

# Kidney Involvement In Monoclonal Gammopathies



**Vecihi Batuman MD FASN**  
**Huberwald Professor of Medicine**  
**Tulane University Medical School and**  
**Chief, Renal Section VA Medical Center**  
**New Orleans, LA**

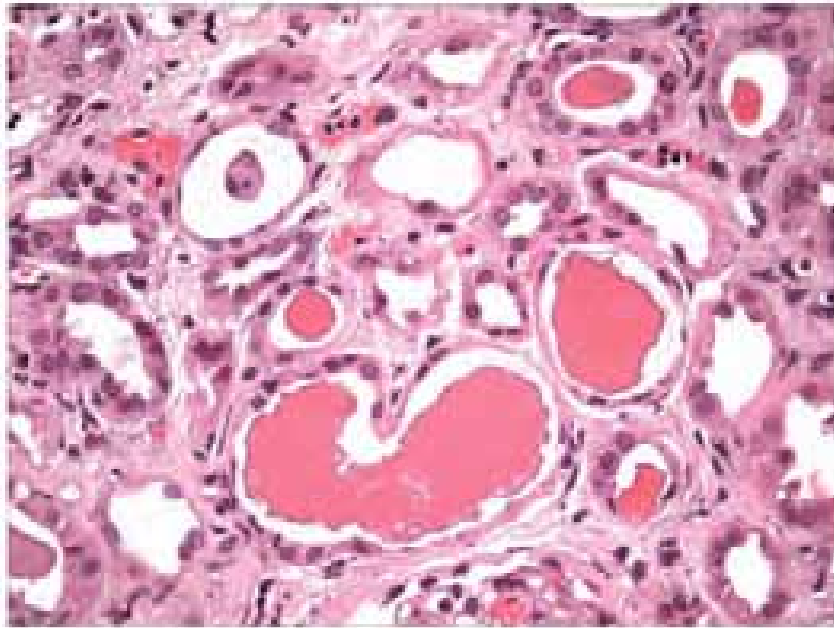
# Objectives

1. Review common types of renal disorders associated with monoclonal gammopathy
2. Discuss myeloma kidney (cast nephropathy)
3. Review recent research on pathophysiology
4. Review experimental approach

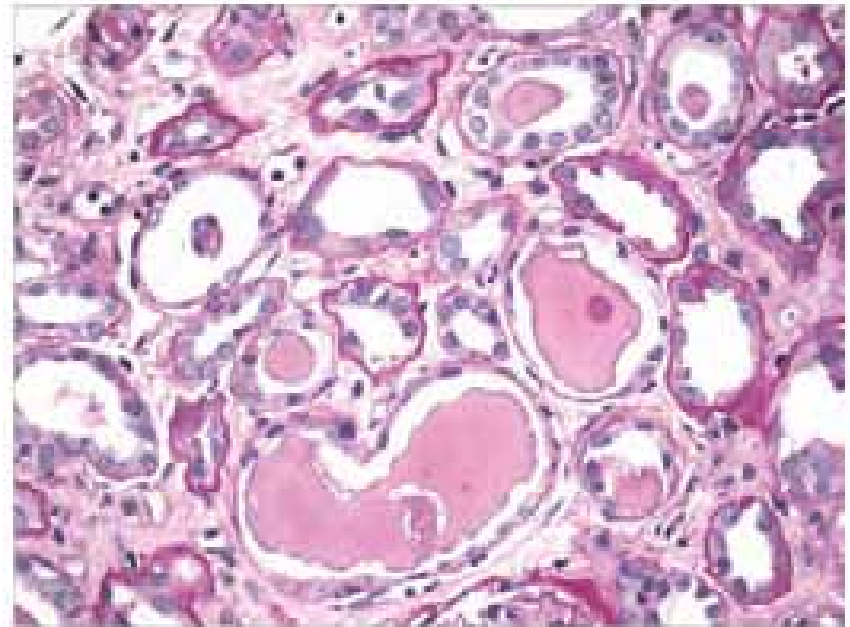
## CASE PRESENTATION

A 60-year-old Caucasian man presents with a 6-week history of fatigue, weight loss, and anorexia is found to have nonoliguric acute kidney injury with a creatinine level of 5.2 mg/dl, increased from a baseline of 1.3 mg/dl 3 months earlier. The patient's past medical history is notable for HIV infection, diabetes, hypertension, and hyperlipidemia. Physical examination reveals a BP of 160/80 mmHg, a weight of 147 lb, and no edema or cutaneous manifestations. His medications include Atripla (efavirenz, tenofovir, and emtricitabine), lisinopril, hydrochlorothiazide, pravastatin, ezetimibe, and an insulin pump.

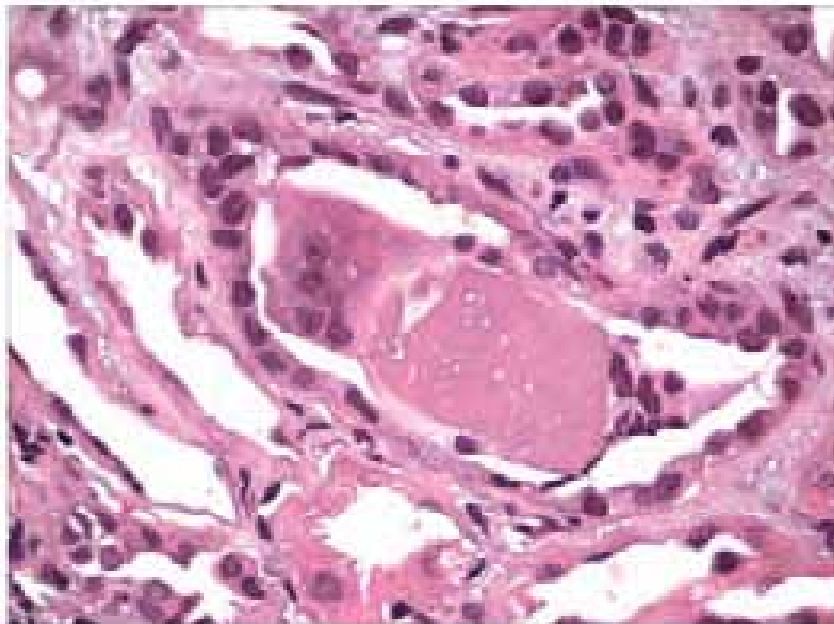
Labs: hematocrit 26.2%, albumin 4.3 g/dl, CD4 count 397 cells/ml, HIV viral load 48 copies/ml, urine protein-to-creatinine ratio 2.51 g. Urinalysis 2 + proteinuria, bland urine sediment. The kidneys are normal in size by ultrasound. The patient's creatinine fails to improve with hydration, and a renal biopsy is performed.



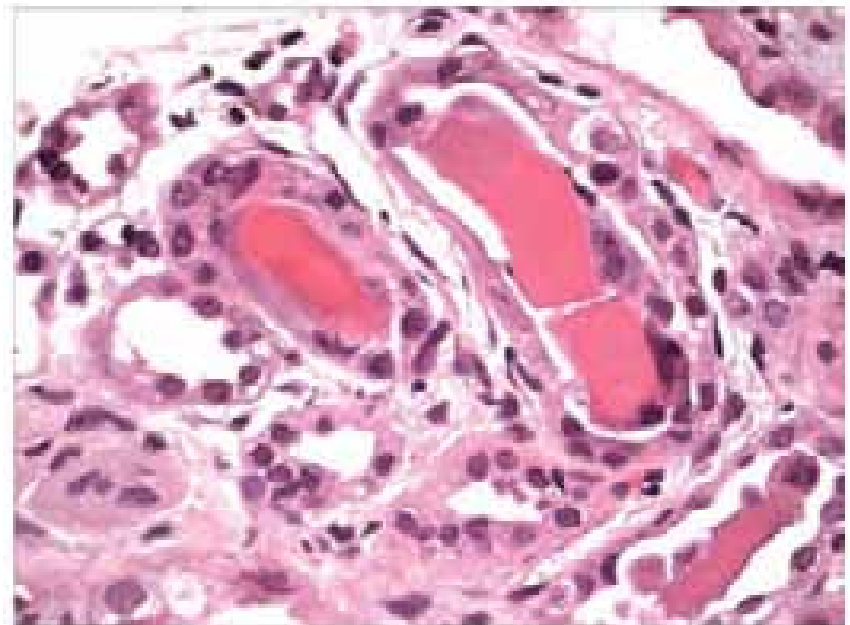
*Figure 1.*



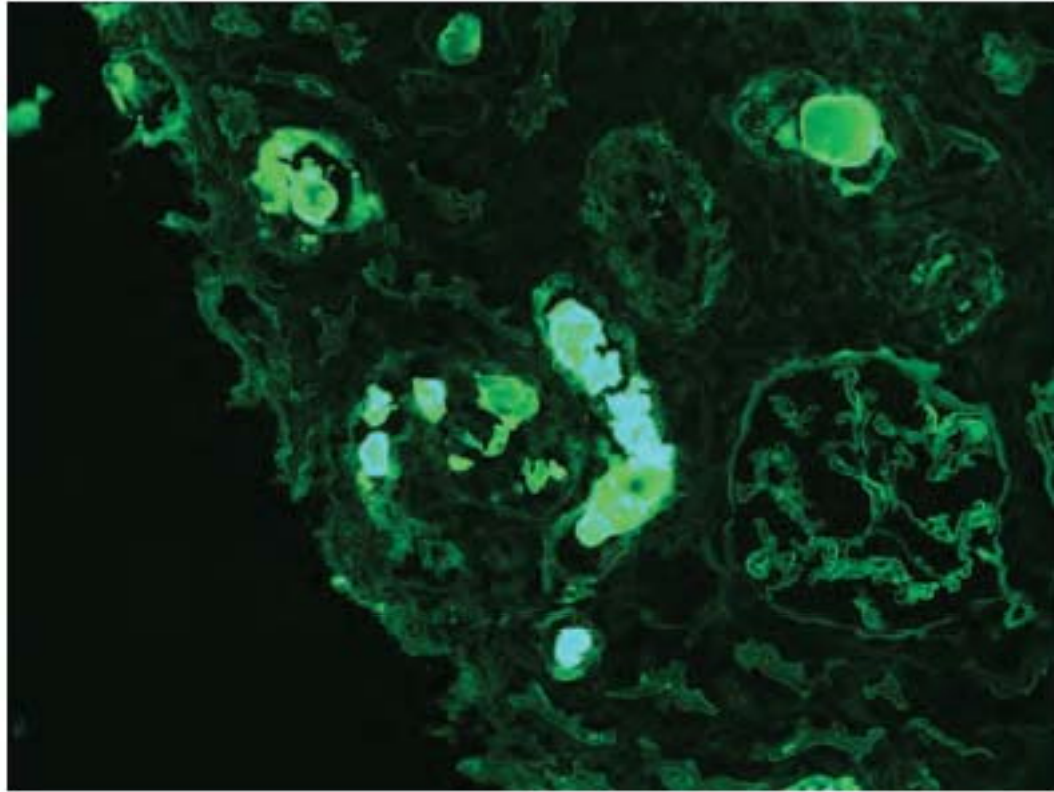
*Figure 2.*



*Figure 3.*



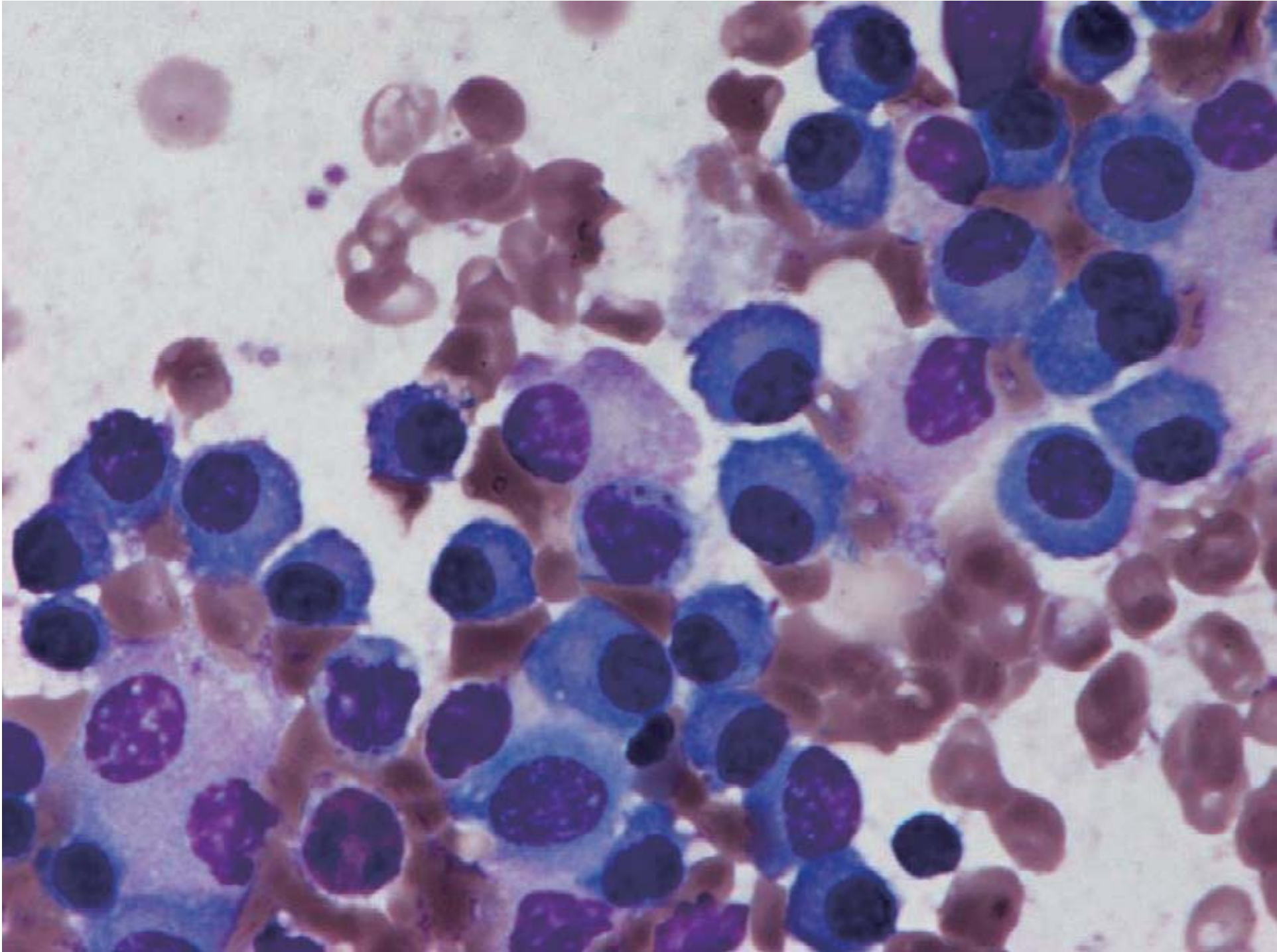
*Figure 4.*



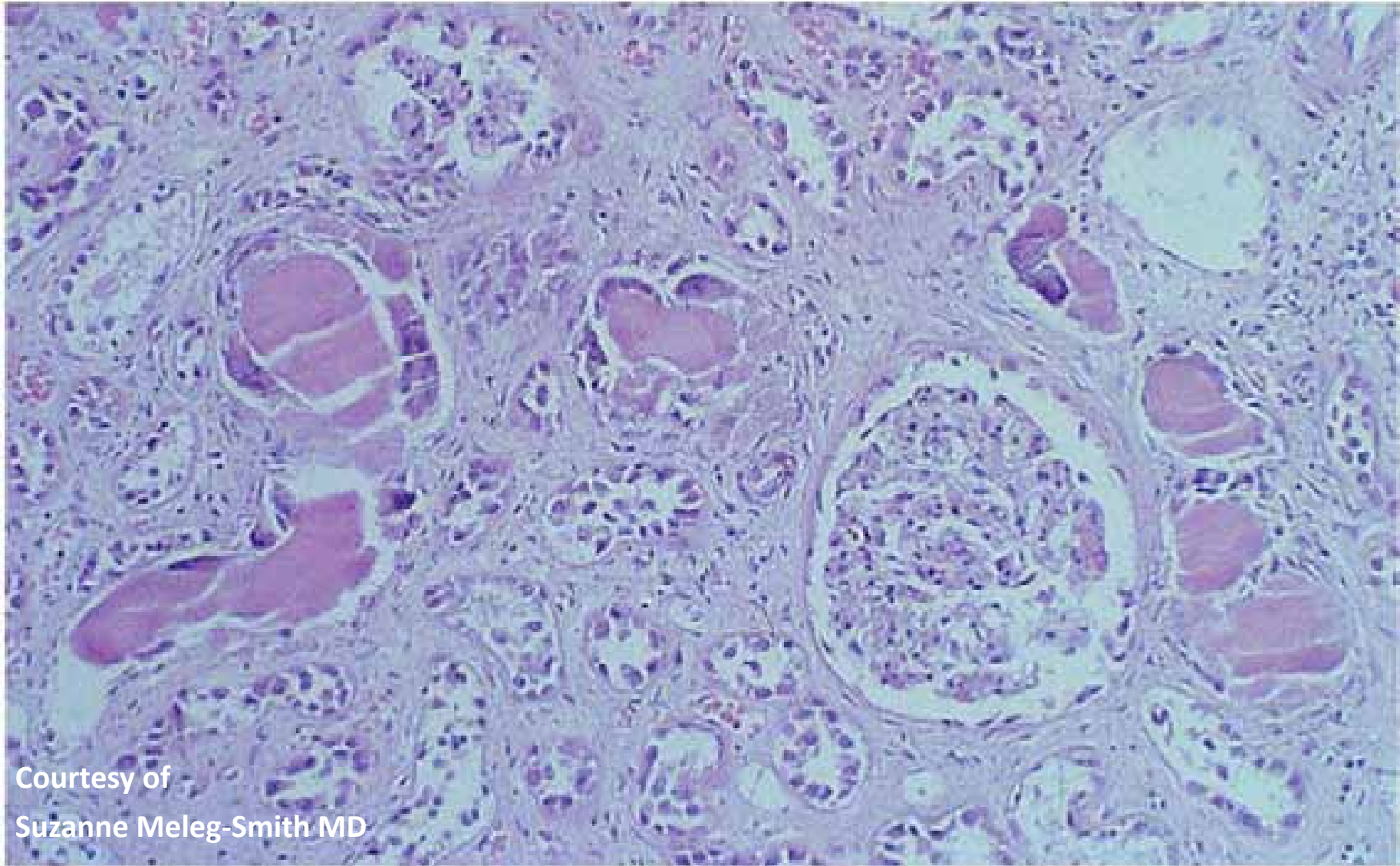
*Figure 5. Kappa light chain*

## **What is the BEST diagnosis?**

- A. Toxic acute tubular necrosis (ATN) related to treatment with tenofovir
- B. HIV-associated nephropathy
- C. Acute interstitial nephropathy
- D. Ischemic ATN
- E. Myeloma cast nephropathy (MCN)



