How do Monoclonal Immunoglobulins Cause Kidney Damage

ASON – Onconephrology Symposium (Sept 17-18, 2026)

Christophe Sirac, Team BioPIC

CNRS UMR 7276 - INSERM U1262 – Control of the Immune Response B and Lymphoproliferations

National Reference Center for AL amyloidosis and other monoclonal Ig deposition diseases

Disclosure

Attralus inc, GateBioscience, Sebia, NanoMedSyn: Research fundings

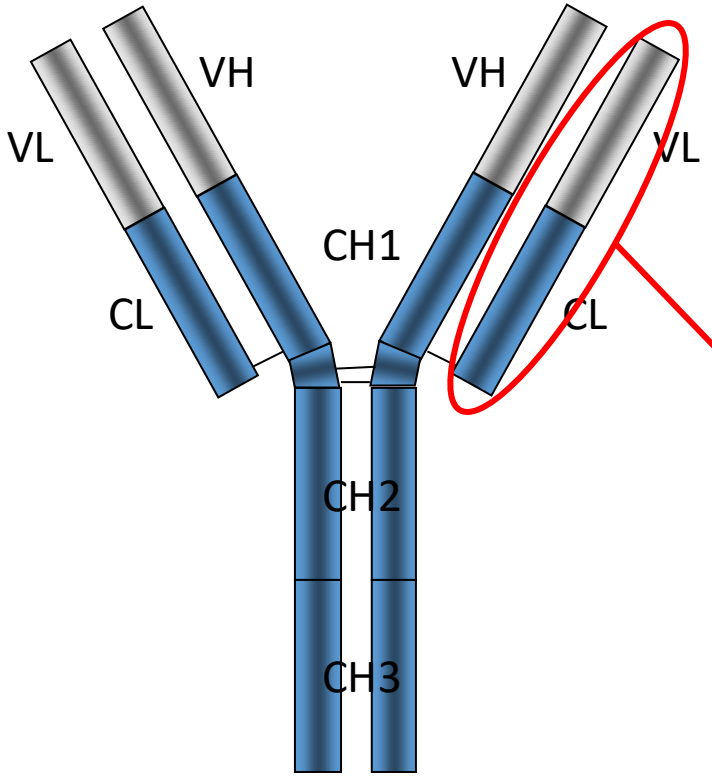
Learning objectives

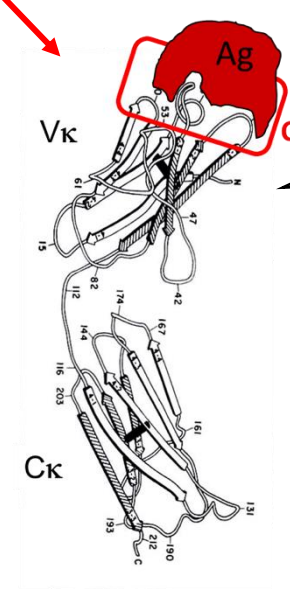
- **Why and how monoclonal Ig (or Ig fragments) deposit into the kidney**
- **What are the molecular mechanisms leading to kidney dysfunction**

General considerations: Ig diversity

Variable domain

Constant domain





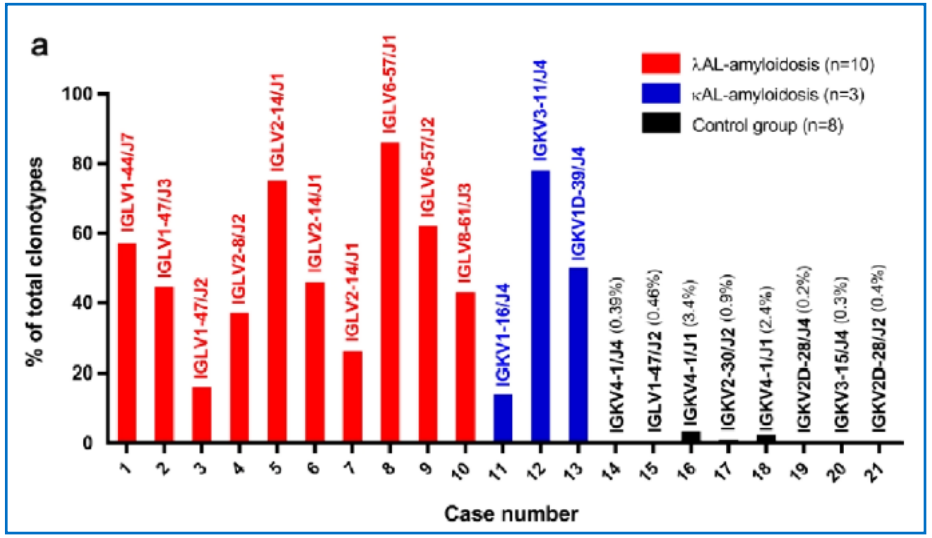
Determinants of monoclonal Ig toxicity ?

Millions of different Ig: All monoclonal LC we studied so far have a different sequence

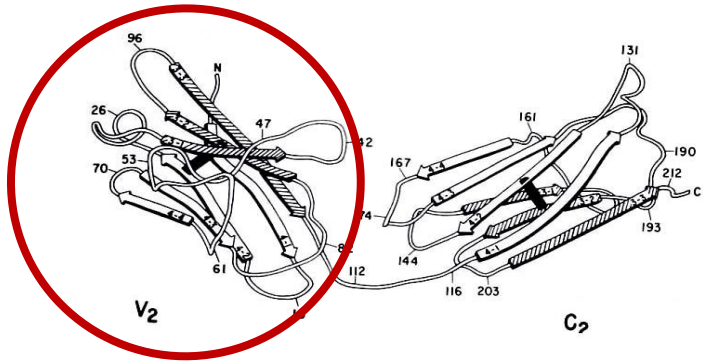
Why monoclonal Ig (or Ig fragments) deposit into the kidney ?

Commonalities

- Excess (even when normal FLC)
- Unique (Monoclonal)
- Often incomplete (abnormal)

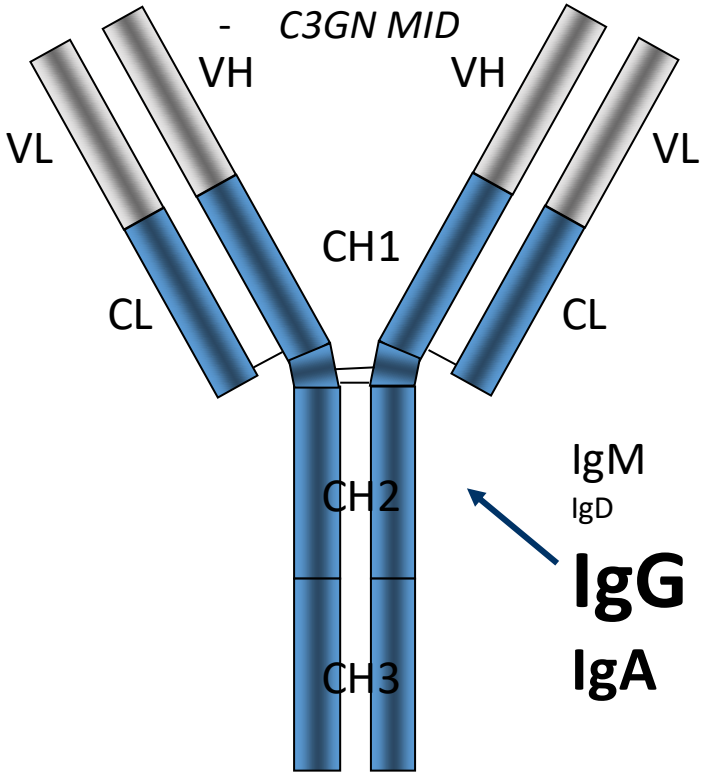


Not all monoclonal Ig and Ig fragments are dangerous
= Role of the Variable domaine



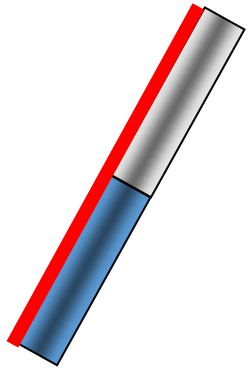
Why monoclonal Ig (or Ig fragments) deposit into the kidney ?

- *LHCDD(?)*
- *Cryo*
- *PGNMID*
- *ITG*
- *C3GN MID*



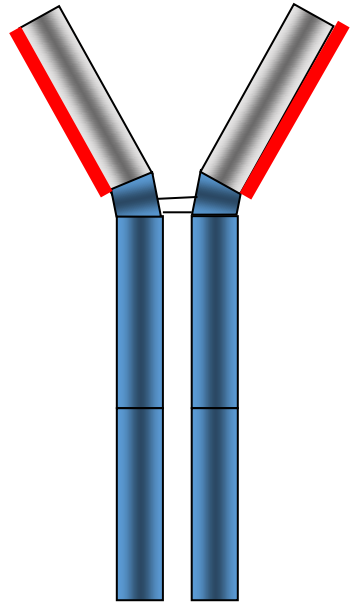
- *LHCDD(?)*
- *AHL Amyloidosis?*

- *LCDD*
- *AL amyloidosis*
- *MCN*
- *Fanconi syndrome*
- *(C3GN, PGNMID)*



Light chain (κ or λ)

- *HCDD*
- *AH amyloidosis*



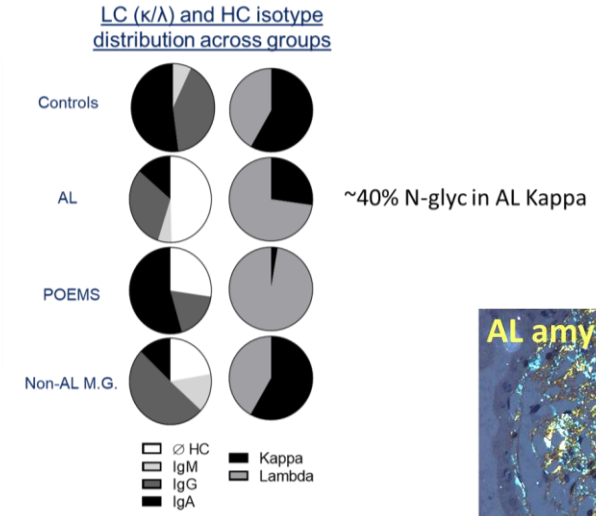
Truncated heavy chain (-CH1)

Tools to understand

Sequence database from the French reference centre

Curated Monoclonal Ig database from patients with full clinical data

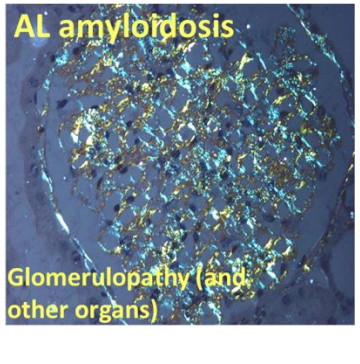
- **735 sequences with full clinical data**
- 265 AL
- 223 non–AL **with organ toxicity**
- 199 **without organ toxic**48 POEMS
- **ity** (Controls)
- 48 POEMS

