CKD-Studien in progress

PD Dr. Eva Schrezenmeier

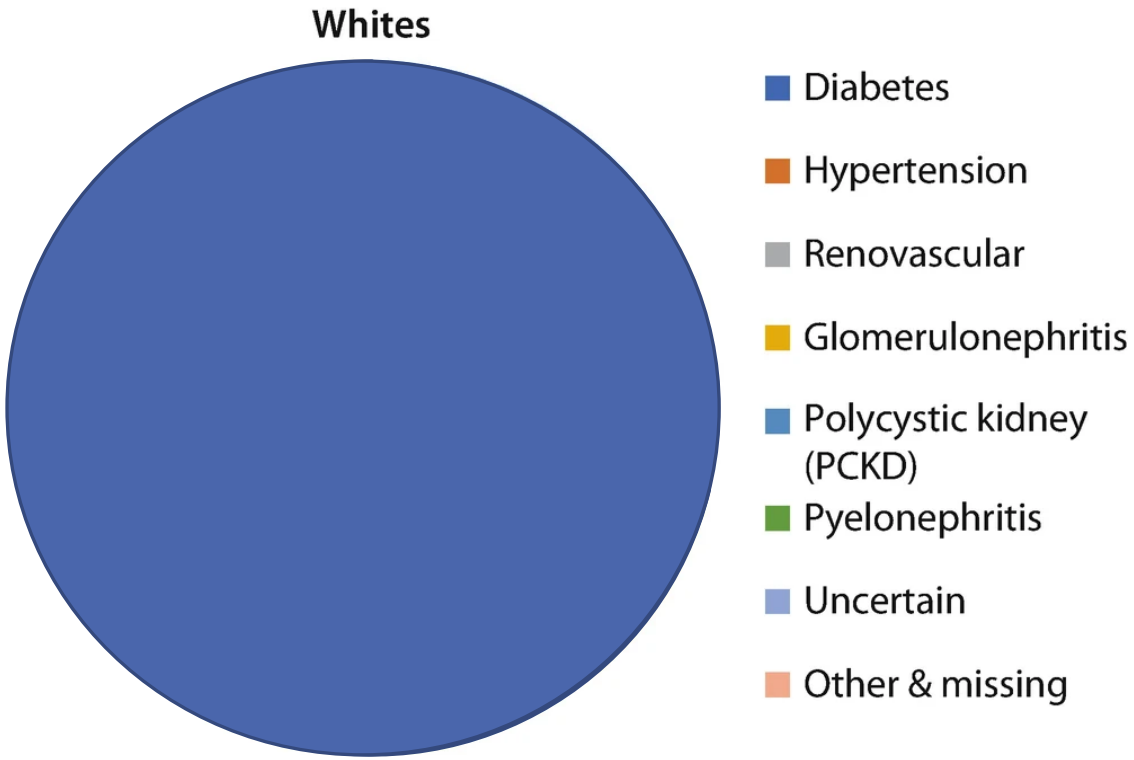
Darlegung potentieller Interessenskonflikte

Der Inhalt des folgenden Vortrages ist Ergebnis des Bemühens um größtmögliche Objektivität und Unabhängigkeit.

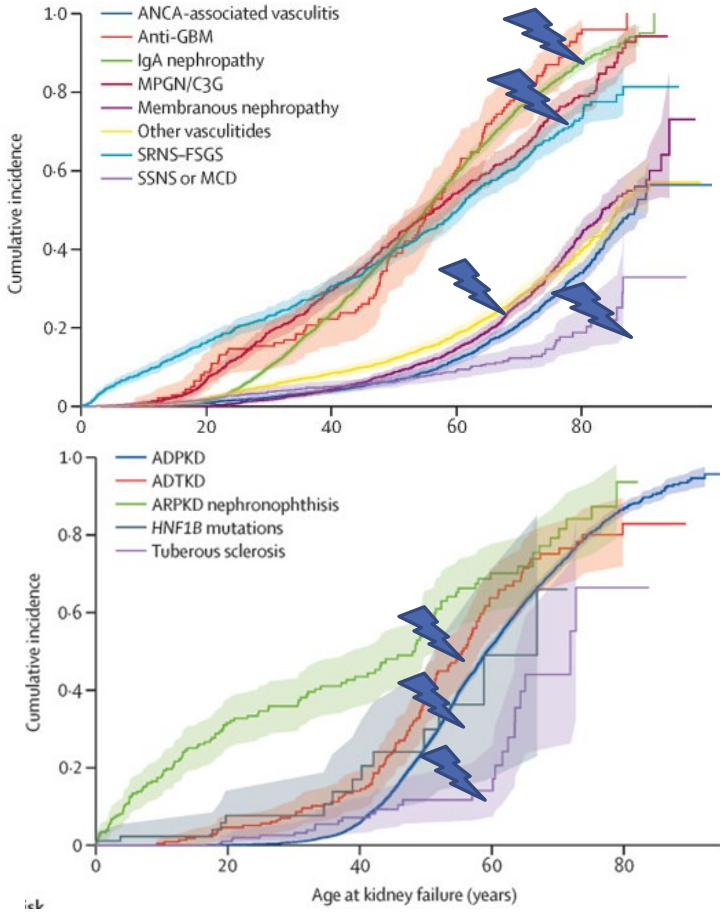
Als Referent weise ich darauf hin, dass es **persönliche Verbindungen** zu Unternehmen gibt, deren Produkte im Kontext des folgenden Vortrages von Interesse sind. Dabei handelt es sich um die folgenden Unternehmen und Verbindungen:

Unternehmen	Verbindungen
Chiesi	Erstattung von Reise- oder Übernachtungskosten
Novartis, AstraZeneca, GSK, Thermofischer	Honorar für Vortrags-, Autoren-, Gutachter- oder Beratungstätigkeiten
HiBio, Alexion	Erhalt von Forschungsgeldern
CSL, AstraZeneca,Argenx	Honorar für Durchführung von Auftragsstudien

Verteilung der Hauptursachen von CKD



Personen weißer Ethnizität
Basierend auf UKRR-2016

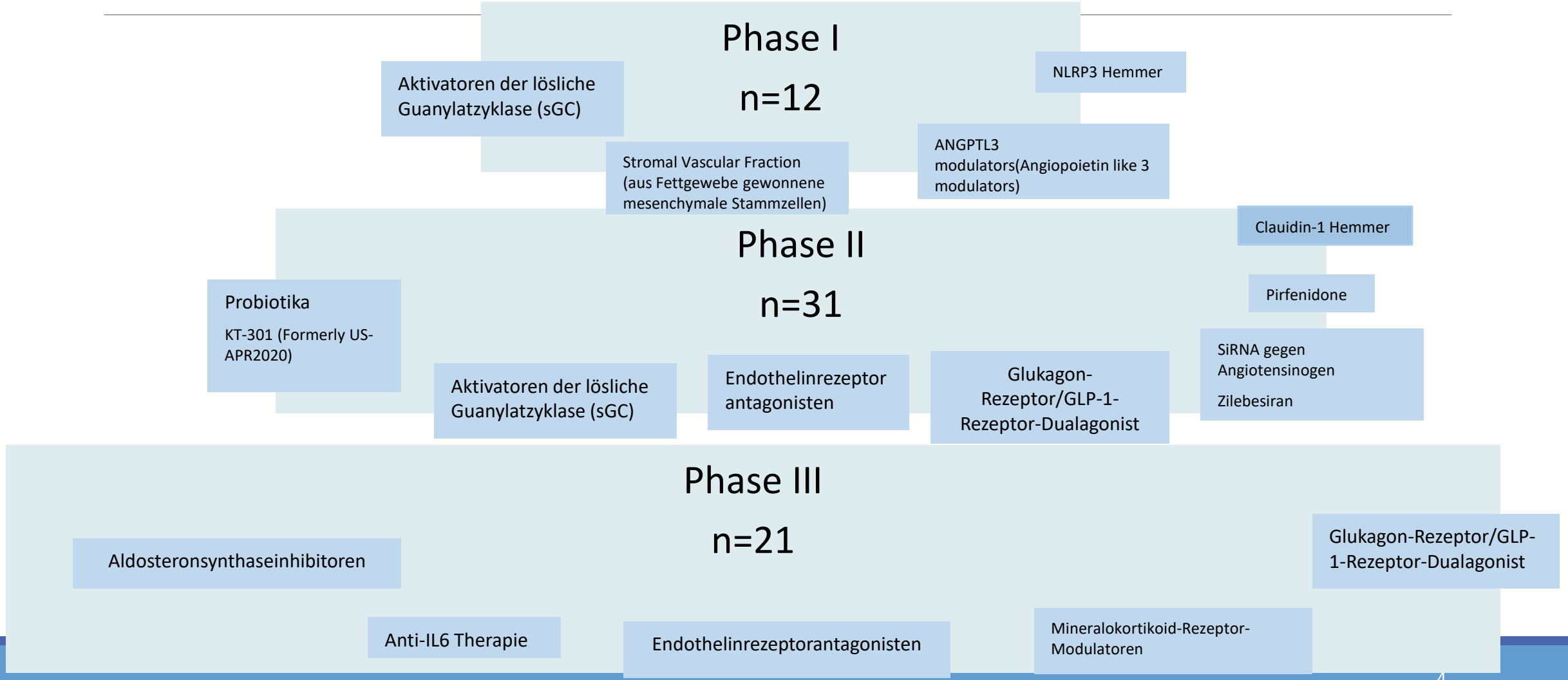


Abro, A. et al. (2022). In: Harber, M. (eds) Primer on Nephrology
Wong K et al. Lancet. 2024

Laufende Studien im Bereich CKD

Showing results for: **CKD** | **Recruiting studies** | **Phase: 1, 2, 3** | **Interventional studies**

+ Synonyms of conditions or disease (9)



Clinicaltrials.gov Abfrage am 5.9.24

Laufende Studien im Bereich CKD

Showing results for: **CKD** | **Recruiting studies** | **Phase: 1, 2, 3** | **Interventional studies**

+ Synonyms of conditions or disease (9)

Phase I

n=12

- Aktivatoren der lösliche Guanylatzyklase (sGC)
- NLRP3 Hemmer
- Stromal Vascular Fraction (aus Fettgewebe gewonnene mesenchymale Stammzellen)
- ANGPTL3 modulators(Angiopoietin like 3 modulators)

Phase II

n=31

- Probiotika
  - KT-301 (Formerly US-APR2020)
- Aktivatoren der lösliche Guanylatzyklase (sGC)
- Endothelinrezeptor antagonisten
- Glukagon-Rezeptor/GLP-1-Rezeptor-Dualagonist
- Clauidin-1 Hemmer
- Pirfenidone
- SiRNA gegen Angiotensinogen
  - Zilebesiran

Phase III

n=21

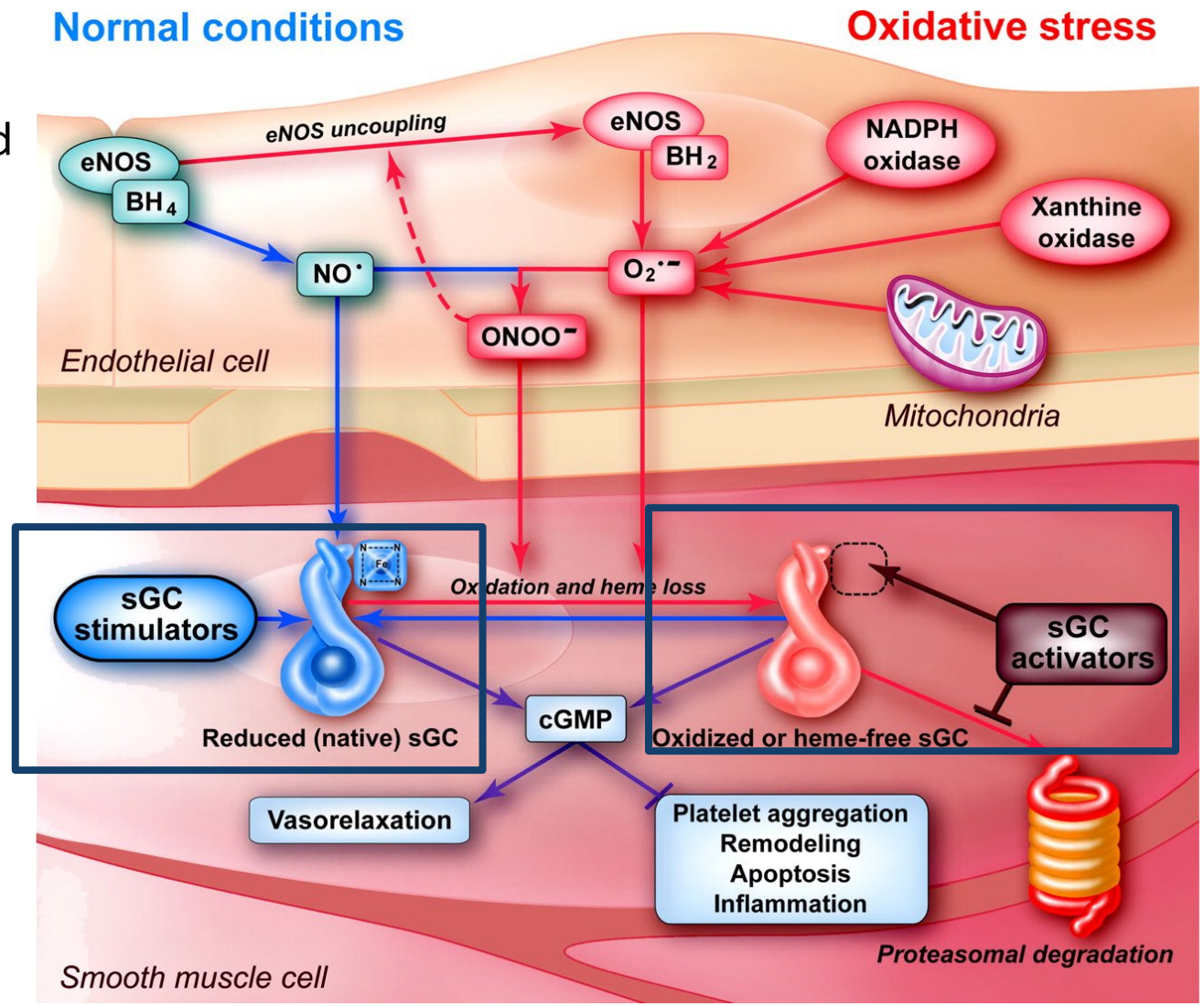
- J. STEGBAUER
  - Aldosteronsynthaseinhibitoren
- Mineralokortikoid-Rezeptor-Modulatoren
- T. SPEER
  - Anti-IL6 Therapie
- J. FLOEGE
  - Endothelinrezeptorantagonisten
- P. ROSSING
  - Glukagon-Rezeptor/GLP-1-Rezeptor-Dualagonist

