: aHUS, C3GN

Avacopan
Nomacopan
Avdoralimab
IFX-1 (vilobelimab)

Inhibitors of Alternative Pathway (small molecules)

Iptacopan
IONIS-FB-LRx
MAC intact (⇩ Risk of *Neisseria meningitidis*)
On-label: IgA
RCTs: IgAN, aHUS, C3GN, LN, idiopathic MN

Danicopan
ALXN2050
BCX9930
PHASE 2 study C3GN & IC-MPGN
Lack of efficacy

C5 inhibitors
On-label: aHUS, PNH; off-label: C3GN, MPGN

Eculizumab → RCTs: STEC-HUS (ECULISHU / ECUSTEC)
Ravulizumab → On-label: aHUS, PNH; RCTs: LN, IgAN
Crovalimab → Binds to C5ß chain; RCTs: aHUS

Biosimilars Ecu
Pozelimab (IgG4 anti-C5 mAb)
Cemdisiran (siRNA targeting C5)
LFG316 (tesidolumab, IgG1 anti-C5 mAb)
Avacincaptad Pegol (pegilated RNA aptamer)
ALXN1720 (anti-C5 minibody)

Note: Meningococal vaccination required, antibiotics prophylaxis advised

Antonucci et al. , Pediatr Nephrol. 2024 May;39(5):1387-1404

Clinical trials on complement inhibitors in kidney diseases

(50% include children)

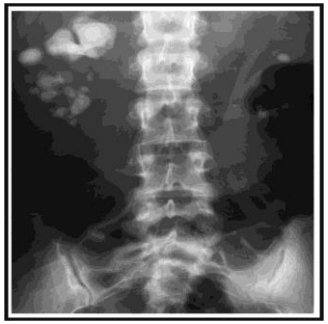
Drug	Target	Mechanism	Clinical trial number
Atypical hemolytic uremic syndrome			
Iptacopan oral	Factor B	Prevents formation of C3 and C5 convertases	**NCT04889430 Phase III, adults**
Pegcetacoplan (s.c.)	C3	Prevents formation of C3 and C5 convertases	NCT05148299 Phase II postBMT-TMA
Crovalimab (i.v. then monthly s.c.)	C5	Prevents formation of C5 convertase	**NCT04858265** **NCT04861259**
Avacopan oral	C5aR1	Blocks anaphylatoxin formation (C3a, C4a and/or C5a)	NCT02464891 Phase II, pts on dialysis
Narsoplimab (i.v. then daily s.c.)	MASP2	Blocks initiation of lectin pathway	**NCT03205995**
C3 glomerulopathy and Immune-complex glomerulonephritis			
Danicopan oral	Factor D	Prevents formation of C3 and C5 convertases	NCT03124368 NCT03369236 Phase II NCT03459443
Iptacopan oral	Factor B	Prevents formation of C3 and C5 convertases	NCT03832114, NCT03955445 **NCT04817618 C3G Phase III adults** Ext 12-18 years **NCT05755386 IC-MPGN Phase III**
Pegcetacoplan (s.c.)	C3	Prevents formation of C3 and C5 convertases	NCT03453619 Basket Phase II NCT04572854 C3G – IC-MPGN Phase II **NCT05067127 C3G – IC-MPGN Phase III**
Avacopan oral	C5aR1	Blocks anaphylatoxin formation (C3a, C4a and/or C5a)	**NCT03301467 (completed)**
BCX9930 oral	Factor D	Prevents formation of C3 and C5 convertases	NCT05162066 Phase II adults, IgAN, MN, C3G, 14 each, terminated/discontinued for BCX10013 once daily
Narsoplimab (i.v. then daily s.c.)	MASP2	Blocks initiation of lectin pathway	NCT02682407 basket Phase II study, 54 adults with IgAN, LN, C3G and MN
IgA nephropathy			
Iptacopan oral	Factor B	Prevents formation of C3 and C5 convertases	NCT03373461 NCT04557462 **NCT04578834 Phase III**
IONIS-FB-LRx	Factor B	Prevents formation of C3 and C5 convertases	NCT04014335 Phase II
ALXN2050 oral	Factor D	Prevents formation of C3 and C5 convertases	NCT05097989 Phase II, 126 adults, IgAN or LN, recruiting
BCX9930 oral	Factor D	Prevents formation of C3 and C5 convertases	NCT05162066 Phase II adults, IgAN, MN, C3G, 14 each, terminated/discontinued for BCX10013 once daily
Avacopan oral	C5aR1	Blocks anaphylatoxin formation (C3a, C4a and/or C5a)	NCT02384317 Phase II, 5 pts, completed: Bruchfeld et al Clin Kidney Journal 2022
Ravulizumab i.v.	C5	Prevents formation of C5 convertase	**NCT04564339 Phase III, 120 adults, IgAN and LN**
Narsoplimab (i.v. then daily s.c.)	MASP2	Blocks initiation of lectin pathway	NCT02682407 basket Phase II study, 54 adults with IgAN, LN, C3G and MN **NCT03608033 ARTEMIS Phase III, 450 adults RCT vs placebo**