# Myeloma Kidney



Courtesy of  
Suzanne Meleg-Smith MD

# Multiple Myeloma and Kidney Involvement

- Sixth most common tumor, 2nd most common hematologic malignancy
- Median Age 71, men > women, African Americans twice as much
- >50,000 pt in America, 20,000 new cases/yr, median survival 3-5 yr
- >11,000 die from MM each yr
- ~ 50% have kidney involvement, ~25% kidney failure
- ~1% ESRD started on dialysis has myeloma kidney
- Independently associated with 2.5-fold increase in all cause mortality
- MM is incurable
- No effective treatment for kidney involvement

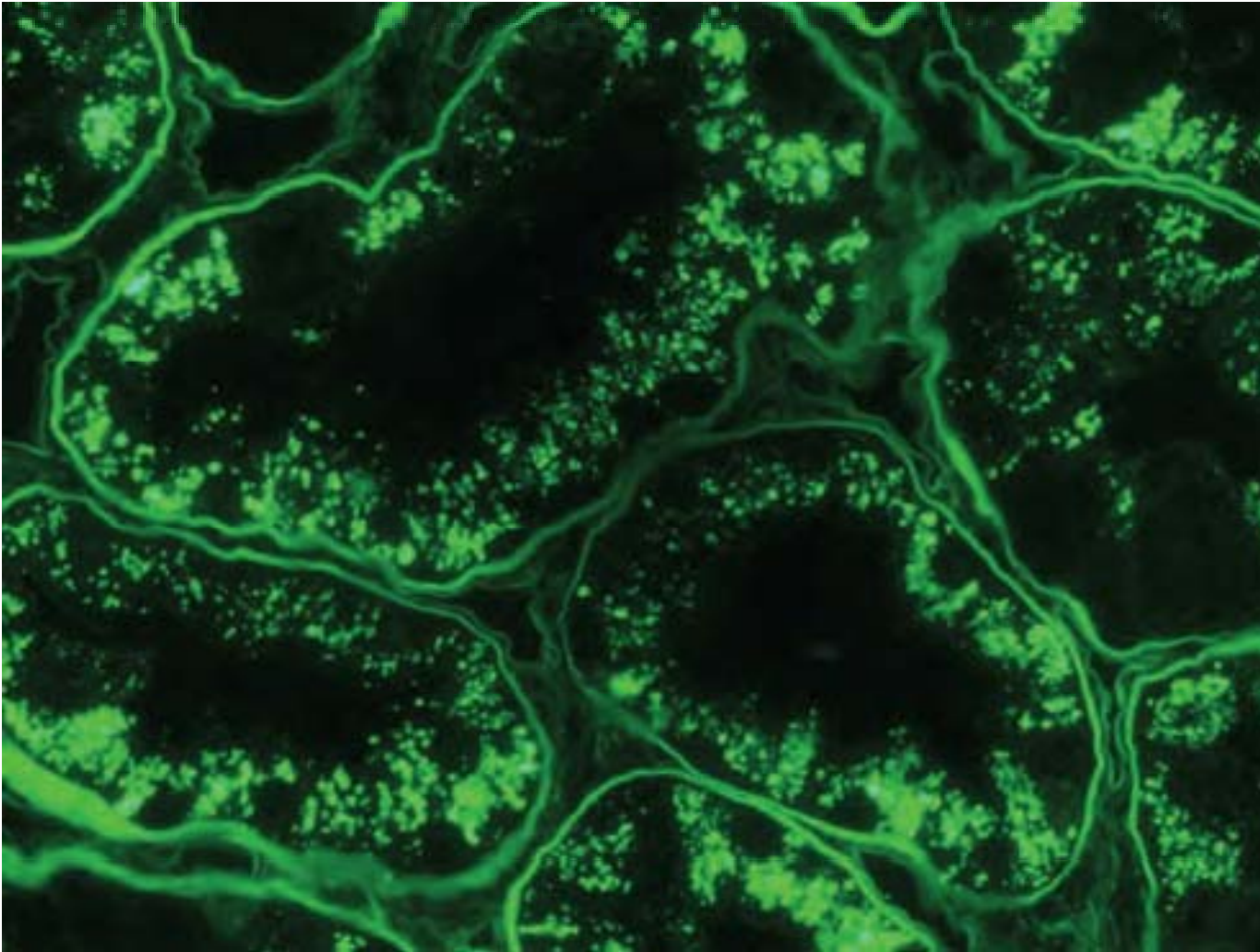
# Types of Kidney Involvement

- Light chain proteinuria
- Renal tubular acidosis
- Myeloma Kidney (Cast Nephropathy)
- Acute Cast Nephropathy
- AL amyloidosis
- LCDD

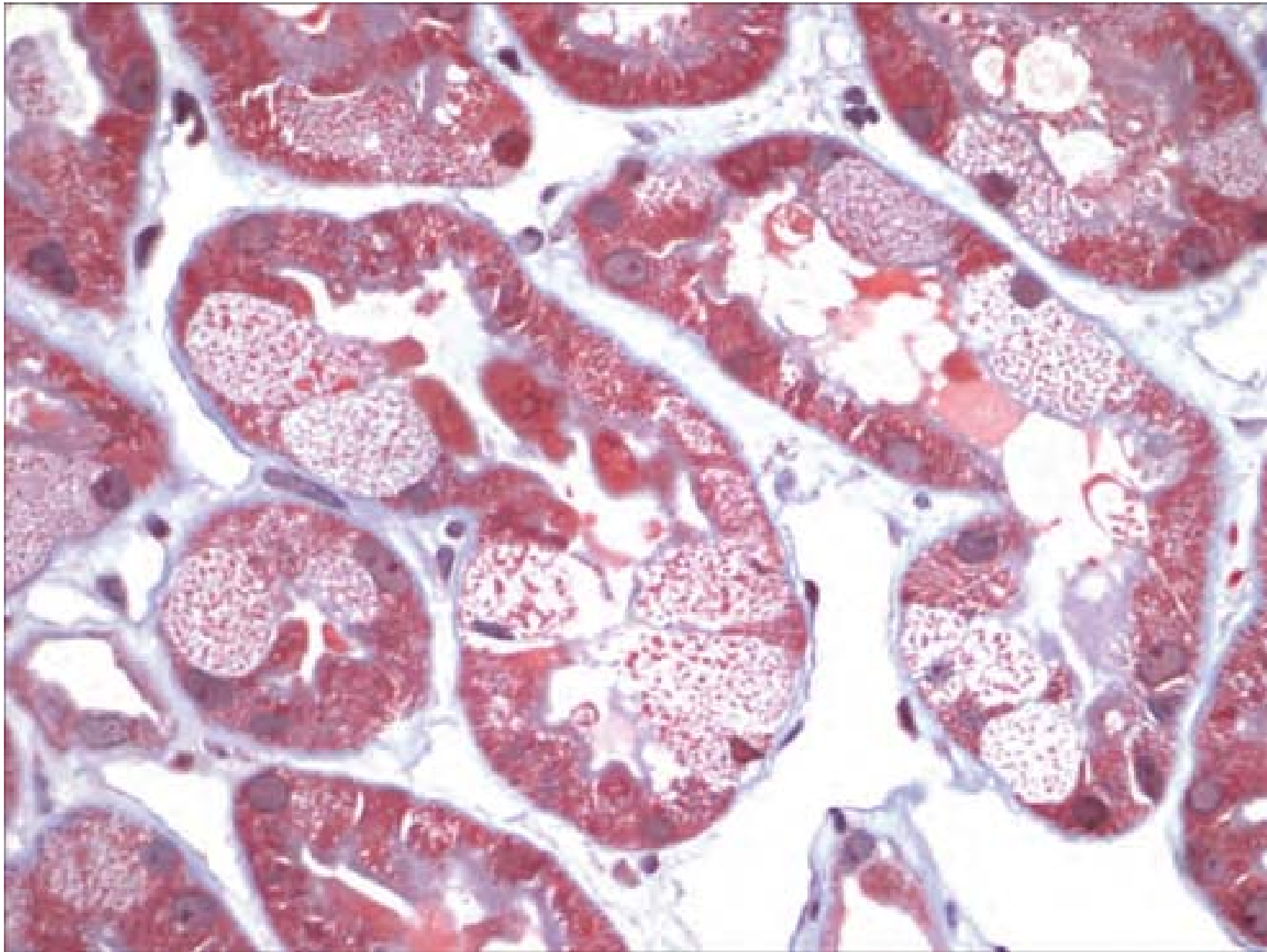
## Kidney involvement in multiple myeloma

- Tubular functional abnormalities
  - Fanconi syndrome
    - Proximal renal tubular acidosis
    - Glycosuria, hypokalemia, hyperuricosuria, amino aciduria
  - Concentrating defect
  - Distal renal tubular acidosis
  - Hypercalcemic nephropathy
  - Low-molecular weight proteinuria

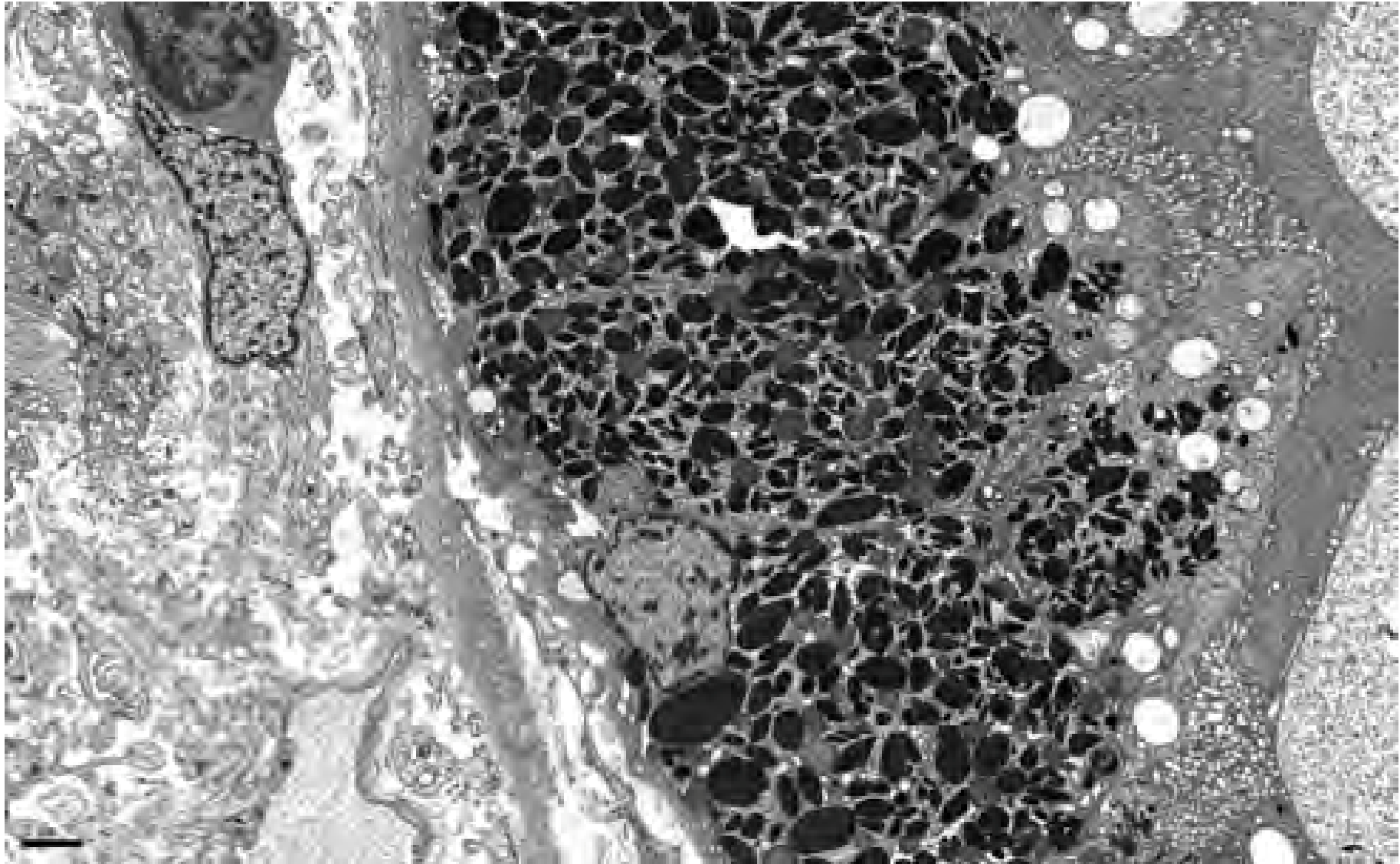
# Kappa Light Chain Fanconi Syndrome



Immunofluorescence performed on paraffin sections after pronase digestion reveals abundant intracellular crystals staining for K-light chain within the tubular epithelial cytoplasm. Staining for all other immune reactants was negative. Magnification, 600.



