

Podocytes – An Innocent Bystander in Cancer

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**Onconeurology
Symposium 2026**



Mass General Brigham



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DISCLOSURES

- **Please state any/all financial disclosures for past 24 months.**

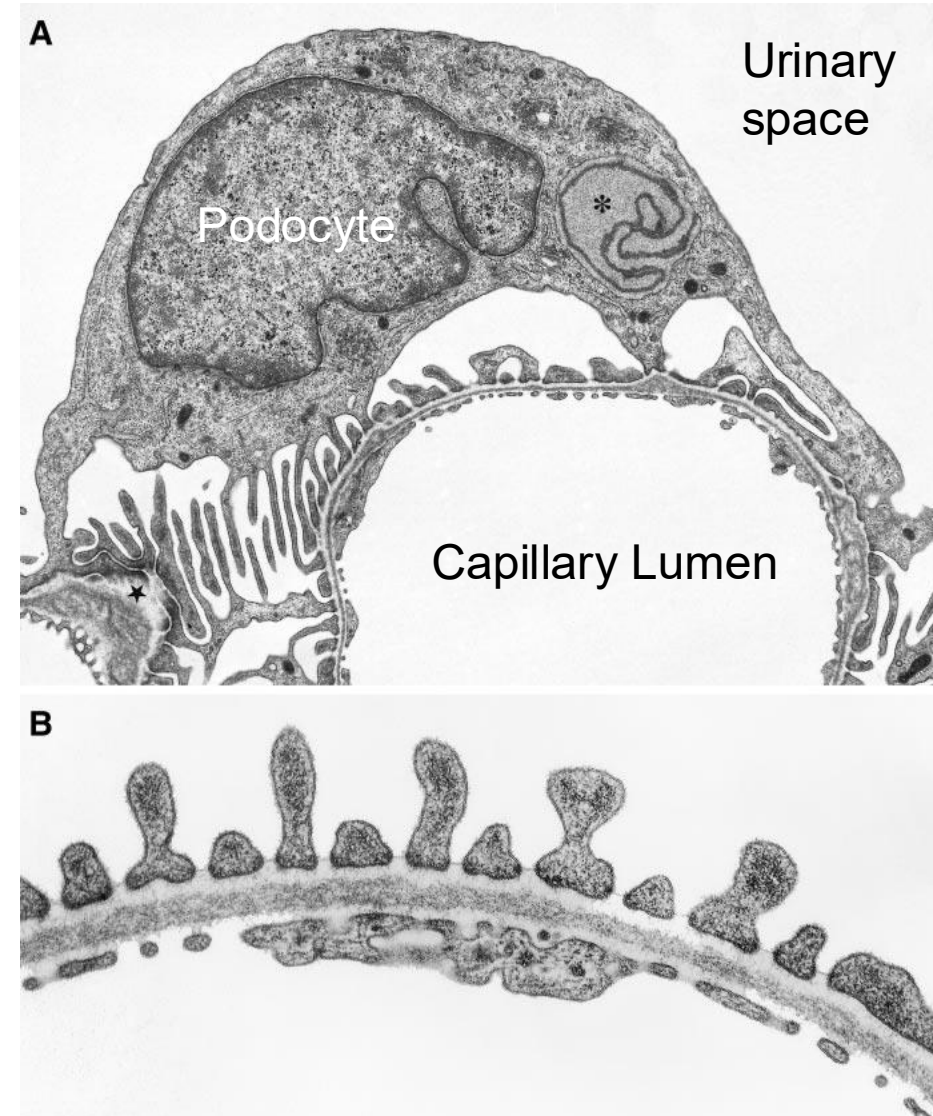
Astrid Weins, MD, PhD

- *Scientific Advisory Board: Vera Therapeutics*
- *Speaker: Genentech, Traverre Therapeutics*
- *Royalties: Elsevier*
- *Patent licensing fees: Euroimmun*

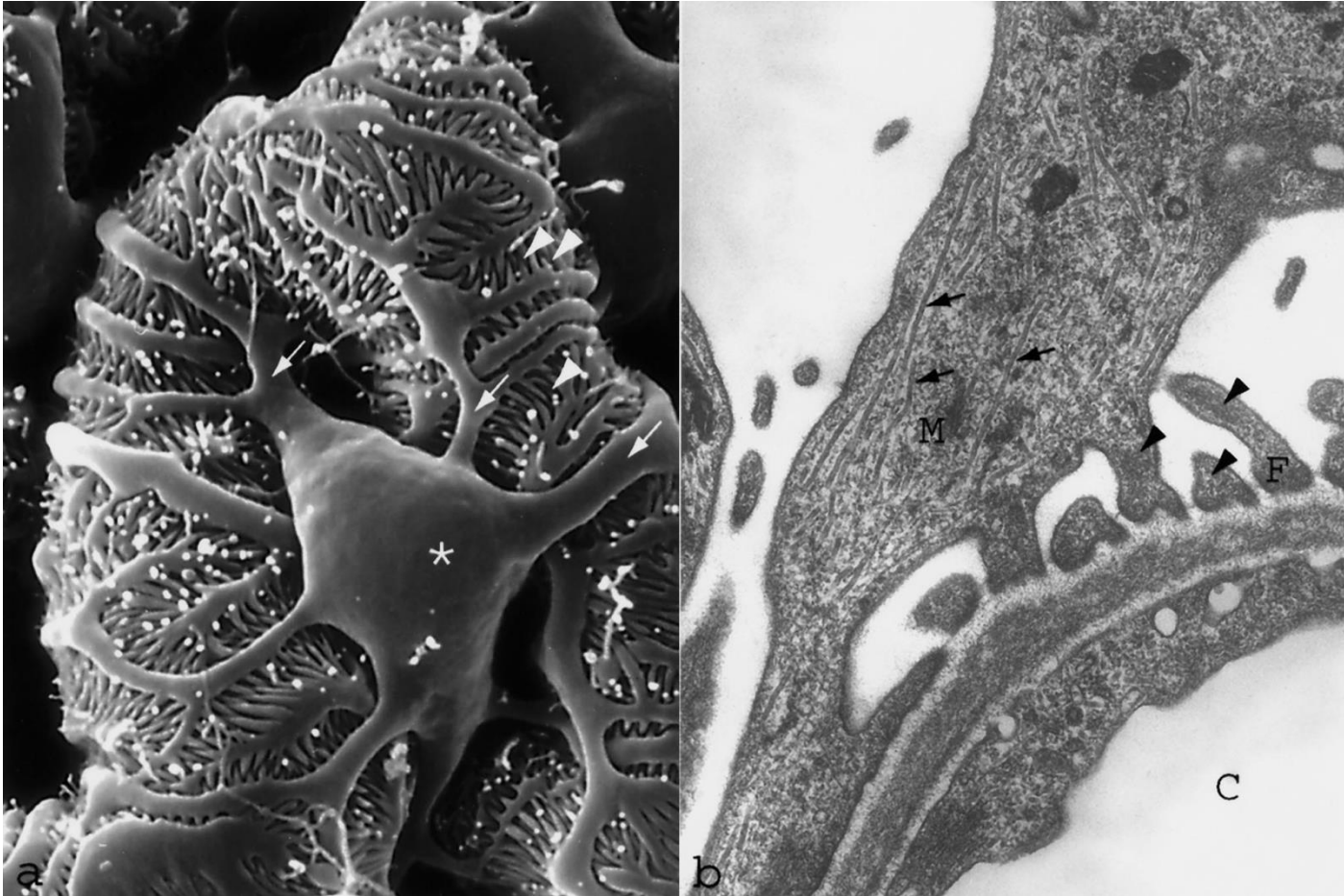
Learning Objectives

1. Understand podocyte vulnerabilities and exposures.
2. Comprehend direct and indirect mechanisms of podocyte injury.
3. Understand associations of paraneoplastic and therapy-related podocyte injury.