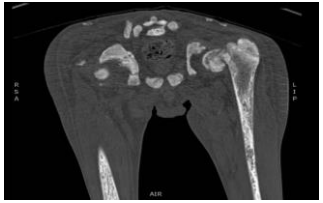
Idiopathic membranous nephropathy			
Iptacopan	Factor B	Prevents formation of C3 and C5 convertases	NCT04154787 Phase II, adults vs RTX
Pegcetacoplan s.c.	C3	Prevents formation of C3 and C5 convertases	NCT03453619 basket Phase II
BCX9930 oral	Factor D	Prevents formation of C3 and C5 convertases	NCT05162066 Phase II adults, IgAN, MN, C3G, 14 each, NOT recruiting/discontinued for BCX10013 once daily
Narsoplimab (i.v. then daily s.c.)	MASP2	Blocks initiation of lectin pathway	NCT02682407 basket Phase II study, 54 adults with IgAN, LN, C3G and MN
Lupus nephritis			
Iptacopan	Factor B	Prevents formation of C3 and C5 convertases	NCT05268289 Phase II
Ravulizumab i.v.	C5	Prevents formation of C5 convertase	NCT04564339 Phase III, 120 adults, IgAN and LN
Narsoplimab (i.v. then daily s.c.)	MASP2	Blocks initiation of lectin pathway	NCT02682407 basket Phase II study, 54 adults with IgAN, LN, C3G and MN
ALXN2050	Factor D	Prevents formation of C3 and C5 convertases	NCT05097989 Phase II, 126 adults, IgAN or LN, recruiting
ANCA-associated vasculitis with renal involvement			
Avacopan	C5aR1	Blocks anaphylatoxin formation (C3a, C4a and/or C5a)	NCT02222155 Phase II NCT01363388 Phase II **NCT02994927 (completed)** Jayne DRW et al NEJM 2021
IFX-1 (vilobelimab) i.v.	C5a	Blocks anaphilatoxin formation	NCT03895801 Phase II, 57 adults with GPA or MPA NCT03712345 Phase II, 20 adults, terminated
Post-BMT thrombotic microangiopathy			
Pegcetacoplan s.c.	C3	Prevents formation of C3 and C5 convertases	NCT05148299 Phase II
Ravulizumab i.v.	C5	Prevents formation of C5 convertase	**NCT04543591 (12 years-adults)** **NCT04557735 (28 days – 17 years)**
Narsoplimab i.v.	MASP2	Blocks initiation of lectin pathway	**NCT04247906** (expanded access, all ages)

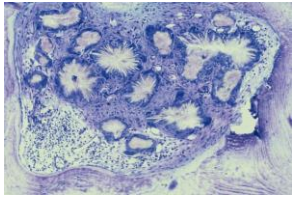
Antonucci et al., Pediatr Nephrol. 2024 May;39(5):1387-1404