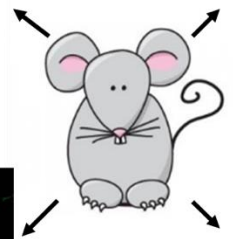


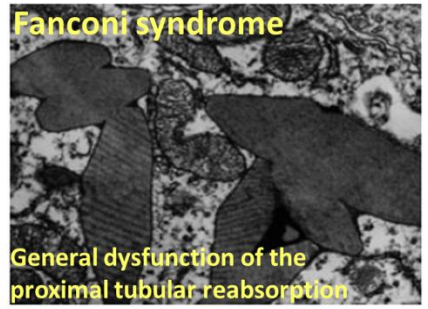
~40% N-glyc in AL Kappa

Bender et al, Blood 2020
Javaugue et al, Kidney Int 2022
Javaugue et al, Kidney int 2025

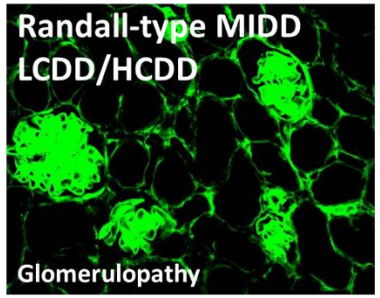
Animal models for MGRS/MGCS

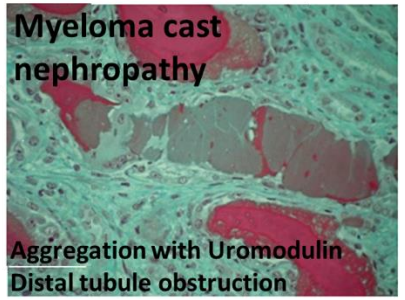






Sirac et al. Blood 2006
Bonaud et al. Blood 2015
Luciani et al. JASN 2016
Bender et al. Blood 2020
Ayala et al. Amyloid 2021
Martinez-Rivas et al. Nat Comm 2025





Sirac et al. Nat Rev Nephrol 2018

Why and how are monoclonal Ig toxic for the kidney?

Tubular diseases

Why and how are monoclonal Ig toxic for the tubules ?

- Non-specific: Organ overload (Multiple Myeloma)
- Specific: Aggregation and Direct toxicity

Why and how are monoclonal Ig toxic for the tubules ?

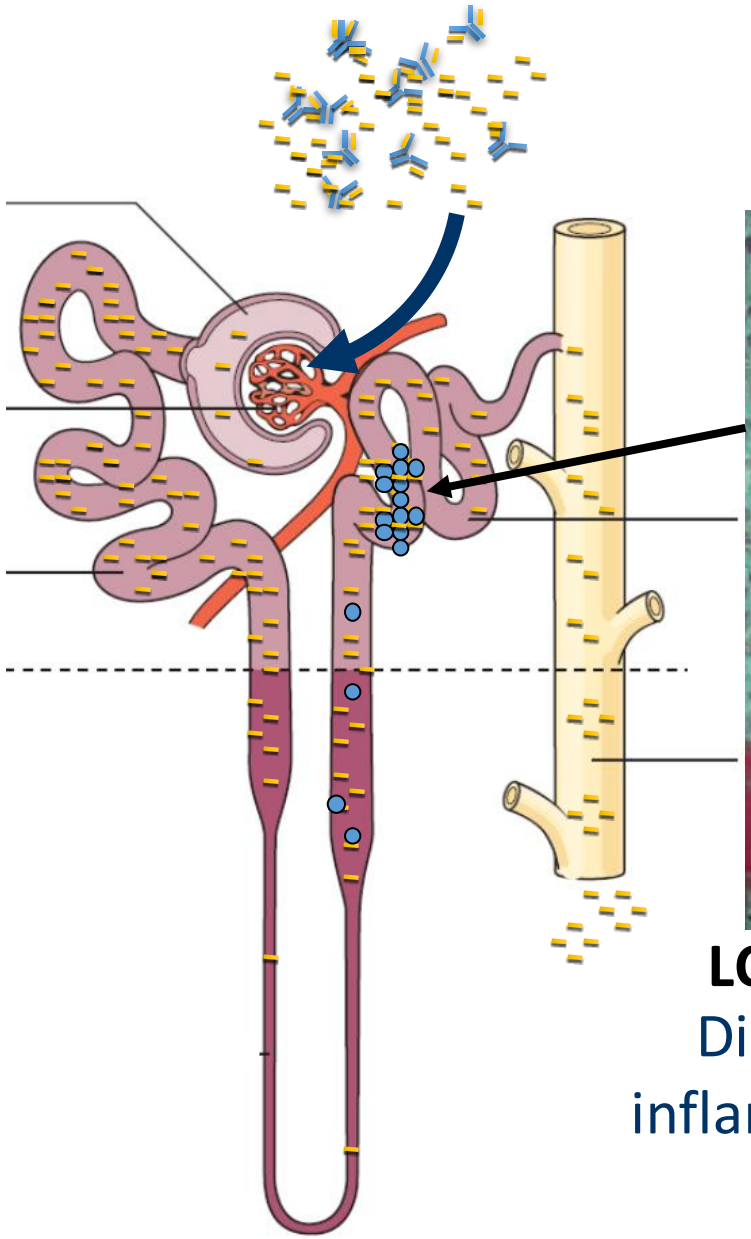
Part 1: Overload

(Multiple myeloma)

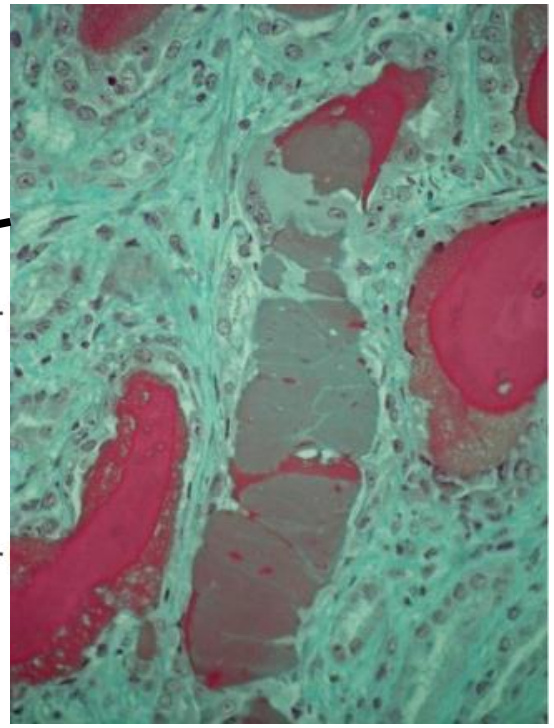
- Myeloma Cast Nephropathy
- LC-induced proximal tubulopathy

Large variety of FLC (κ = λ)
Role of the V domain ?

Why and how are monoclonal Ig toxic for the tubules ?