The Podocyte – a privileged and vulnerable cell



The arborized structure of podocytes relies on a specialized cytoskeleton



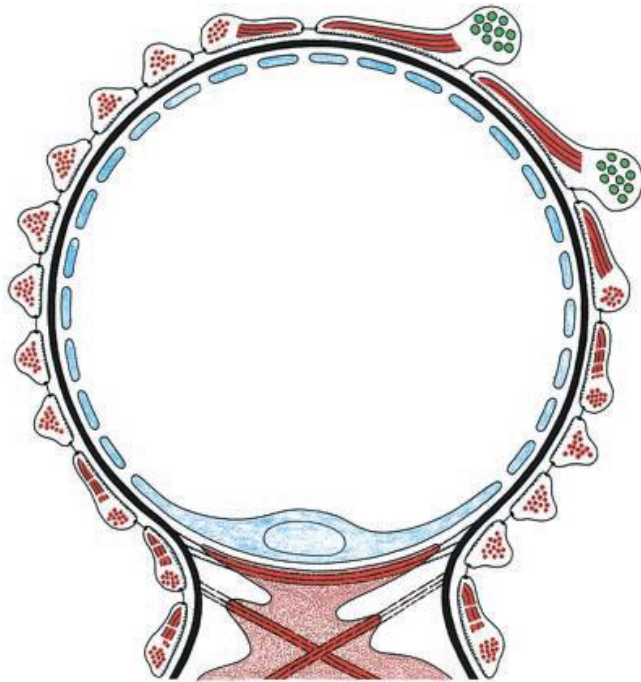
Asterisk: Podocyte cell body

Arrows: Microtubules in major processes

Arrowheads: Actin filament bundles in foot processes

Kobayashi et al, 2001

Cytoskeletal organization of podocyte processes



Major processes:

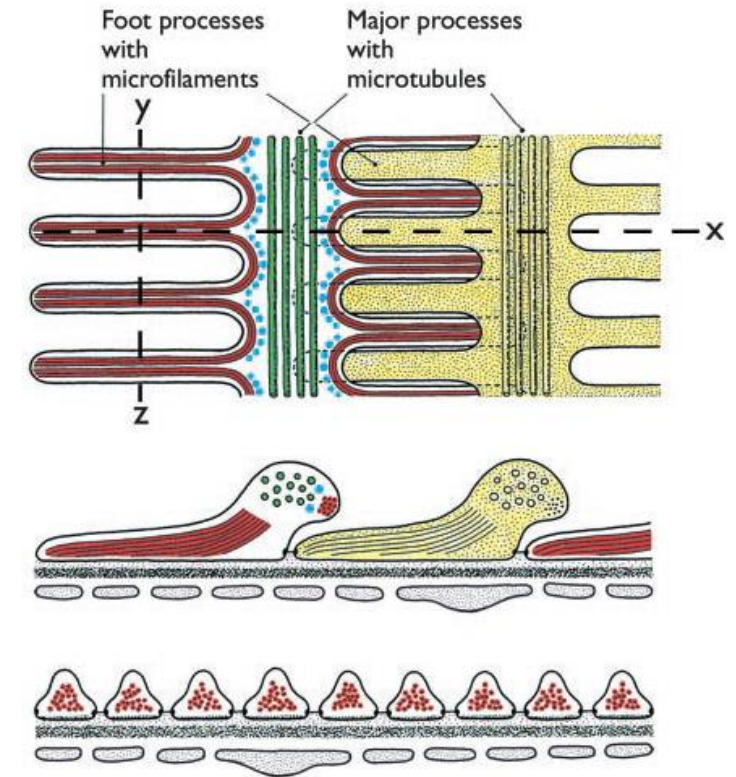
- Microtubules (tubulin)
- Intermediate filaments (vimentin, plectin)

Foot processes:

- Microfilaments (actin)

Dynamic response to outside forces happens mostly in foot processes by rearrangement of their actin cytoskeleton (Ca^{2+} /Rho-K).

Major processes remain mostly static.



Pavenstaedt et al, 2001

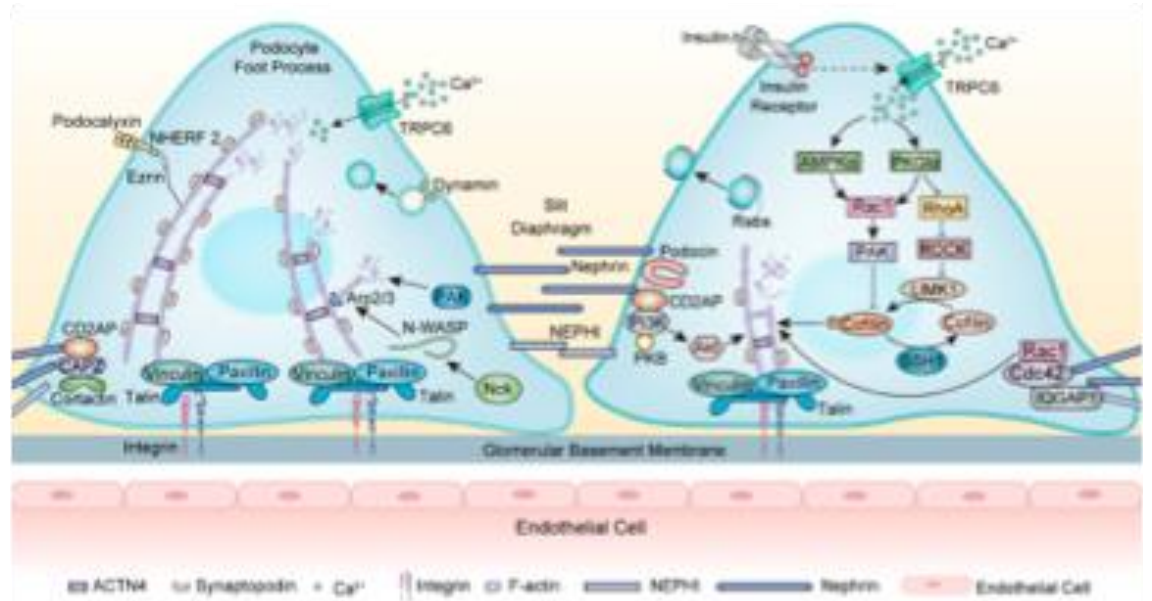
Disruption of the cytoskeleton leads to foot process effacement

Microtubules

- facilitate **intracellular transport of organelles, proteins (including nephrin!), molecules (including ATP!) and vesicles.** (*Gibbs et al, 2015*)
- crucial for maintaining **cell shape, polarity and structural integrity.** (*Kobayashi et al, 2001*)
- essential for **podocyte foot process formation and maintenance** (*Kobayashi et al, 2001*)

Actin

- plays dominant role in **establishing and maintaining foot processes**
- central **actin bundles** and a **network of cortical actin**
- in a highly dynamic state of **constant assembly and disassembly**
- strongly **sensitive and responsive to mechanical stress** enhance **adhesion to the extracellular matrix** (*Endlich et al, 2024*)
- engaged in **generating tensile forces**



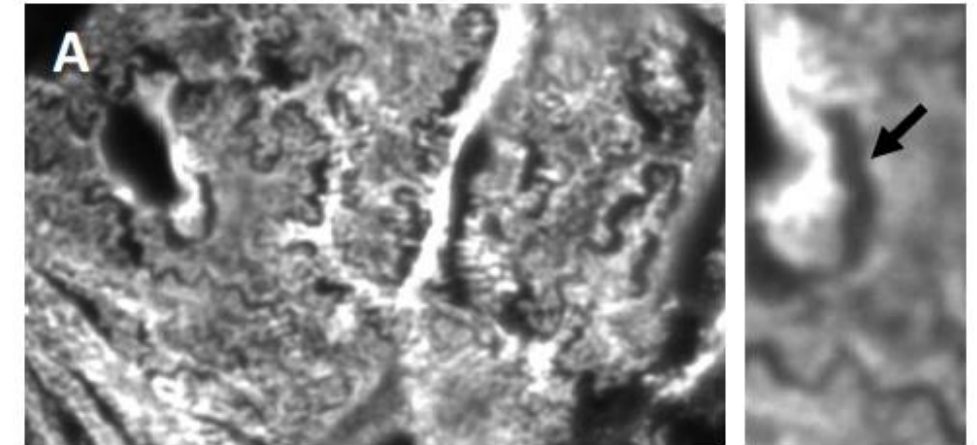
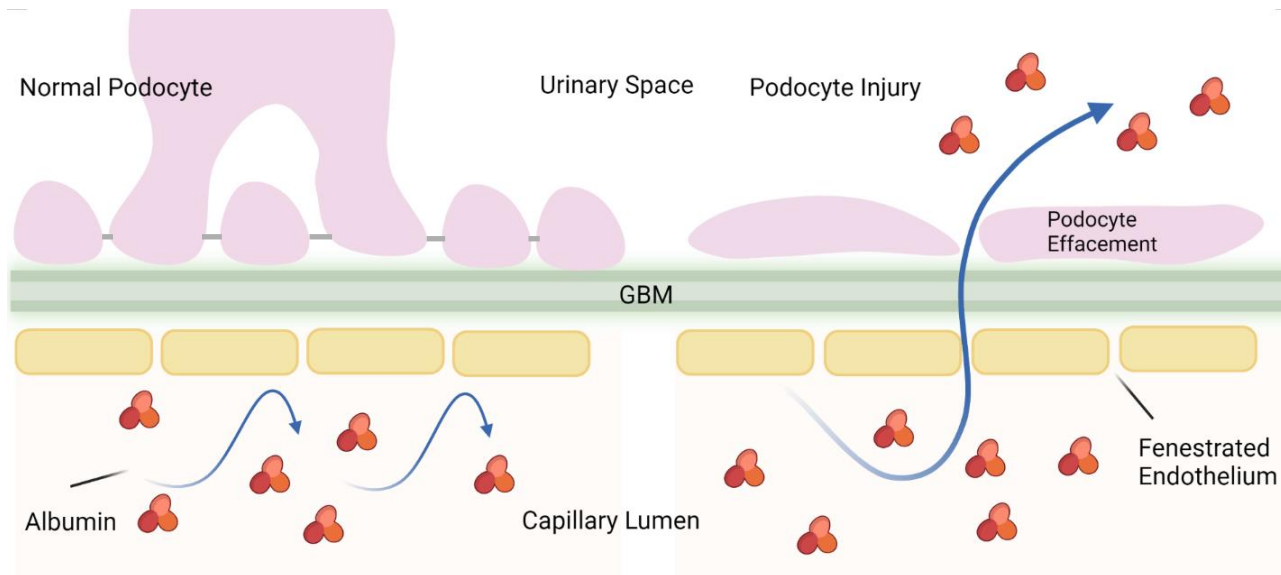
The pathophysiology of proteinuria via slit diaphragm loss