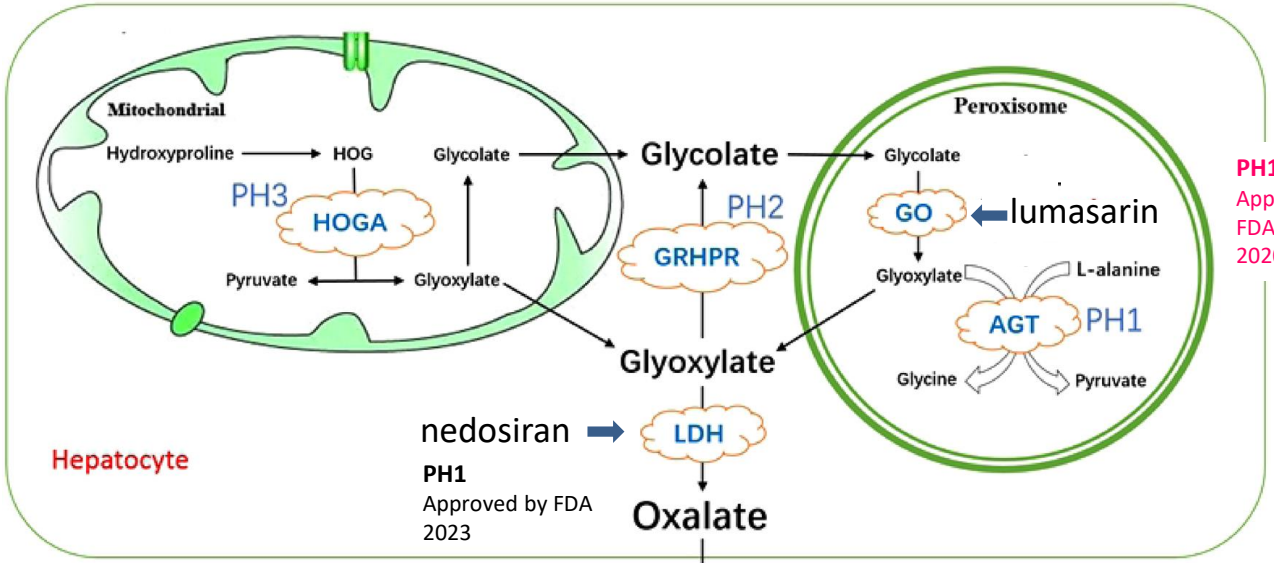
Primary hyperoxaluria type 1

Pathogenesis and mechanisms of siRNA therapy: lumasiran, nedosiran

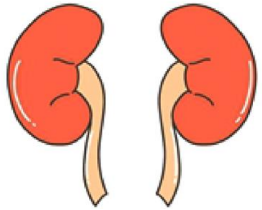








PH1
Approved by FDA & EMA
2020



AGT = alanine:glycoxylate aminotransferase

GO = glycolate oxidase

LDH = lactate dehydrogenase

Glycolate is soluble, excreted renally and does not precipitate

Adapted from Gang et al. Front. Pediatr., 10 January 2023

Multicenter Long-term Real World Data on Treatment with Lumasiran in Patients With Primary Hyperoxaluria Type 1

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Methods and cohort

- Multicenter
- 33 genetically proven PH1, 13 on dialysis
- 14 adults, 14 females
- Age at starting treatment: 2day-59yrs
- Lumasiran treatment 6-27m (med 18)*

*** Lumasiran dosing:**

1) <10Kg= Loading: 6mg/kg monthly for 3 doses; Then 3mg/Kg once monthly (Begin after 1m of loading)
2) 10-20Kg= Loading: 6mg/Kg monthly for 3 doses; Then 6mg/Kg quarterly (Begin after 1m of loading)
3) >20Kg= Loading: 3mg/Kg monthly for 3 doses; Then 3mg/Kg quarterly (Begin after 1m of loading)

Findings

Results are expressed as Mean (SD)

Patients with preserved kidney function

	At baseline	At 3 months	At 12 months	At 18 months
Mean urine oxalate (mmol/1.73m²/d)	1.88 (0.8)	0.73 (0.26)**	0.72 (0.3)**	0.65 (0.2)**
Mean urine glycolate (mmol/1.73m²/d)	2.13 (2.3)	3.54 (1.3)**	5.09 (2.6)**	5.88 (5.7)**
Mean plasma oxalate (mmol/1.73m²/d)	10.65 (4.0)	6.96 (4.1)	9.31 (3.6)	9.9 (3.6)
Mean plasma glycolate (mmol/1.73m²/d)	67.21 (88.2)	85.43 (46.8)	315.8 (302.8)**	240.9 (174)**

Mean eGFR (ml/min/1.73m²)			
70.6 (25.5)	Vitamin B6	74.1 (27.7)
71.3 (18.8)	Non Vitamin B6	86.4 (25.4)

** means significantly different as compared to baseline

Dialysis patients

Mean plasma oxalate (mmol/1.73m²/d)	78.0 (40.2)	37.2 (16.9)**	43.1 (16.3)	59.3 (23.8)
Mean plasma glycolate (mmol/1.73m²/d)	197.2 (220)	337.4 (294)**	443.3 (638)	259.5 (271)

