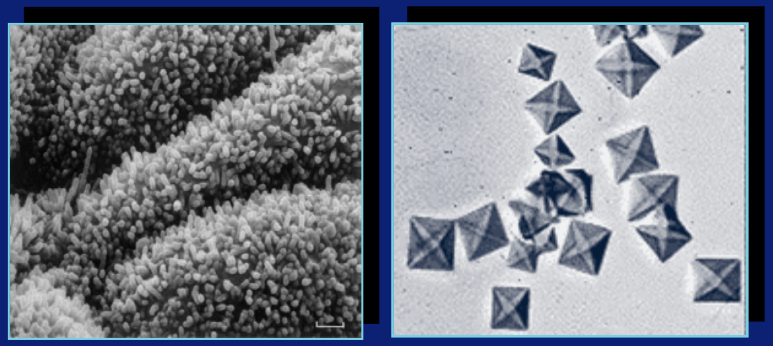
Erasmus MC
University Medical Center Rotterdam

University of Antwerp

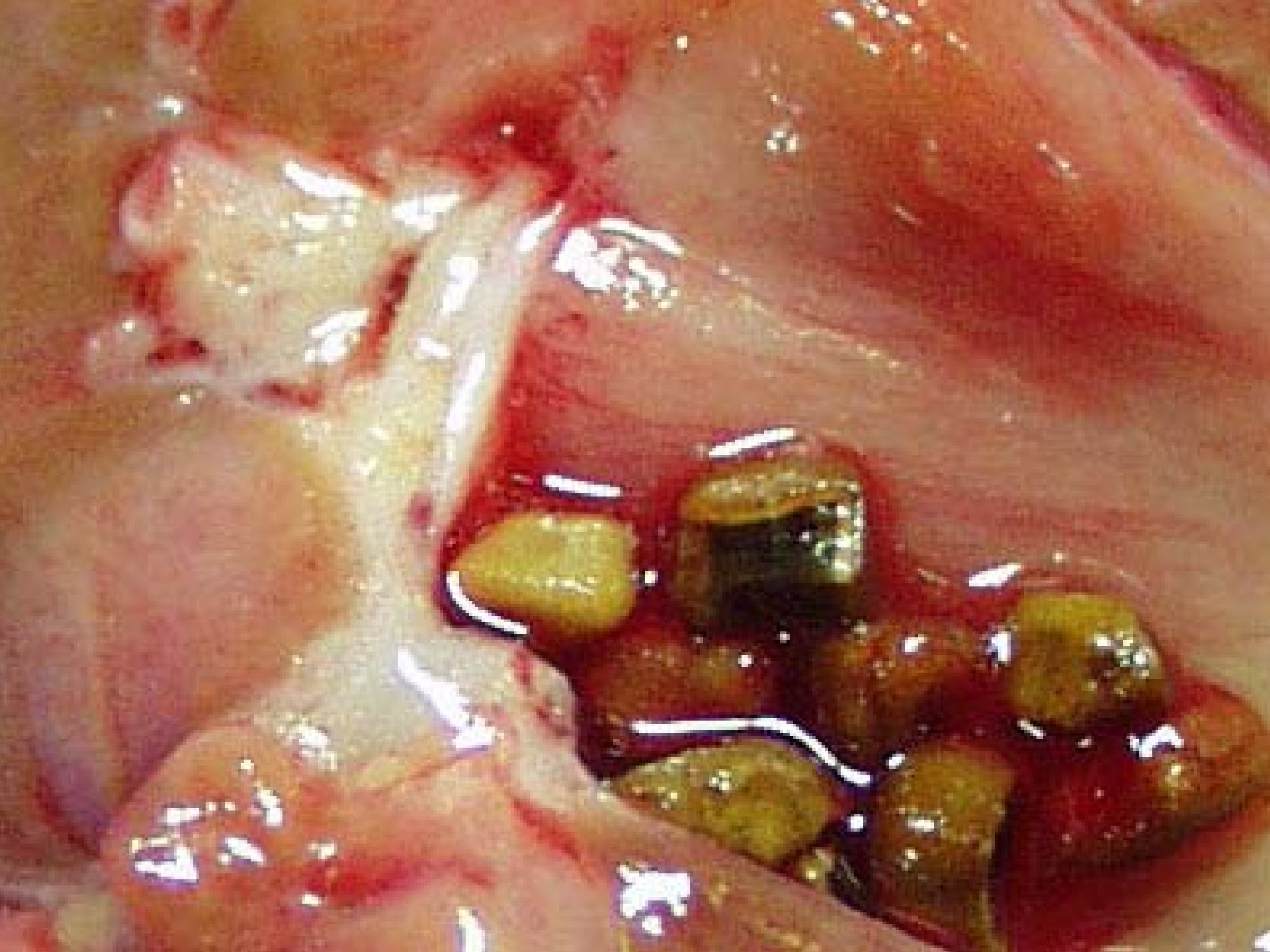
Cellular responses to calcium oxalate



Nephrolithiasis is caused by the formation and retention of crystals in the kidney