Clinicaltrials.gov Abfrage am 5.9.24

Aktivatoren der lösliche Guanylatzyklase (sGC)

- CKD ist oft mit oxidativem Stress und einer verminderten Verfügbarkeit von Stickstoffmonoxid (NO) verbunden
- sGC-Aktivatoren können die oxidierte und hämfreie Form von sGC aktivieren
- Wiederherstellung der cGMP-Produktion auch unter oxidativem Stress wiederherstellen

- Verbesserung des renalen Blutflusses
- Reduktion von Proteinurie und Nierenschäden
- Anti-fibrotische und anti-inflammatorische Effekte
- Verbesserung der Endothelfunktion



Stasch JP, Pacher P, Evgenov OV. Soluble guanylate cyclase as an emerging therapeutic target in cardiopulmonary disease. Circulation. 2011 May 24;123(20):2263-73. doi: 10.1161/CIRCULATIONAHA.110.981738. PMID: 21606405; PMCID: PMC3103045.

Efficacy, Safety, and Dosing of Avenciguat in Diabetic and Nondiabetic Chronic Kidney Disease

JASN
Journal of the American Society of Nephrology

PRESPECIFIED POOLED ANALYSIS

2 Randomized Controlled Trials

diabetic and non-diabetic

Double Blind
(Placebo-controlled)

INCLUSION CRITERIA

- eGFR ≥20 and eGFR <90 *mL/min/1.73 m²*
- UACR ≥200 and UACR <3500 *mg/g*
- On ACEi or ARB

BASELINE CHARACTERISTICS

- 62 years Mean age
- eGFR 44 *mL/min/1.73 m²* Mean
- UACR 719 *mg/g* Median 10-hr
- n=500

RANDOMIZATION

20 weeks

	UACR change (95% CI) (from baseline in in 10-hr urine) PRIMARY END POINT	UACR change (from baseline in 1st morning voided urine) SECONDARY END POINT
Avenciguat 1 mg TID n=125	-15.5% (-26.4, -3.0)	-19.4% (-30.0,-7.3)
Avenciguat 2 mg TID n=126	-13.2% (-24.6, -0.1)	-15.5% (-26.9,-2.5)
Avenciguat 3 mg TID n=127	-21.5% (-31.7,-9.8)	-23.4% (-33.5, -11.8)

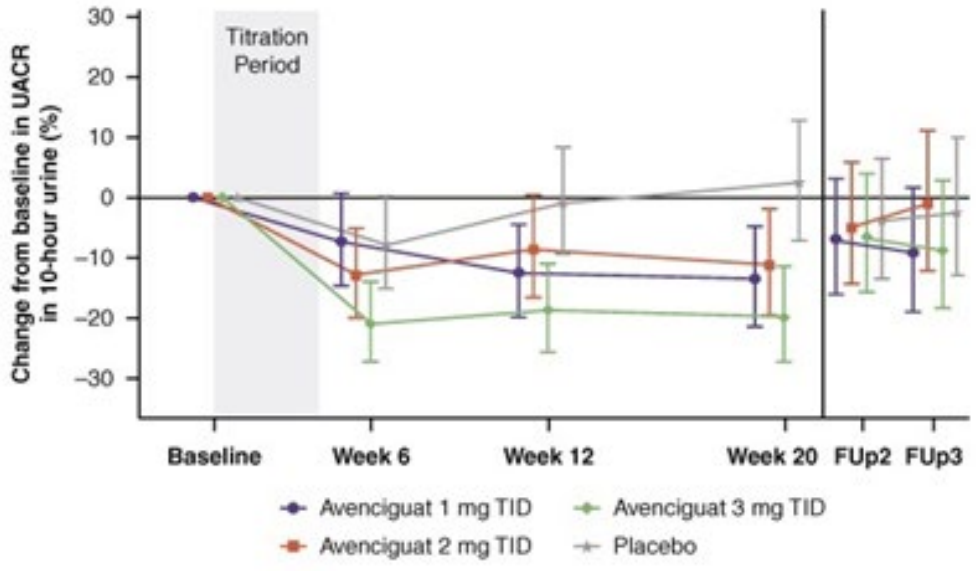
Avenciguat was well tolerated; overall frequency of adverse events was low and clinically comparable to placebo

Conclusions: Avenciguat (a novel, potent soluble guanylyl cyclase activator) was effective in lowering albuminuria and was well tolerated in patients with CKD.

Hiddo J.L. Heerspink, David Cherney, Abdul Halim Abdul Gafor, et al. ***Effect of Avenciguat on Albuminuria in Patients with CKD: Two Randomized Placebo-Controlled Trials.*** JASN doi: 10.1681/ASN.0000000000000418. ***Visual Abstract by Edgar Lerma, MD, FASN***

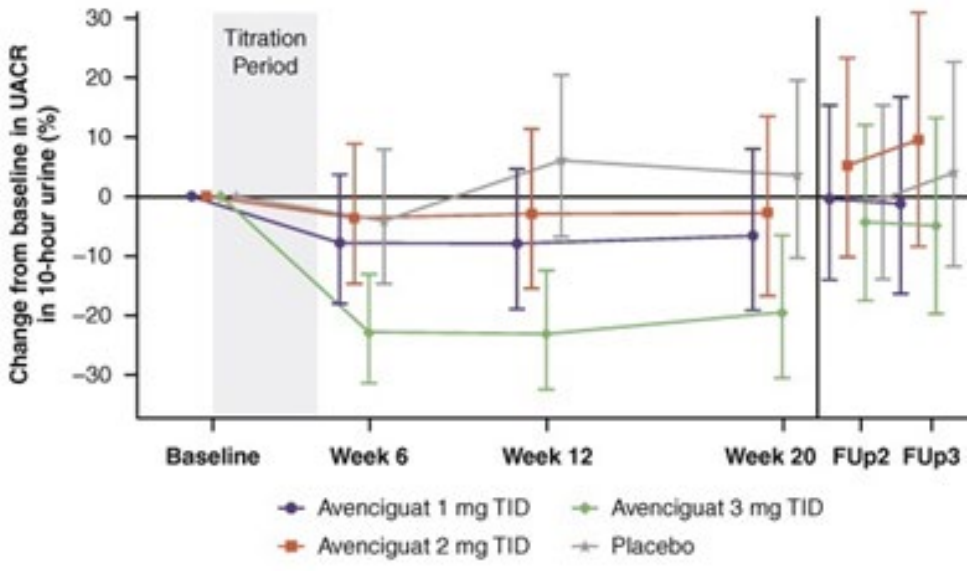
Change from baseline in UACR up to week 20

ALL



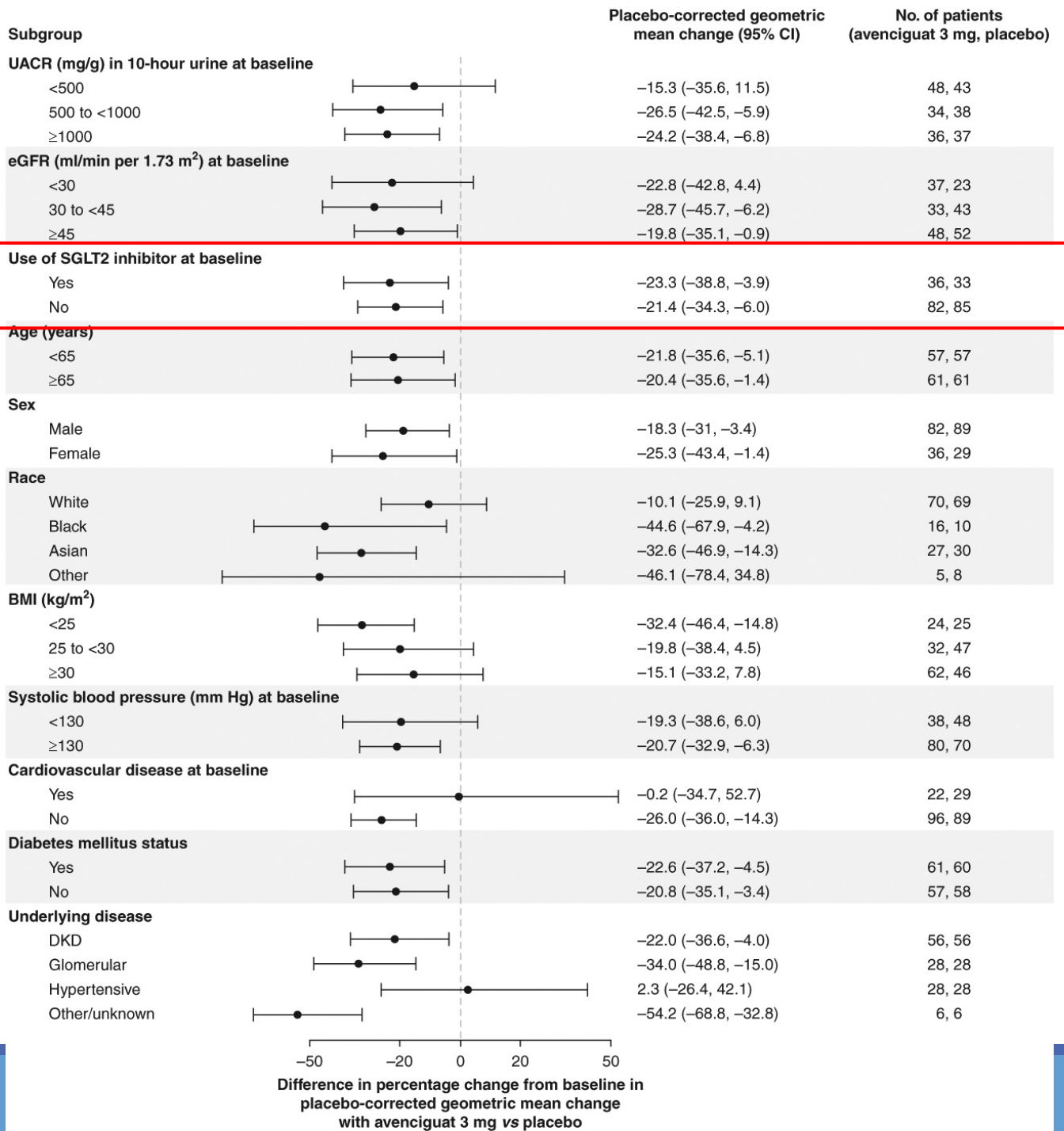
No. of patients:						
Avenciguat 1 mg TID	121	120	117	112	108	108
Avenciguat 2 mg TID	114	112	105	105	99	102
Avenciguat 3 mg TID	118	116	112	107	102	104
Placebo	118	117	112	110	103	106

DKD



No. of patients:						
Avenciguat 1 mg TID	57	56	55	52	52	51
Avenciguat 2 mg TID	53	52	46	46	43	44
Avenciguat 3 mg TID	56	55	53	48	45	46
Placebo	56	56	54	53	51	53

Heerspink HJL, Cherney D, Gafor AHA, Górriz JL, Pergola PE, Tang SCW, Desch M, Iliev H, Sun Z, Steubl D, Nangaku M. Effect of Avenciguat on Albuminuria in Patients with CKD: Two Randomized Placebo-Controlled Trials. J Am Soc Nephrol. 2024 May 25;35(9):1227–39. doi: 10.1681/ASN.0000000000000418. Epub ahead of print. PMID: 38795055; PMCID: PMC11387026.