KI REPORTS
Kidney International Reports

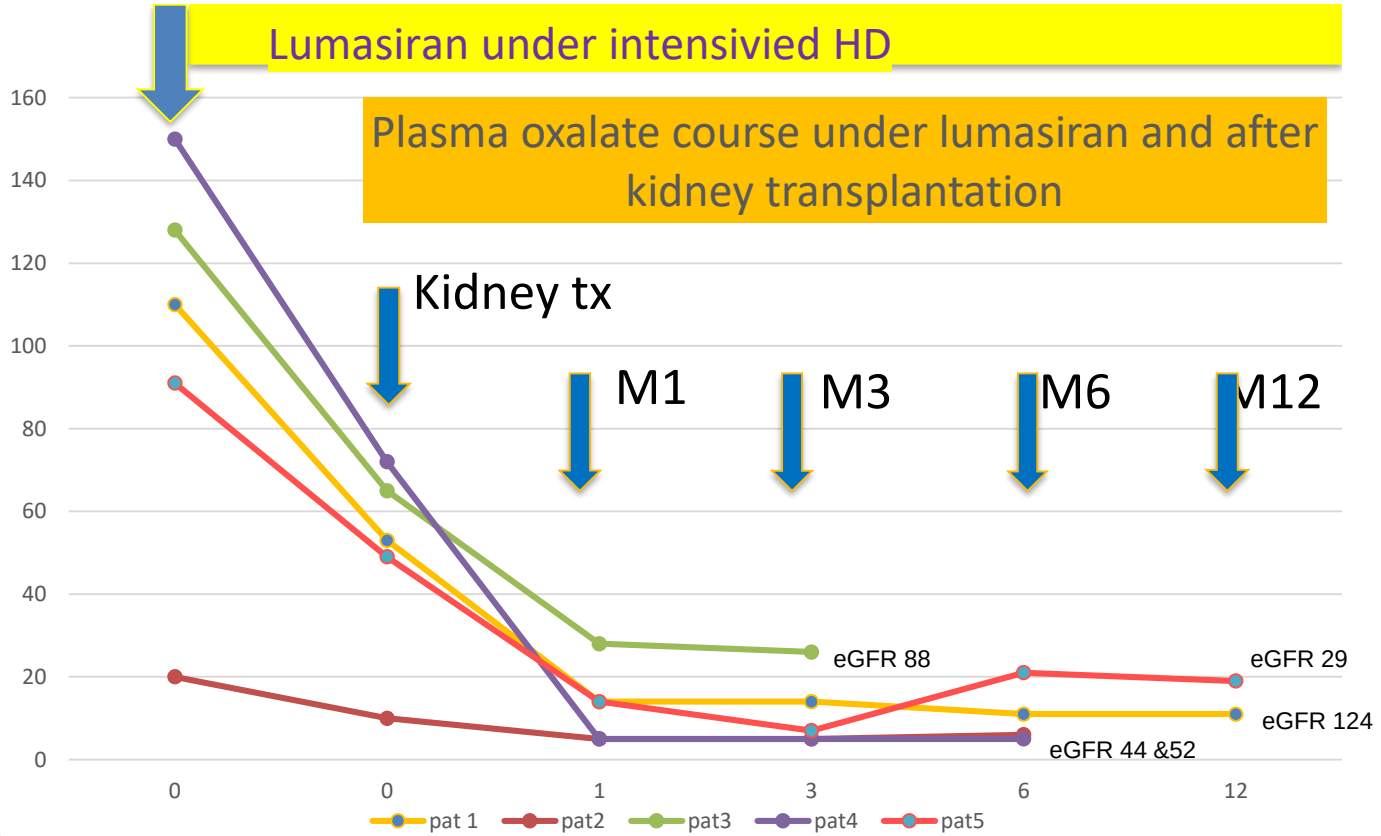
Martin-Higueras C et al. 2023

Visual abstract by:
Abdul Qader, MD
@md_abdulqader83

Conclusion Lumasiran treatment is safe and efficient. Not all patients with preserved kidney function experienced satisfactory reduction of urinary oxalate excretion in quarterly dosing. On whether or not a dosage (interval) adjustment is advisable needs clarification. In dialysis, lack of plasma oxalate reduction may relate to dissolving systemic oxalate deposits.