Foot process effacement and loss of filtration surface

Focal defects in podocyte coverage (SD loss or cell loss)

→ **albuminuria**

Increased hydraulic conductivity and ineffective reflection



Sustained or severe podocyte injury leads to irreversible podocyte loss

Lessons from animal models:

Sustained podocyte injury that leads to podocyte loss eventually results in segmental or global glomerulosclerosis.

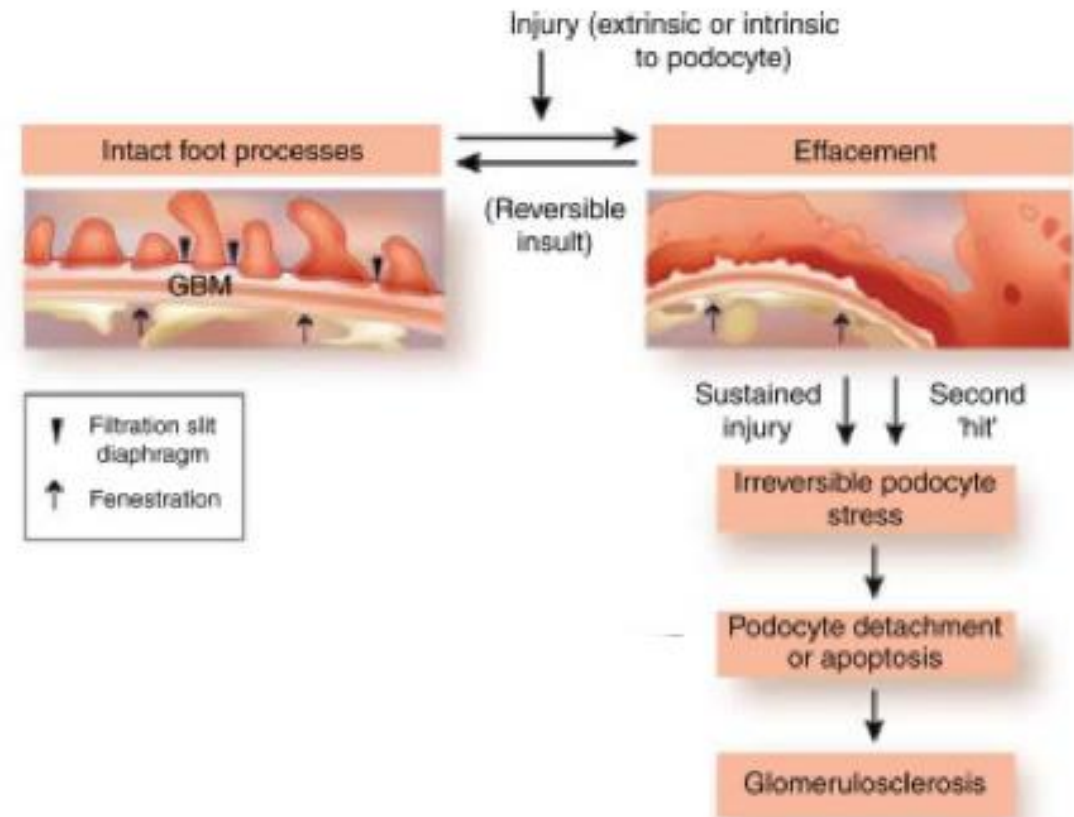
A second hit or preexisting podocyte vulnerability may exacerbate the injury.

Toxic podocyte depletion (*Wiggins*)
(diphtheria toxin)

Adriamycin nephropathy (*Hakrrouch/Weins*)

Uninephrectomy model (*Kriz*)

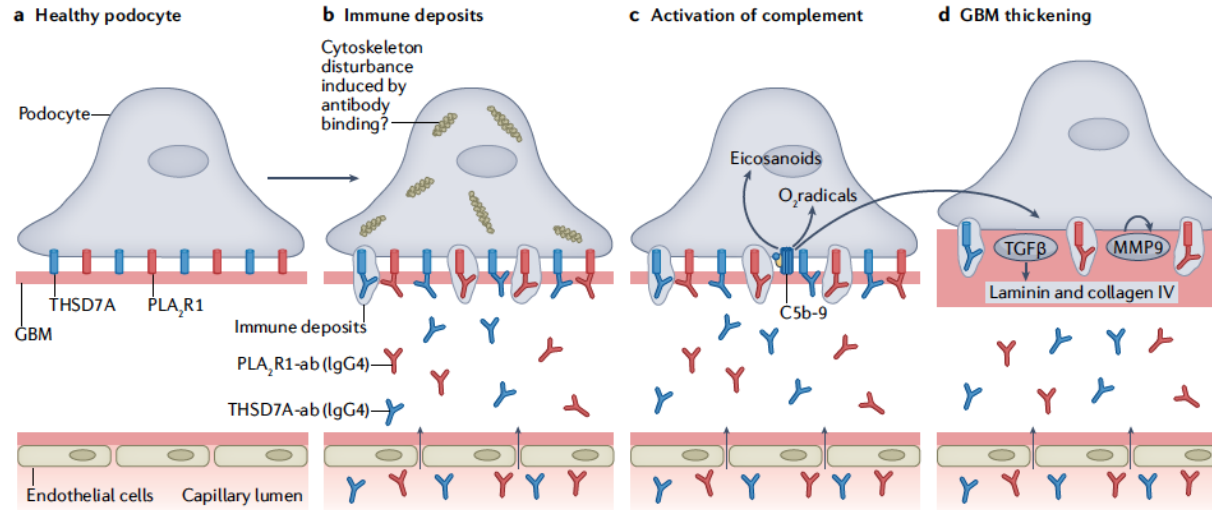
CD25/LMB2 model (*Ichikawa*)



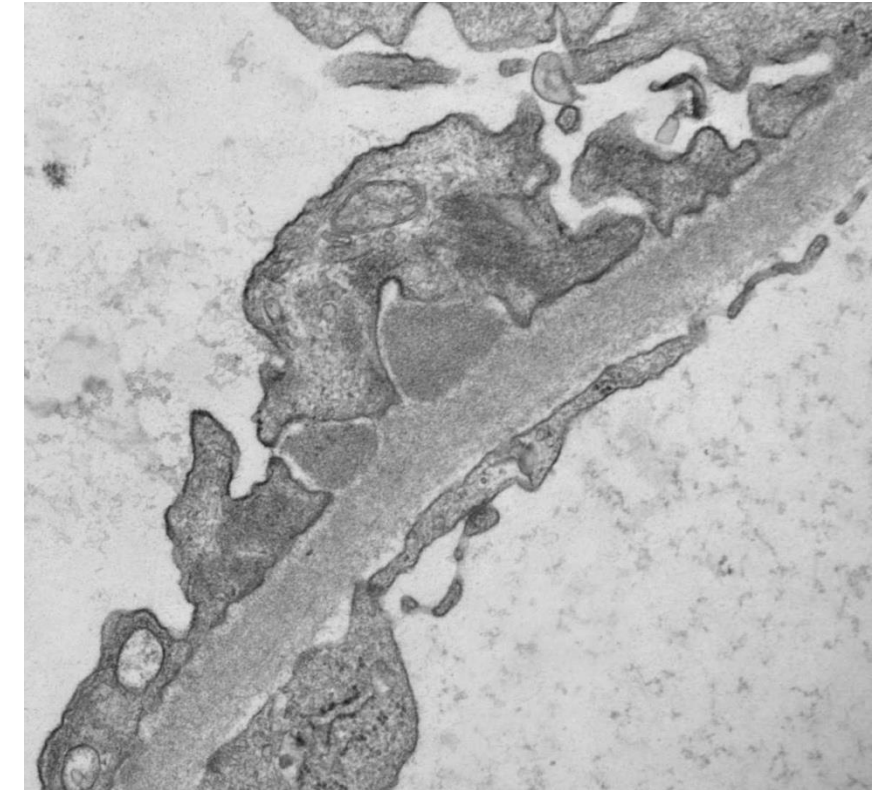
D'Agati, Kidney International, 2008.