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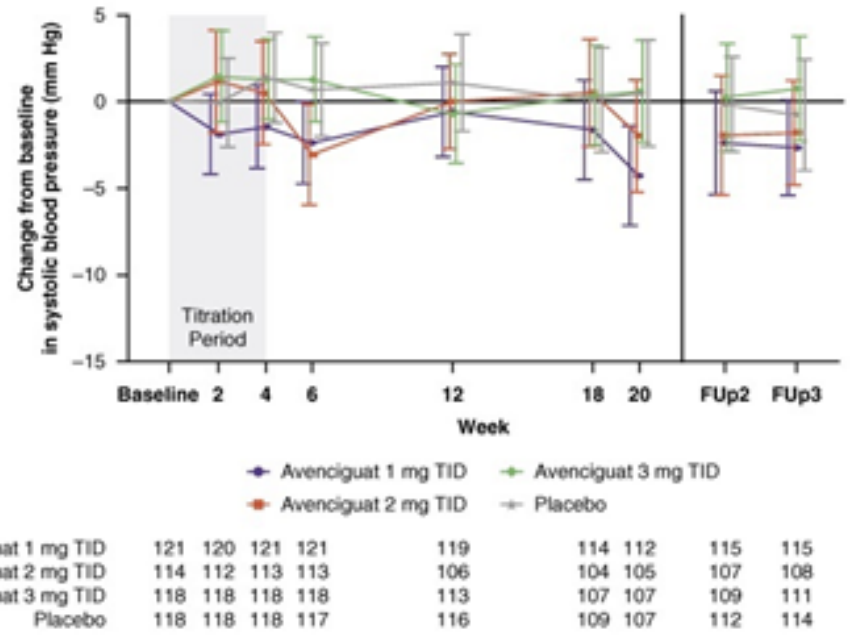
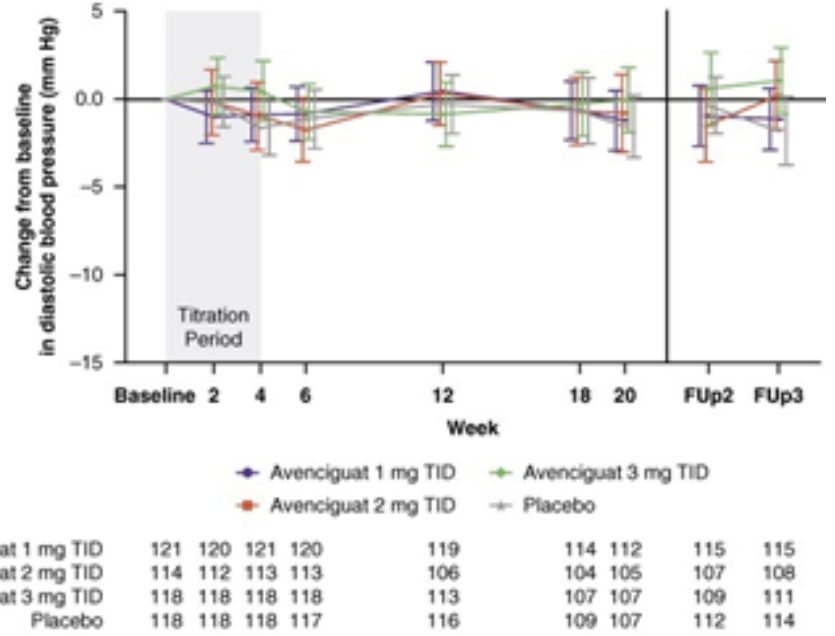
Change from baseline in systolic and diastolic BP

systolic BP



Avenciguat 1 mg TID	121	120	121	121	119	114	112	115	115
Avenciguat 2 mg TID	114	112	113	113	106	104	105	107	108
Avenciguat 3 mg TID	118	118	118	118	113	107	107	109	111
Placebo	118	118	118	117	116	109	107	112	114

diastolic BP



Avenciguat 1 mg TID	121	120	121	120	119	114	112	115	115
Avenciguat 2 mg TID	114	112	113	113	106	104	105	107	108
Avenciguat 3 mg TID	118	118	118	118	113	107	107	109	111
Placebo	118	118	118	117	116	109	107	112	114

Hypotonie als einzig relevantes AE

Heerspink HJL, Cherney D, Gafor AHA, Górriz JL, Pergola PE, Tang SCW, Desch M, Iliev H, Sun Z, Steubl D, Nangaku M. Effect of Avenciguat on Albuminuria in Patients with CKD: Two Randomized Placebo-Controlled Trials. J Am Soc Nephrol. 2024 May 25;35(9):1227–39. doi: 10.1681/ASN.0000000000000418. Epub ahead of print. PMID: 38795055; PMCID: PMC11387026.

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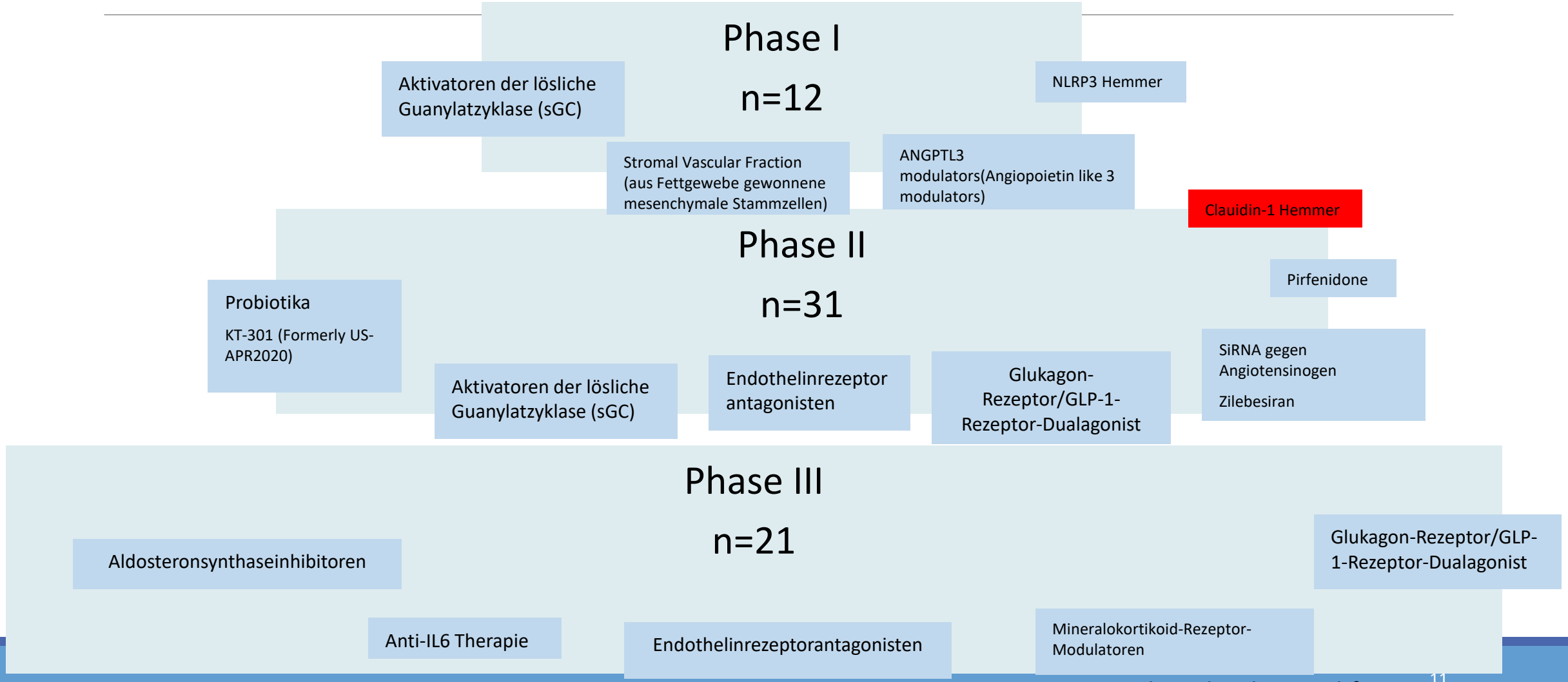


Clinicaltrials.gov Abfrage am 5.9.24

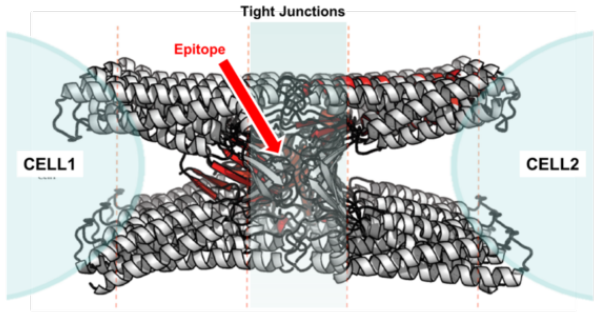
Fibrosehemmung durch gezielte Blockade von extrajuctionalem Claudin-1

Healthy

CLDN1 in Tight Junctions

CLDN1 is an integral part of TJs

CLDN1 epitope (loop) is masked in the TJs of epithelial cells



Epithelial Injury or De-differentiation

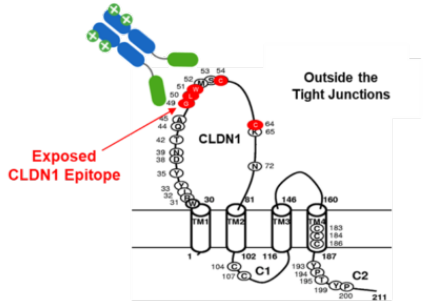
Pathological

CLDN1 Exposed

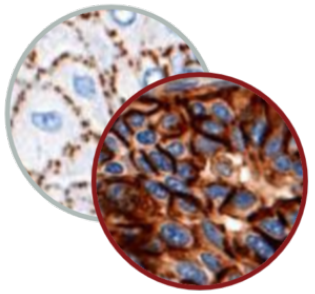
CLDN1 overexpression

Exposed CLDN1 outside of TJs

Anti-CLDN1 Ab binds the exposed epitope and **restores a healthy ECM**



Outcome



Carcinogenesis / Fibrogenesis

Restored ECM with Healthy Permeability and Resolved Tissue Function

- CLDN1-Überexpression induziert *epithelial-mesenchymal transition*
- CLDN1 ist in vielen Krebsarten überexprimiert, darunter hepatozelluläres Karzinom und Plattenepithelkarzinome.