Kidney International Reports 2024 9114-133DOI: (10.1016/j.ekir.2023.10.004)

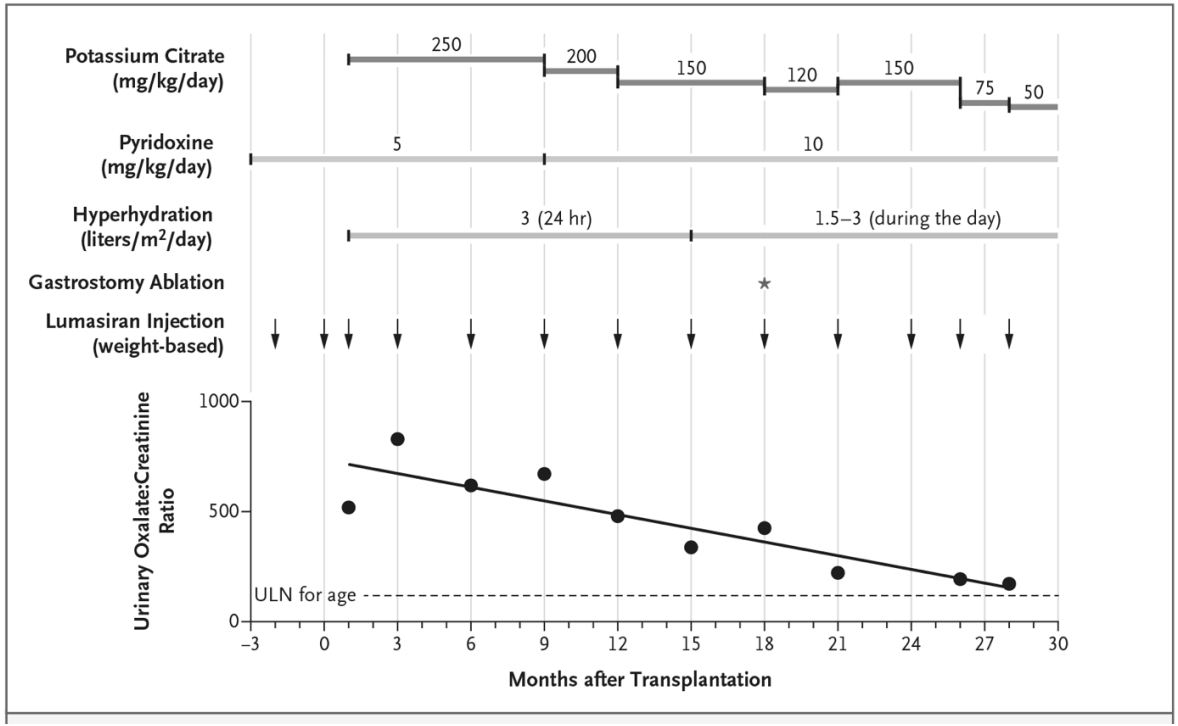
Isolated kidney transplantation under lumasiran therapy in primary hyperoxaluria type 1: a report of five cases



Sellier-Leclerc AL et al, NDT 2023

CORRESPONDENCE

Lumasiran, Isolated Kidney Transplantation, and Continued Vigilance



Bacchetta J, et al. N Engl J Med. 2024

Nedosiran Safety and Efficacy in PH1: Interim Analysis of PHYOX3

30 months

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Methods and cohort

- Multicenter open-label extension phase III study
- PH1 patients on monthly Nedosiran
- No Transplant, dialysis or systemic oxalosis
- N=13
  Female 53.8%
- 23 years (median)

Follow up: 30 months

Results

PH1: Primary Hyperoxaluria Type 1
SAE: serious adverse events

Stable range of GFR over time
62-84.2 mL/min/1.73m²

OXALATE in urine
Mean 24-h urine oxalate excretion decreased by at least 60%

from month 2 onwards

OXALATE in urine
Normal/ near-normal 24-h urine oxalate excretion
76.9% (10/13)

Eligible for ↓ hyperhydration/ stopping co-meds
84.6% (N=11)

↓ annualized stone events compared to baseline
0.37 vs 1.28

Adverse Events
100%
Mild to moderate, mostly at the injection site

SAEs
N=3 (23%)
Not treatment related
No deaths

KI REPORTS
Kidney International Reports

Groothoff J et al, 2024

Visual Abstract by:
S. Sudha Mannemuddhu, MD, FAAP
@drM_Sudha

Conclusion: Nedosiran was well tolerated in patients with PH 1, and treatment resulted in a sustained, substantial reduction in urine oxalate excretion for at least 30 months in this long-term study. No safety signals were identified to date. The PHYOX3 study is ongoing.