Podocyte injury via subepithelial immune complex formation

Early phase of subepithelial immune complex formation in MN



- Immune complexes build up at the base of the foot process (subepithelial)
- Lifting of podocytes off the GBM
- Foot process effacement and apical dislodging of the slit diaphragm



BWH Renal Pathology

Podocyte Injury in Cancer Patients - Associations

Paraneoplastic

Diffuse Podocytopathy

- anti-Nephrin (lymphoma, thymoma)

Membranous Nephropathy

- Anti-NELL1

Collapsing Glomerulopathy

- *APOL1* HR alleles
- Ischemia/Vasculopathy/TMA

Paraprotein/Light chain-Associated

- Crystal storing podocytopathy
- Light chain deposition
- AL amyloidosis

Therapy-related

Diffuse Podocytopathy

- Immune Check Point Inhibition (anti-nephrin)
- NSAIDs
- Anti-EGFR, VEGF-I, BCR-Abl Inhibition
- Tyrosine Kinase Inhibition
- Antibody Drug Compounds (MT blockers etc)

Membranous Nephropathy

- FAT1 (SCT)
- NSAIDs

Collapsing Glomerulopathy

- Bisphosphonates
- *APOL1* HR alleles
- Vasculopathy/TMA
- As a Complication of Diffuse Podocytopathy

Case 1 – Proteinuria after ADC targeting B7-H4

50 y/o WF with metastatic adenocystic carcinoma

Treated with cisplatin x3 cycles (SCr rose from pre-cisplatin baseline of 0.8 mg/dl to 1.4, then improved back to baseline)

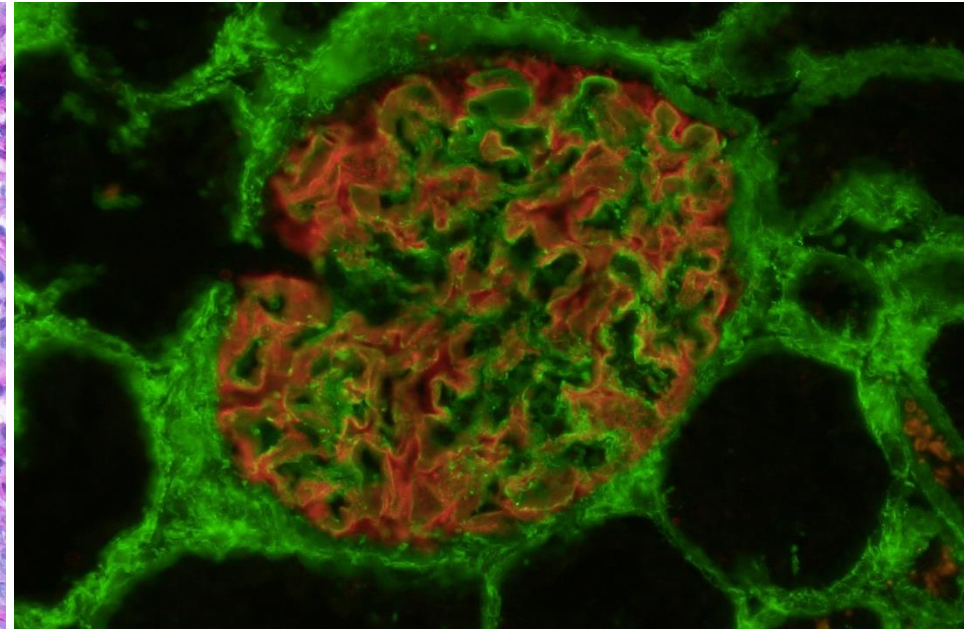
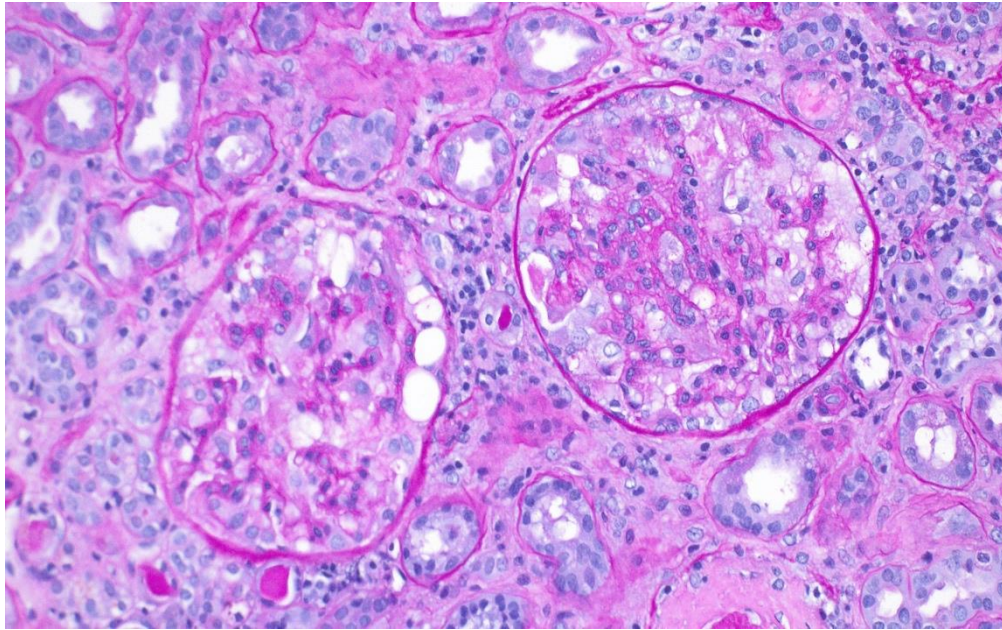
Enrolled in clinical trial with **microtubule assembly blocker ADC targeting B7-H4**

Soon developed new-onset proteinuria; 24 hr urine protein rose quickly up to 12 g

Developed periorbital edema, pedal edema, ascites, hyperlipidemia

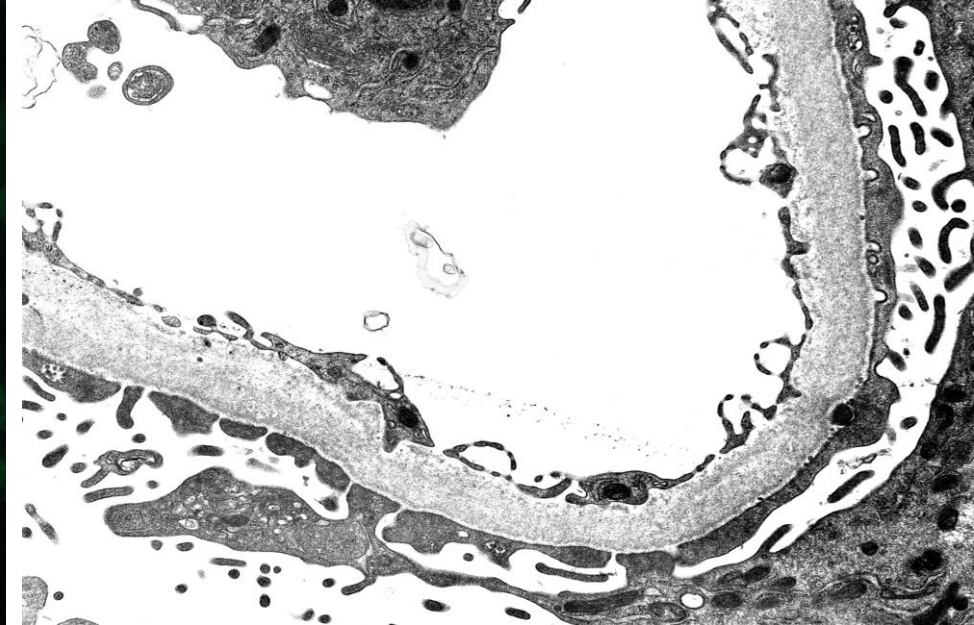
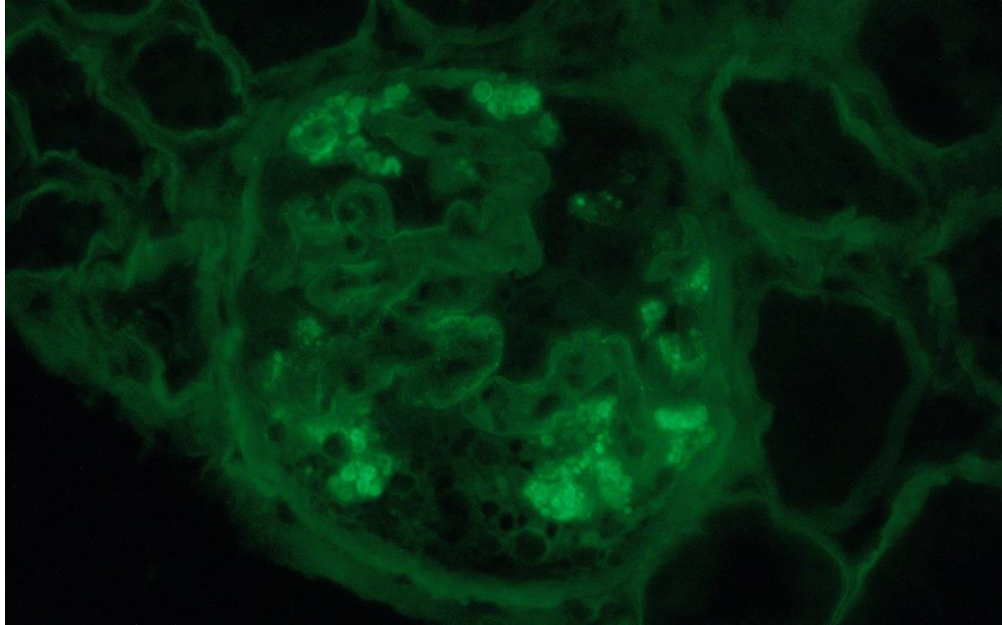
Serologic evaluation: neg/normal dsDNA, C3/C4, ANCA, antiPLA2R, THSD7A, ANA, hepatitis, cryoglobulins, sFLC, SPEP and IF. RF was 25.