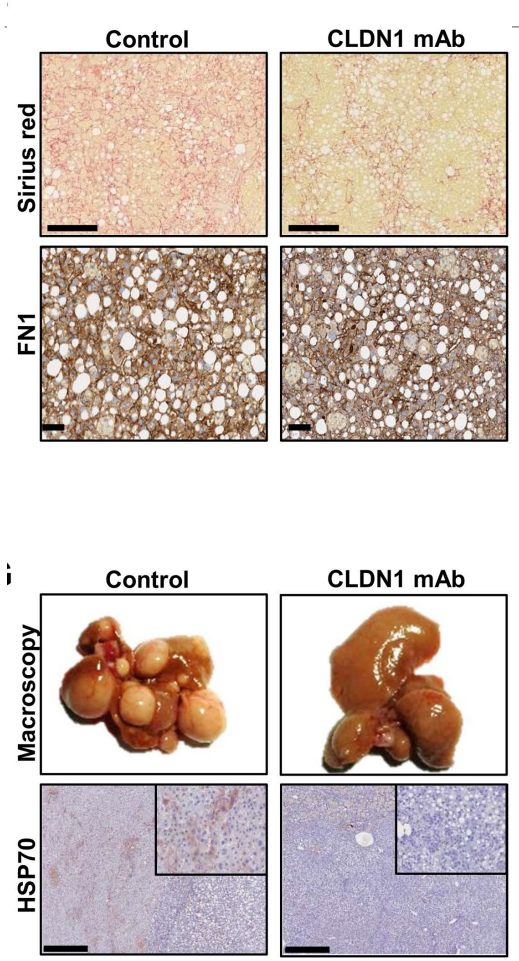
https://alentis.ch/cldn1-old/

accessed 30.08.2024

Leber

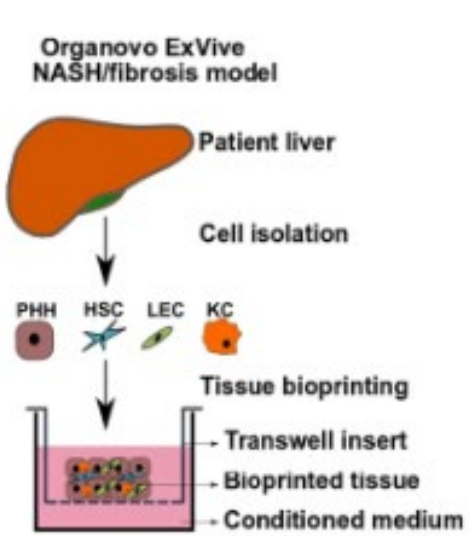
mouse
NASH

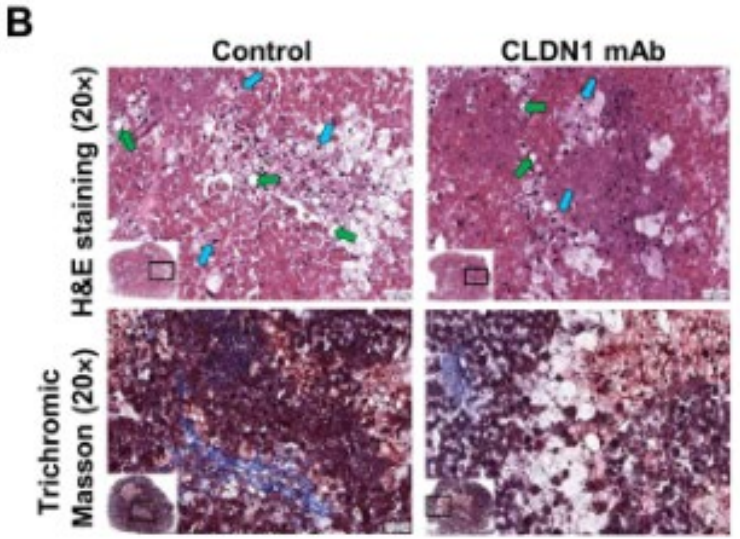
treatment with an antibody against nonjunctional claudin-1

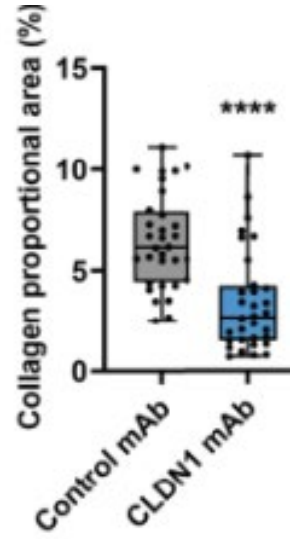


human

treatment with an antibody against nonjunctional claudin-1





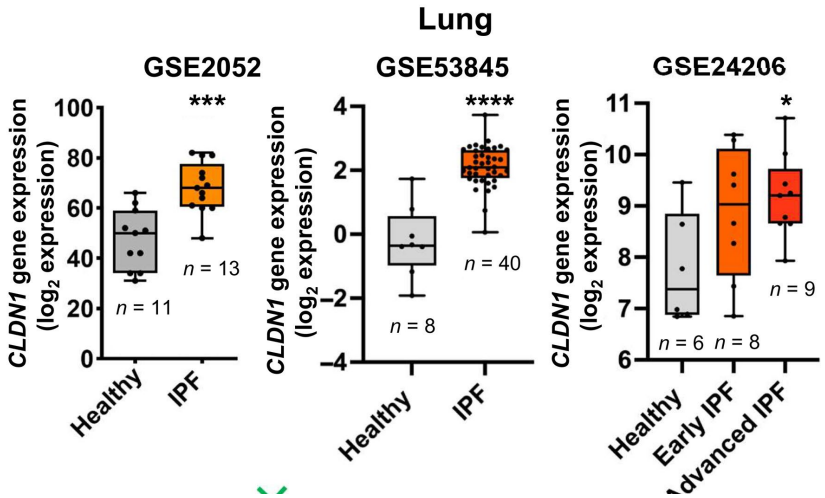


Roehlen N, Saviano A, El Saghire H et al. A monoclonal antibody targeting nonjunctional claudin-1 inhibits fibrosis in patient-derived models by modulating cell plasticity. Sci Transl Med. 2022 Dec 21;14(676):eabj4221. doi: 10.1126/scitranslmed.abj4221. Epub 2022 Dec 21. PMID: 36542691.

Lunge

Late Breaking Abstract – Claudin-1 is a potential airway-centric therapeutic target for pulmonary fibrosis

Abstract European Respiratory Society 2023
Geoffrey Teixeira



FDA Grants Orphan Drug Status to Alentis' Lixudebart for Idiopathic Pulmonary Fibrosis

7 June 2024 |

In a significant advancement for the treatment of Idiopathic Pulmonary Fibrosis (IPF), **Alentis Therapeutics** has announced that the U.S. Food and Drug Administration (FDA) has granted Orphan Drug designation to its investigational drug **lixudebart** (ALE.F02). Alentis Therapeutics is a clinical-stage biotechnology firm dedicated to developing treatments targeting **Claudin-1** positive (CLDN1+) tumors and **organ fibrosis**.

Dr. Luigi Manenti, Chief Medical Officer at Alentis, emphasized the critical need for new IPF treatments, noting that the Orphan Drug status highlights the potential of lixudebart to address this unmet medical need. According to Dr. Manenti, the company has completed the necessary IND-enabling studies and believes that their highly specific antibody, which targets CLDN1 in fibrotic lungs, could potentially alter the disease's trajectory.

https://synapse.patsnap.com/article/fda-grants-orphan-drug-status-to-alentis-lixudebart-for-idiopathic-pulmonary-fibrosis, accessed 30 august 2024

Niere

RECRUITING

NCT05939947

A Clinical Trial of **ALE.F02** in Patients With Advanced Liver Fibrosis and/or Mild Cirrhosis

Conditions

Advanced Liver Fibrosis | Liver Cirrhosis

Locations

San Antonio, Texas, United States
Munich, Germany
Bucharest, Romania
Cluj-Napoca, Romania

Show all 6 locations

RECRUITING

NCT06047171

Rescue of Nephrons With **ALE.F02** (RENAL-F02)

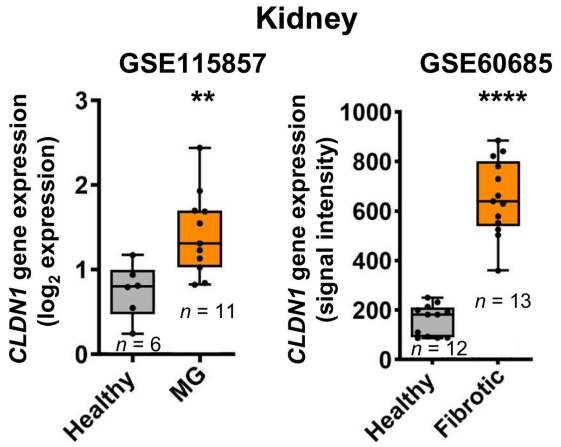
Conditions

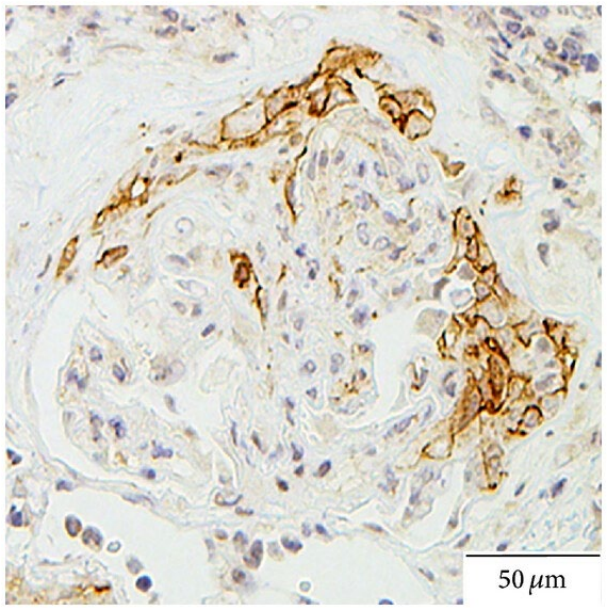
Glomerulonephritis Rapidly Progressive

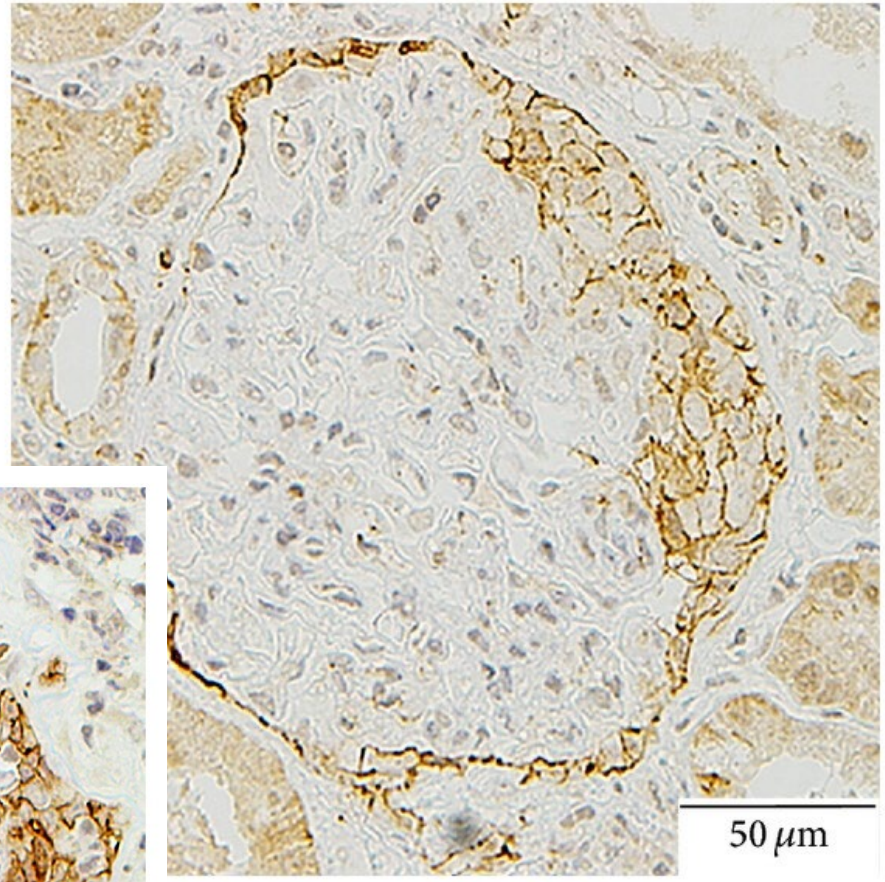
Locations

Prague, Czechia
Praha 4, Czechia
Aalborg, Denmark
Aarhus, Denmark

Show all 46 locations







Koda R, Yoshino A, Imanishi Y, Kawamoto S, Ueda Y, Yaoita E, Kazama JJ, Narita I, Takeda T. Expression of tight junction protein claudin-1 in human crescentic glomerulonephritis. Int J Nephrol. 2014;2014:598670. doi: 10.1155/2014/598670. Epub 2014 Apr 27. PMID: 24868462; PMCID: PMC4020360.
https://clinicaltrials.gov; accessed 30 August 2024