Kidney International Reports 2024 91387-1396DOI: (10.1016/j.ekir.2024.02.1439)

Table 2 | Recommended management and monitoring of patients with PH1 on RNAi therapy

Group[a]	Start	Cessation criteria after 6 months of therapy	Six-monthly analyses for 5 years and cessation criteria
Group A ($VB6^-$, eGFR >30)	We recommend starting therapy	Uox >1.5 UL or less than a 30% reduction in Uox[b] or a deterioration of the clinical condition or evidence of a SAE[c]	SAE or deterioration in clinical condition related to RNAi therapy[c]
Group B ($VB6^+$, eGFR >30)	We suggest starting therapy, based on patient characteristics (not fully VB6 responsive, severe disease)	Uox >1.5 UL or <30% reduction Uox[b]; or deterioration of clinical condition or evidence of a SAE[c]	SAE or deterioration in clinical condition related to RNAi therapy[c]
Group C ($VB6^-$, eGFR <30)	We recommend starting therapy	Decrease in Pox <20% from baseline or deterioration of clinical condition or evidence of a SAE[c]	Stop if decrease in Pox is <20%[d,e] from baseline: discuss options if the decrease in Pox is <30% from baseline[d,e]. Also stop treatment if there is evidence of an SAE OR deterioration in clinical condition related to RNAi therapy[c]
Group D ($VB6^+$, eGFR <30)	We suggest starting therapy based on patient characteristics (not fully VB6 sensitive, rapidly deteriorating kidney function in case of eGFR 20–30)	Decrease in Pox <20% from baseline[d,f] or deterioration of clinical condition as assessed by a committee; or evidence of a SAE[c]	Stop therapy if the decrease in Pox is <20%[2,4]; discuss options if the decrease in Pox is <30%[d,f]. Also stop treatment if there is evidence of a SAE or deterioration in clinical condition related to RNAi therapy[c]
Group E (no genetic diagnosis, eGFR <30)	We recommend starting therapy with monthly monitoring of Pox levels	Decrease Pox <20% of baseline or deterioration of clinical condition as assessed by a committee; or evidence of a SAE[c]. Also stop therapy if the suspected PH diagnosis is not confirmed genetically	Not applicable
Group F (no ongoing clinical disease)	We suggest starting therapy in adults and recommend starting therapy in children	Uox >1.5 UL or <30% reduction Uox of baseline; or deterioration of clinical condition as assessed by a committee; or evidence of a SAE[c]	SAE or deterioration in clinical condition related to RNAi therapy[c]
Group G (full $VB6^+$)	We do not recommend starting therapy	Not applicable	Not applicable

https://www.weforum.org/agenda/2021/07/how-we-can-inspire-people-connections-ocean/

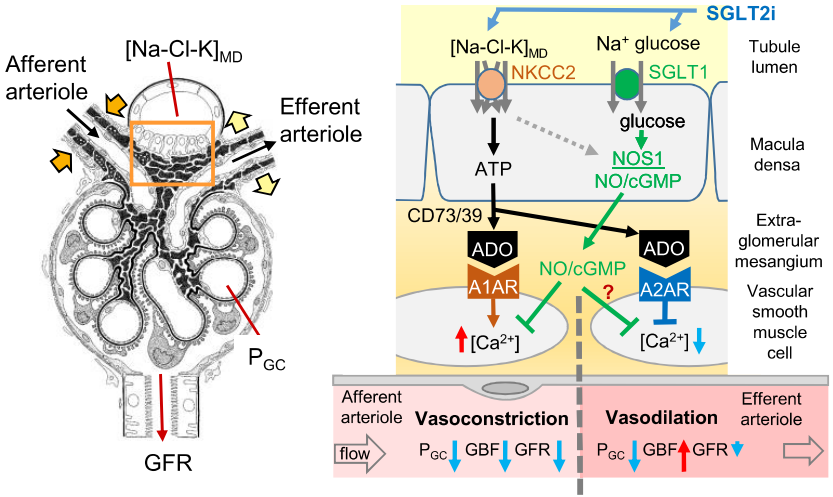
Thank you for your attention!


Paediatric
Kidney
Week
european
society for
paediatric
nephrology
4th Cycle - 3rd IPNA-ESPN
Master for Junior Classes
13-14 October 2025
57th ESPN Annual Meeting
15-18 October 2025
Athens, Greece
Congress Organizer
oic
group