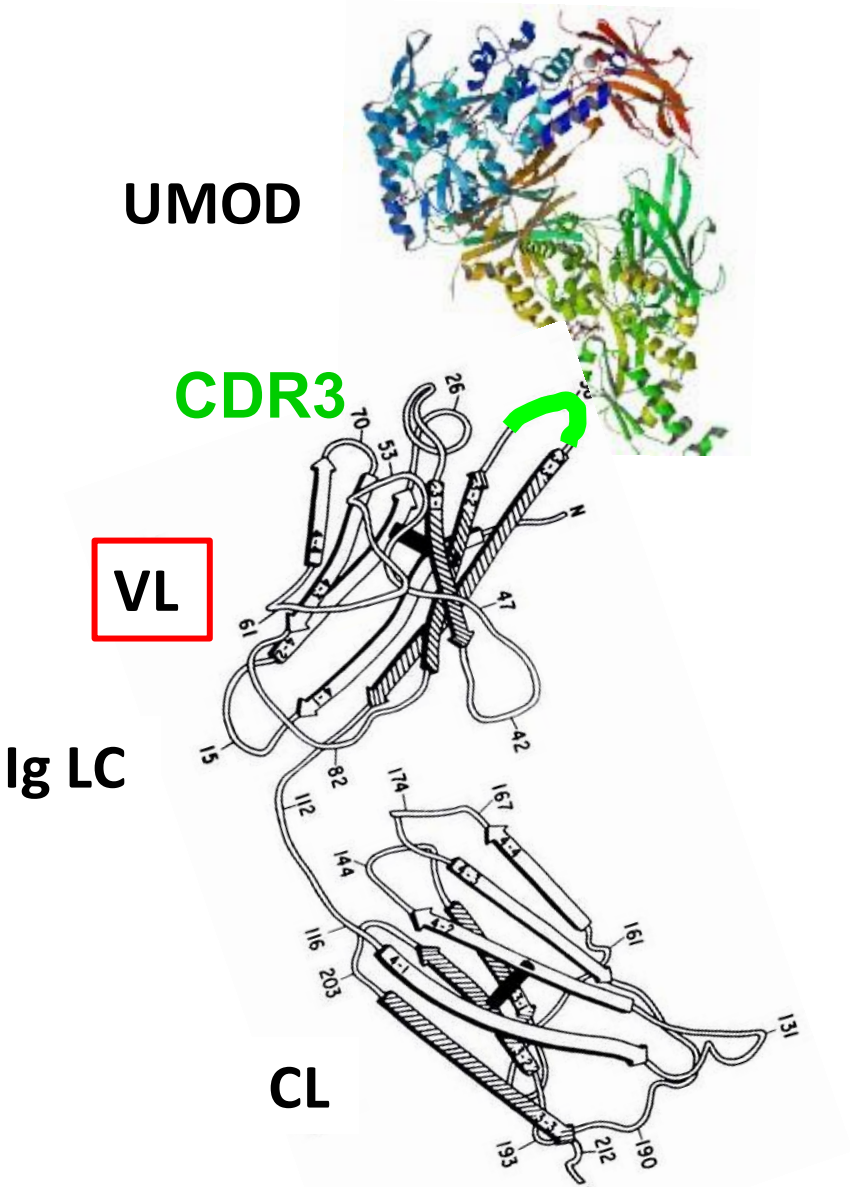


Myeloma cast nephropathy



LC/UMOD precipitation

Distal tubules obstruction, inflammation, tubulointerstitial fibrosis



Paul Sanders' group

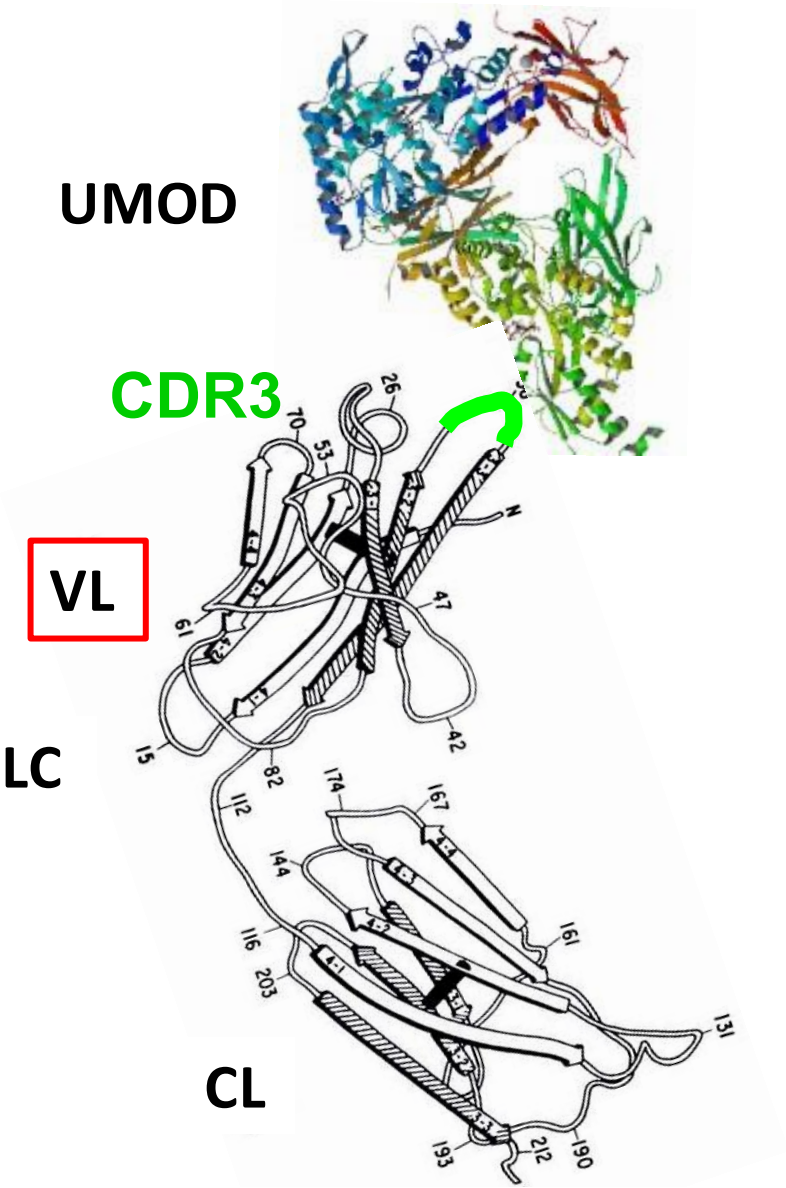
Why and how are monoclonal Ig toxic for the tubules ?

But,

- Most LC can cause casts when in excess while CDR3 highly variable

- One of the best UMOD binder: LC from a patient with Fanconi syndrome, without casts…

Quantity matters more than LC features



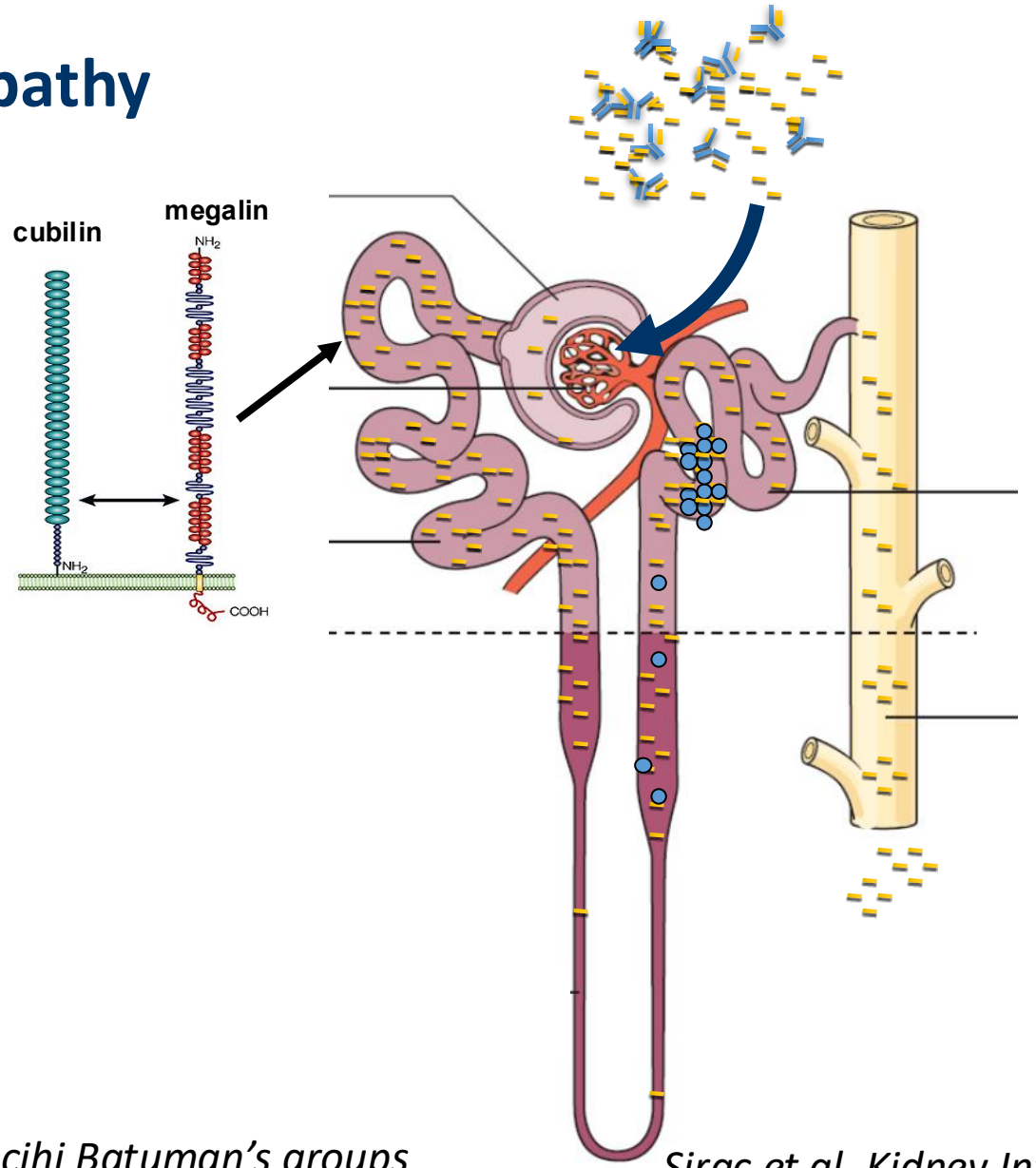
Paul Sanders' group

Why and how are monoclonal Ig toxic for the tubules ?

LC-induced Proximal tubulopathy

Excessive reabsorption of FLC leading to

- Oxydative stress
- Apoptosis
- TLR/STAT1/NF-κB activation
- Inflammatory (IL6, IL8, MCP-1) and pro-fibrotic (TGFβ) signals release by tubular cells