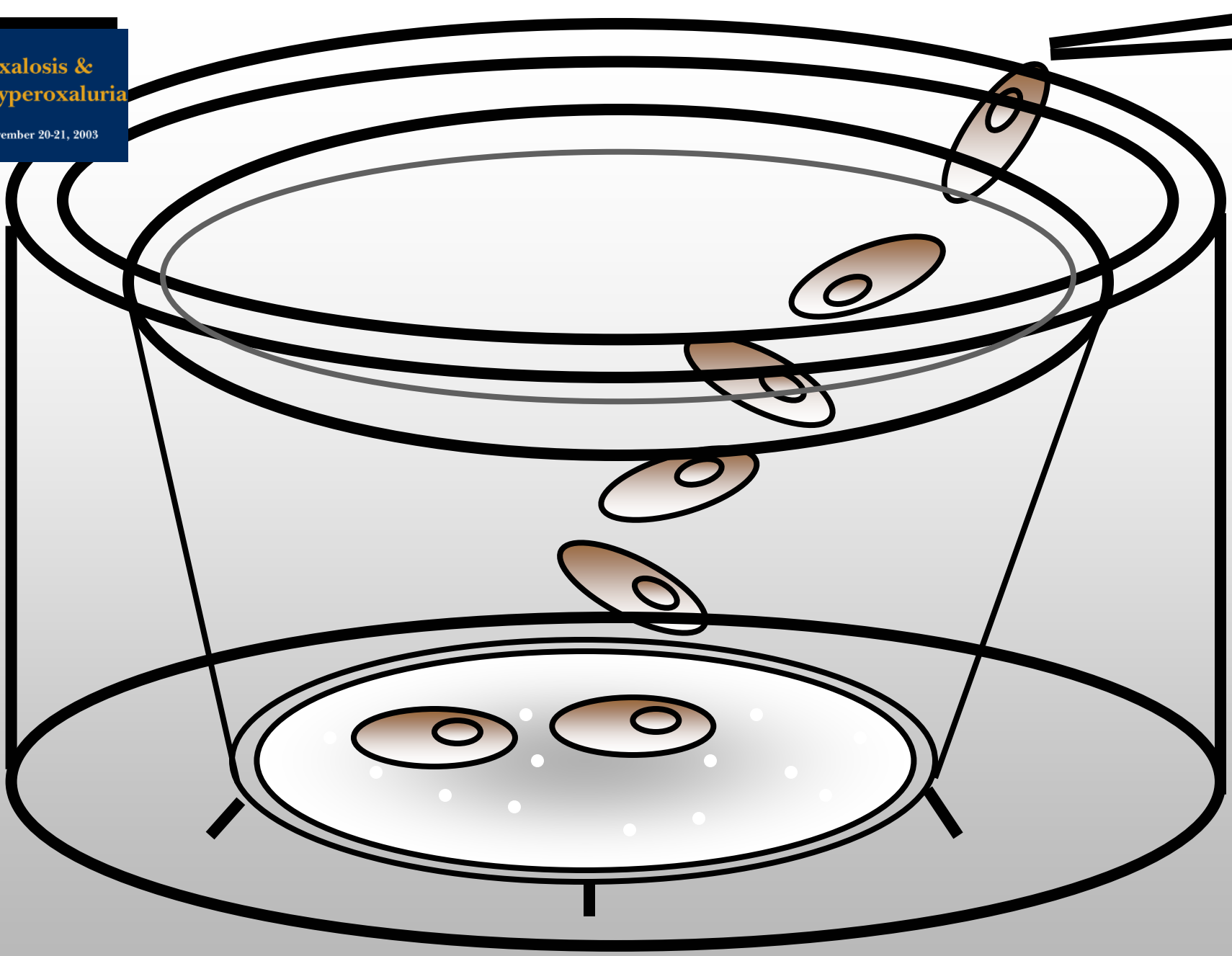
crystal formation
is physiologic