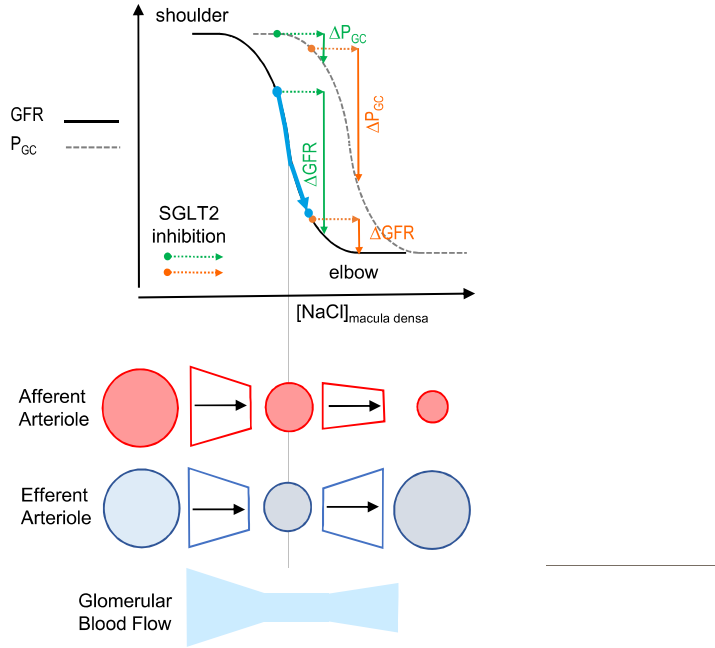
SGLT2 Inhibitors

- ✓ SGLT2i inhibit Na-Glucose reabsorption in proximal tubules
- ✓ Overwhelming evidence for broad nephroprotective efficacy in adults with CKD
- ✓ Activate tubulo-glomerular feedback (TGF) and reduce hyperfiltration-mediated kidney injury

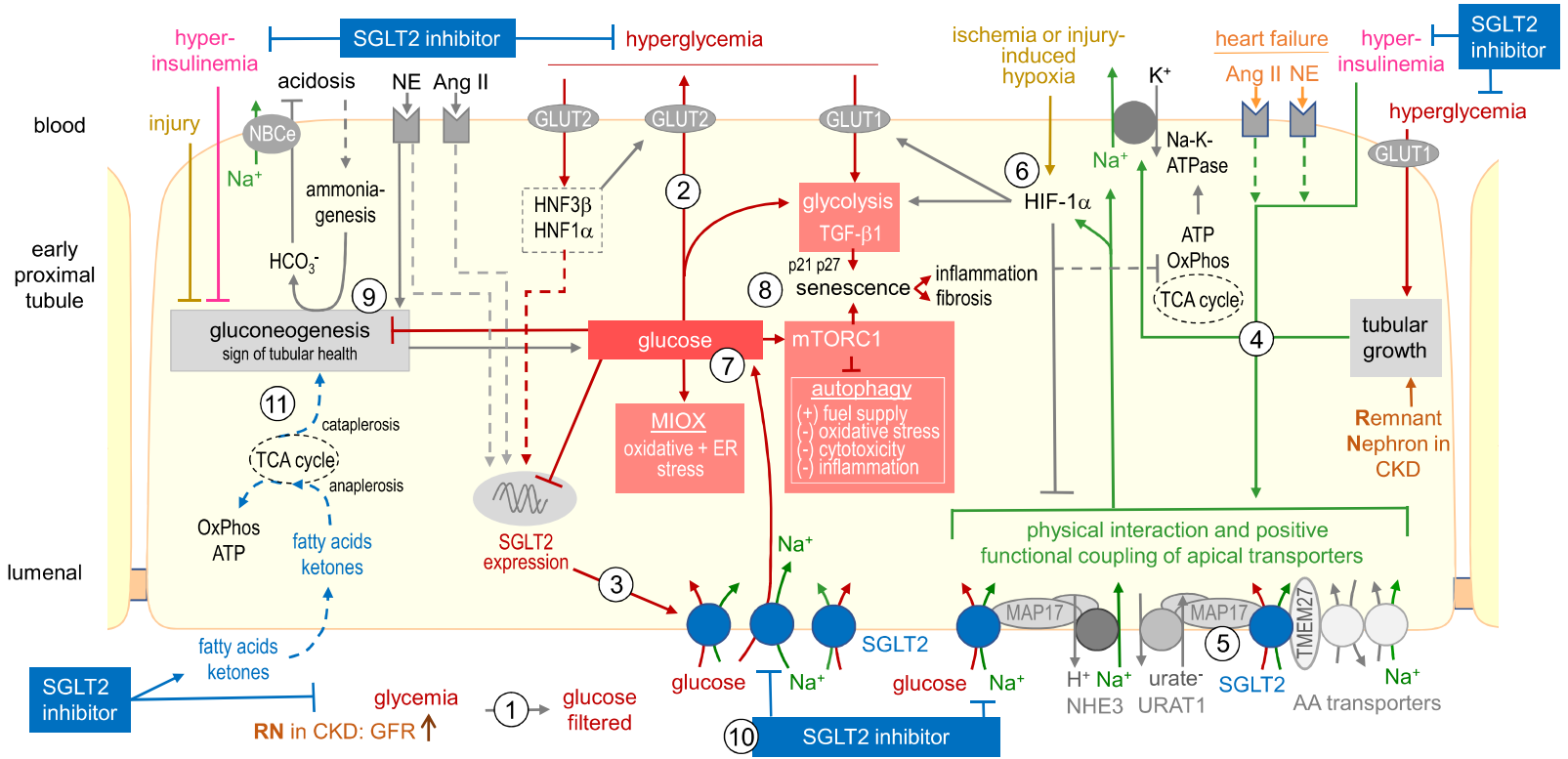
SGLT2i induced TGF via NaCl sensing at macula desna (MD)