Alan Solomon, Paul Sanders, Vecihi Batuman's groups

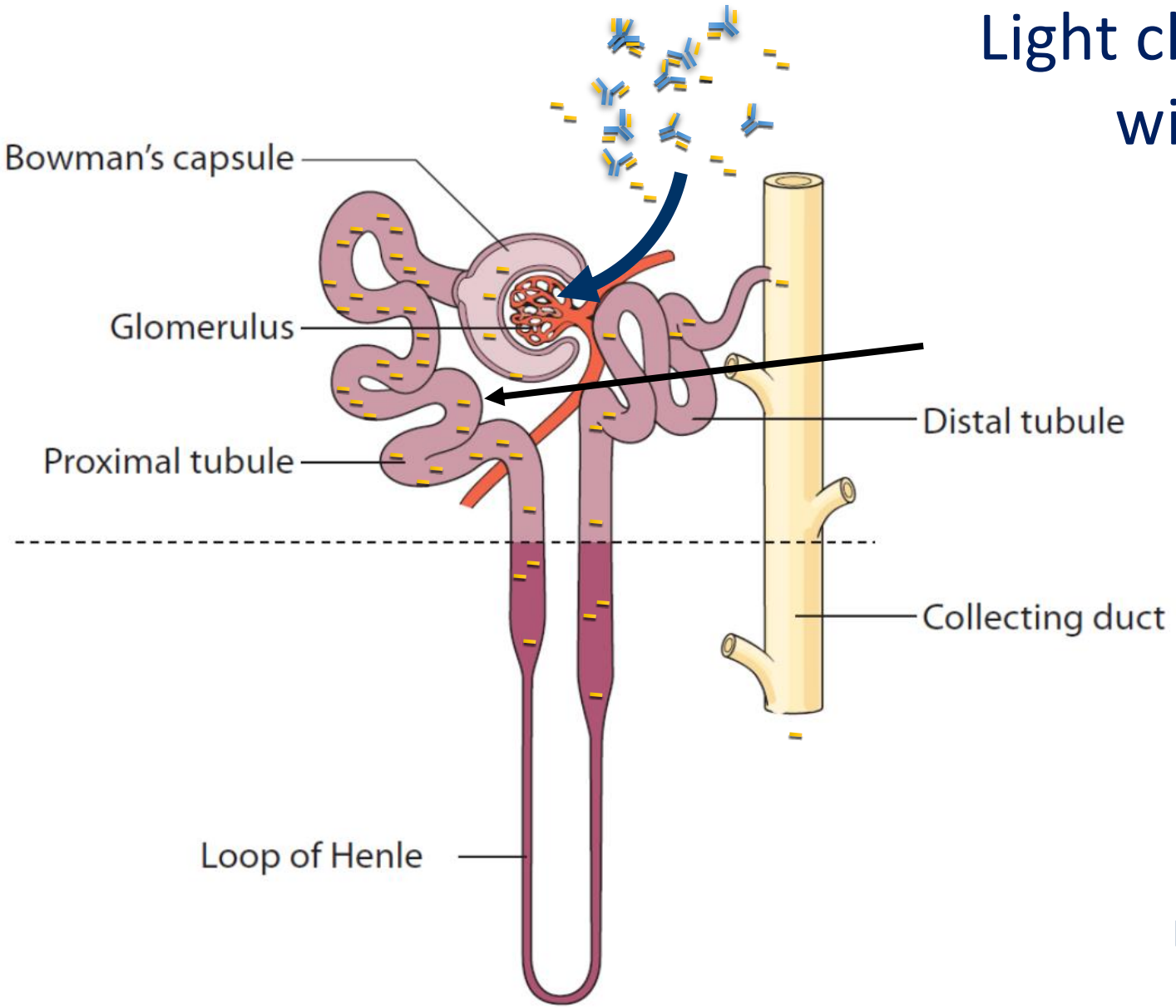
Sirac et al. Kidney Int Rep, 2021

Part 2: Aggregation and Direct toxicity

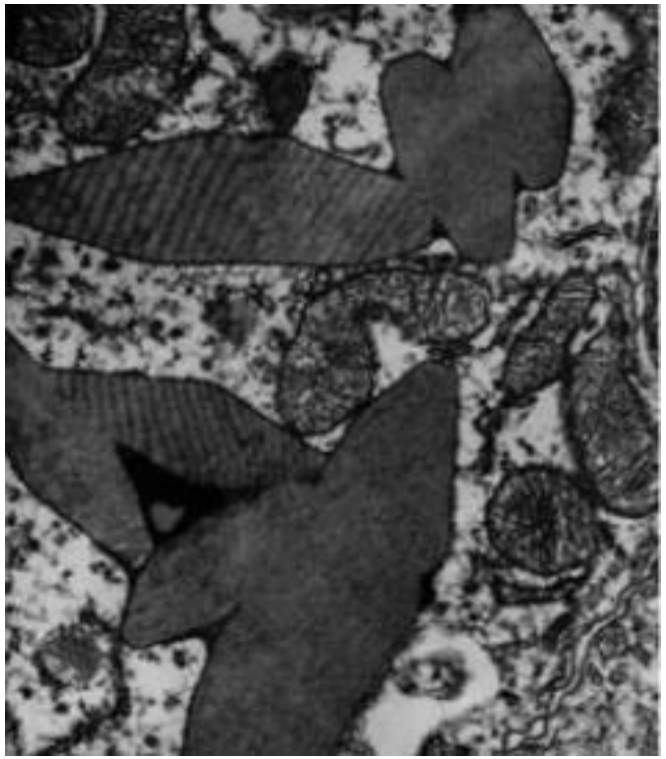
(MGUS/SMM more frequent than MM: MGRS)

- LC-induced proximal tubulopathy with Fanconi syndrome

Why and how are monoclonal Ig toxic for the tubules ?



Light chain proximal tubulopathy with Fanconi Syndrome

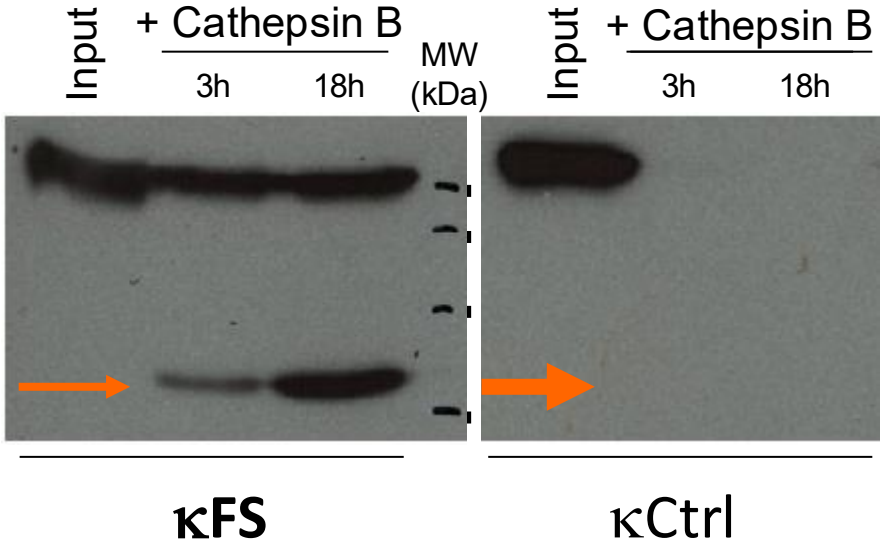


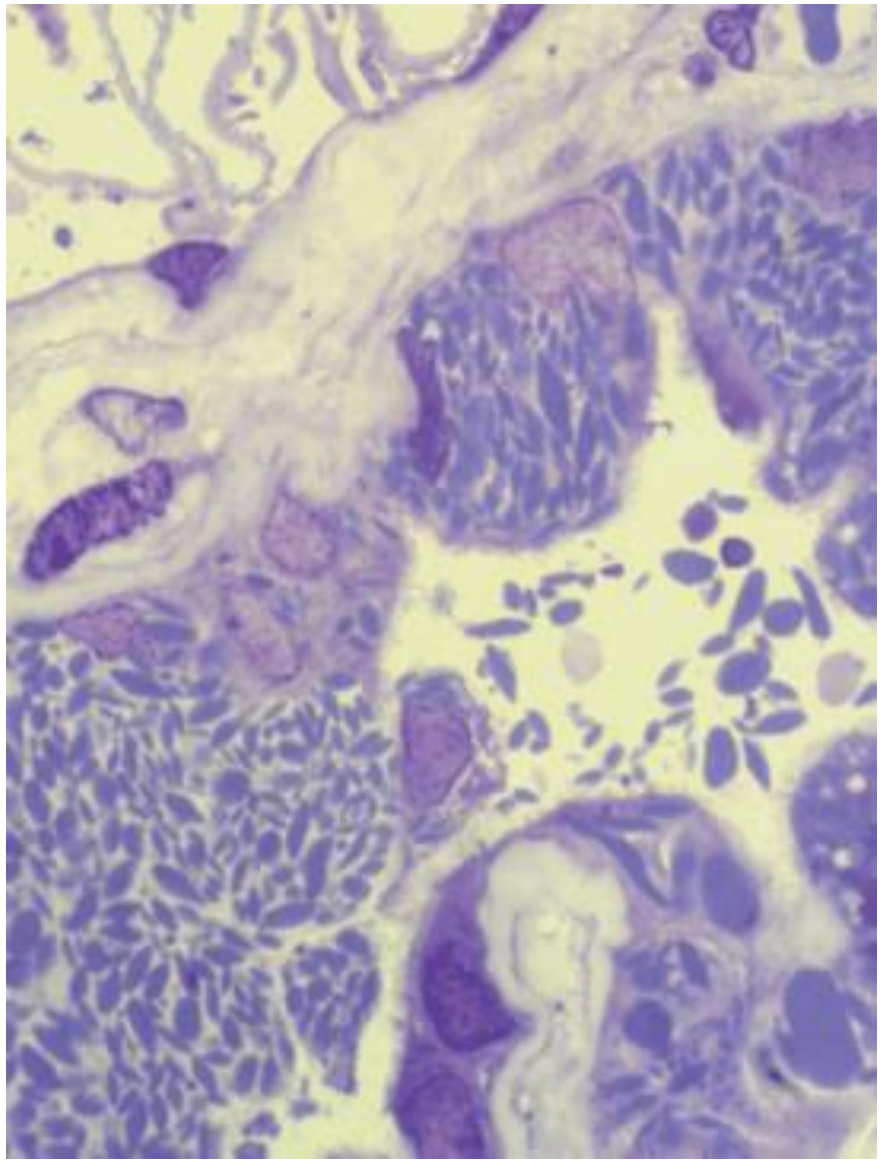
Generalized dysfunction of the proximal tubule reabsorption (LMW proteinuria, glucosuria, phosphaturia, aminoaciduria…)

Why and how are monoclonal Ig toxic for the tubules ?

LC-induced Fanconi Syndrome

- κ >> λ
- Intracellular crystals (Lysosomes)
- **70% Vκ1-33 and Vκ1-39 *(with hydrophobic residues in CDR?)***
- Resistance to intracellular proteolysis

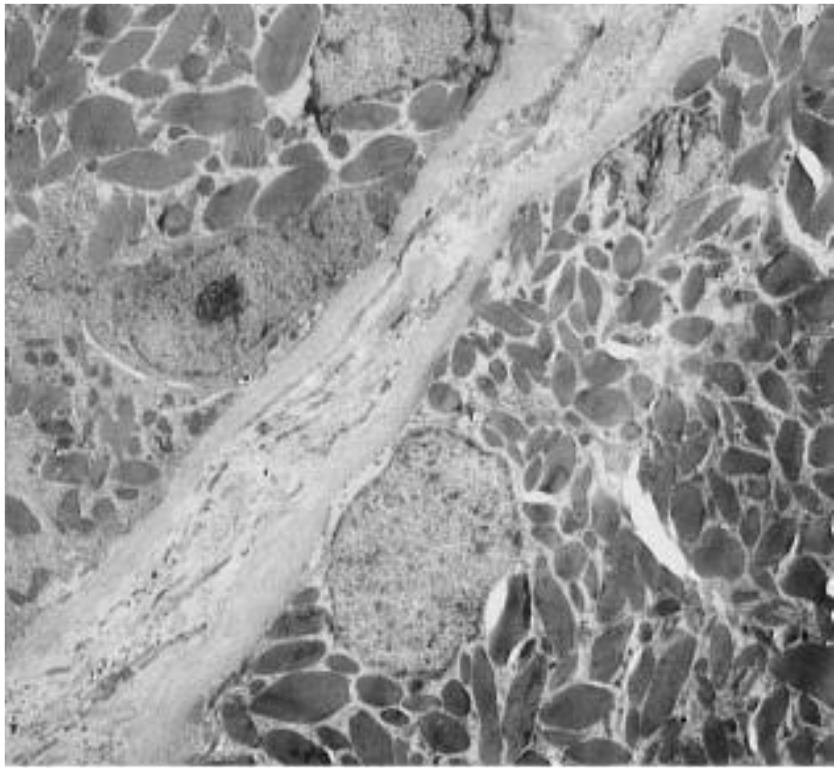




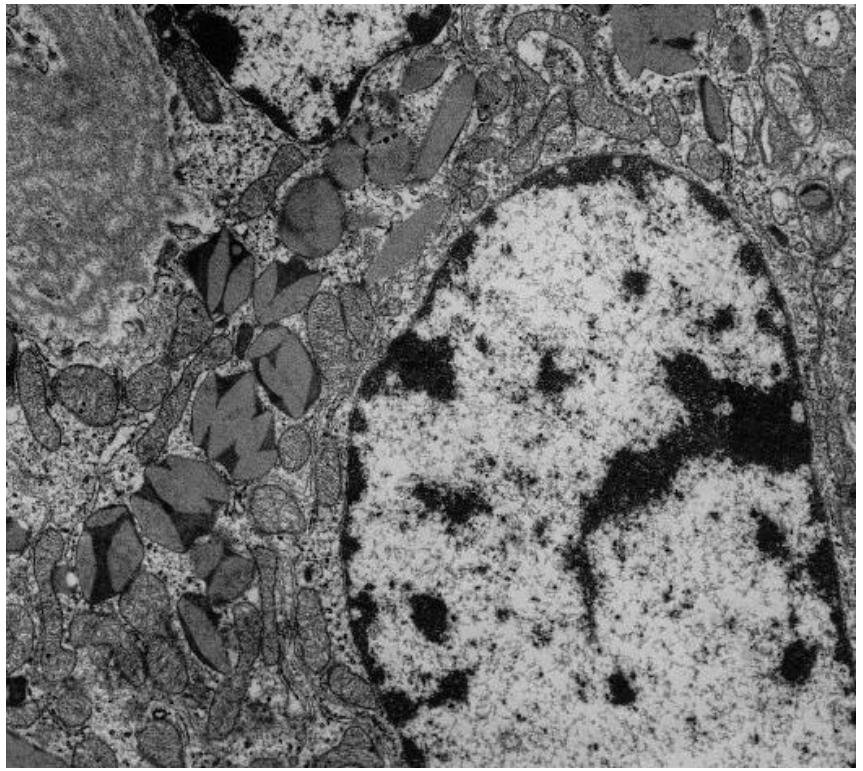
Sirac et al, 2006 Blood - Luciani et al, 2016 JASN

Why and how are monoclonal Ig toxic for the tubules ?