**The proximal tubular epithelia appear swollen and contain intracellular crystalline inclusions. Magnification, 600 (trichrome)**

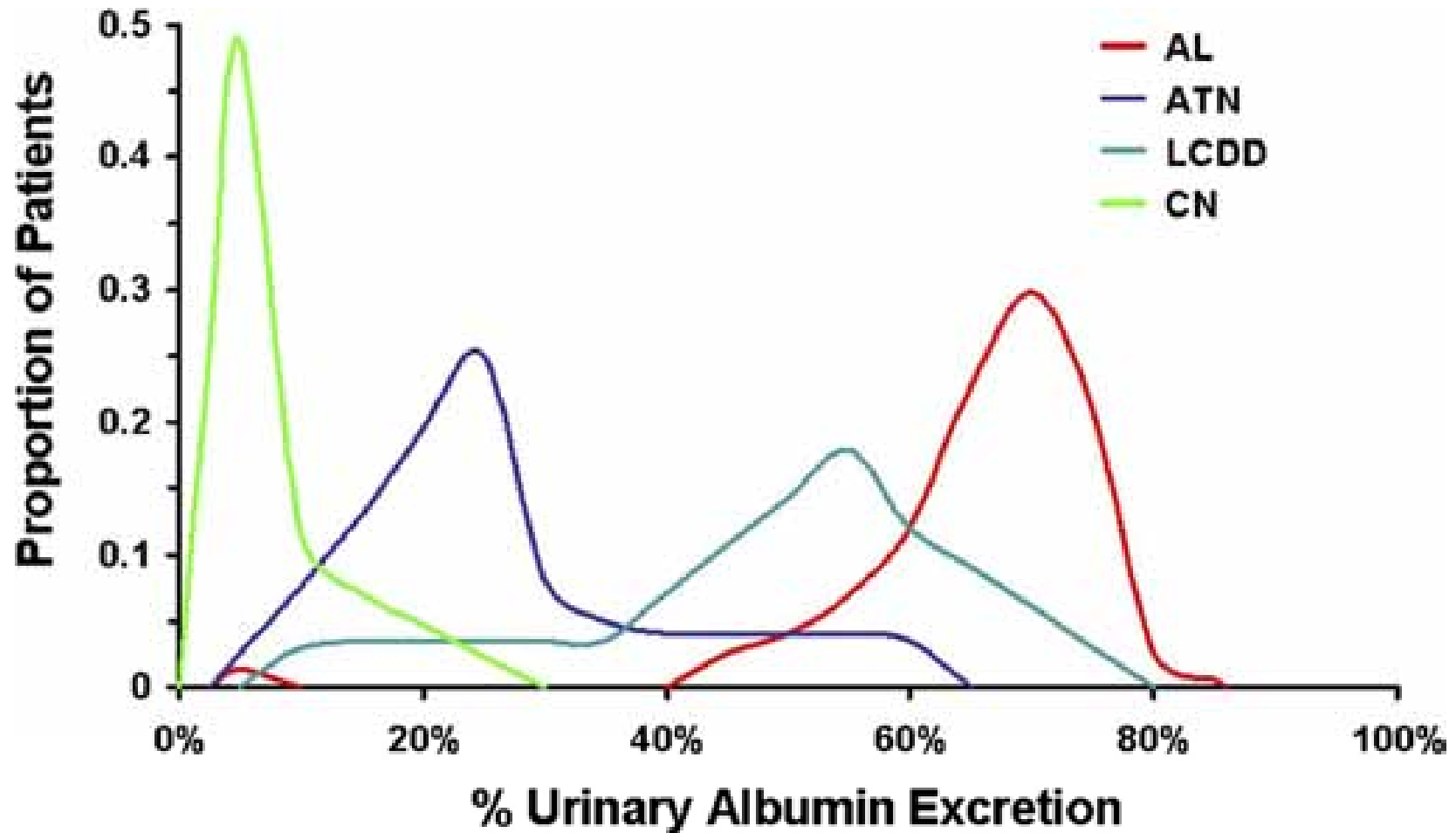


**Abundant, markedly electron-dense, rounded and angulated intracellular crystals within the cytoplasm of proximal tubular epithelium**



**Higher magnification of the intracellular crystals reveals a regular periodicity. Many of the crystals are larger than the adjacent mitochondria.**

**Distribution curves of percentage of urinary albumin excretion (%UAE) obtained from 24-hour urine collections.**

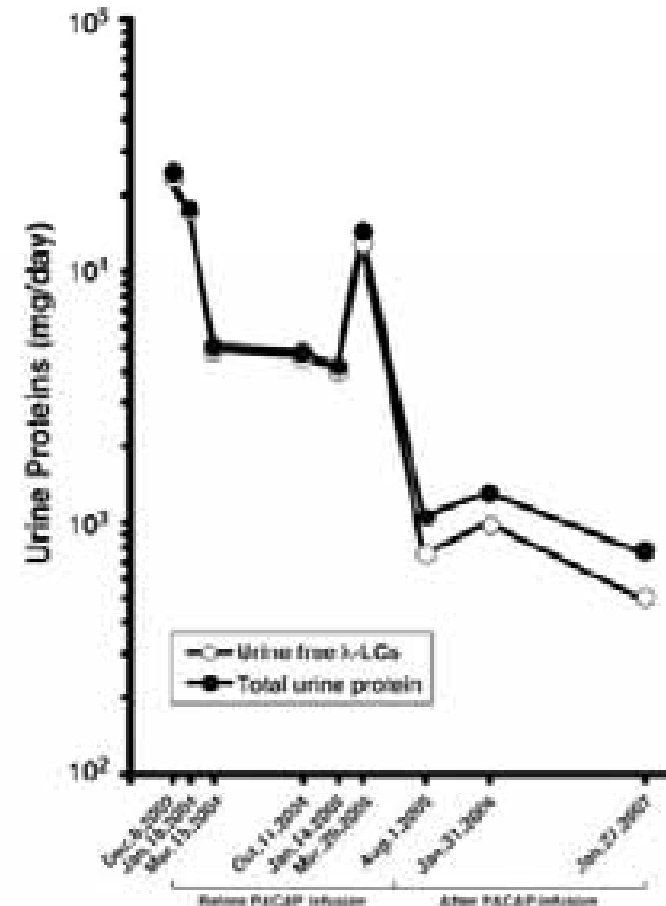


# Free Light Chain Excretion in a Patient with Myeloma Kidney

**Table 1 – Lambda light-chain immunoglobulins and total protein in the urine of a patient with multiple myeloma and myeloma kidney**

Date	Free lambda light chains in urine (mg/day)	Total protein (mg/day)
12/6/03	<b>21,347</b>	<b>21,584</b>
1/18/04	17,784	17,952
3/15/04	4,968	5112
10/11/04	4,665	4873
1/14/05	4,092	4312
3/29/05 <sup>a</sup>	13,200	ND
8/1/05 <sup>b</sup>	751	1068
1/31/06	1,013	1331
1/27/07	520	781

<sup>a</sup> Before PACAP infusion.  
<sup>b</sup> After PACAP infusion.



**Table 1: Classification of Kidney disease in MM according to primary site of injury [2, 35, 42, 43]**

<b>Glomerular</b>	<b>Tubular</b>	<b>Interstitial</b>	<b>Other Causes</b>
<ul style="list-style-type: none"> <li>• Primary Amyloidosis (AL or AH) •</li> <li>Monoclonal Ig deposition:               <ul style="list-style-type: none"> <li>- Light chain deposition disease</li> <li>- Heavy chain deposition disease</li> <li>- Light &amp; heavy chain deposition disease</li> </ul> </li> <li>• Miscellaneous (cryoglobulinemia and proliferative glomerulonephritis)</li> </ul>	<ul style="list-style-type: none"> <li>- Myeloma kidney (Light chain cast nephropathy)</li> <li>- Distal tubular dysfunction</li> <li>- Proximal tubule dysfunction or acquired Fanconi syndrome</li> </ul>	<ul style="list-style-type: none"> <li>- Plasma cell infiltration</li> <li>- Interstitial nephritis</li> </ul>	<ul style="list-style-type: none"> <li>- Hyperuricemia</li> <li>- Hypercalcemia</li> <li>- Drugs (e.g. NSAIDs)</li> </ul>

# Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant

Nelson Leung,<sup>1,2</sup> Frank Bridoux,<sup>3</sup> Colin A. Hutchison,<sup>4</sup> Samih H. Nasr,<sup>5</sup> Paul Cockwell,<sup>4</sup> Jean-Paul Fermand,<sup>6</sup> Angela Dispenzieri,<sup>2</sup> Kevin W. Song,<sup>7</sup> and Robert A. Kyle,<sup>2</sup> on behalf of the International Kidney and Monoclonal Gammopathy Research Group

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**Table 1. Pathologic classification of diseases with tissue deposition or precipitation of monoclonal Ig**

Organized	Nonorganized (granular)			
	Fibrillar	Microtubular	MIDD (Randall type)	Other
Crystals				
Myeloma cast nephropathy	Light chain amyloidosis	Type I and type II cryoglobulinemic glomerulonephritis	LCDD	Proliferative GN with monoclonal Ig deposits
Light chain proximal tubulopathy (with or without Fanconi syndrome)	Nonamyloid	Immunotactoid GN	LHCDD	Waldenström
Crystal-storing histiocytosis	Fibrillary GN*	GOMMID	HCDD	Macroglobulinemia

GN indicates glomerulonephritis; GOMMID, glomerulonephritis with organized microtubular monoclonal Ig deposits; LCDD, light-chain deposition disease; LHCDD, light- and heavy-chain deposition disease; and HCDD, heavy-chain deposition disease.

\*Mostly associated with polyclonal IgG deposits.

Other than cast nephropathy and hypercalcemia, MM is not required for the development of the other kidney diseases.

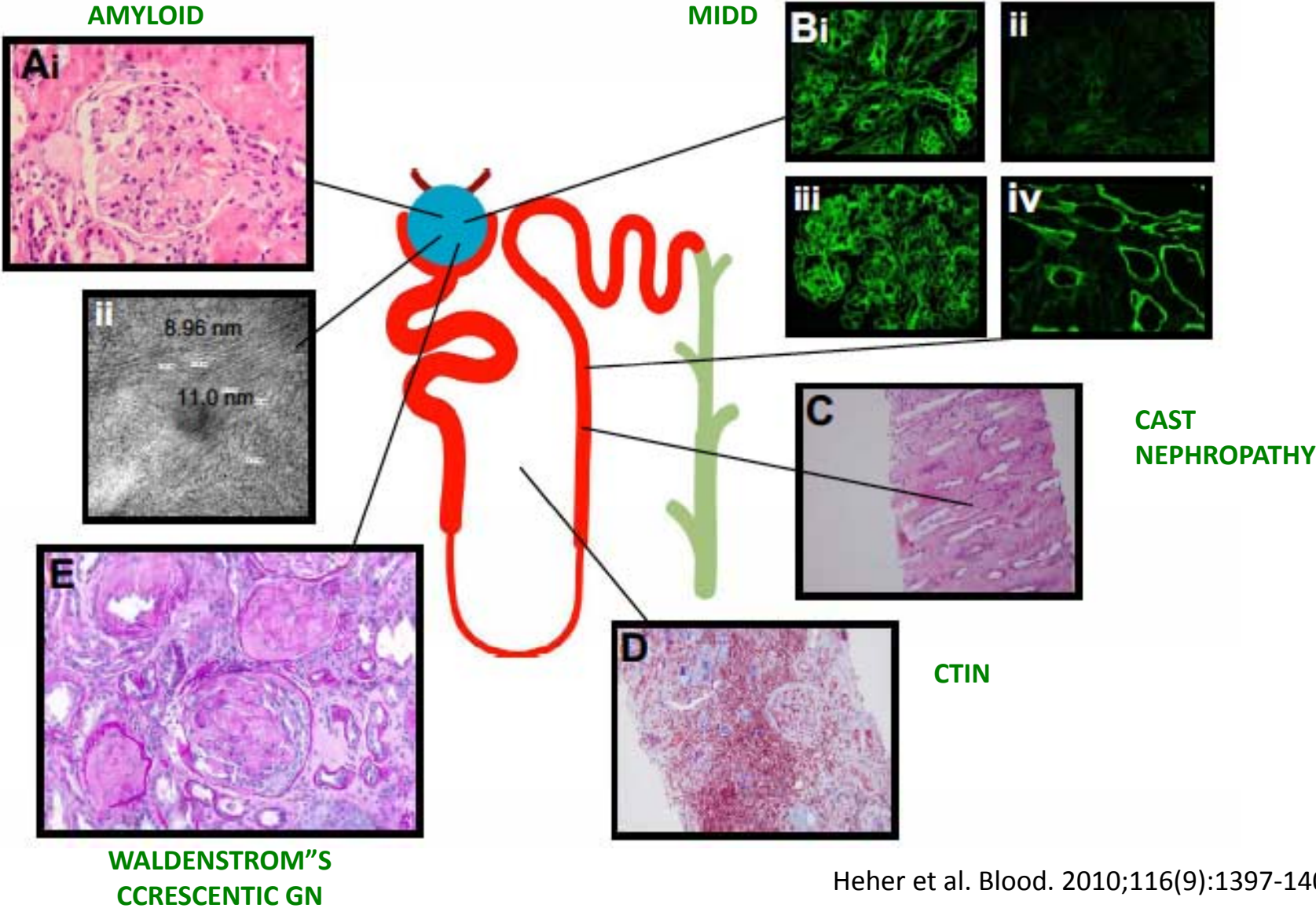
# Ig-dependent mechanisms of renal failure in plasma cell dyscrasias

Ig-dependent mechanisms	
Mechanism	Details
Cast nephropathy (myeloma kidney)	Risk factors include light chain myeloma with > 10 g/day of monoclonal Ig excretion, IgD myeloma, volume depletion, sepsis, medications (see "Medication toxicity" below)
MIDD	Often associated with kappa light chains. Systemic syndrome may be present.
AL amyloidosis	Often associated with nephrotic-range albuminuria and lambda light chains. Systemic syndrome may be present.
Glomerulonephritis	Membranoproliferative, diffuse proliferative, crescentic, cryoglobulinemic all recognized
Tubulointerstitial nephritis	May also result from non-Ig mechanisms.
Minimal change or membranous glomerulopathy	Albuminuria is typically present, in addition to light chain proteinuria
Henoch-Scholein purpura/IgA nephropathy	Associated with IgA myeloma
Immunotactoid and fibrillary glomerulopathy	Rare conditions
Intracapillary monoclonal deposits of IgM thrombi	Associated with Waldenström macroglobulinemia
TMA	Paraprotein causes endothelial injury with resulting TMA
Hyperviscosity syndrome	Most common with Waldenström macroglobulinemia

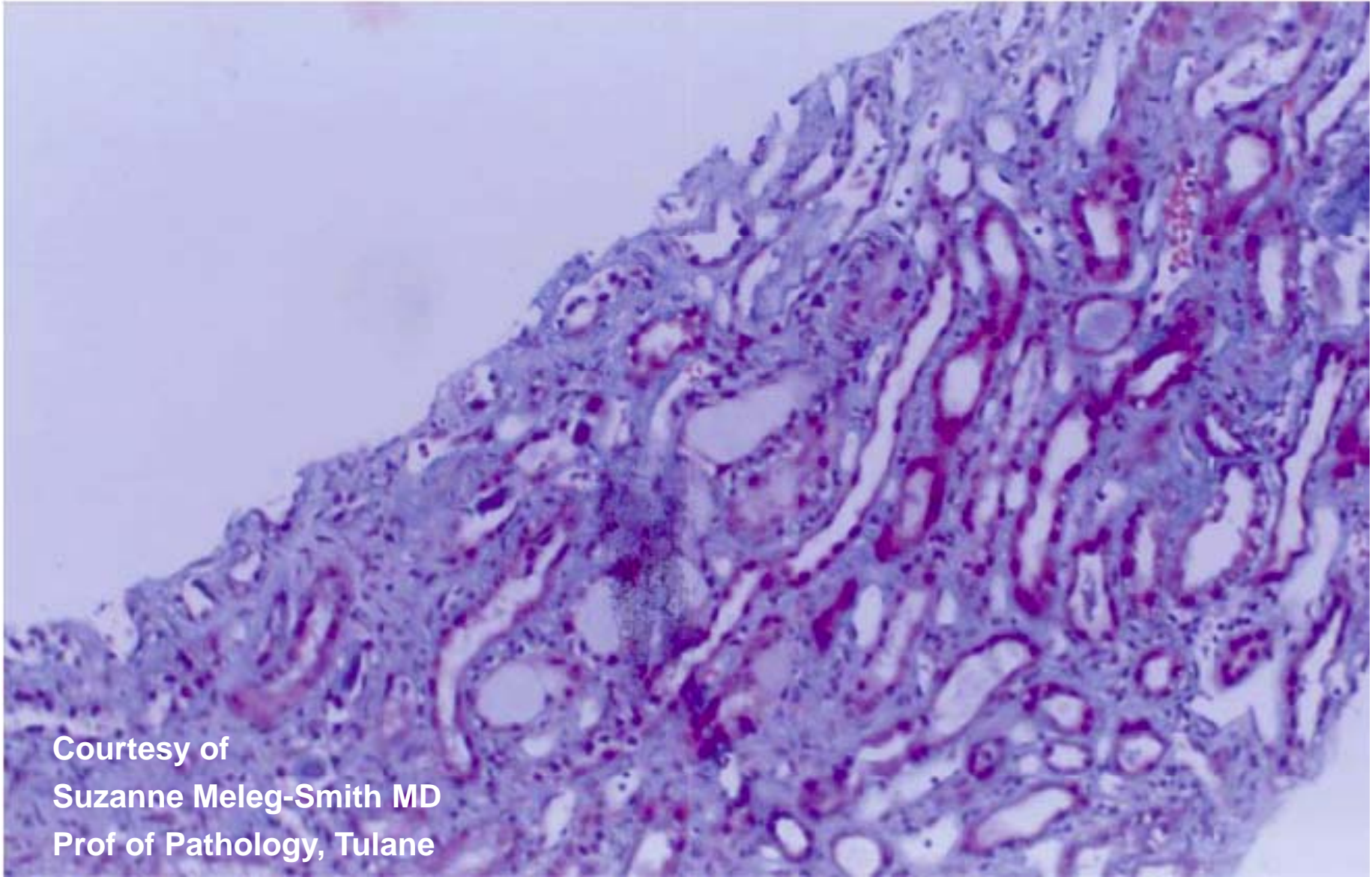
# Ig-independent mechanisms of renal failure in plasma cell dyscrasias