GFR and pressure in glomerular capillaries as a function of $NaCl_{MD}$ ± SGLT2i



Vallon V. Nephrol Dial Transplant. 2024



- ✓ Induce a fasting-like metabolic response => optimize kidney's energy substrate utilization
- ✓ Regulate autophagy and maintenance of cellular homeostasis
- ✓ Attenuate sympathetic hyperactivity
- ✓ Improve vascular health and microvascular function

Vallon V. Nephrol Dial Transplant. 2024

A multi-institutional study found a possible role of anti-nephrin antibodies in post-transplant focal segmental glomerulosclerosis recurrence.

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Cohort

Kidney transplant recipients with FSGS from 1986 to 2022: **109 patients**

Excluded
- Secondary FSGS: 8 patients
- No genetic testing: 56 patients

Stocked plasma/serum samples and graft biopsies

14 presumed primary FSGS;
11 recurrent FSGS and
3 non-recurrent FSGS
8 genetic FSGS

Methods

1 hour biopsy, Graft biopsy

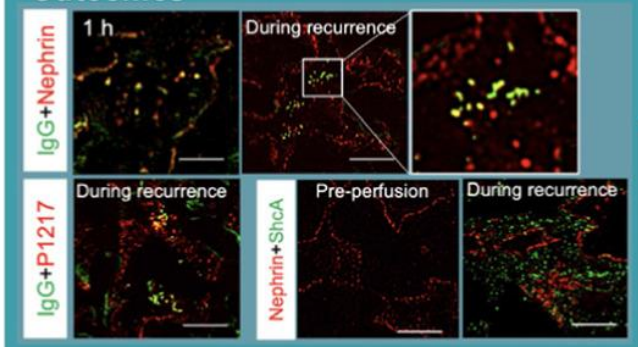
IF staining;
IgG, IgG subclass, p-nephrin, ShcA and nephrin

SIM observation

Plasma or Serum

ELISA
anti-nephrin antibodies

Outcomes

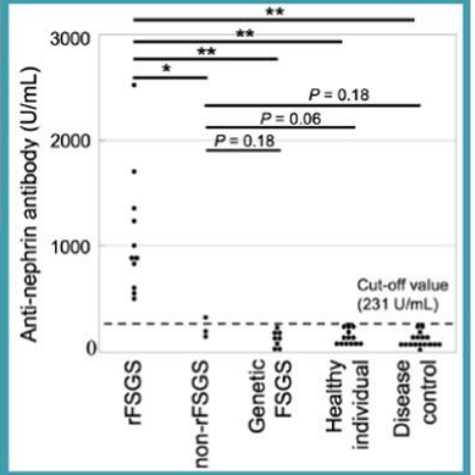


Results of IF

rFSGS: recurrent FSGS

	rFSGS n=11	non-rFSGS n=3	Genetic FSGS n=8
IgG co-localized with nephrin	11 (100%)	0 (0%)	0 (0%)
p-nephrin↑	11 (100%)	0 (0%)	0 (0%)
ShcA ↑	11 (100%)	0 (0%)	0 (0%)

positive anti-nephrin Ab; 11/11 (100 %) patients with recurrent FSGS



Shirai, 2023

CONCLUSION Circulating anti-nephrin antibodies are a possible candidate for circulating factors involved in the pathogenesis of post-transplant recurrent FSGS, and this may be mediated by nephrin phosphorylation.

- In this study, circulating antinephrin autoantibodies were common in patients with MCD or idiopathic nephrotic syndrome and appeared to be markers of disease activity.
- Their binding at the slit diaphragm induced podocyte dysfunction and nephrotic syndrome, which highlights their pathophysiological significance.