Mouse models to help unravel the disease (1)



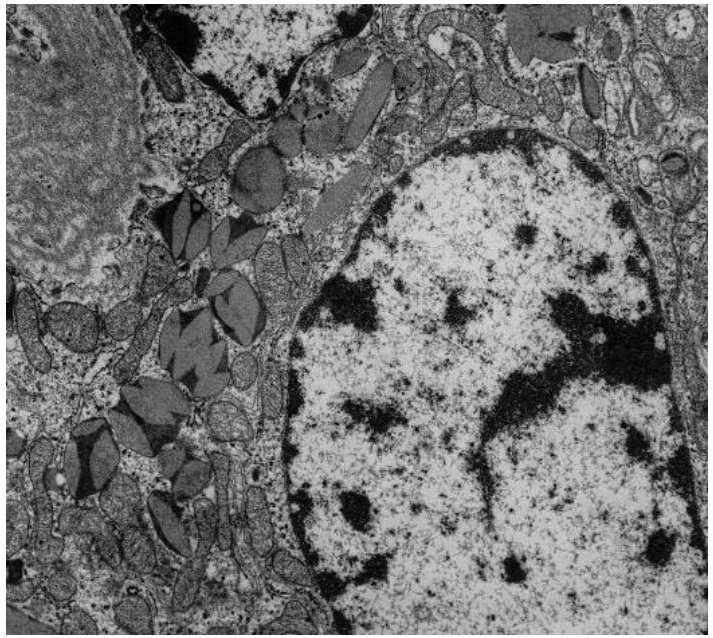
Patient κFS



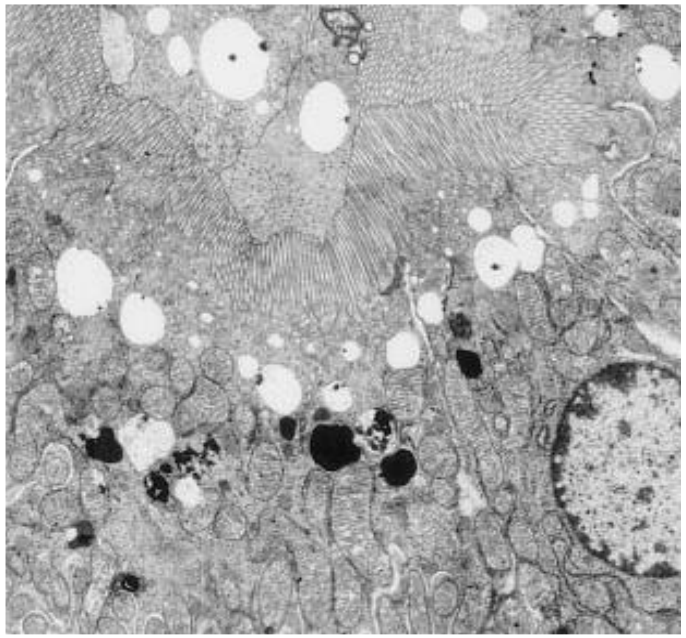
Mouse κFS

Decourt et al. Blood 1999
Sirac et al. Blood 2006

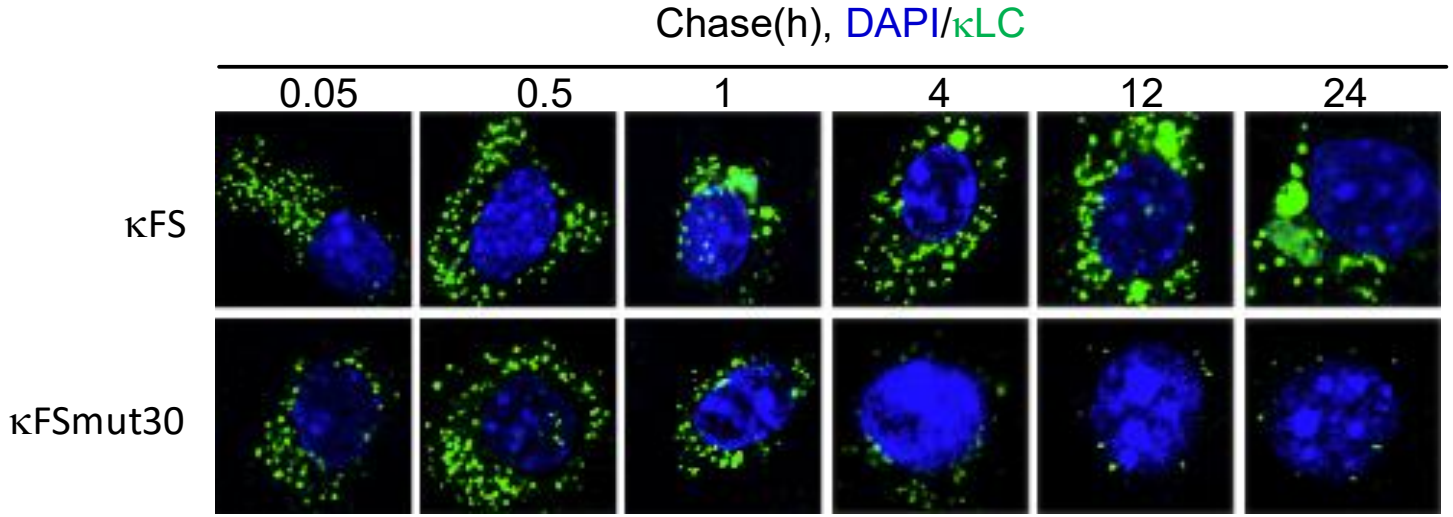
Why and how are monoclonal Ig toxic for the tubules ?



Mouse κFS



Mouse κFSmut30

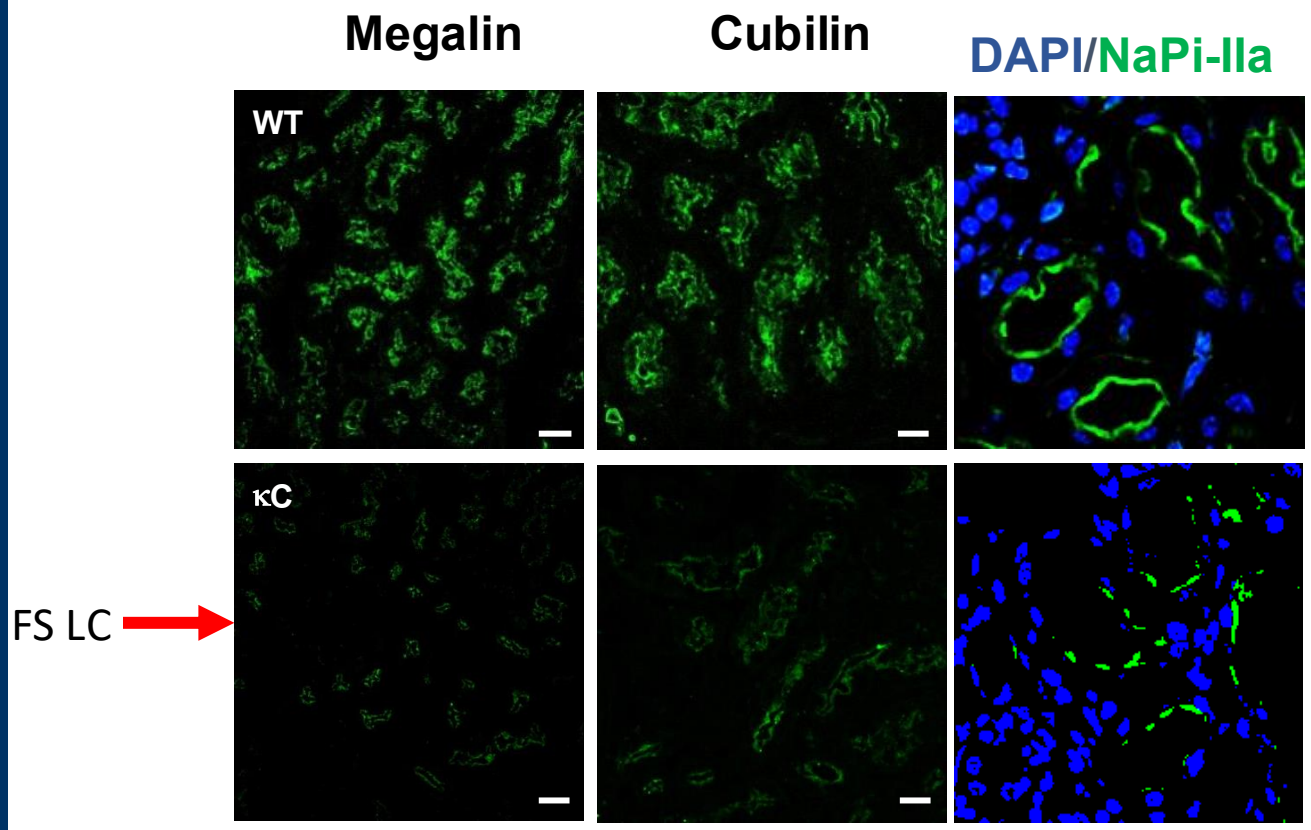


Highly specific: A single AA substitution eliminates toxicity

Decourt et al, Blood 1999
Sirac et al, Blood 2006
Luciani et al, JASN 2016

Why and how are monoclonal Ig toxic for the tubules ?

- Generalized dysfunction of tubular reabsorption: why?