Mechanism	Details
Volume depletion or sepsis	Can cause acute tubular necrosis and/or precipitate cast nephropathy
Hypercalcemia	Can precipitate cast nephropathy
Tumor lysis syndrome	Uric acid or phosphate nephropathy
Medication toxicity	Zoledronate: acute renal failure Pamidronate: collapsing focal segmental glomerulosclerosis Nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, loop diuretics, or IV contrast can precipitate cast nephropathy
Direct parenchymal invasion by plasma cells	Associated with advanced or aggressive myeloma
Pyelonephritis	Immunodeficiency from myeloma, deficient Ig, and chemotherapy all contribute

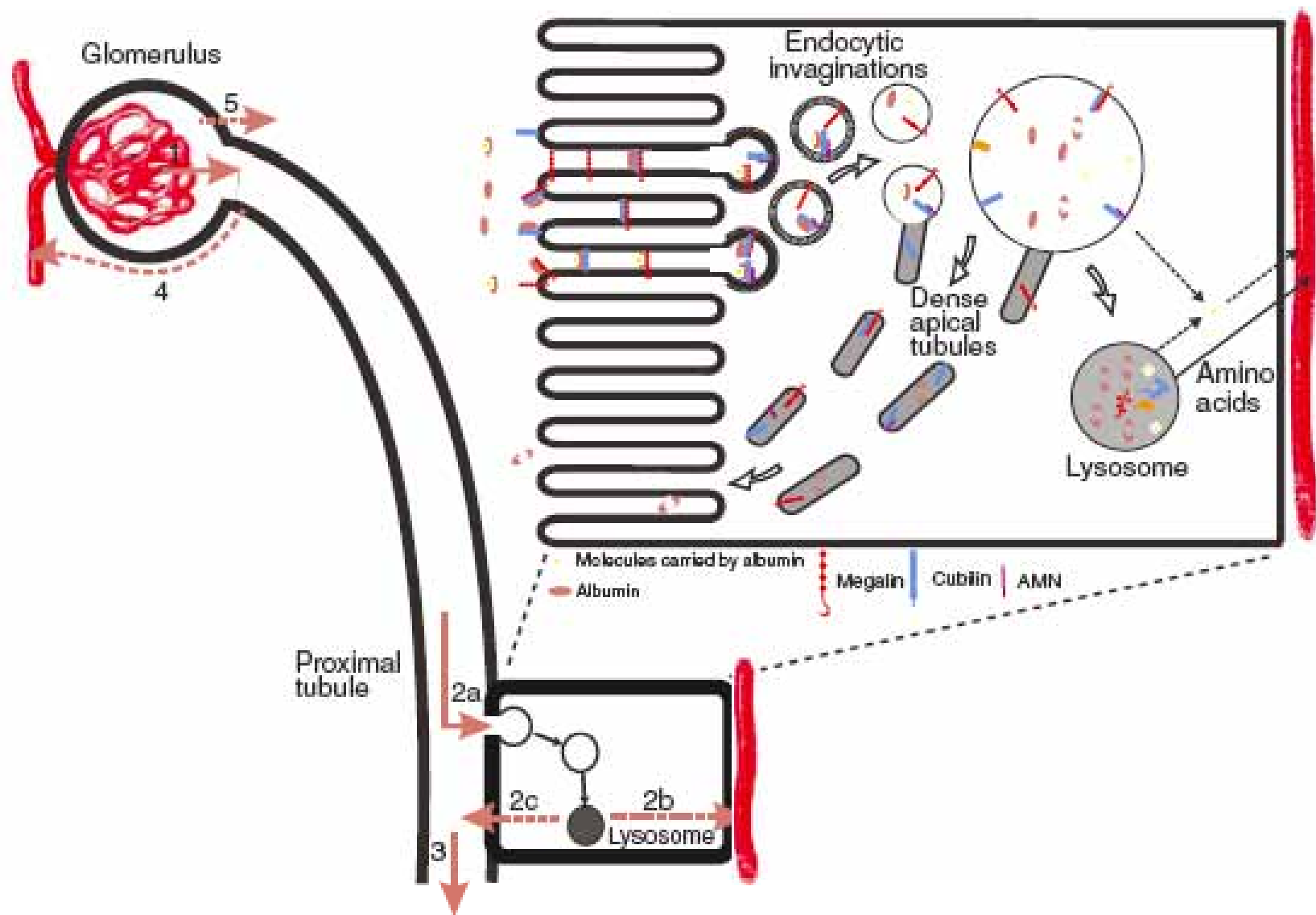
Three distinct syndromes account for most cases of Ig-mediated kidney disease but virtually all nephropathologic syndromes have been observed

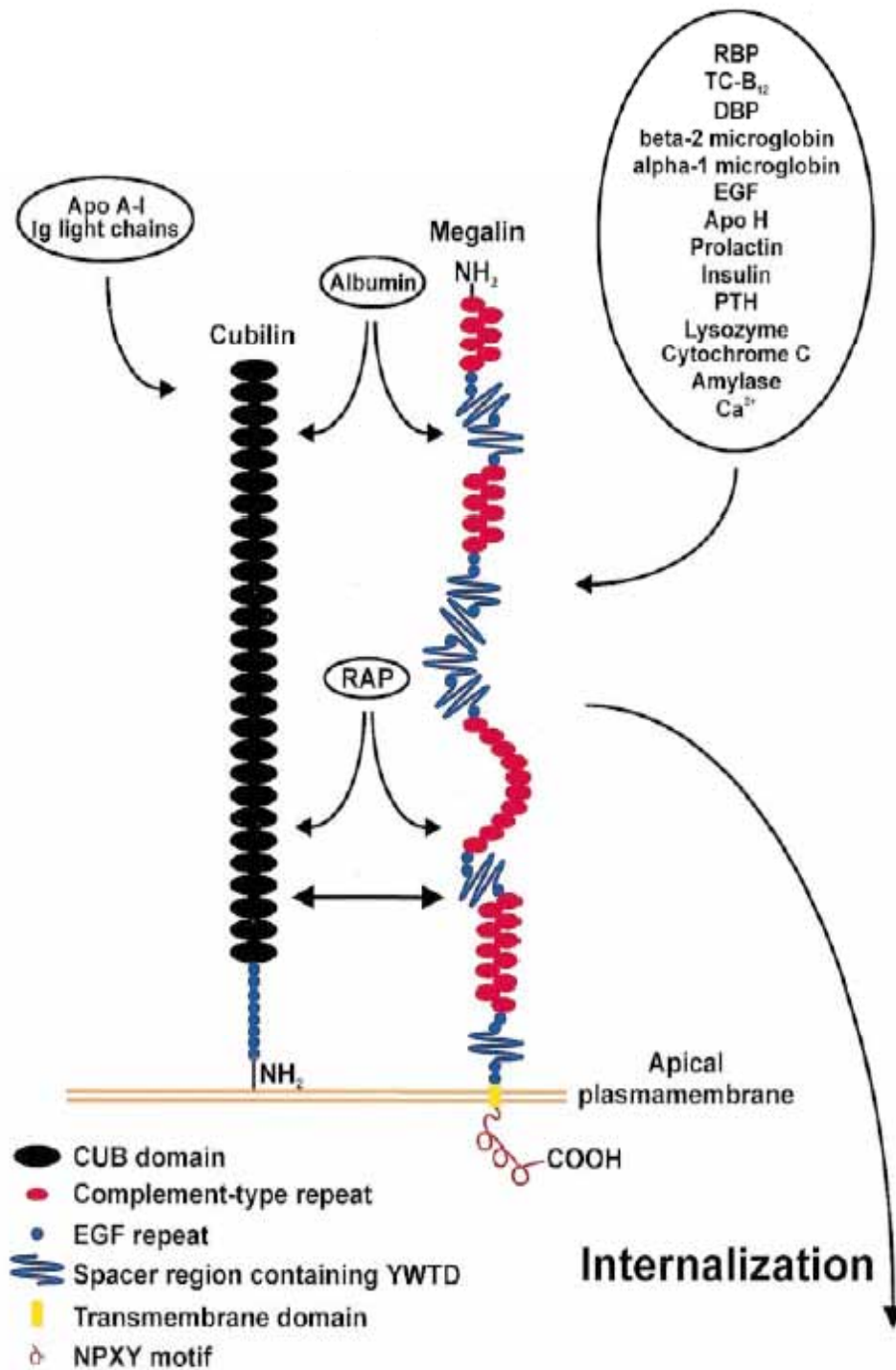


# Myeloma Kidney



Courtesy of  
Suzanne Meleg-Smith MD  
Prof of Pathology, Tulane





Apo A-I  
Ig light chains

Albumin

RAP

Megalin  
NH<sub>2</sub>

RBP  
TC-B<sub>12</sub>  
DBP  
beta-2 microglobulin  
alpha-1 microglobulin  
EGF  
Apo H  
Prolactin  
Insulin  
PTH  
Lysozyme  
Cytochrome C  
Amylase  
Ca<sup>2+</sup>

Cubilin

Apical  
plasmamembrane

COOH

- CUB domain
- Complement-type repeat
- EGF repeat
- Spacer region containing YWTD
- Transmembrane domain
- NPXY motif

Internalization

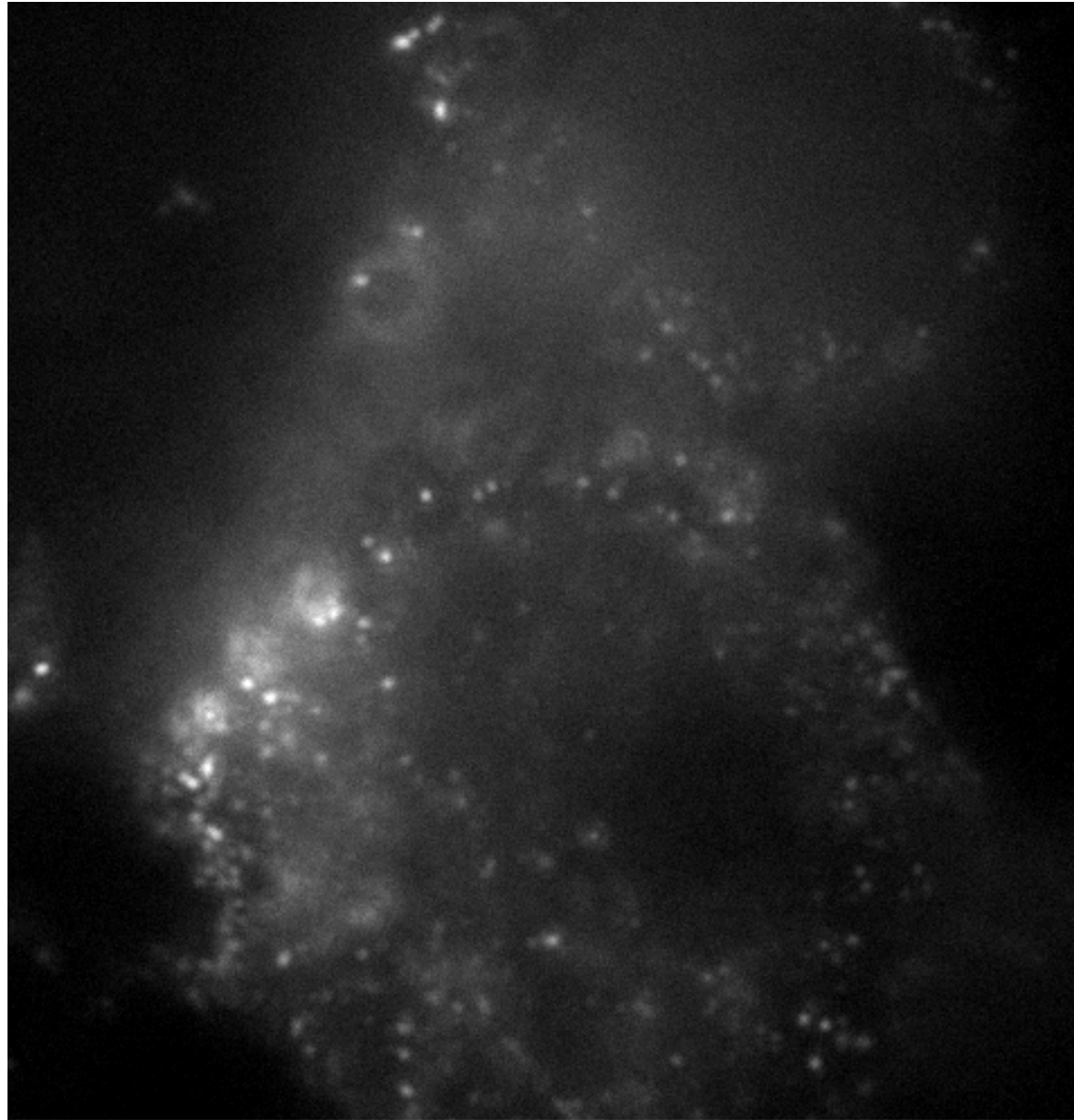
*Kidney International, Vol. 62 (2002), pp. 1977–1988*

## Endocytosis of light chains induces cytokines through activation of NF- $\kappa$ B in human proximal tubule cells

**SULE SENGUL, CRAIG ZWIZINSKI, ERIC E. SIMON, ADITI KAPASI, PRAVIN C. SINGHAL, and VECIHI BATUMAN**

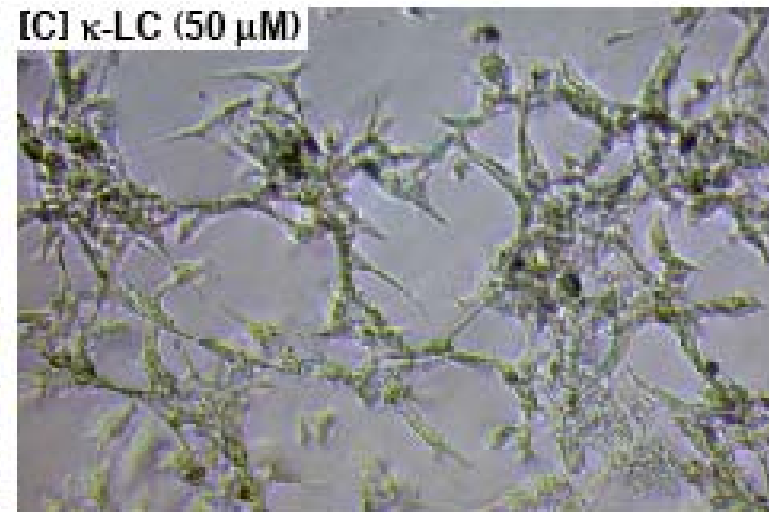
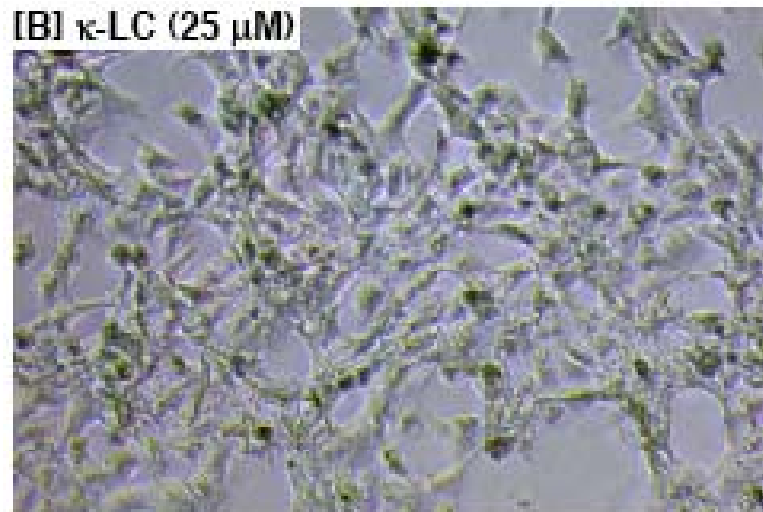
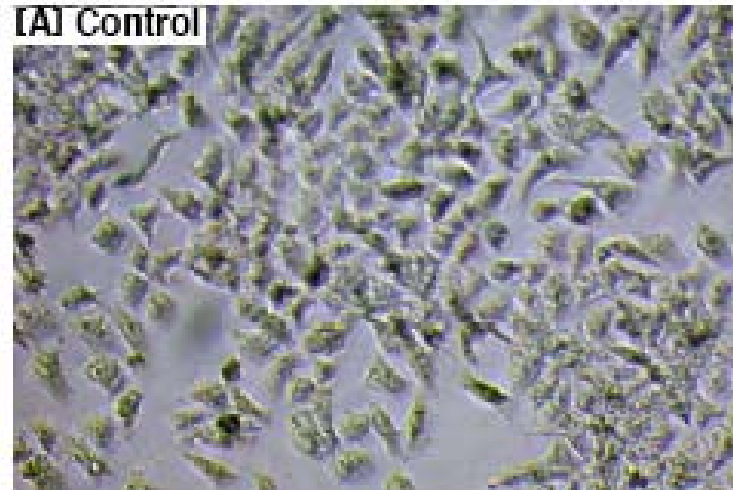
*Department of Medicine, Section of Nephrology, Tulane Medical Center, Tulane Cancer Center, and Veterans Administration Medical Center, New Orleans, Louisiana; and Long Island Jewish Medical Center, New Hyde Park, Long Island, New York, USA*