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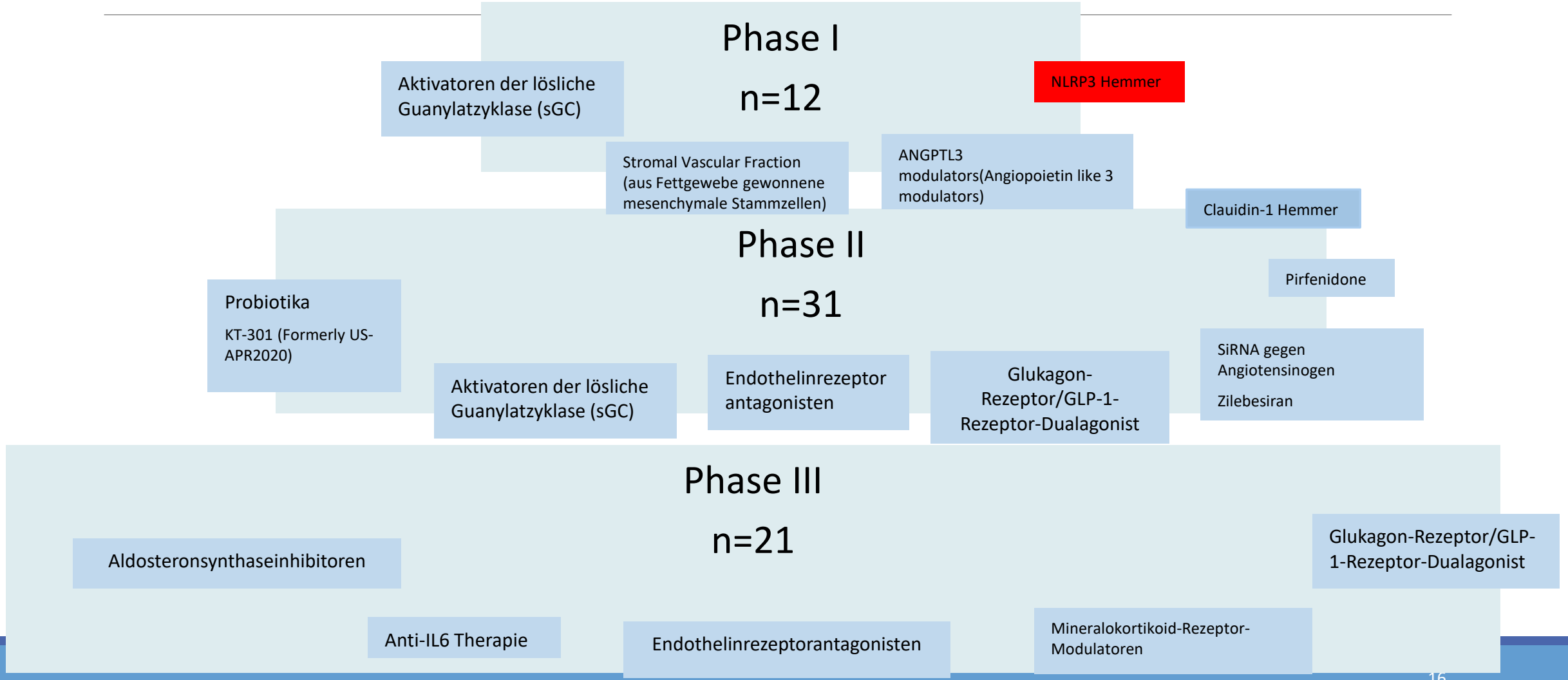


Clinicaltrials.gov Abfrage am 5.9.24

A Phase 1b Study to Assess the Safety, Tolerability, and Pharmacodynamics of AZD4144 in Participants With Established Atherosclerotic Cardiovascular and Chronic Kidney Disease.

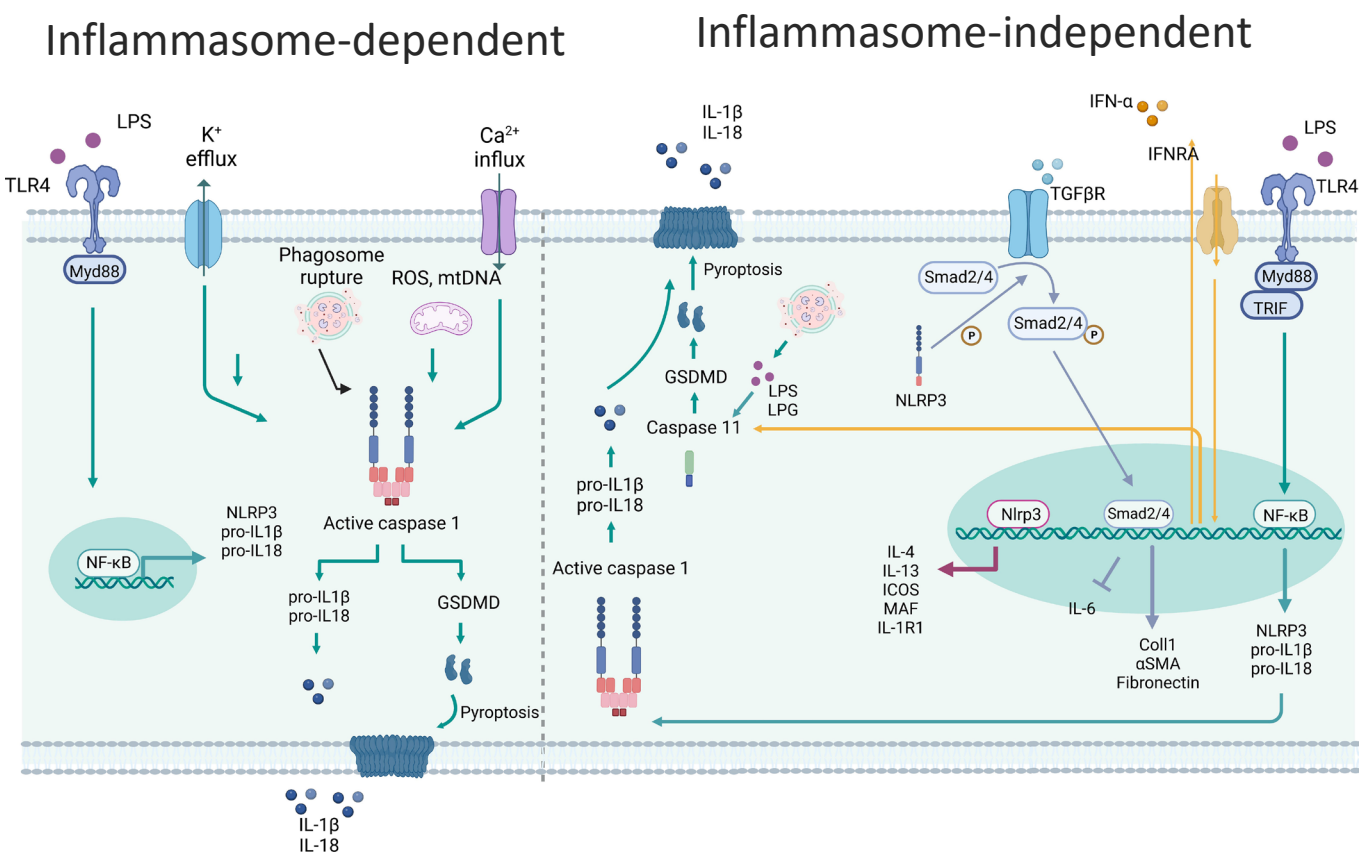
ClinicalTrials.gov ID NCT06675175

Sponsor AstraZeneca

Information provided by AstraZeneca (Responsible Party)

Last Update Posted 2024-11-05

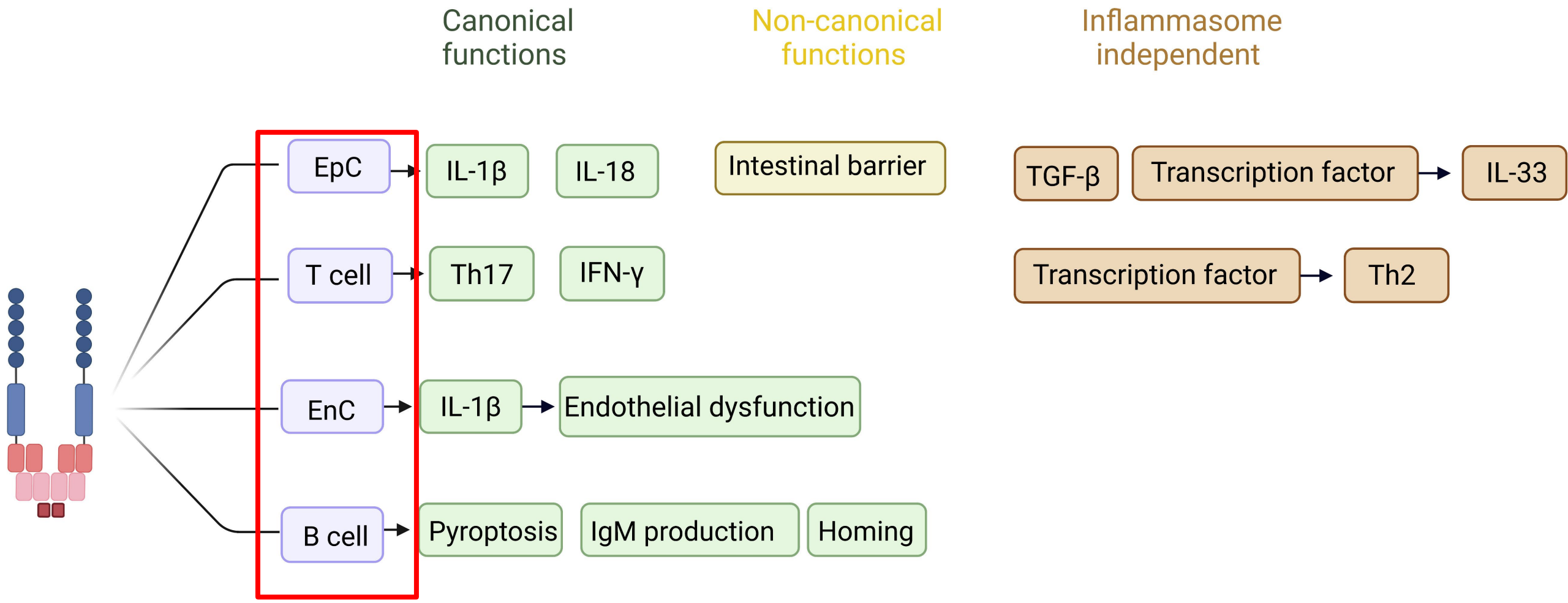
NLRP3-Hemmer



- Aktivierung über TLR4
- Initiiert Bildung des Inflammasom-Komplexes
- Aktivierung von Caspase-1
- Fördert Reifung und Freisetzung von IL-1β und IL-18
- Verursacht pyroptotische Zelllyse durch Gasdermin D
- Wichtige Rolle bei Entzündungsreaktion
- Beteiligt an Pathogenese entzündlicher Erkrankungen

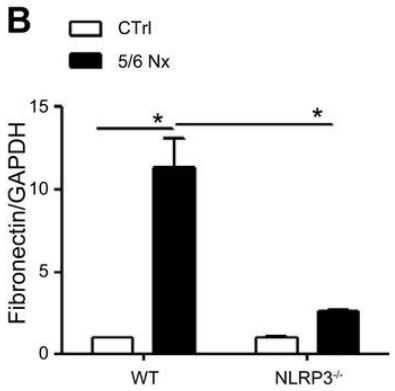
Honda TSB, Ku J, Anders HJ. Cell type-specific roles of NLRP3, inflammasome-dependent and -independent, in host defense, sterile necroinflammation, tissue repair, and fibrosis. Front Immunol. 2023 Jul 25;14:1214289. doi: 10.3389/fimmu.2023.1214289. PMID: 37564649; PMCID: PMC10411525.

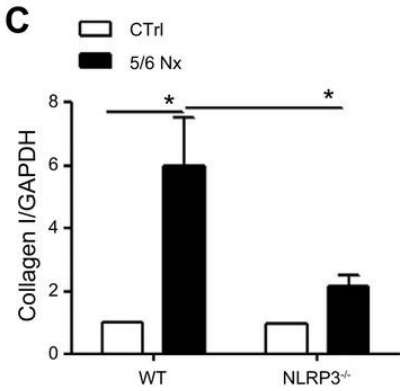
NLRP3-Hemmer

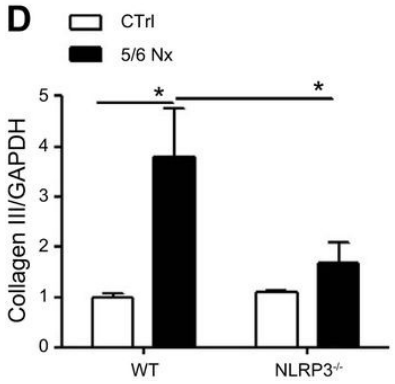


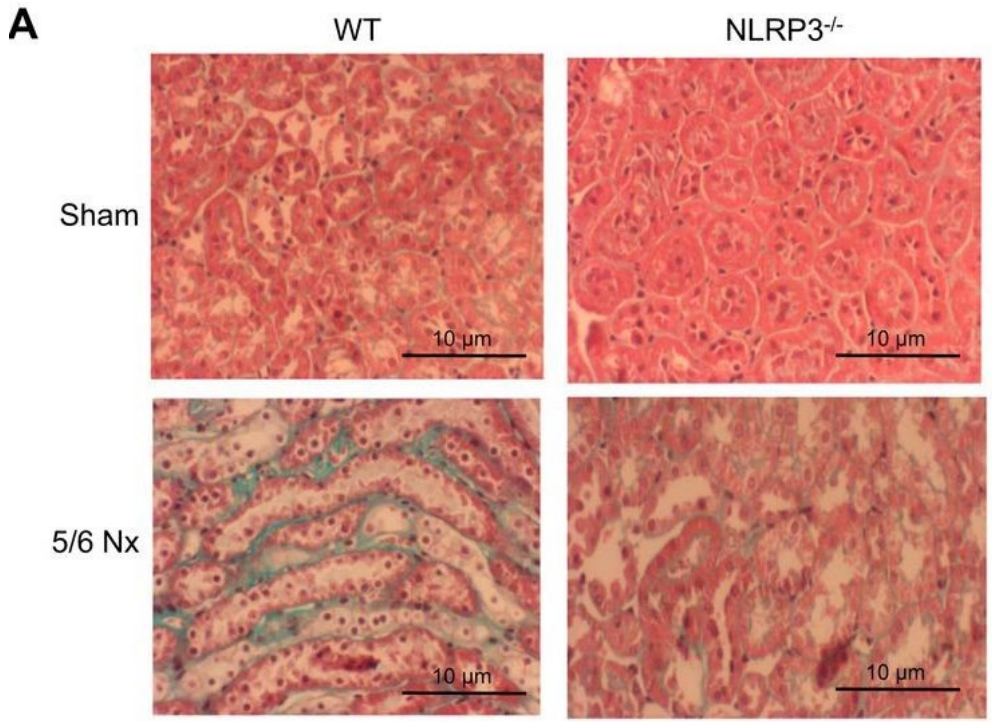
Honda TSB, Ku J, Anders HJ. Cell type-specific roles of NLRP3, inflammasome-dependent and -independent, in host defense, sterile necroinflammation, tissue repair, and fibrosis. Front Immunol. 2023 Jul 25;14:1214289. doi: 10.3389/fimmu.2023.1214289. PMID: 37564649; PMCID: PMC10411525.