PAS



IgG/
nephrin

Albumin



EM

Case 1: Kidney Biopsy Diagnosis

DIFFUSE PODOCYTOPATHY WITH EXTENSIVE FOOT PROCESS EFFACEMENT AND COLLAPSING FEATURES, LIKELY REPRESENTING A TOXIC PODOCYTOPATHY IN THE SETTING OF ADC THERAPY

No significant overlapping staining of IgG with Nephrin is seen; an anti-nephrin-mediated podocytopathy/minimal change disease can be ruled out

ADCs can enter the podocyte via intrinsic receptors

B7-H4

Tissue factor

nephron
**Experimental
Nephrology**

Original Paper

Nephron Exp Nephrol 2010;116:e72–e83
DOI: [10.1159/000319320](https://doi.org/10.1159/000319320)

The Cytoplasmic Domain of Tissue Factor Restricts Physiological Albuminuria and Pathological Proteinuria Associated with Glomerulonephritis in Mice

Jim Apostolopoulos Leon Moussa Peter G. Tipping

Centre for Inflammatory Diseases

Key Words

Tissue factor · Podocyte · Albuminuria · Proteinuria · Glomerulonephritis

Abstract

Background/Aims: Tissue factor (TF) is a transmembrane protein that is essential for coagulation. TF is expressed on podocytes and its cytoplasmic domain has cell signalling functions in epithelial cells. **Methods:** Mice lacking the cyto-

Clinical & Experimental Immunology
The Journal of Translational Immunology

Clinical and Experimental Immunology ORIGINAL ARTICLE doi:10.1111/cei.12452

B7x/B7-H4 modulates the adaptive immune response and ameliorates renal injury in antibody-mediated nephritis

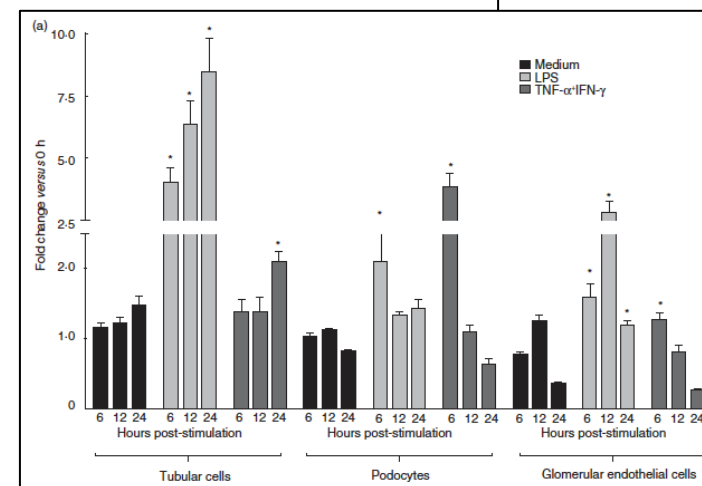
R. D. Pawar,^{*1} B. Gollav,¹ Y. Xia,^{*1} L. Herlitz,² J. Doerner,³ S. Chalmers,¹ K. Ghosh,¹ X. Zang⁴ and C. Putterman^{*1}

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Summary

Kidney disease is one of the leading causes of death in patients with lupus and other autoimmune diseases affecting the kidney, and is associated with deposition of antibodies as well as infiltration of T lymphocytes and macrophages, which are responsible for initiation and/or exacerbation of inflammation and tissue injury. Current treatment options have relatively limited efficacy; therefore, novel targets need to be explored. The co-inhibitory molecule, B7x, a new member of the B7 family expressed predominantly by non-lymphoid tissues, has been shown to inhibit the proliferation, activation and functional responses of CD4 and CD8 T cells. In this study, we found that B7x was expressed by intrinsic renal cells, and was up-regulated upon stimulation with inflammatory triggers. After passive administration of antibodies against glomerular antigens, B7x^{-/-} mice developed severe renal injury accompanied by a robust adaptive immune response and kidney up-regulation of inflammatory mediators, as well as local infiltration of T cells and macrophages. Furthermore, macrophages in the spleen of B7x^{-/-} mice were polarized to an inflammatory phenotype. Finally, treatment with B7x-immunoglobulin (Ig) in this nephritis model decreased kidney damage and reduced local inflammation. We propose that B7x can modulate kidney damage in autoimmune diseases including lupus nephritis and anti-glomerular basement membrane disease. Thus, B7x mimetics may be a novel therapeutic option for treatment of immune-mediated kidney disease.

Keywords: B7x, co-inhibition, co-stimulation, nephritis, T cells



Case 2 – Proteinuria after Stem Cell Transplant

64yo WF with AML, s/p allogeneic PBSCT

Course complicated by multi-organ cGvHD

Referral for new nephrotic range proteinuria

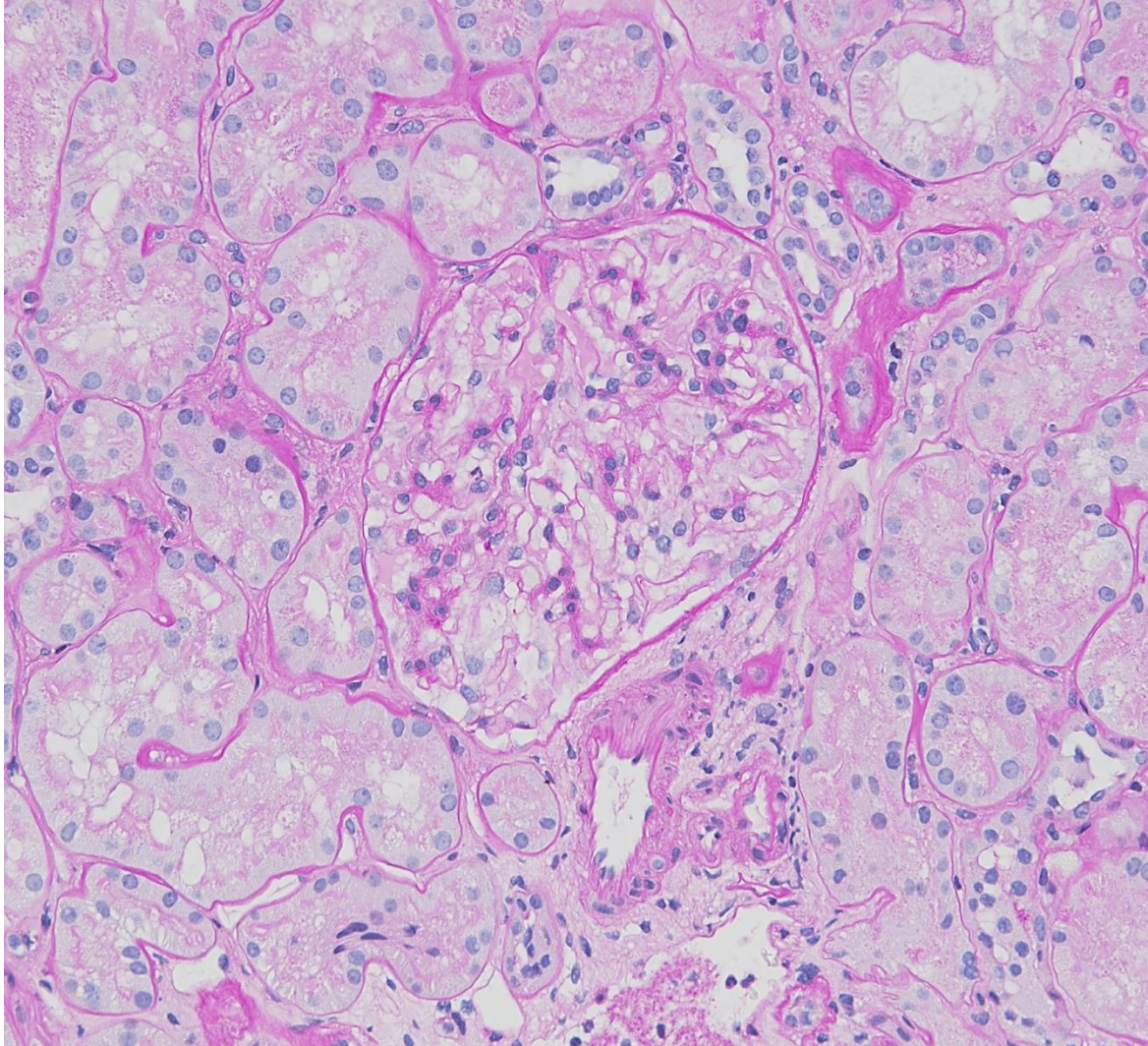
Labs: SCr 0.83; eGFR 79; serum albumin 2.9