## ENDOCYTOSIS OF LIGHT CHAINS IN PTC

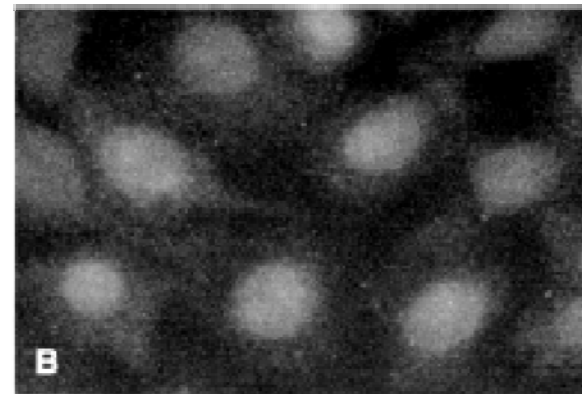
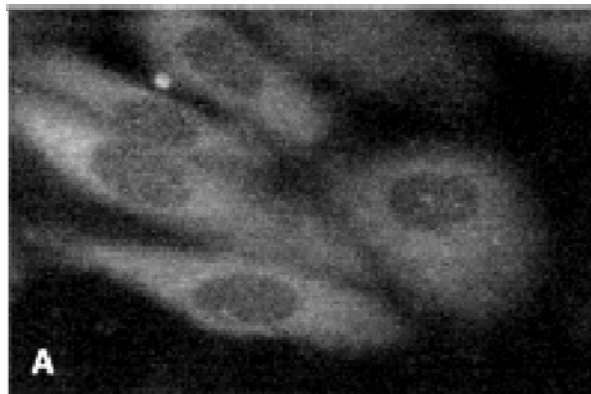
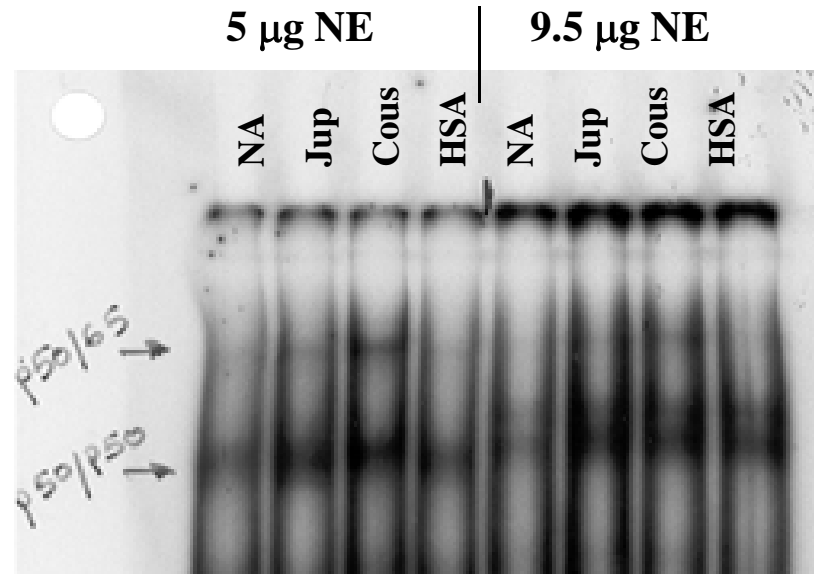


Sengul et al *Kidney International*, Vol. 62 (2002), pp. 1977–1988

# Cytotoxicity of Myeloma Light Chains



# LCs Activate NF- $\kappa$ B



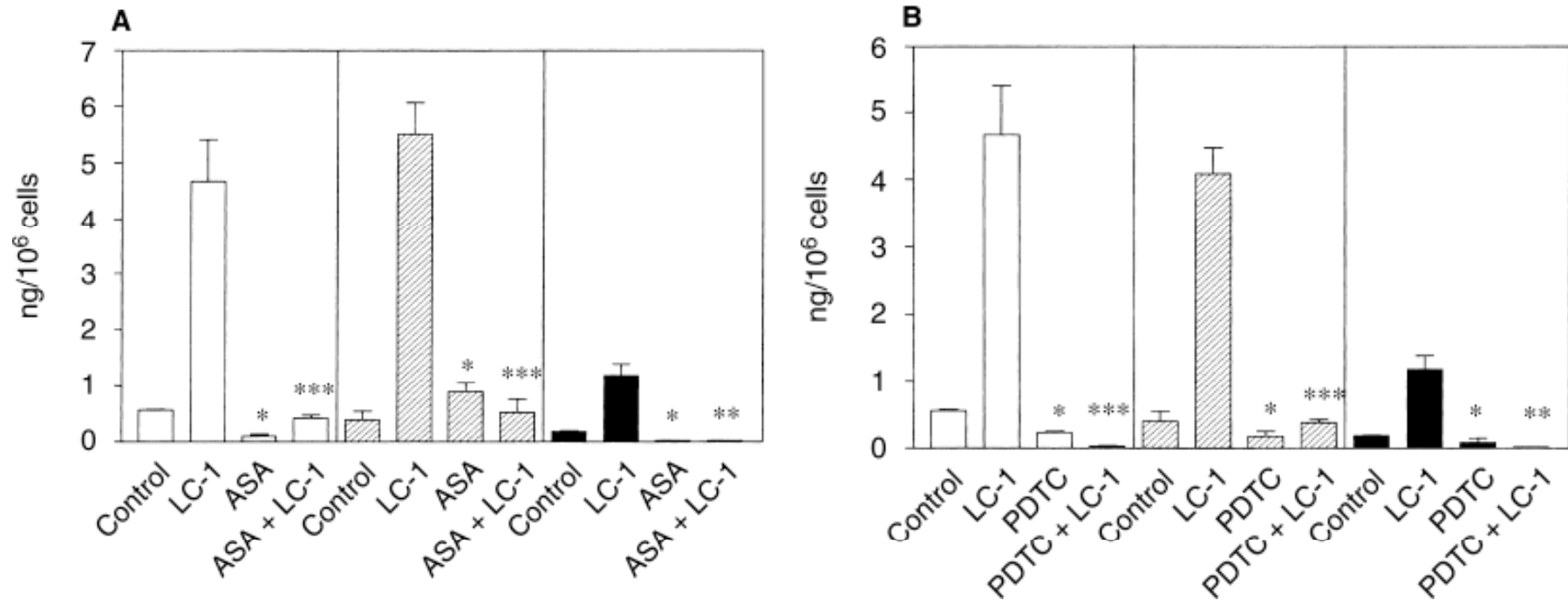
*Am J Physiol Renal Physiol* 284: F1245–F1254, 2003.  
First published February 11, 2003; 10.1152/ajprenal.00350.2002.

## Role of MAPK pathways in light chain-induced cytokine production in human proximal tubule cells

**Sule Sengul**<sup>1,2</sup> **Craig Zwizinski**<sup>1,2</sup> and **Vecihi Batuman**<sup>1,2,3</sup>

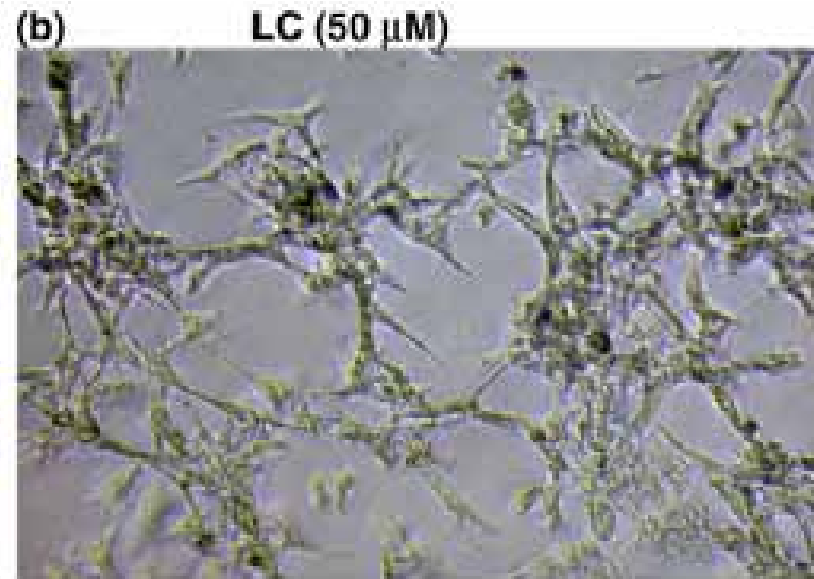
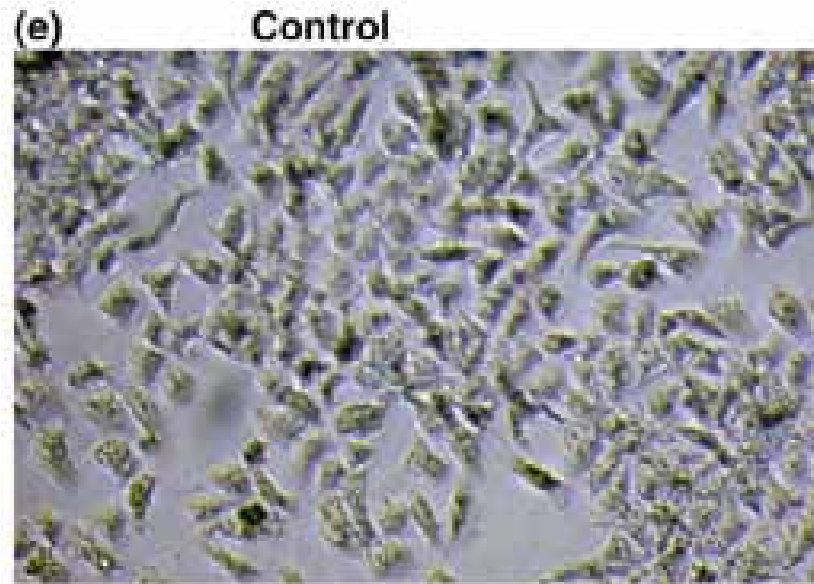
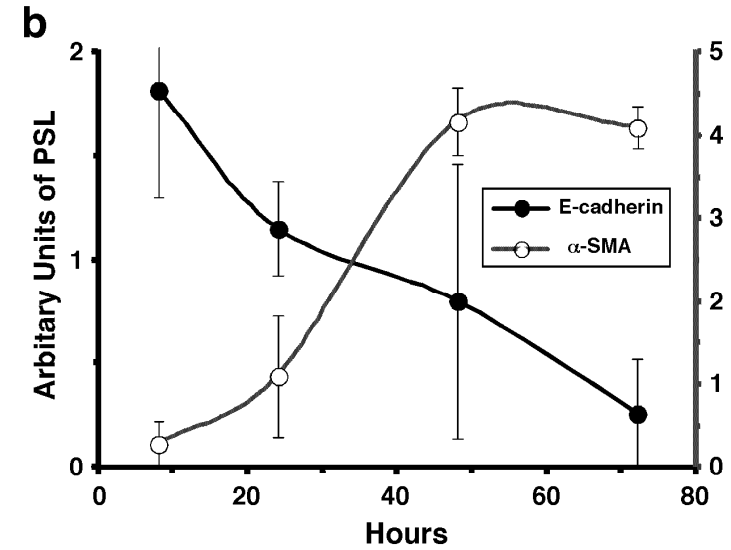
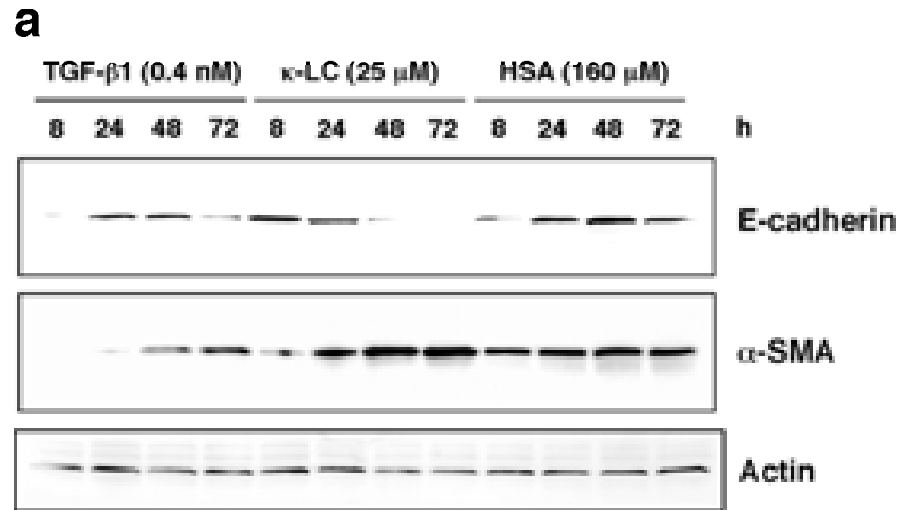
<sup>1</sup>Section of Nephrology, Department of Medicine, Tulane Medical Center, <sup>3</sup>Tulane Cancer Center, and <sup>2</sup>Veterans Administration Medical Center, New Orleans, Louisiana 70112

**Effects of NF-κB inhibitors aspirin (ASA) and pyrrolidineditiocarbamate (PDTC) on LC-1 stimulated IL6, IL-8 and MCP-1 production.**

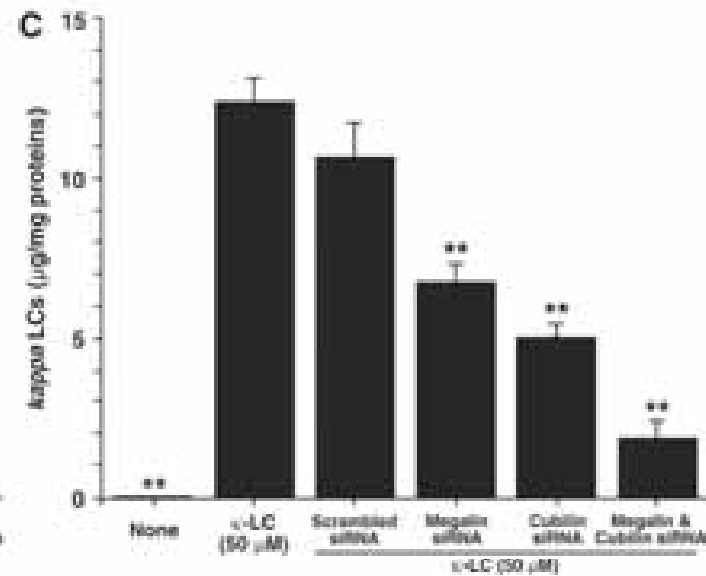
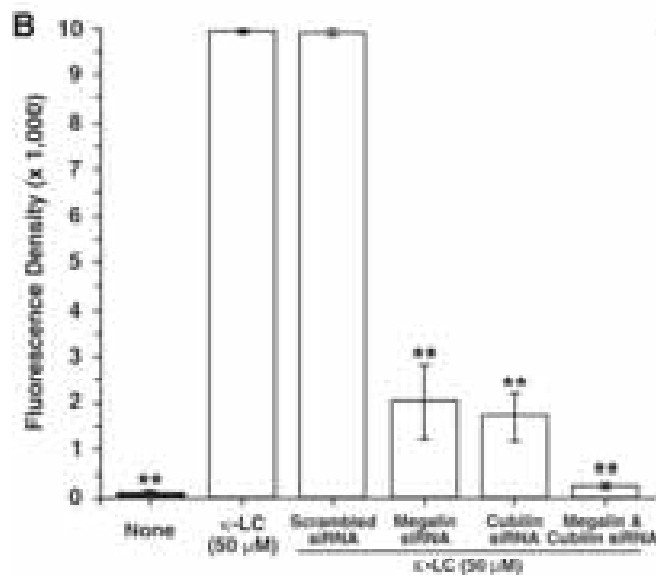
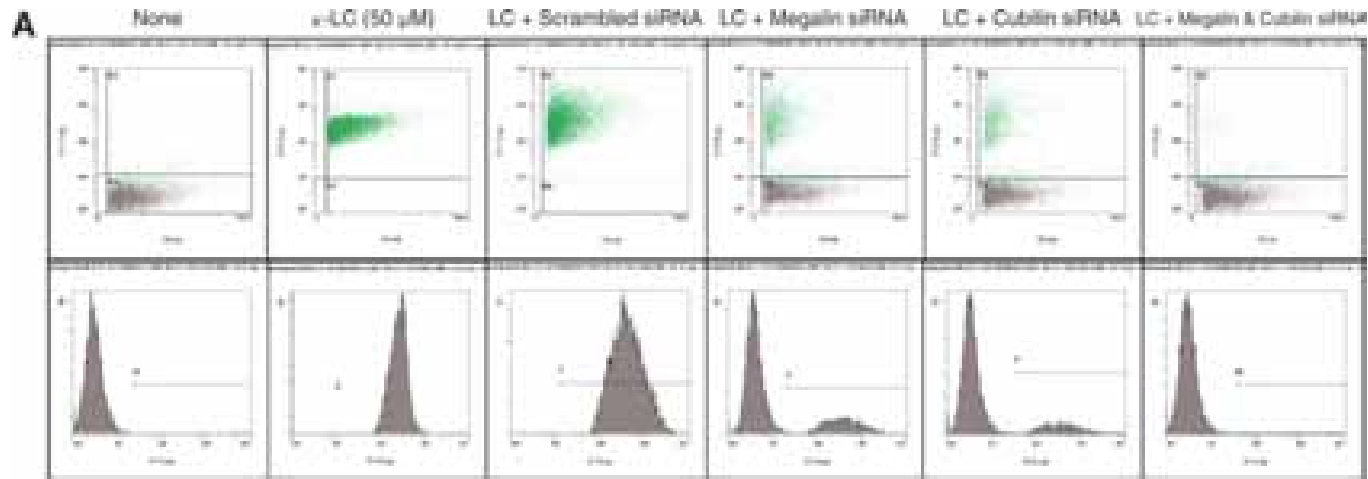