Fibrosehemmung durch NLRP3-Hemmung bei Mäusen nach 5/6 Nephrektomie





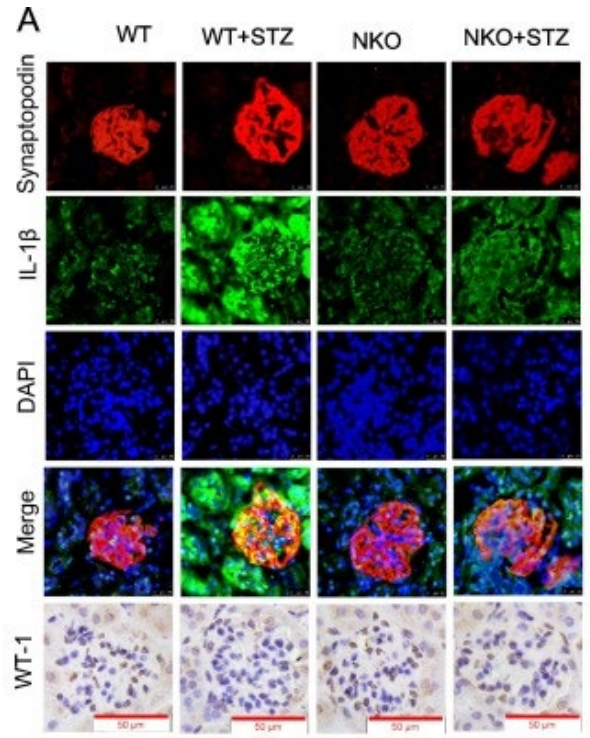


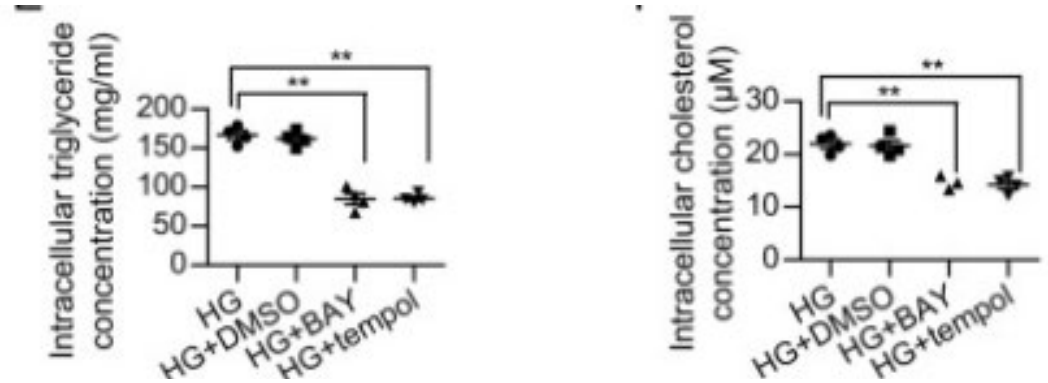


Gong W, Mao S, Yu J, Song J, Jia Z, Huang S, Zhang A. NLRP3 deletion protects against renal fibrosis and attenuates mitochondrial abnormality in mouse with 5/6 nephrectomy. Am J Physiol Renal Physiol. 2016 May 15;310(10):F1081-8. doi: 10.1152/ajprenal.00534.2015. Epub 2016 Feb 17. PMID: 26887832.

Fibrosehemmung durch NLRP3-Hemmung bei diabetischen Mäusen?

Die Hemmung des NLRP3-Inflammasoms lindert Podozytenschäden, indem sie die Lipidakkumulation bei diabetischer Nephropathie unterdrückt.





NLRP3 inflammasome specific inhibitors

Wu M, Yang Z, Zhang C, Shi Y, Han W, Song S, Mu L, Du C, Shi Y. Inhibition of NLRP3 inflammasome ameliorates podocyte damage by suppressing lipid accumulation in diabetic nephropathy. Metabolism. 2021 May;118:154748. doi: 10.1016/j.metabol.2021.154748. Epub 2021 Mar 4. PMID: 33675822.

Podocyte-specific Nlrp3 inflammasome activation promotes diabetic kidney disease.

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

AIM

Define the role podocyte Nlrp3 in diabetic kidney disease (DKD).

METHODS

In vivo: We determined the role of podocyte NLRP3 for sterile inflammation and glomerular dysfunction in experimental DKD using gain- and loss-of-function approaches

Streptozotocin podocyte-specific mouse models

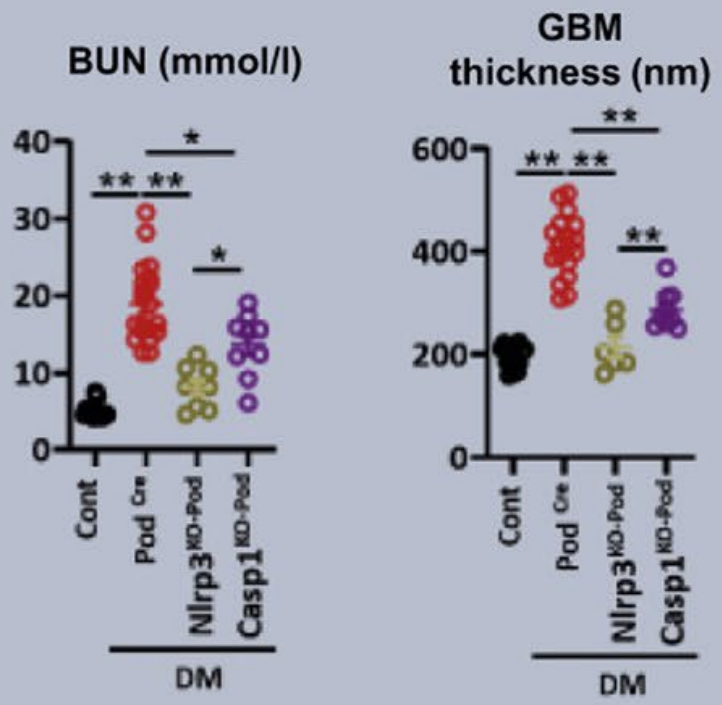
- control: wild type (Pod^{Cre})
- Nlrp3 gain-of-function: $Nlrp3^{V\text{-}Pod}$
- Nlrp3 loss-of-function: $Nlrp3^{KO\text{-}Pod}$
- Caspase-1 loss-of-function: $Casp1^{KO\text{-}Pod}$

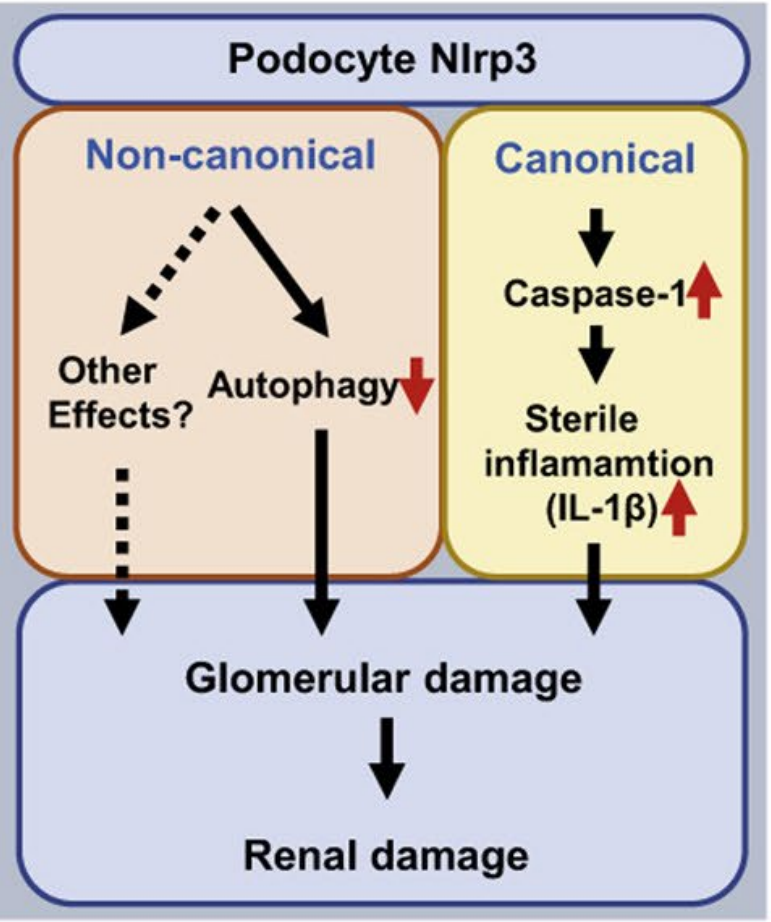
Endpoints (*ex vivo*):
- Kidney function
- Morphological analysis
- Cell death
- Autophagy

In vitro: Effect of Nlrp3 versus caspase-1 inhibitor on autophagy was tested in mouse primary podocytes.