Urinalysis: 3+ protein; 24h urine 6.4g/day

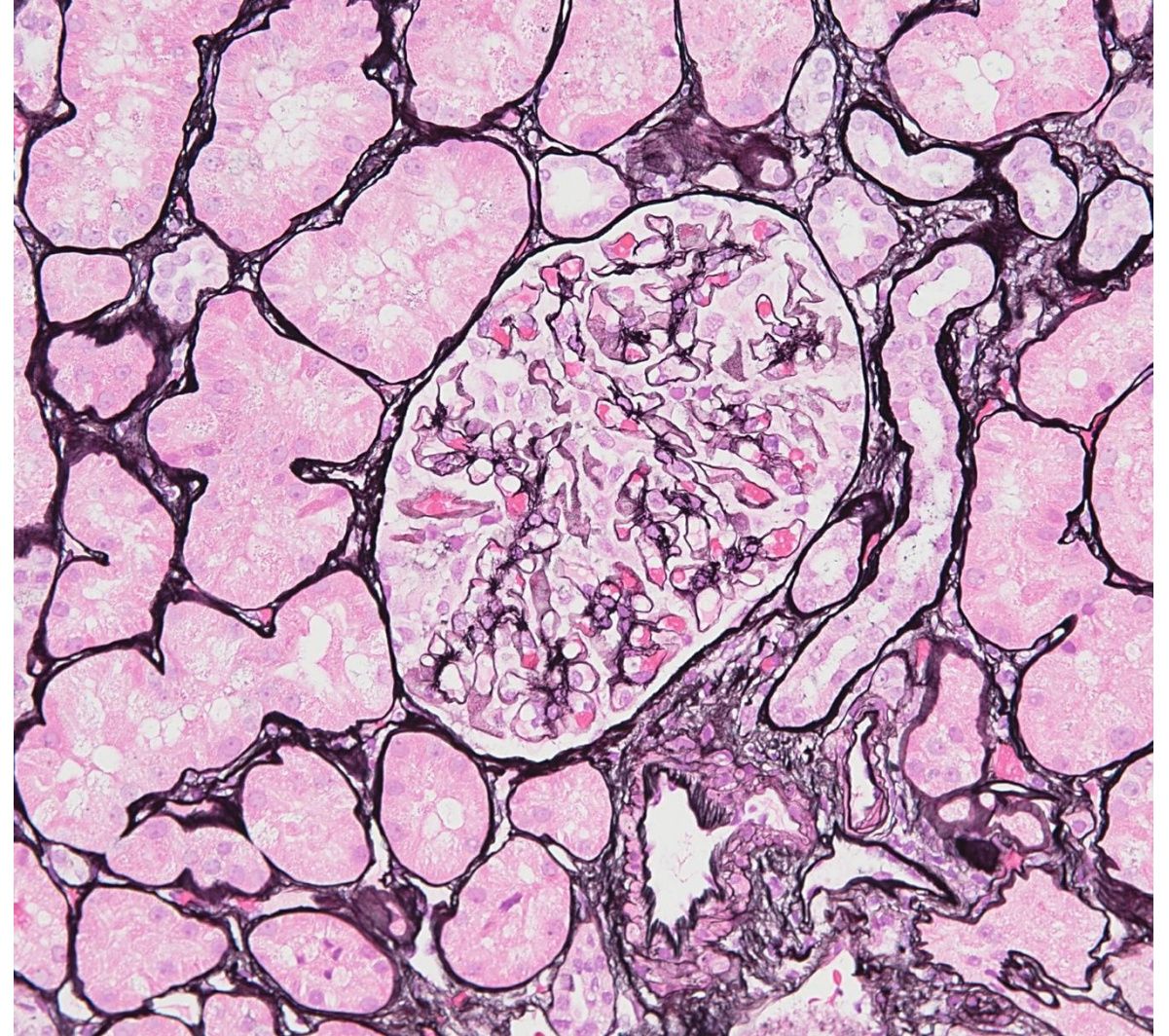
Referred for kidney biopsy

Case 2: Kidney Biopsy Findings

PAS

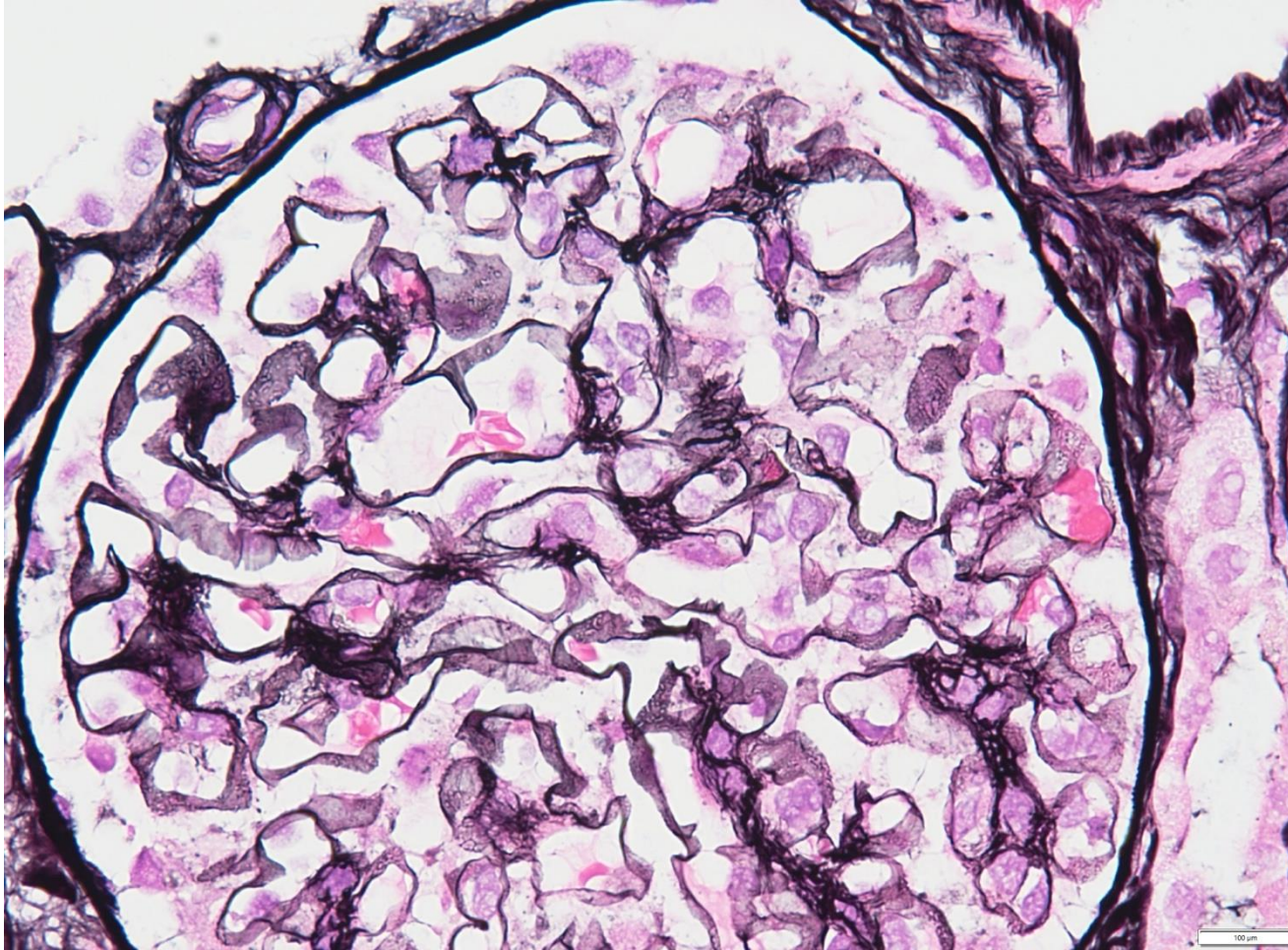


JMS

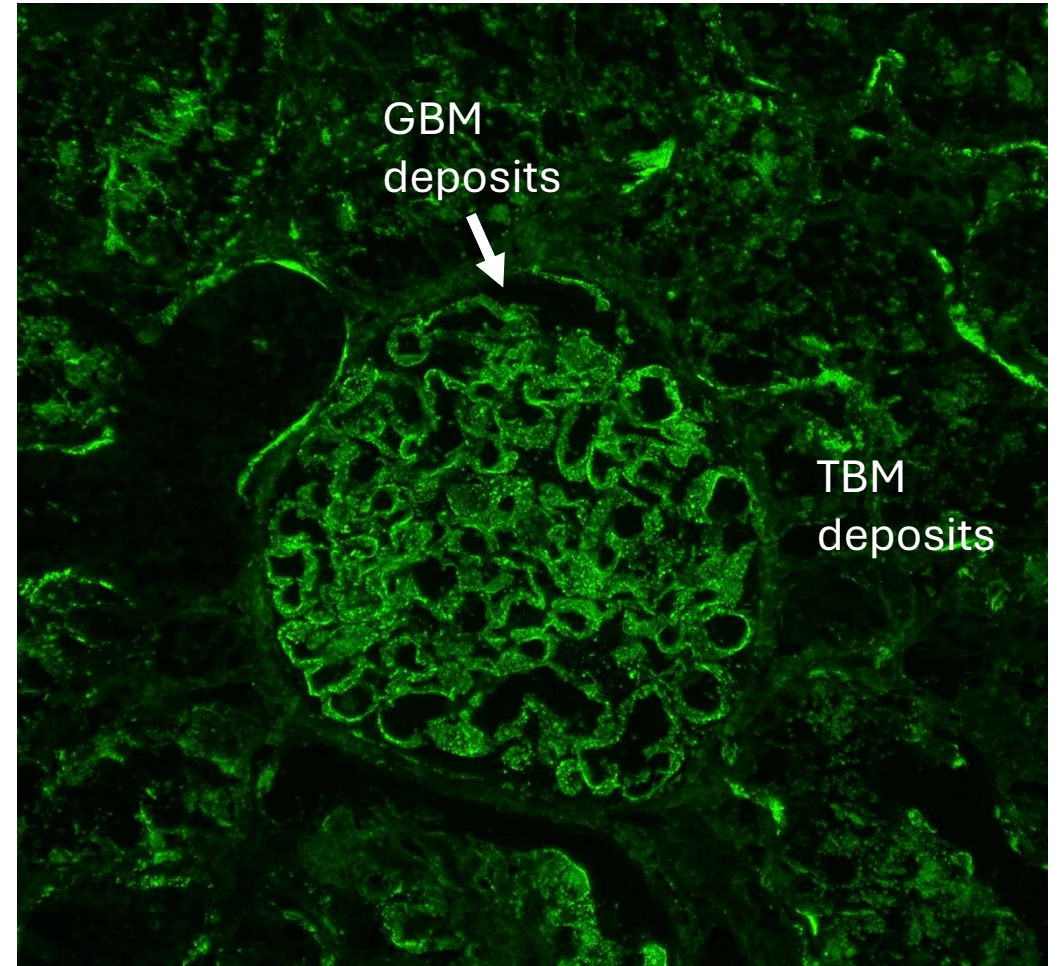


Case 2: Kidney Biopsy Findings

JMS – 40x: segmental craters

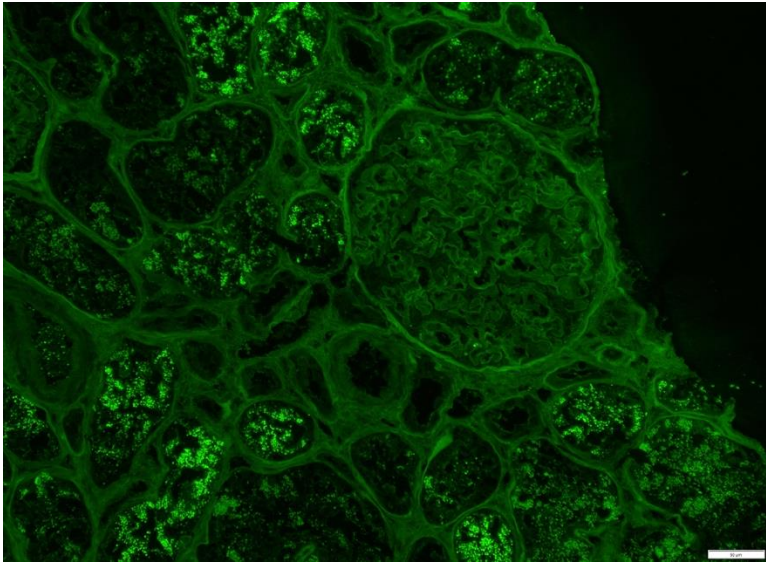


IgG: granular deposits

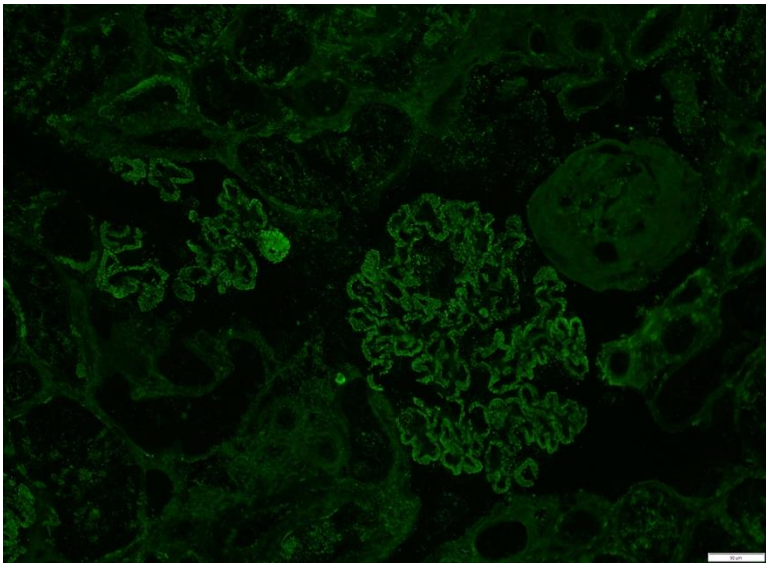


Case 2: Kidney Biopsy Findings

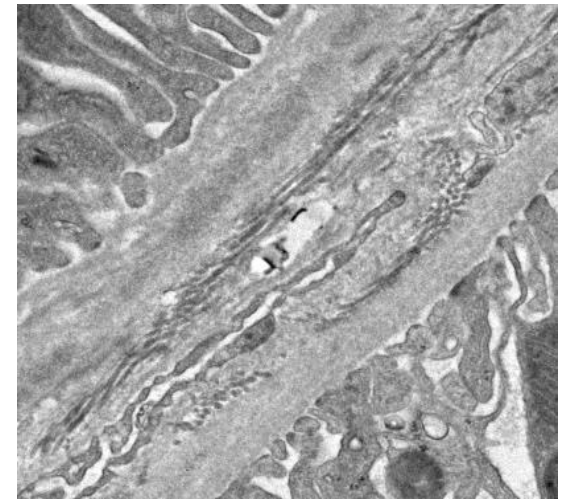
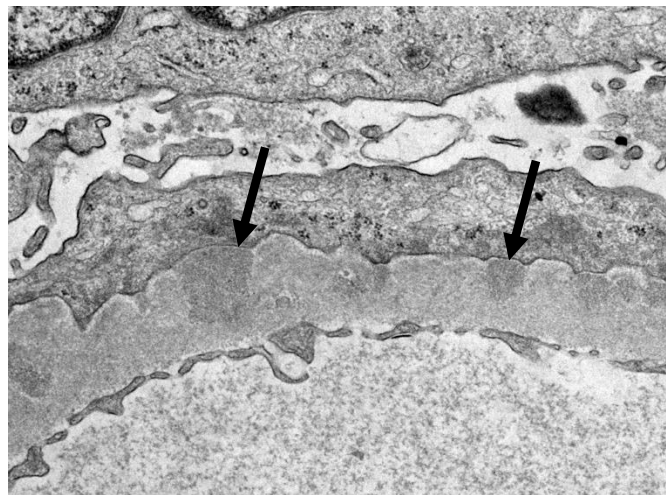
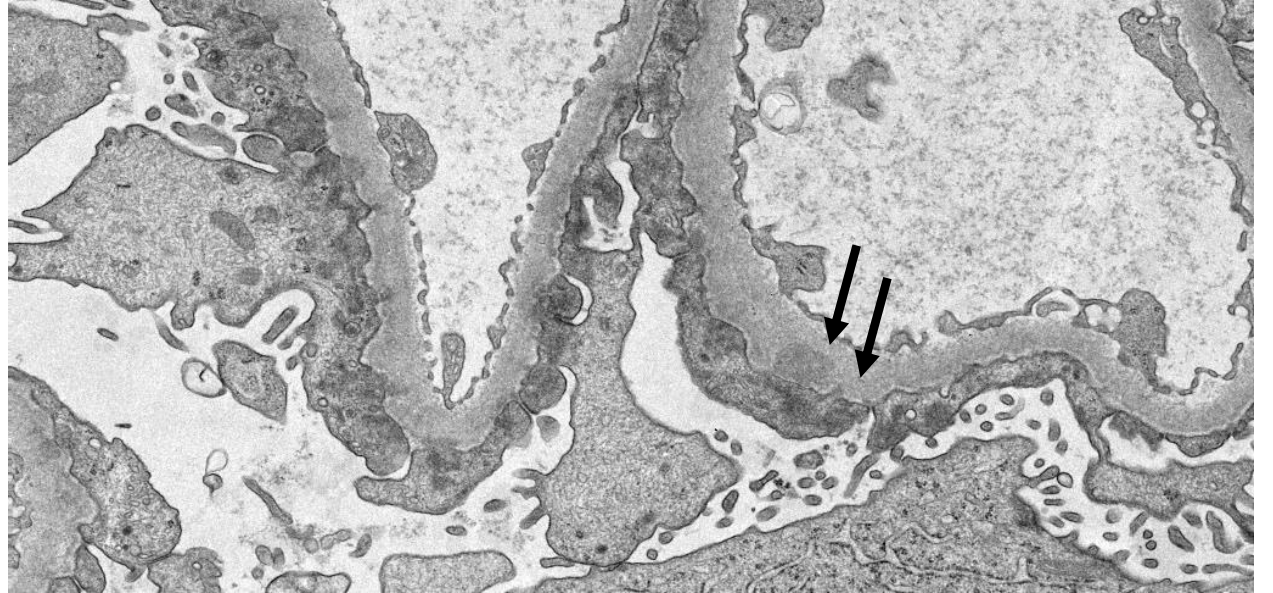
Alb



PLA2r



EM

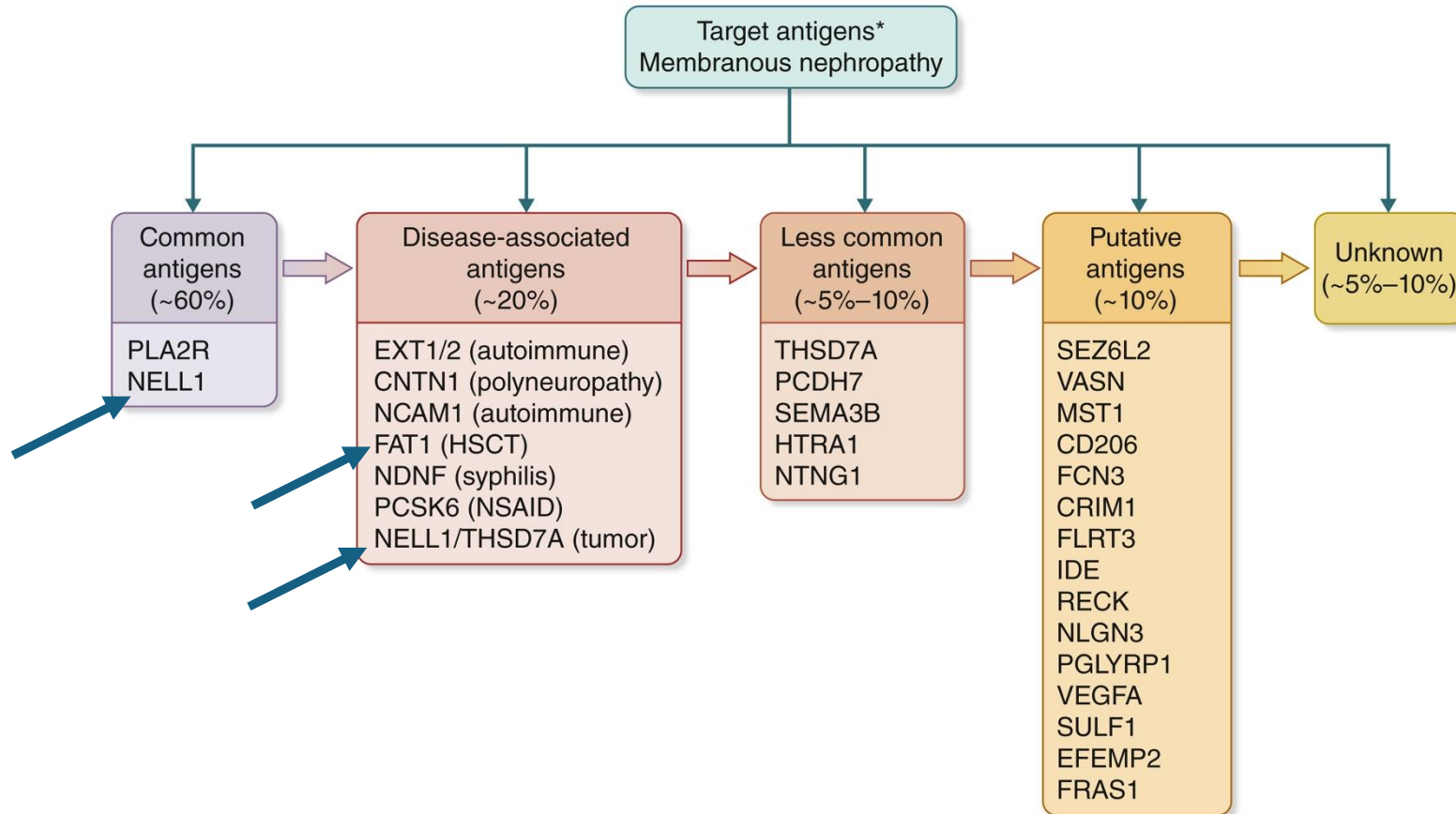


Case 2: Kidney Biopsy Diagnosis

MEMBRANOUS NEPHROPATHY, STAGE II

- THE DEPOSITS ARE REACTIVE FOR POLYCLONAL IgG WITH PREDOMINANCE OF IgG4, AND ONLY DIM REACTIVITY FOR PLA2R