Sengul et al. *Kidney International* (2002) 62, 1977–1988;

# EMT in LC-exposed PTC

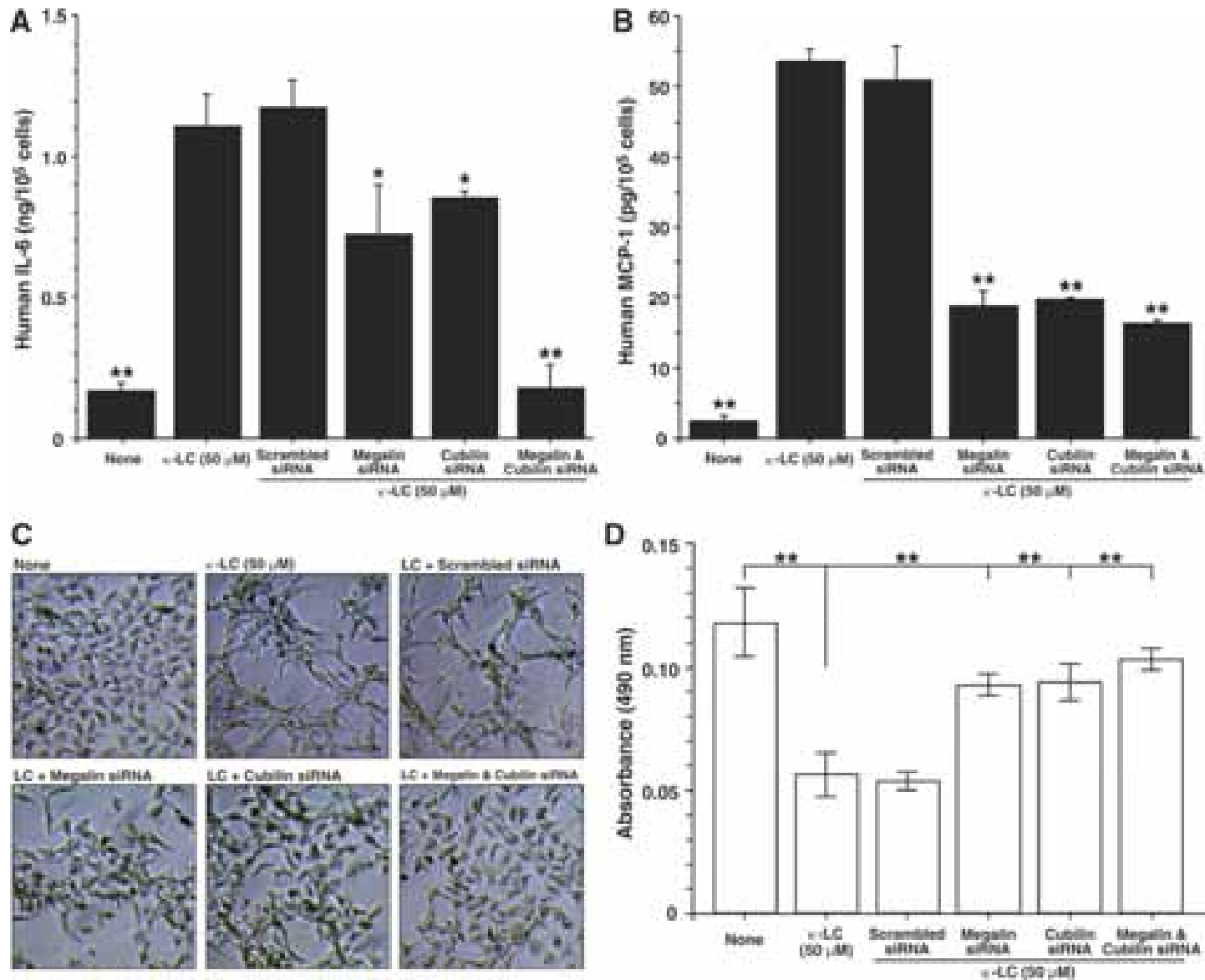


# Effect of silencing megalin and/or cubilin on light chain (LC) endocytosis and cytotoxicity in human renal PTECs

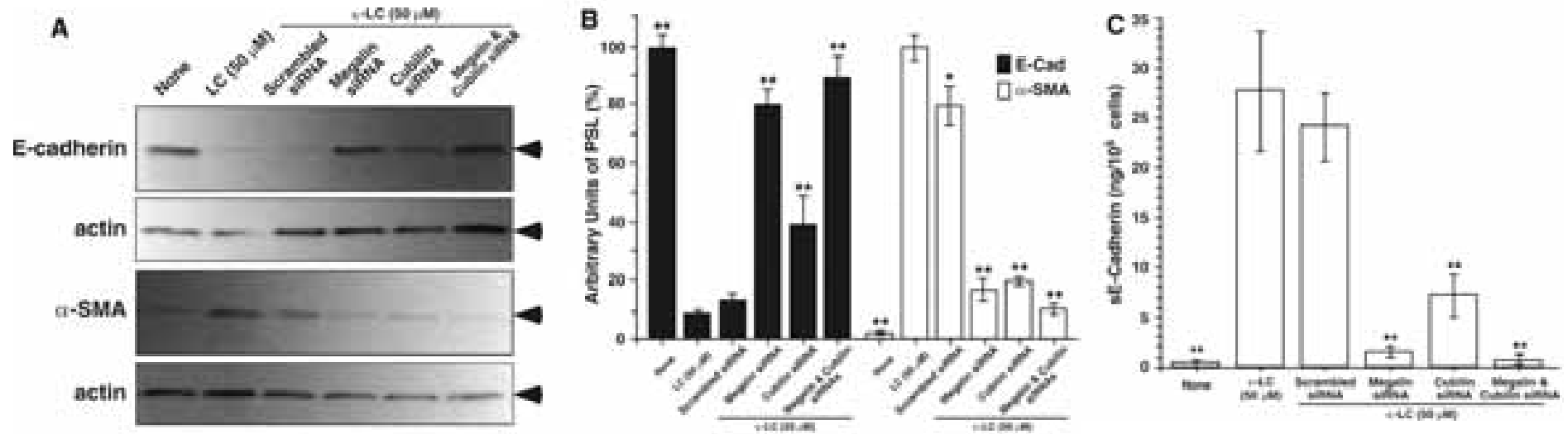


Li, M. et al. Am J Physiol Renal Physiol 295: F82-F90 2008

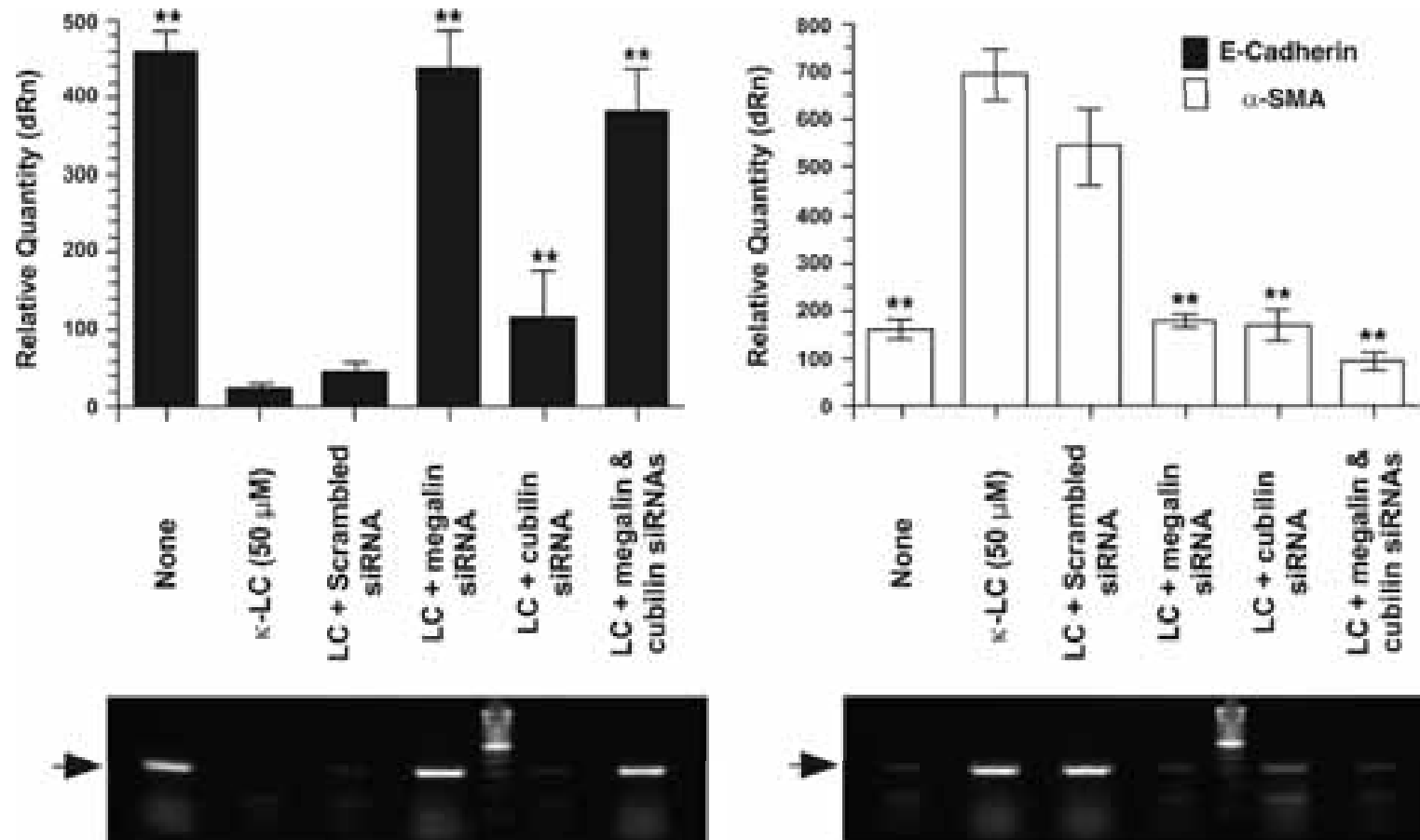
## Silencing megalin and cubilin genes inhibits cytokine production and ameliorates LC cytotoxicity in human renal PTECs



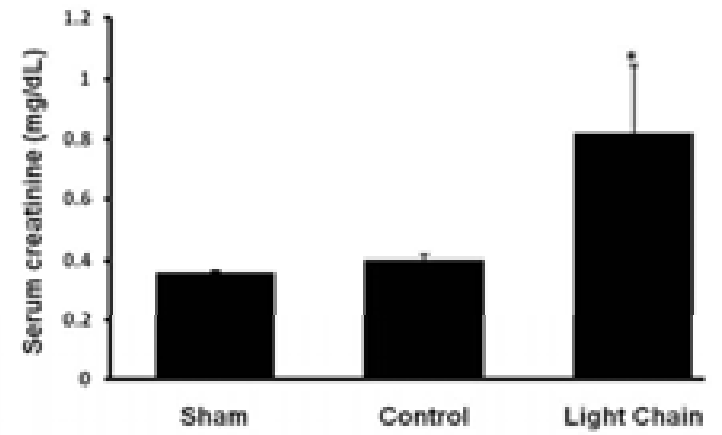
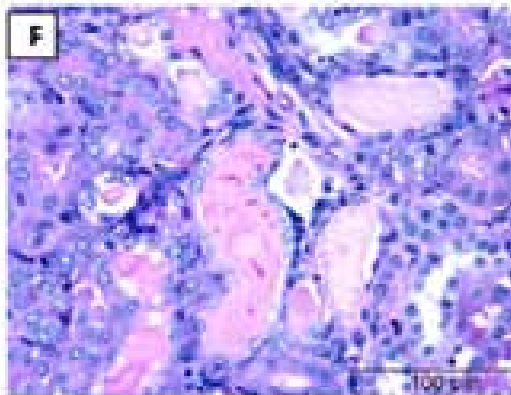
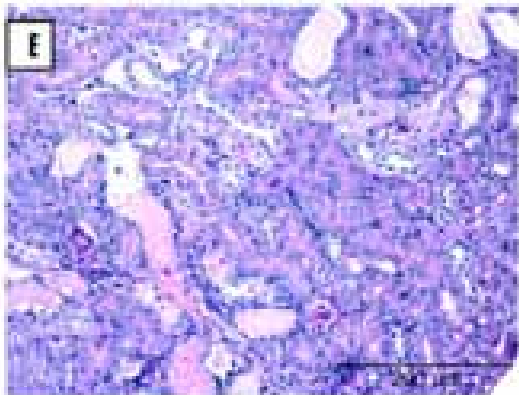
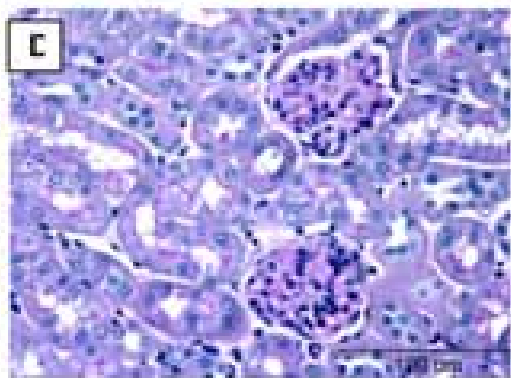
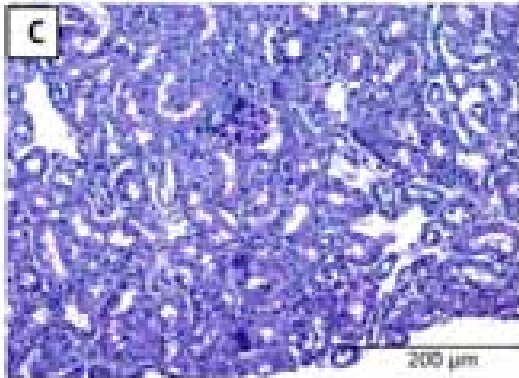
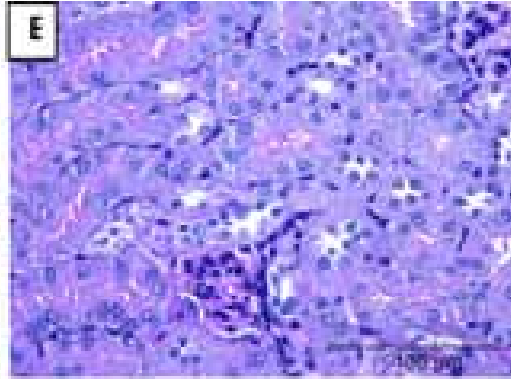
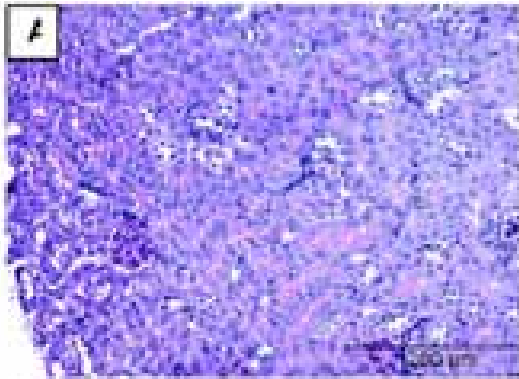
# Effect of megalin and/or cubilin interference on the protein levels of E-cadherin and $\alpha$ -smooth muscle actin (SMA) in LC-exposed human renal PTECs