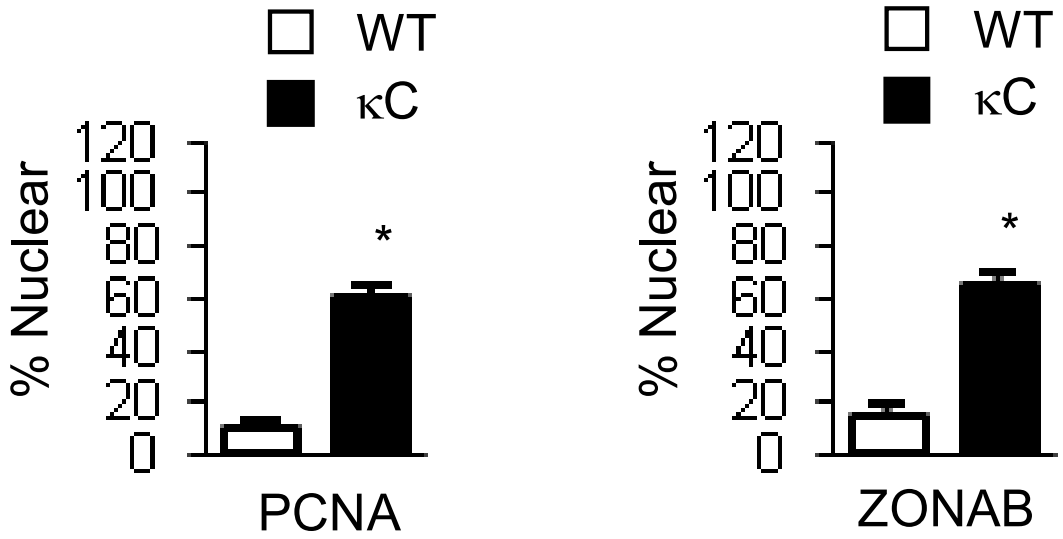


- Defective recycling of **all** apical receptors and transporters

Olivier Devuyst's group

Why and how are monoclonal Ig toxic for the tubules ?

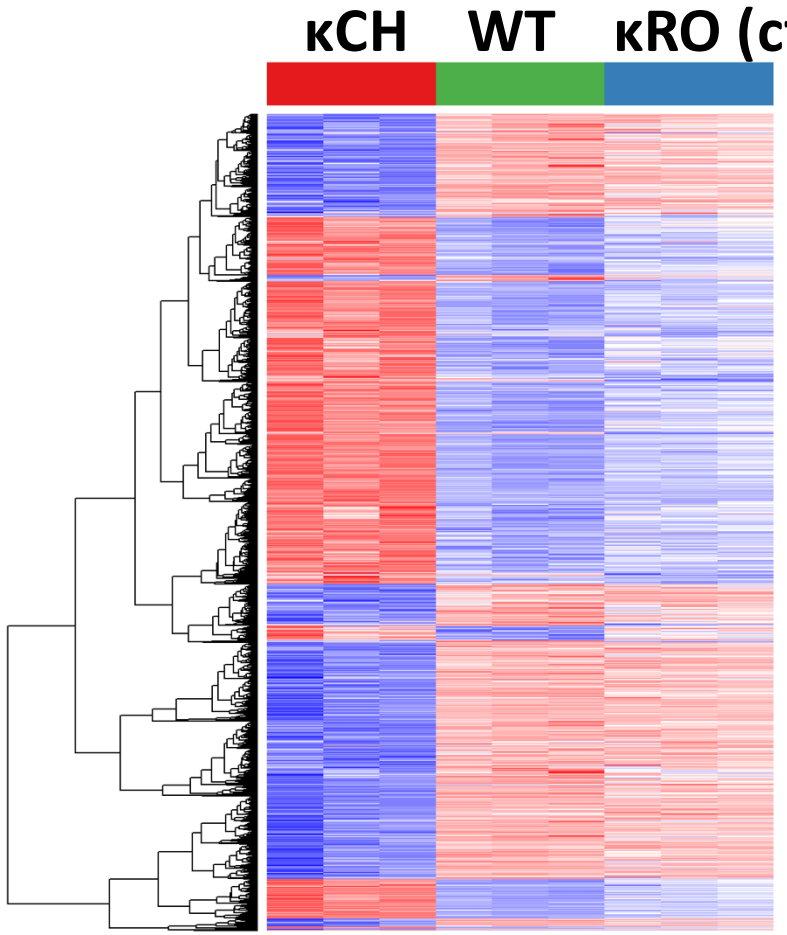
➢ LC induces Proliferation/Dedifferentiation of PT cells



↑ PCNA/ZONAB

Not able to reabsorb anymore > Full blown Fanconi syndrome

Transcriptomic on proximal tubules



Luciani, Sirac et al. JASN 2016, unpublished data

Why are monoclonal Ig toxic for the kidney ?

Glomerular diseases

Why and how are monoclonal Ig toxic for the glomeruli ?

Aggregation and Direct toxicity

- Aggregation → Mechanical constraints (disruption of the tissue)

- Abnormal Ig → Direct cellular stress/toxicity

Extracellular deposits

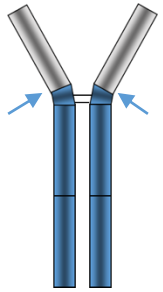
Few monoclonal Ig involved

Isotypes and/or V genes associated with a specific disease

Toxicity/aggregation = set of mutations (Not recurrent)

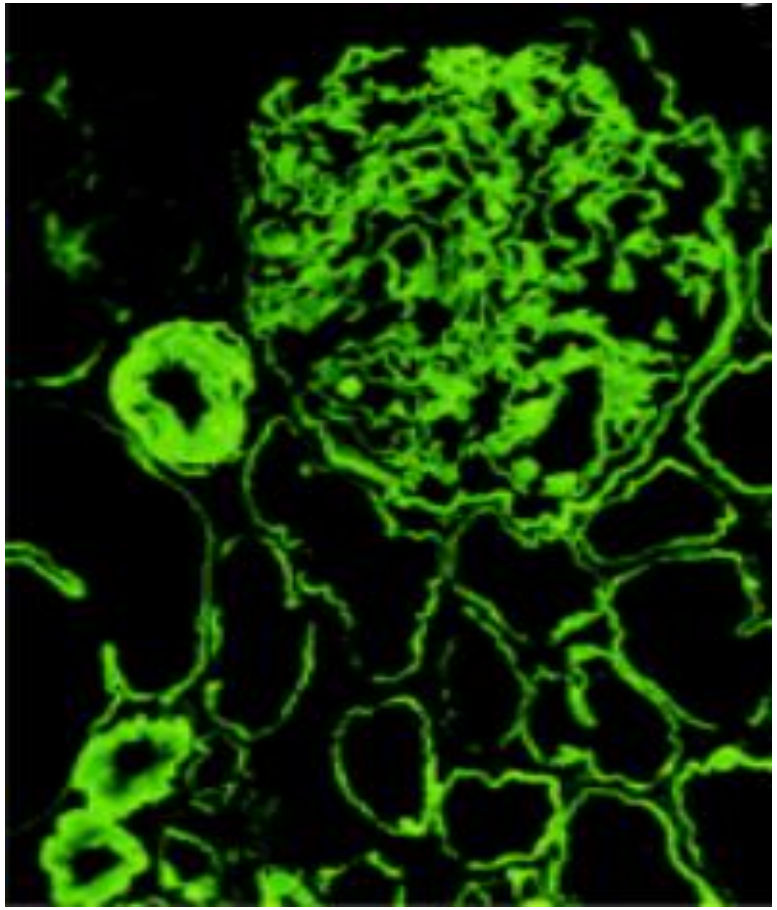
Why and how are monoclonal Ig toxic for the glomeruli ?

Monoclonal Ig Deposition Disease (LCDD/HCDD)



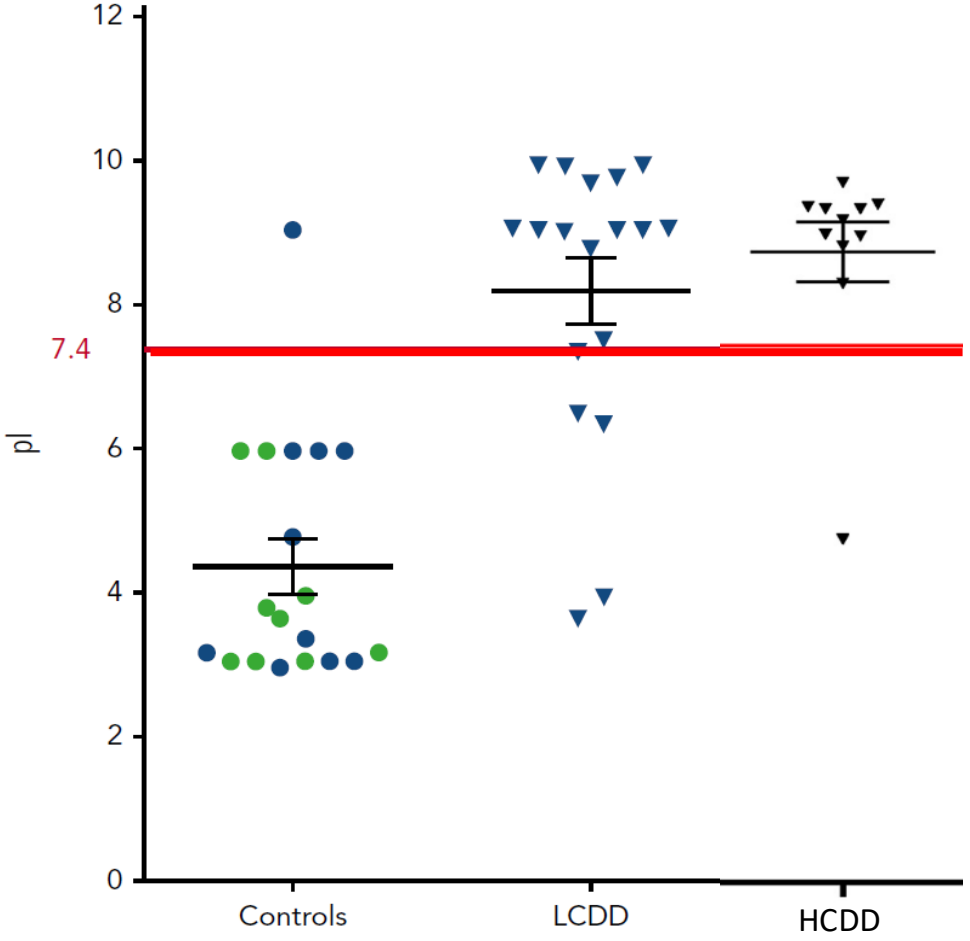
- MGUS > MM
- LCDD : κ > λ / HCDD: Deletion of CH1
- No VL usage bias
- No recurrent structural peculiarities
- Common feature: pI >> 7 (positive charges at physiologic pH) and N-glycosylation (50-60% of LCDD κ LC)

LCDD/HCDD



Gallo et al., Am J Pathol 1996,
Kaplan et al., BJH 2007,
Bridoux et al. Kidney int 2017
Joly et al. Blood, 2019