Endpoints (*in vitro*): → Autophagy

RESULTS





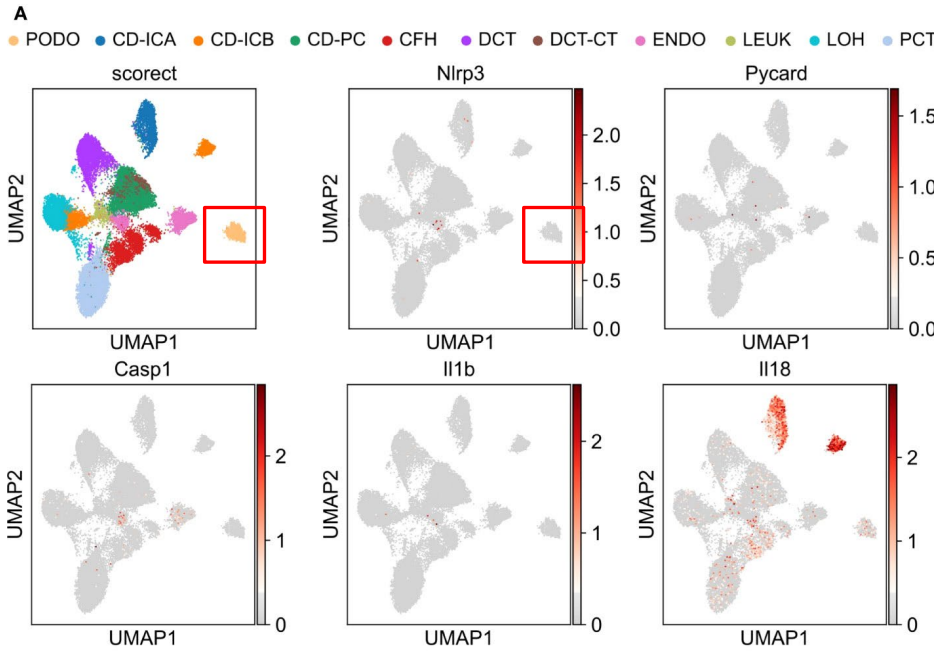
Shahzad, Isermann et al, 2022

CONCLUSION

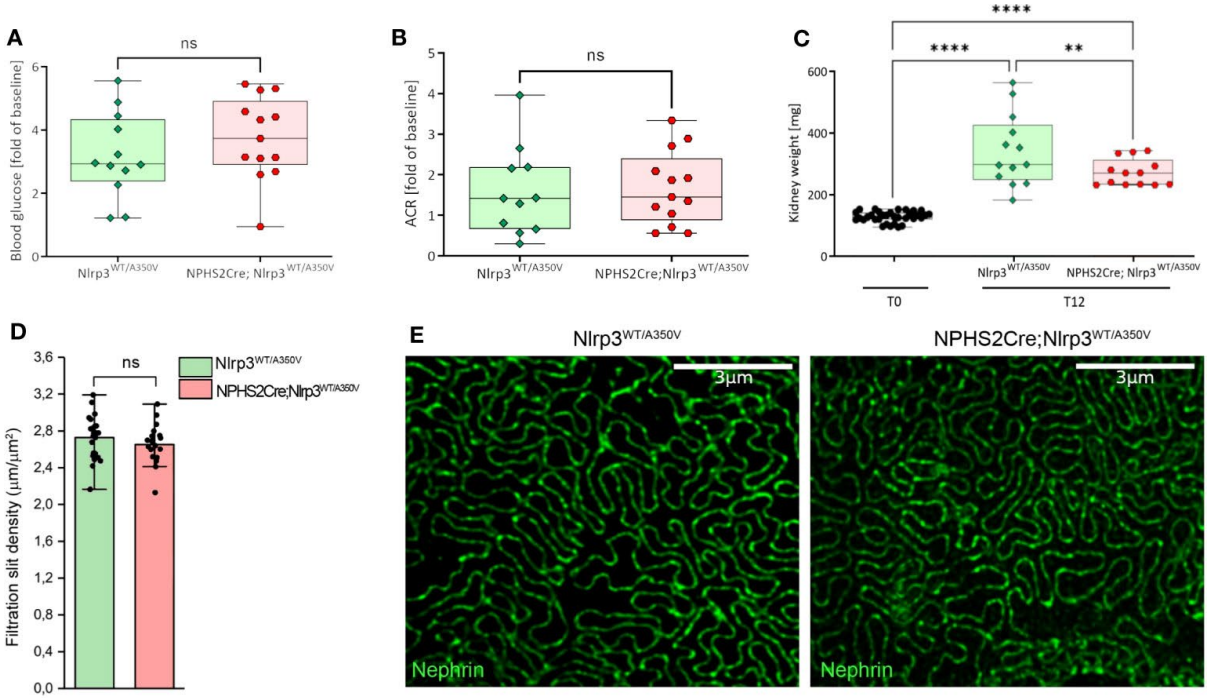
- Podocyte NLRP3 is both sufficient and required for sterile inflammation and glomerular damage in experimental DKD.
- These data support an "immune-cell like" function of podocytes.
- NLRP3 regulates canonical and non-canonical effects. Hence, pharmaceutically targeting NLRP3 is expected to be superior to inhibition of caspase-1 mediated cytokine maturation.

No NLRP3 inflammasome activity in kidney epithelial cells, not even when the NLRP3-A350V Muckle-Wells variant is expressed in podocytes of diabetic mice

Unbiased single-cell RNA sequencing of diabetic human and healthy murine kidneys indicates the absence of canonical NLRP3 inflammasome



Introduction of a podocyte-specific Nlrp3WT/A350V mutation does not aggravate the phenotype after STZ/uNX treatment.

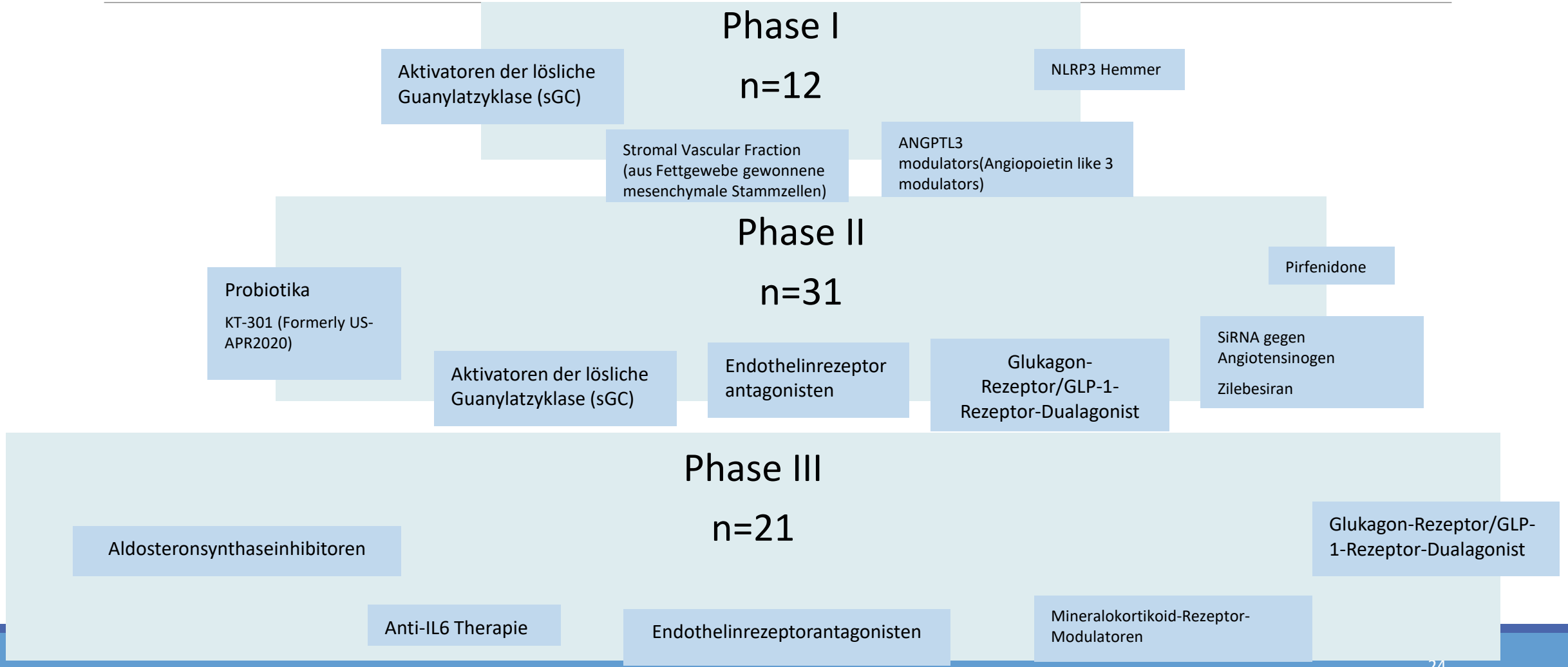


Kunte SC, Marschner JA, Klaus M, Honda T, Li C, Motrapu M, Walz C, Angelotti ML, Antonelli G, Melica ME, De Chiara L, Semeraro R, Nelson PJ, Anders HJ. No NLRP3 inflammasome activity in kidney epithelial cells, not even when the NLRP3-A350V Muckle-Wells variant is expressed in podocytes of diabetic mice. Front Immunol. 2023 Aug 23;14:1230050. doi: 10.3389/fimmu.2023.1230050. PMID: 37744356; PMCID: PMC10513077.

Laufende Studien im Bereich CKD

Showing results for: **CKD** | **Recruiting studies** | **Phase: 1, 2, 3** | **Interventional studies**

+ Synonyms of conditions or disease (9)



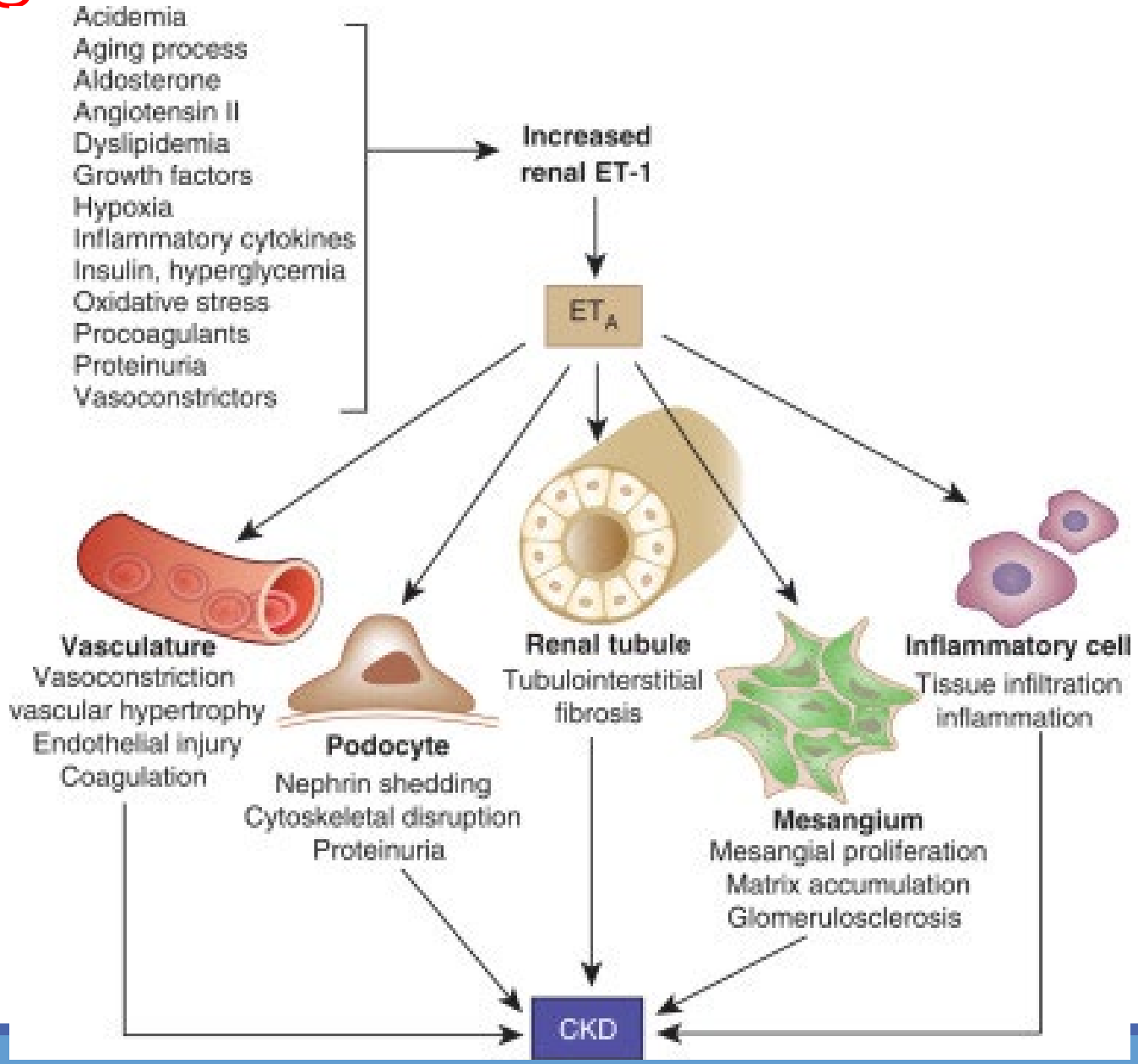
Clinicaltrials.gov Abfrage am 5.9.24

Aktuell laufende Studien an der Charité, Klinik mit Scherpunkt Nephrologie und internistische Intensivmedizin – Kontaktaufnahme jederzeit! Nephrologie-studien@charite.de

Studie/Indikation	Substanzklasse	Ansprechpartner Immer: nephrologie-studien@charite.de
Hypertonie	Aldosteronsynthasehemmer	Markus.vandergiet@charite.de
CKD (und Hypertonie)	Aldosteronsynthasehemmer	eva-vanessa.schrezenmeier@charite.de Markus.vandergiet@charite.de
Alport-Syndrom	SGLT2i, Farnesoid-X-R-Agonist	jan.halbritter@charite.de
ANCA-Vaskulitis	CAR T Zellen Iptacopan, Claudin-AK (Fibrosehemmung), Biomarker-Studien	adrian.schreiber@charite.de
Anti-GBM Erkrankung	Imlifidase	adrian.schreiber@charite.de
IgAN	rec TACI Ravulizumab	adrian.schreiber@charite.de
SLE	CAR T Zellen	eva-vanessa.schrezenmeier@charite.de
COVID bei Risikogruppen (NTX)	Molnupiravir	eva-vanessa.schrezenmeier@charite.de
MCD	CD40L/BTKi, Register (FOrMe Regsiter)	eva-vanessa.schrezenmeier@charite.de
ADPKD	SGLT2i, IGF1R-Antikörper Phase 1 und 2	jan.halbritter@charite.de
AKI mit ausbleibender Erholung; Pat. mit V.a. akut interst. Nephritis	Diagnostik-Studien	philipp.enghard@charite.de