- ABUNDANT SUBEPITHELIAL AND INTRAMEMBRANOUS DEPOSITS AND TUBULAR BASEMENT MEMBRANE DEPOSITS
- THE POSSIBILITY OF AN IMMUNE COMPLEX MEDIATED NEPHROPATHY AS AN EXPRESSION OF cGVHD WITH ANTIBODIES AGAINST THE PROCADHERIN FAT1 SHOULD BE CONSIDERED

Antigen Identification in Membranous Nephropathy is important!



Sethi S, Madden B. **Mapping antigens of membranous nephropathy: almost there** Kidney International, 103, 469-472

Case 2: Mass Spectrometry Report

MN Target Antigen ID, LC MS, Ts

Interpretation

Kidney, needle biopsy for membranous nephropathy mass spectrometry (BS26-041330; 08/11/2026):

MASS SPECTROMETRY

Liquid chromatography tandem mass spectrometry (LC MS/MS) was performed on peptides extracted from glomeruli that were microdissected from the paraffin-embedded specimen.

LC MS/MS detected a peptide profile consistent with **Procadherin FAT1 (FAT1)**. These findings support the diagnosis of FAT1-associated Membranous Nephropathy (MN).

Take Home Points

- ★ Podocytes are uniquely susceptible postmitotic cells due to their structure, and their position on the outside of the capillaries within the kidney filter.
- ★ If a drug is filtered, it encounters podocytes!
- ★ Podocyte injury can be direct or indirect/secondary to other glomerular injury (TMA, immune complexes etc).
- ★ Podocyte injury can be associated with the cancer itself or can be therapy-related.
- ★ It is important to consider not only the toxicity of the drug itself, but also how the drug may enter the podocyte (ADCs, receptor-driven mechanism and uptake etc)!
- ★ There is more to monoclonal gammopathies than amyloid!
- ★ Genetic predisposition may worsen the disease, and lead to irreversible podocyte loss!