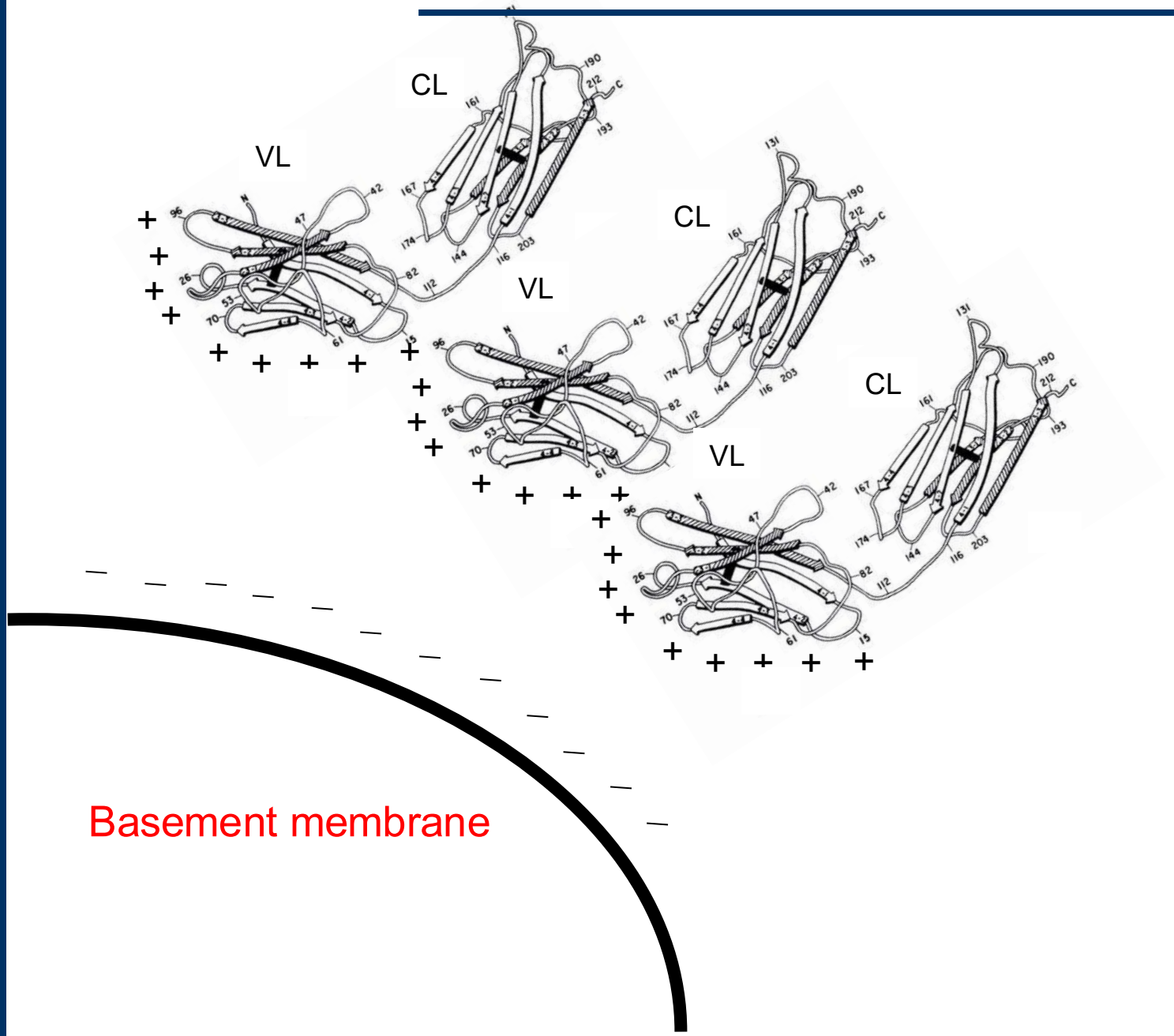
Why and how are monoclonal Ig toxic for the glomeruli ?



Pi of V domains involved?

Gallo et al., Am J Pathol 1996
Kaplan et al., BJH 2007
Bridoux et al. Kidney Int 2017
Joly et al. Blood 2019

Why and how are monoclonal Ig toxic for the glomeruli ?



Aggregation

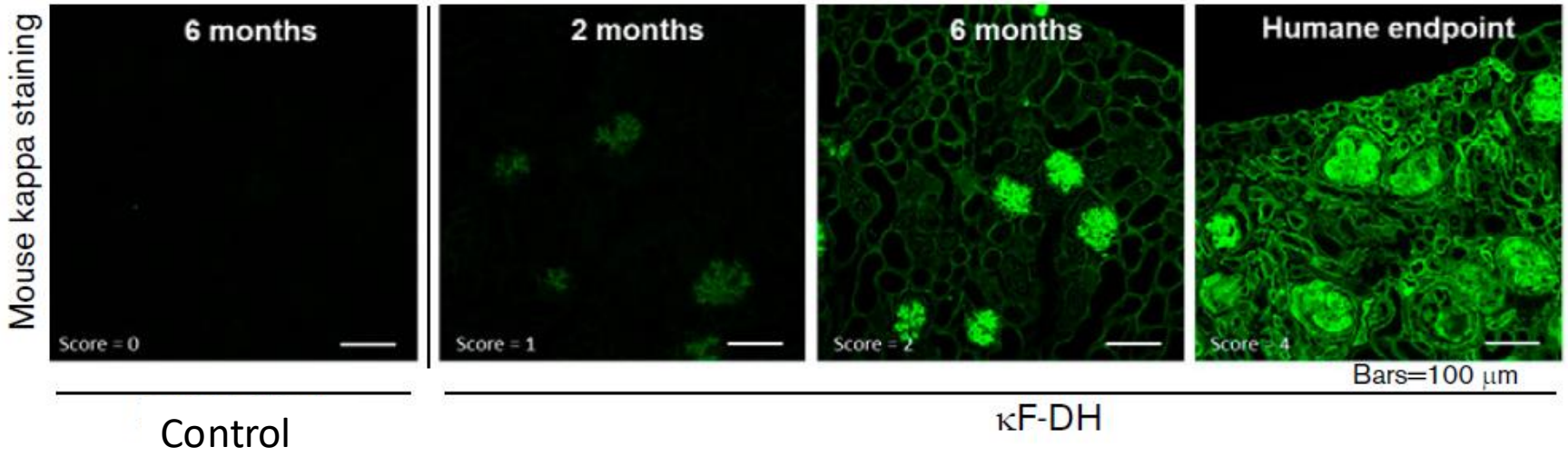
↓

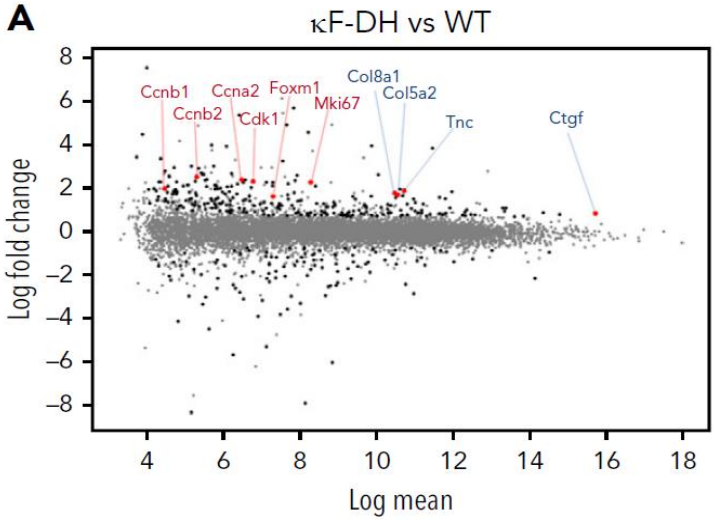
✓Hydrophobic residues
✓N-glycosylation
✓ Amino-acid deletion

Cogne *et al*., J Clin Invest 1991,
Rocca *et al*. Clin Exp Immunol 1993,
Decourt *et al*. Clin Exp Immunol 1996
Joly *et al.* Blood 2019
…

Why and how are monoclonal Ig toxic for the glomeruli ?

Mouse models to help unravel the disease (2)





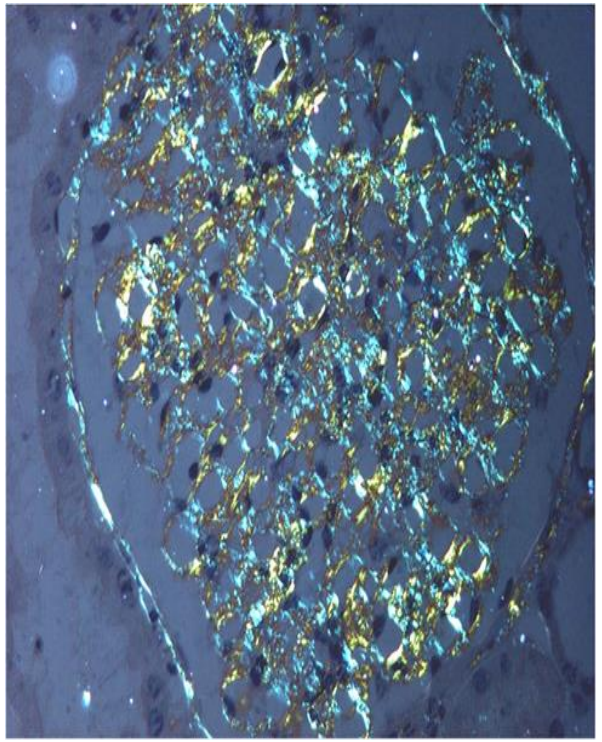
- Increased production of abnormal extracellular matrix (glomerulosclerosis)
- Increased proliferation (renewal of tissue)

Bender et al, Blood 2020

Why and how are monoclonal Ig toxic for the glomeruli ?