Endothelinrezeptorantagonisten bei CKD

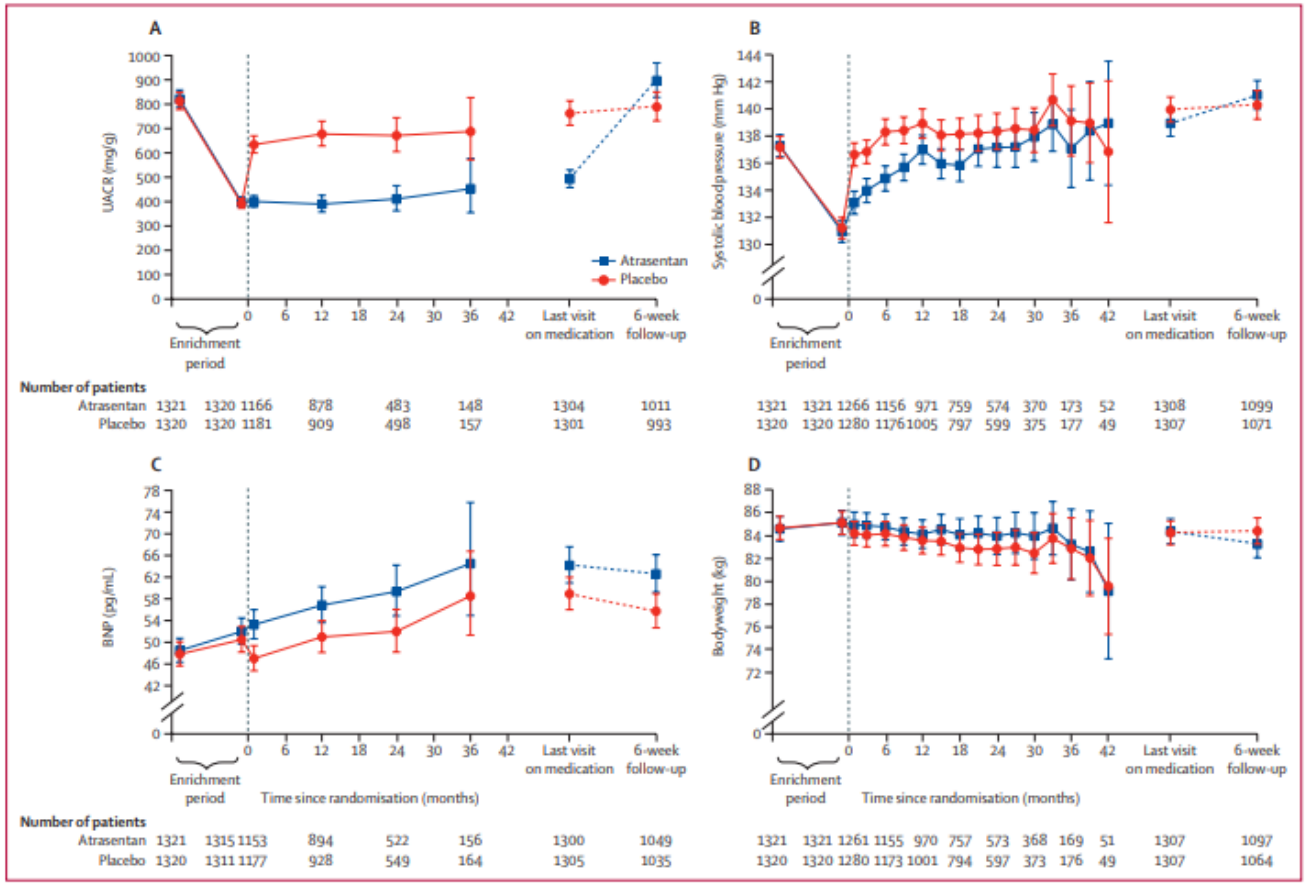
- ET-1
  - ist ein starker Vasokonstriktor
  - trägt zur Erhöhung des Blutdrucks bei
  - erhöht die glomeruläre Permeabilität
  - führt zu einer Dysfunktion der Podozyten
  - fördert Fibrose



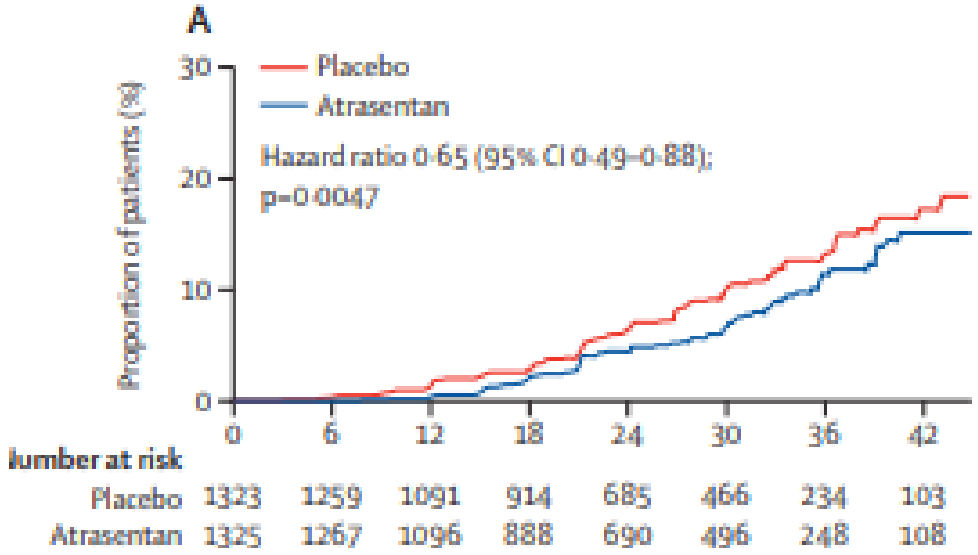
Kohan, D Kindey International 2014

It´s a long story….SONAR- abgebrochen

Hauptproblem: Fluid retention, Anämie

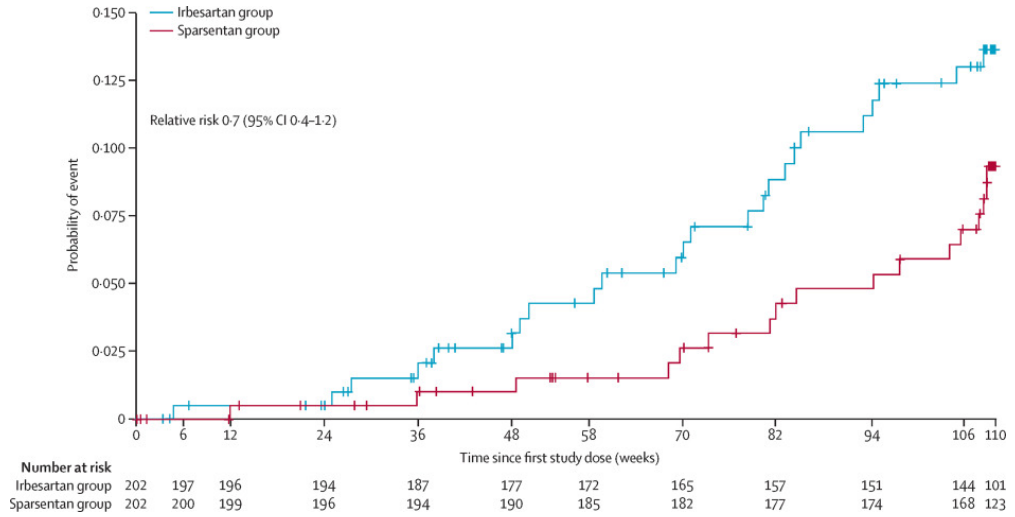


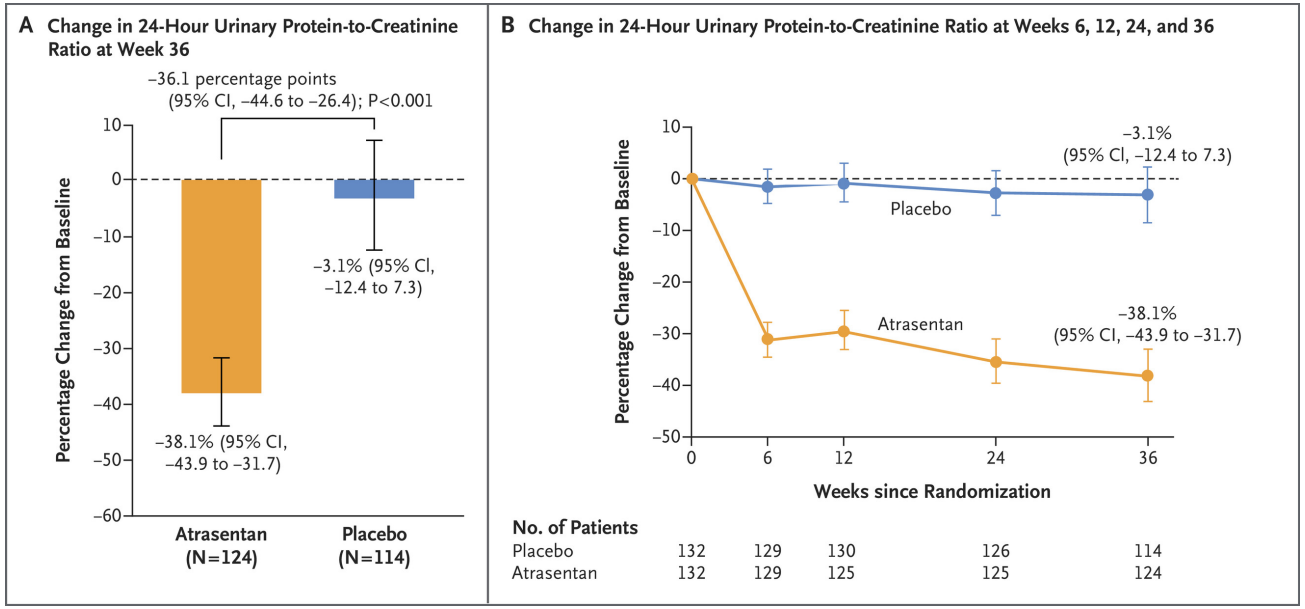
Verdopplung des Serumkreatinins oder eGFR <15 mL/min pro 1,73 m² über ≥90 Tage anhaltend, chronische Dialyse über ≥90 Tage, Nierentransplantation oder Tod aufgrund von KF



Heerspink HJL, Parving HH, Andress DL, Bakris G, Correa-Rotter R, Hou FF, Kitzman DW, Kohan D, Makino H, McMurray JJV, Melnick JZ, Miller MG, Pergola PE, Perkovic V, Tobe S, Yi T, Wigderson M, de Zeeuw D; SONAR Committees and Investigators. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. Lancet. 2019 May 11;393(10184):1937-1947. doi: 10.1016/S0140-6736(19)30772-X. Epub 2019 Apr 14. Erratum in: Lancet. 2019 May 11;393(10184):1936. doi: 10.1016/S0140-6736(19)30939-0. PMID: 30995972.

Sparsentan und Atrasentan bei IgA-NP





Time to reach the composite kidney failure endpoint of confirmed 40% eGFR reduction, end-stage kidney disease, or all-cause mortality

Rovin BH et al. Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active-controlled, phase 3 trial. Lancet. 2023 Dec 2;402(10417):2077-2090. doi: 10.1016/S0140-6736(23)02302-4. Epub 2023 Nov 3. PMID: 37931634.

Heerspink HJL, Jardine M, Kohan DE, Lafayette RA, Levin A, Liew A, Zhang H, Lodha A, Gray T, Wang Y, Renfurm R, Barratt J; ALIGN Study Investigators. Atrasentan in Patients with IgA Nephropathy. N Engl J Med. 2024 Oct 25. doi: 10.1056/NEJMoa2409415. Epub ahead of print. PMID: 39460694.

Nahe Zukunft…

NCT05003986 Recruiting

Study of **Sparsentan** Treatment in Pediatrics With Proteinuric Glomerular Diseases

Conditions

Alport Syndrome | Focal Segmental Glomerulosclerosis | IgA Vasculitis | Immunoglobulin A Nephropathy | Minimal Change Disease

Locations

Study to Investigate Efficacy, Safety, and Tolerability of **Zibotentan**/Dapagliflozin Compared to Dapagliflozin in Participants With Chronic Kidney Disease and High Proteinuria (ZENITH High Proteinuria)

Conditions

Chronic Kidney Disease With High Proteinuria

Locations

- Huntsville, Alabama, United States
- Bakersfield, California, United States
- Sun City West, Arizona, United States
- Huntington Park, California, United States

Show all 296 locations

NCT05834738 Recruiting

Randomized, Double-blind, Placebo-controlled, Crossover Study of **Atrasentan** in Subjects With IgA Nephropathy

Conditions

IgA Nephropathy | Immunoglobulin A Nephropathy

Locations

- Birmingham, Alabama, United States
- Oak Brook, Illinois, United States
- Atlanta, Georgia, United States
- Boston, Massachusetts, United States

Show all 30 locations