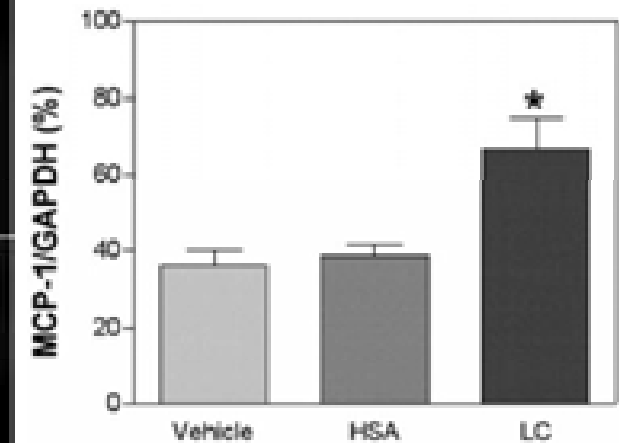
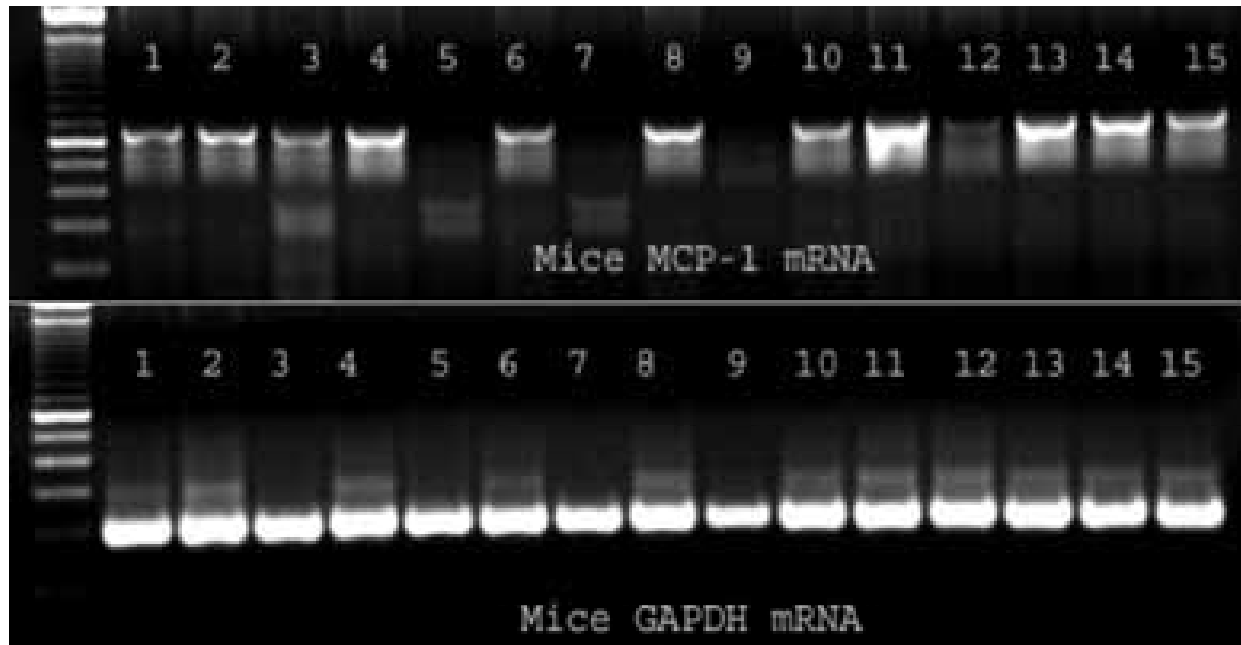
**Real-time RT-PCR analysis of E-cadherin and  $\alpha$ -SMA expression after megalin and/or cubilin siRNA transfection in LC-exposed human renal PTECs**

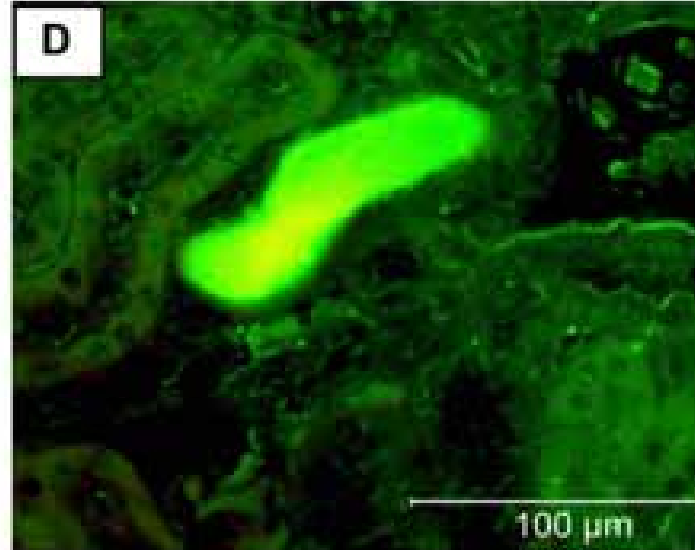
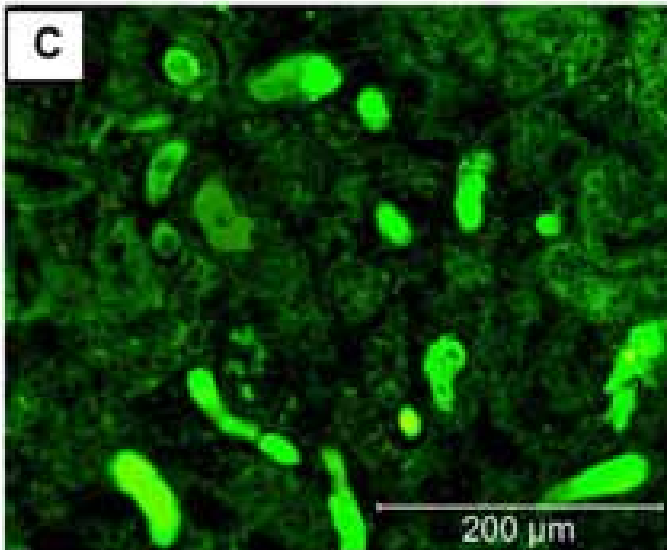
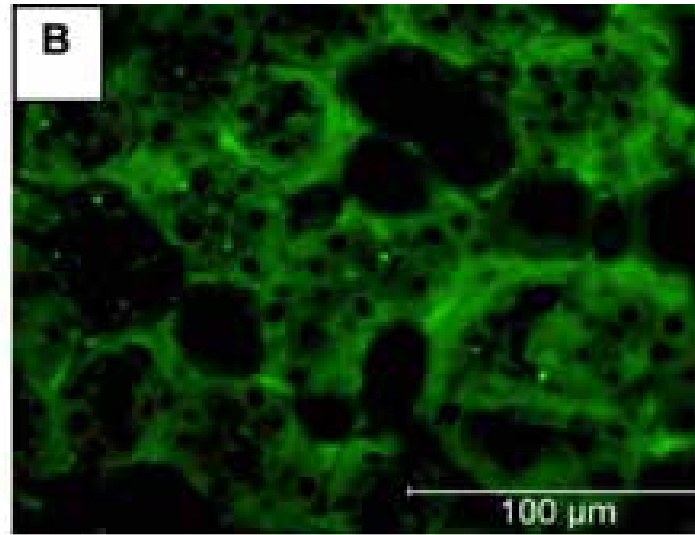
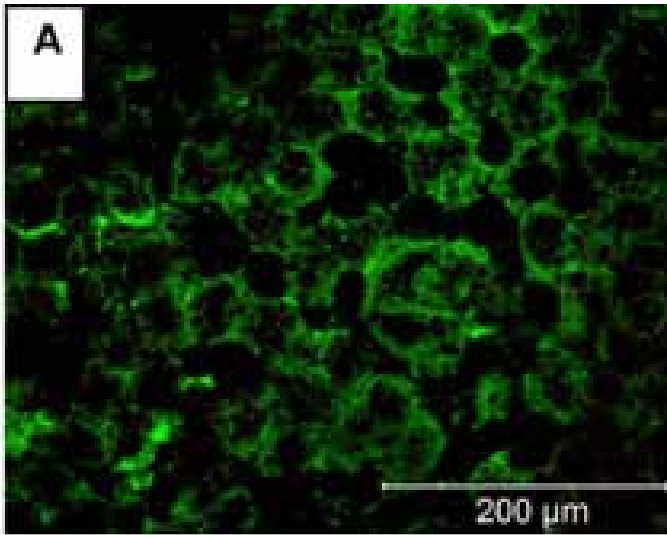


Li, M. et al. Am J Physiol Renal Physiol 295: F82-F90 2008

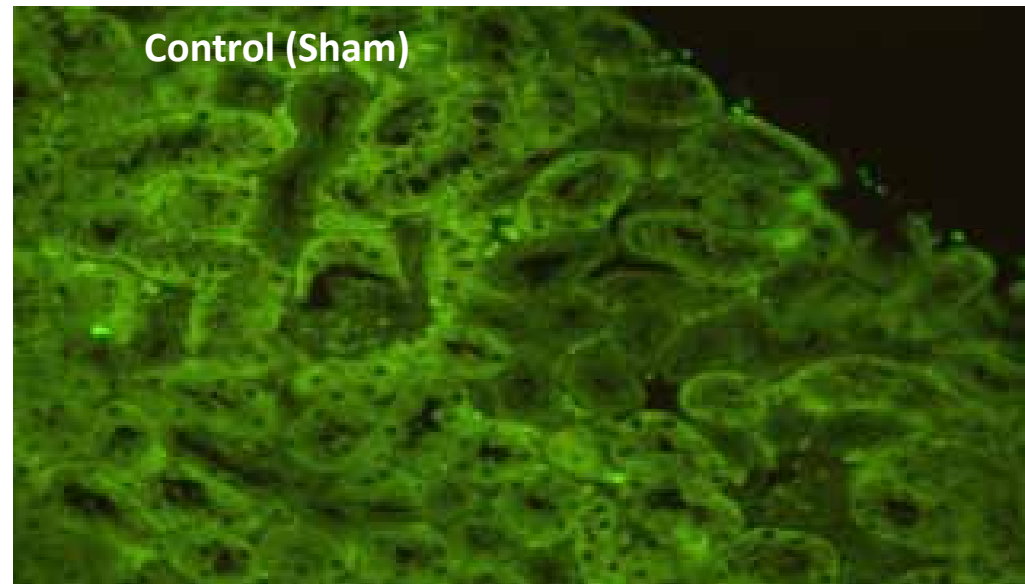
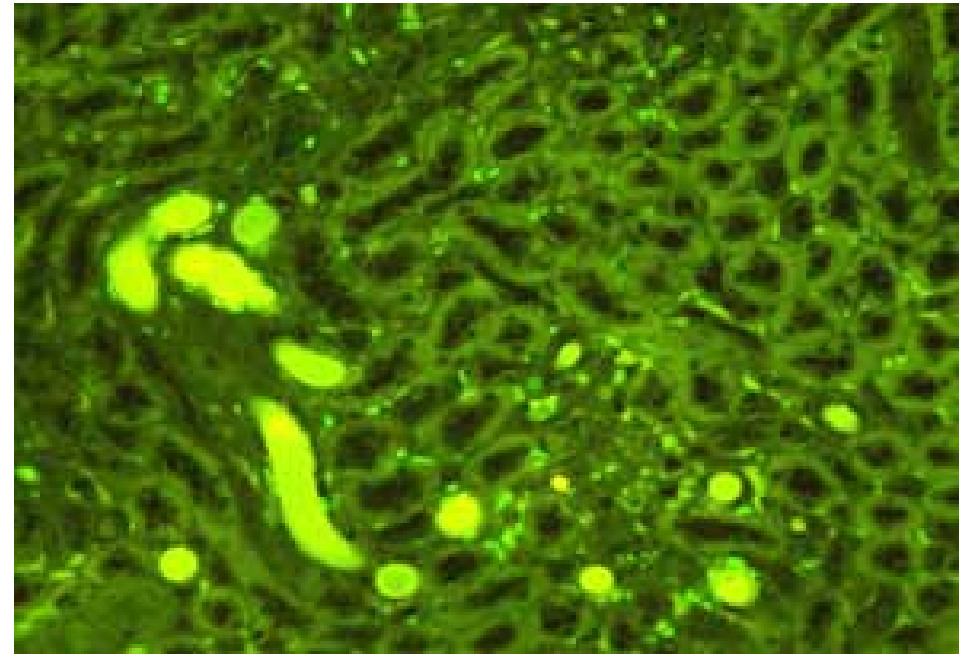
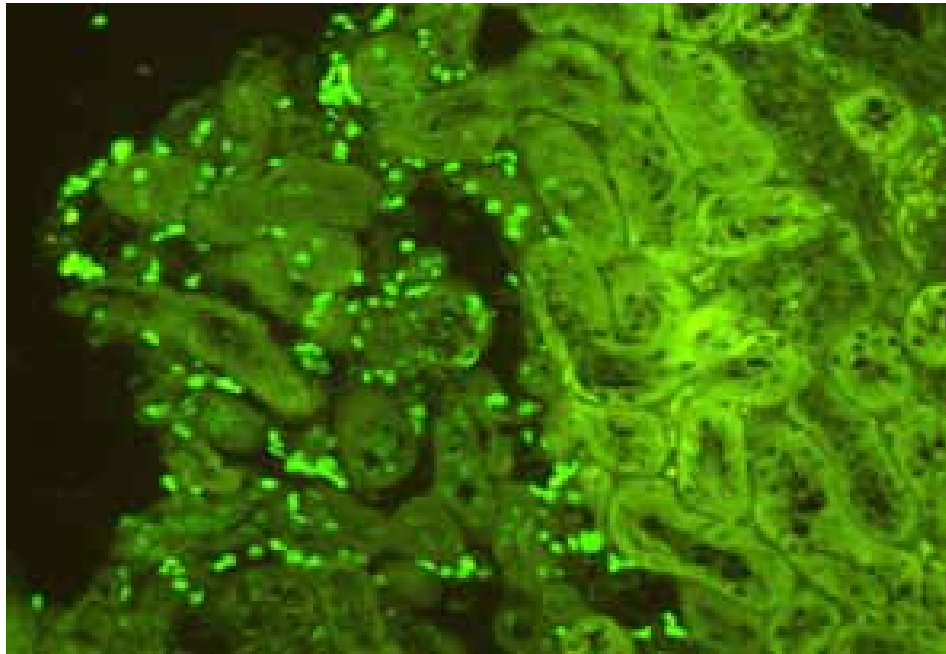