AL Amyloidosis

- MGUS >> MM
- λ > κ
- VL bias (5 VL germline = ~60% cases)
- No VL bias for organ tropism
- Mutations increasing fibrillogenesis (too many/no reccurence)
- N-glycosylation (~40% of AL κ LC)

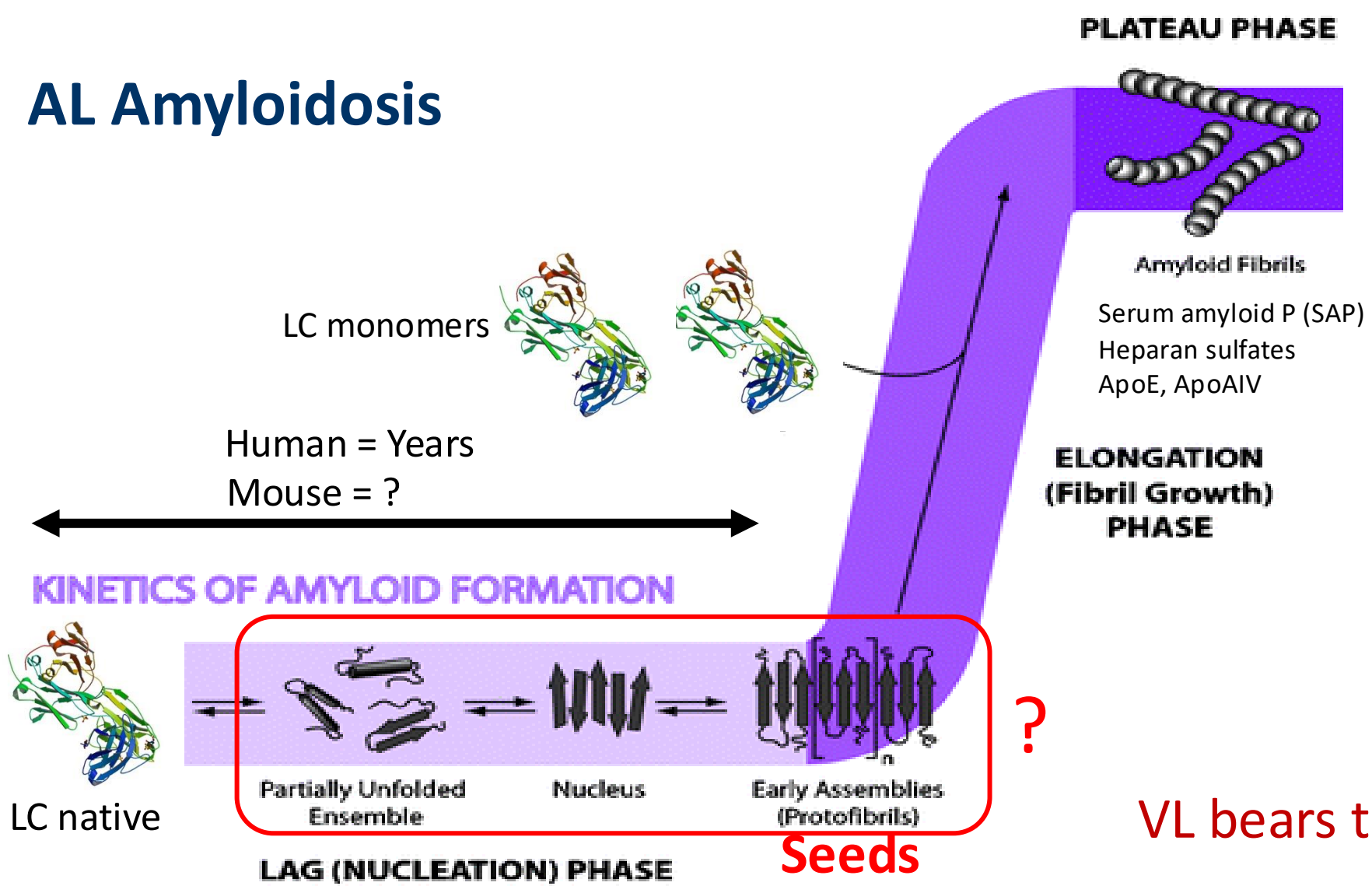


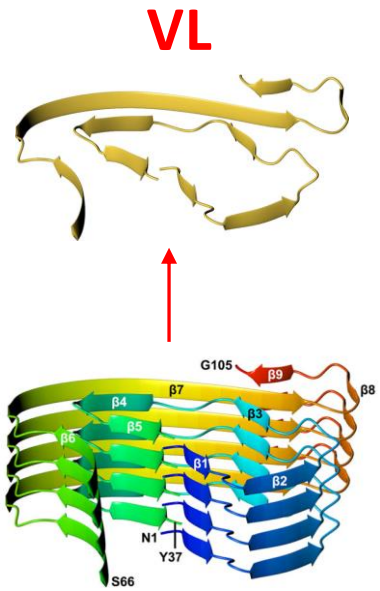
Ig +
GAGs + SAP
+ ApoE etc…

The only conformational disease

Why and how are monoclonal Ig toxic for the glomeruli ?

AL Amyloidosis





VL bears the amyloidogenicity

Adapted from Wilson et al. 2008 and Swuec et al, 2020

Why and how are monoclonal Ig toxic for the glomeruli ?

Nucleus/protofibrils formation

2 hypotheses:

- LC are degraded (proteases) in the tissue/serum releasing the amyloidogenic VL

- Tissue environment (chaperones?) allows unfolding of LC and fibril formation (then CL is degraded)

In search for the factors allowing amyloid seeding

Why and how are monoclonal Ig toxic for the glomeruli ?

Mouse models to help unravel the disease (3)

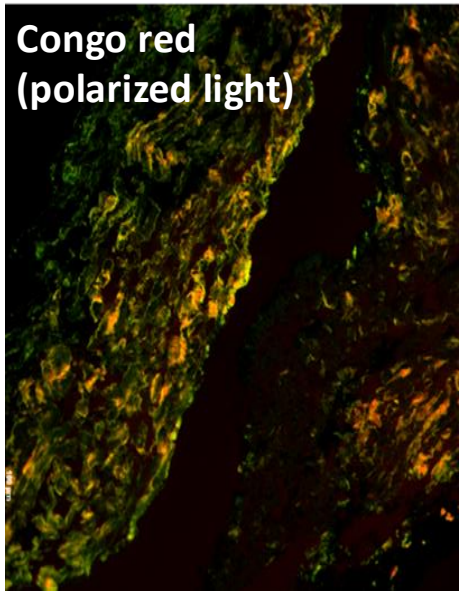
nature communications

Article https://doi.org/10.1038/s41467-025-58307-2

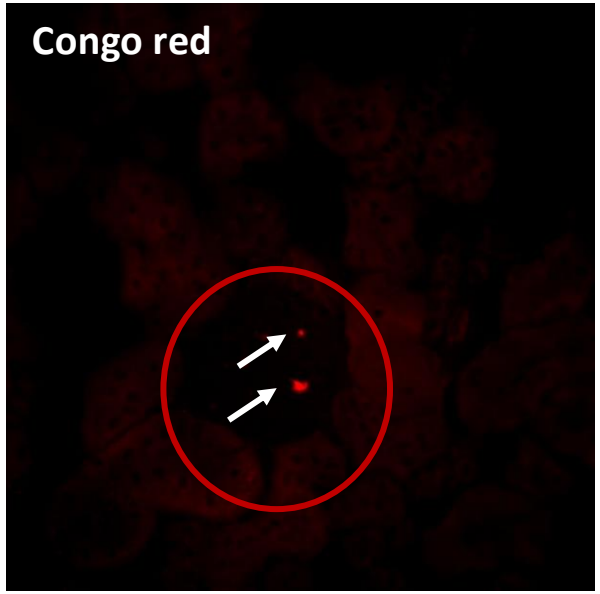
A mouse model of cardiac immunoglobulin light chain amyloidosis reveals insights into tissue accumulation and toxicity of amyloid fibrils

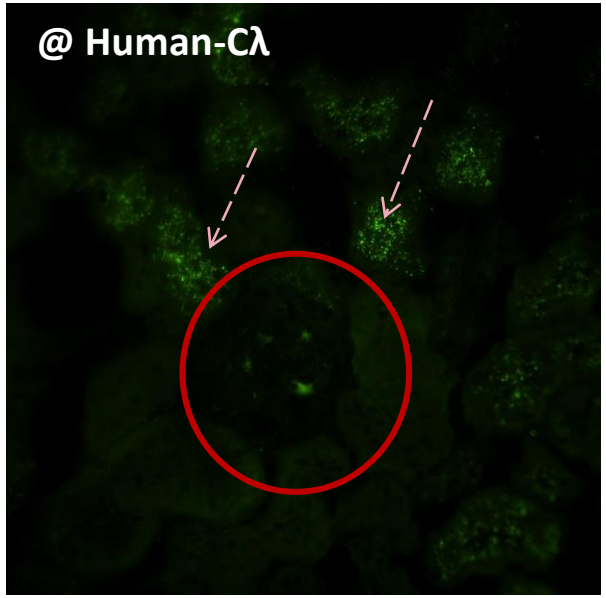
Martinez-Rivas et al, Nat Comm 2025

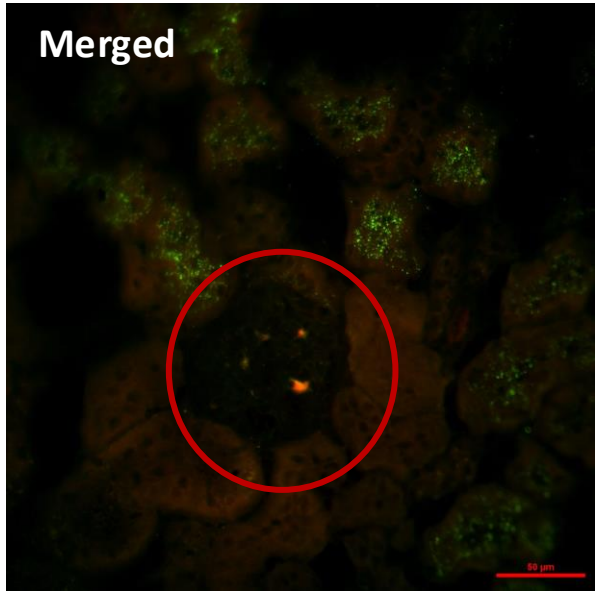
Heart



Kidney







Only traces of amyloidosis in kidney…

AL Amyloidosis

Direct toxicity of soluble AL LC in the kidney ?

- Demonstrated in heart: highly similar to LCPT (Oxydative stress, Apoptosis, lysosomal dysfunction) but no obvious endocytosis

- In Kidney: No information except Guillermo Herrera's work (Macrophage phenotype, MMP production)

Conclusions/Perspectives

Why and how are monoclonal Ig toxic for the kidney

- Specific structural peculiarities (aggregation or conformational disease): **AI tools to predict** (MigAlert, Lictor, AbAmy, VLamypred…)
- Obstruction/Disruption of tissue
- Direct toxicity (how?)

What are the molecular mecanisms leading to kidney dysfunction

> Phenotypic modification of targeted cells (dedifferentiation/production of matrix/Inflammatory signals/ apoptosis)

Gemma Martinez-Rivas
Roussine Codo
Karolina Swiderska
Alessio Lampis
Sébastien Bender
Pauline Duchatelet
Adriana Hémery
Nikolaj Nielsen

Lab Task Force

Arnaud Jaccard
Virginie Pascal
Murielle Roussel
Vincent Javaugue
Frank Bridoux
Séléna Teillaud

Clinical Task Force

CRIBL Lab Lab retreat 2026

+ Pathology crew: Sihem Kaaki, Cécile Ory, Alexia Rinsant, Oumayma Hachani, Laurence Richard, Emilie Pinault, Aurore Danigot

THANKS