# MCP-1 in kidney of mice treated with light chains (*i.p.*)

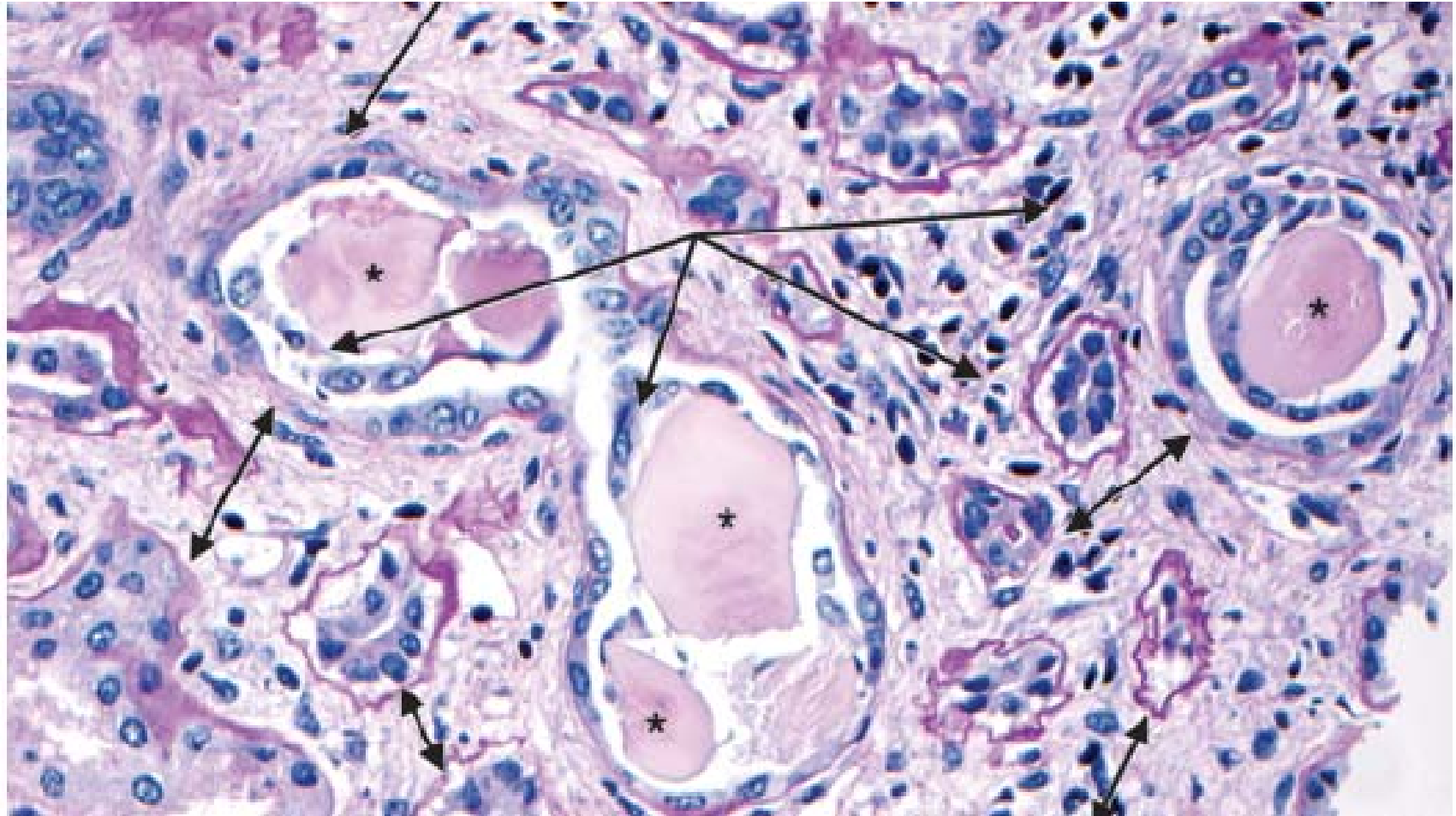


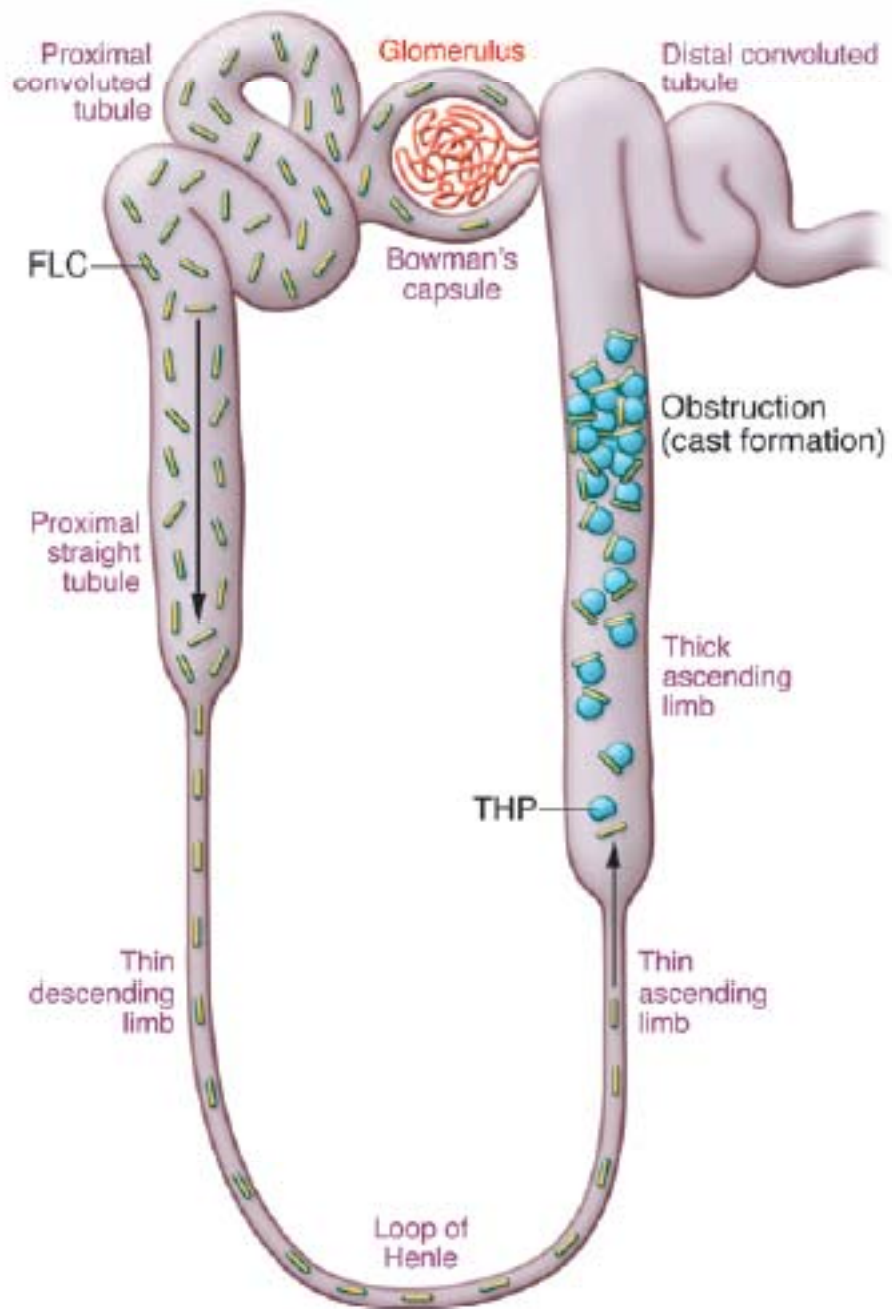
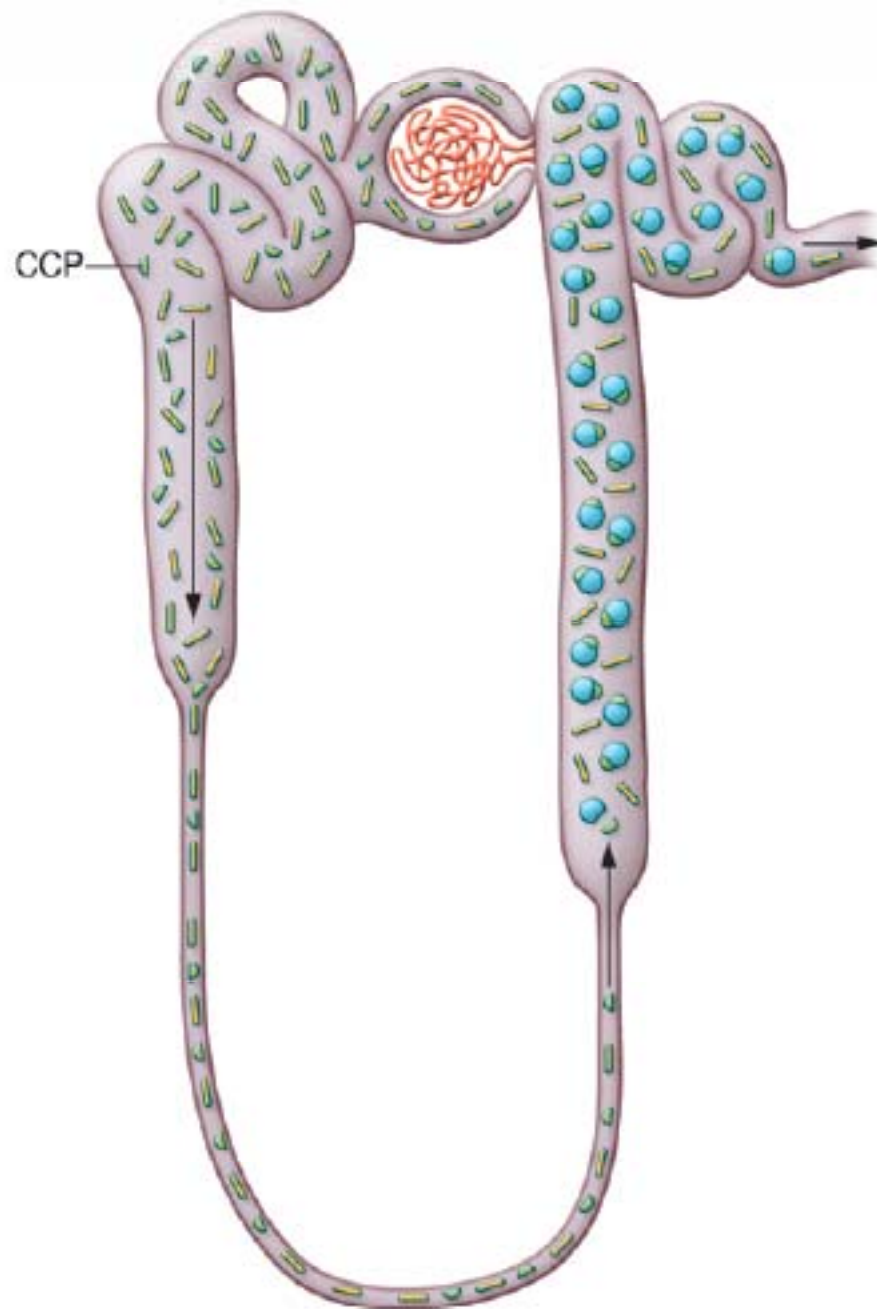


# Apoptosis in $\kappa$ -LC and control mice



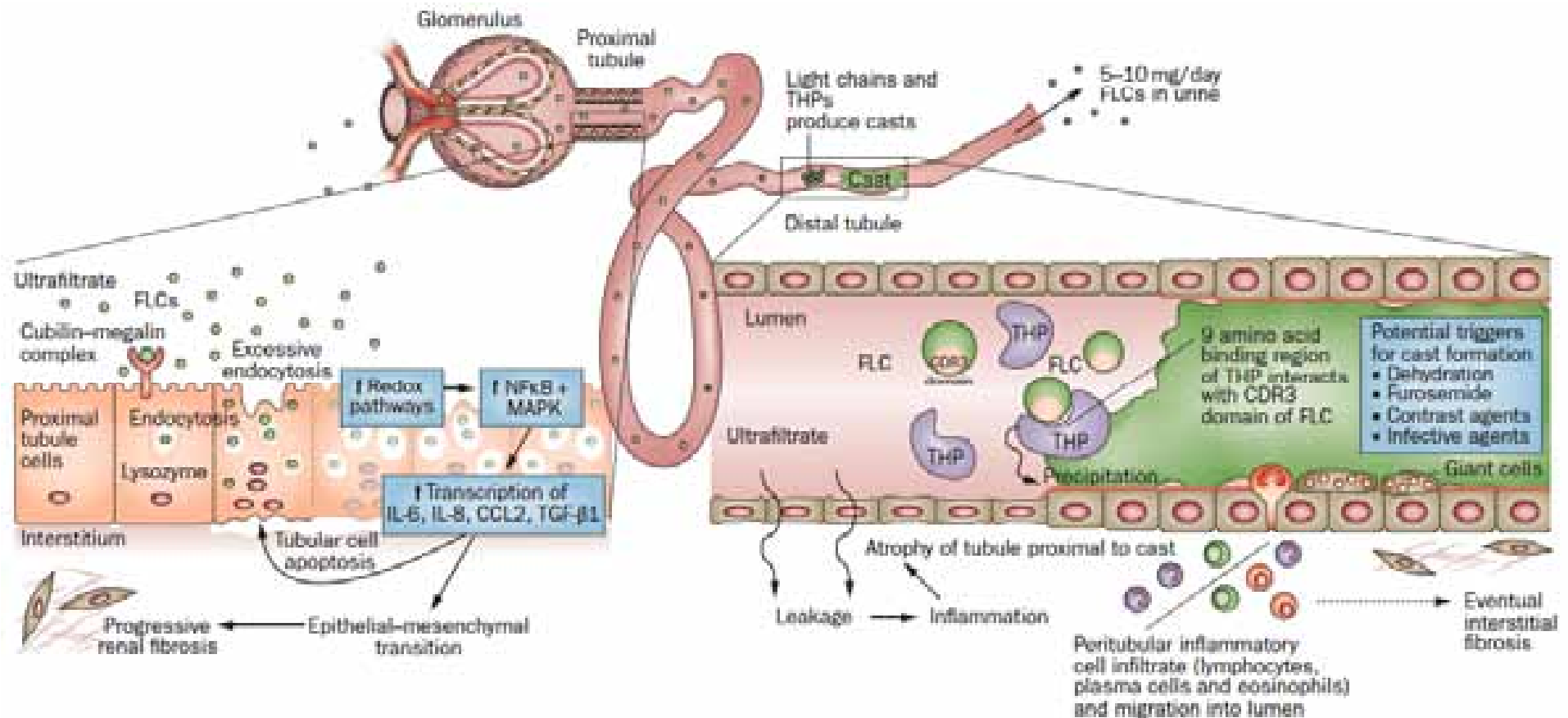
# Cast Nephropathy



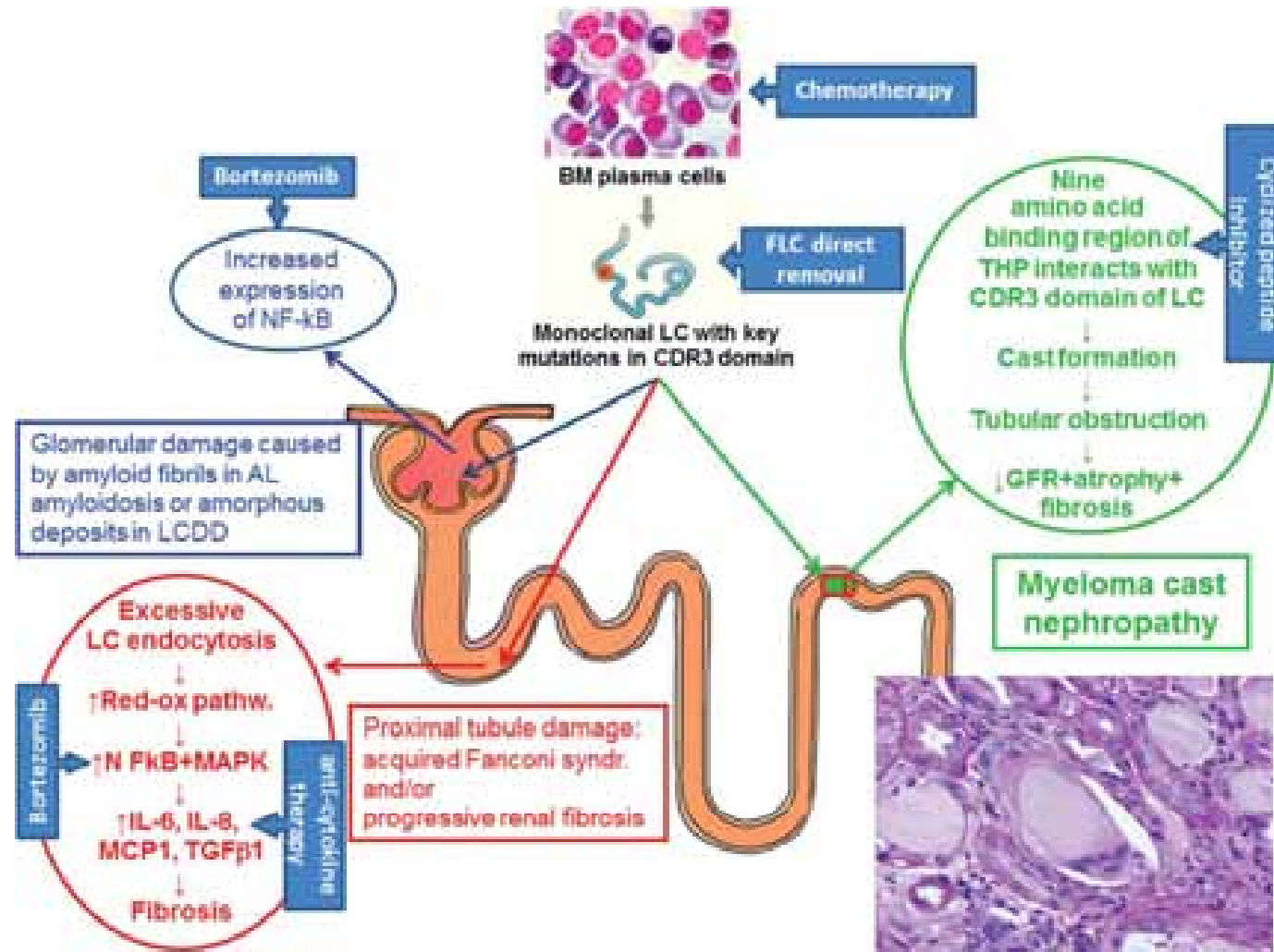
**A****B**

# The pathogenesis and diagnosis of acute kidney injury in multiple myeloma

Colin A. Hutchison, Vecihi Batuman, Judith Behrens, Frank Bridoux, Christophe Sirac, Angela Dispenzieri, Guillermo A. Herrera, Helen Lachmann and Paul W. Sanders on behalf of the International Kidney and Monoclonal Gammopathy Research Group *Nat. Rev. Nephrol.* **8**, 43–51 (2012)



# Treatment Strategies Based on the Mechanisms of FLCs-induced kidney injury



Davenport A , and Merlini G Nephrol. Dial. Transplant. 2012;27:3713-3718

THANK YOU!



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## ***People who actually did the work:***

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- *Craig Zwizinski.PhD*
- *Min Li, MD PhD*
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- *Kristine E Gullo*

## ***Collaborators:***

- *Jerome L Maderdrut PhD*
- *Tina Thethi, MD*
- *Zubaida Saifudeen MD*
- *Samir El-Dahr MD*
- *Eric E Simon MD*
- *Sule Sengul, MD*

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