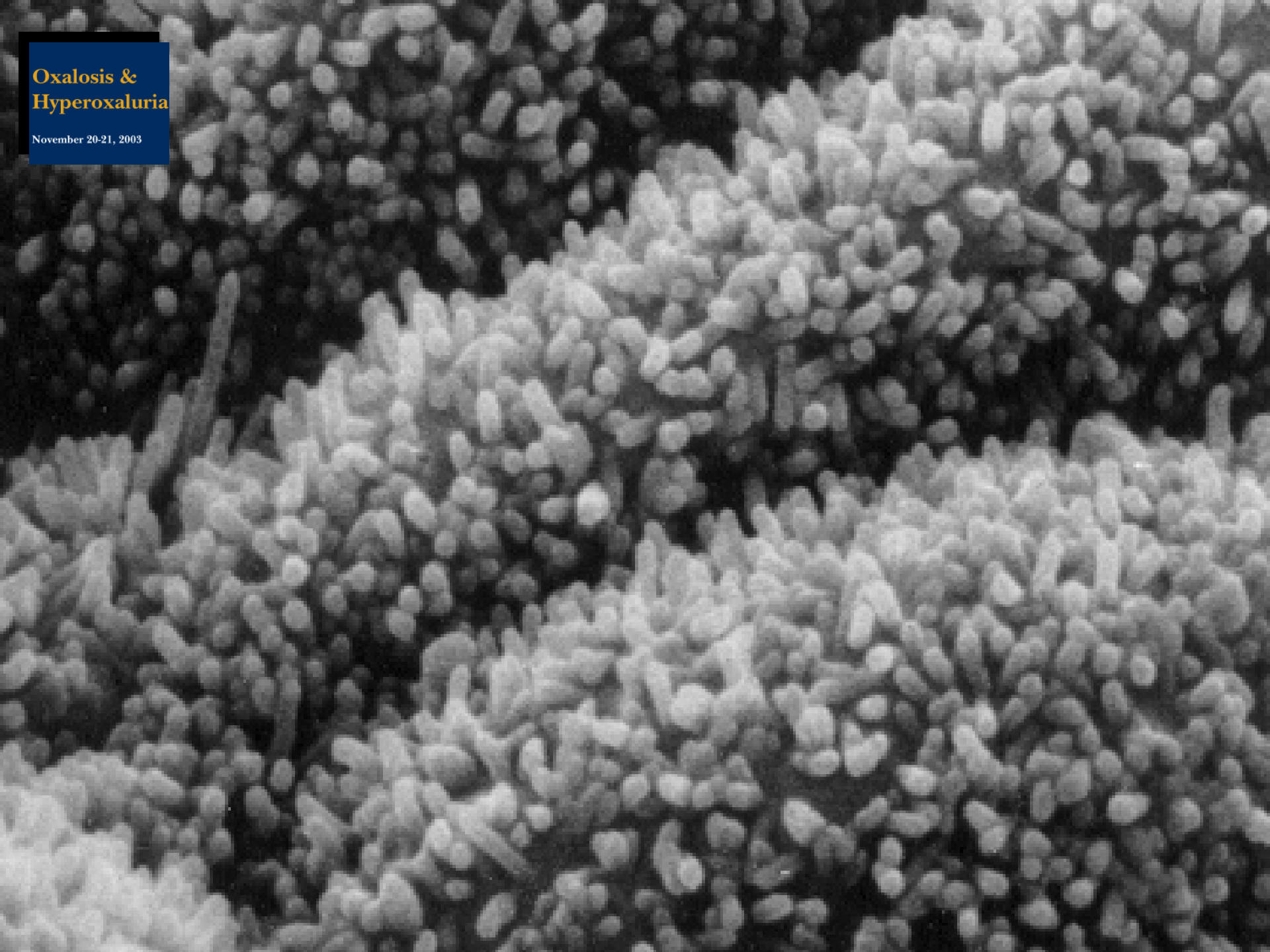
crystal retention
is pathologic

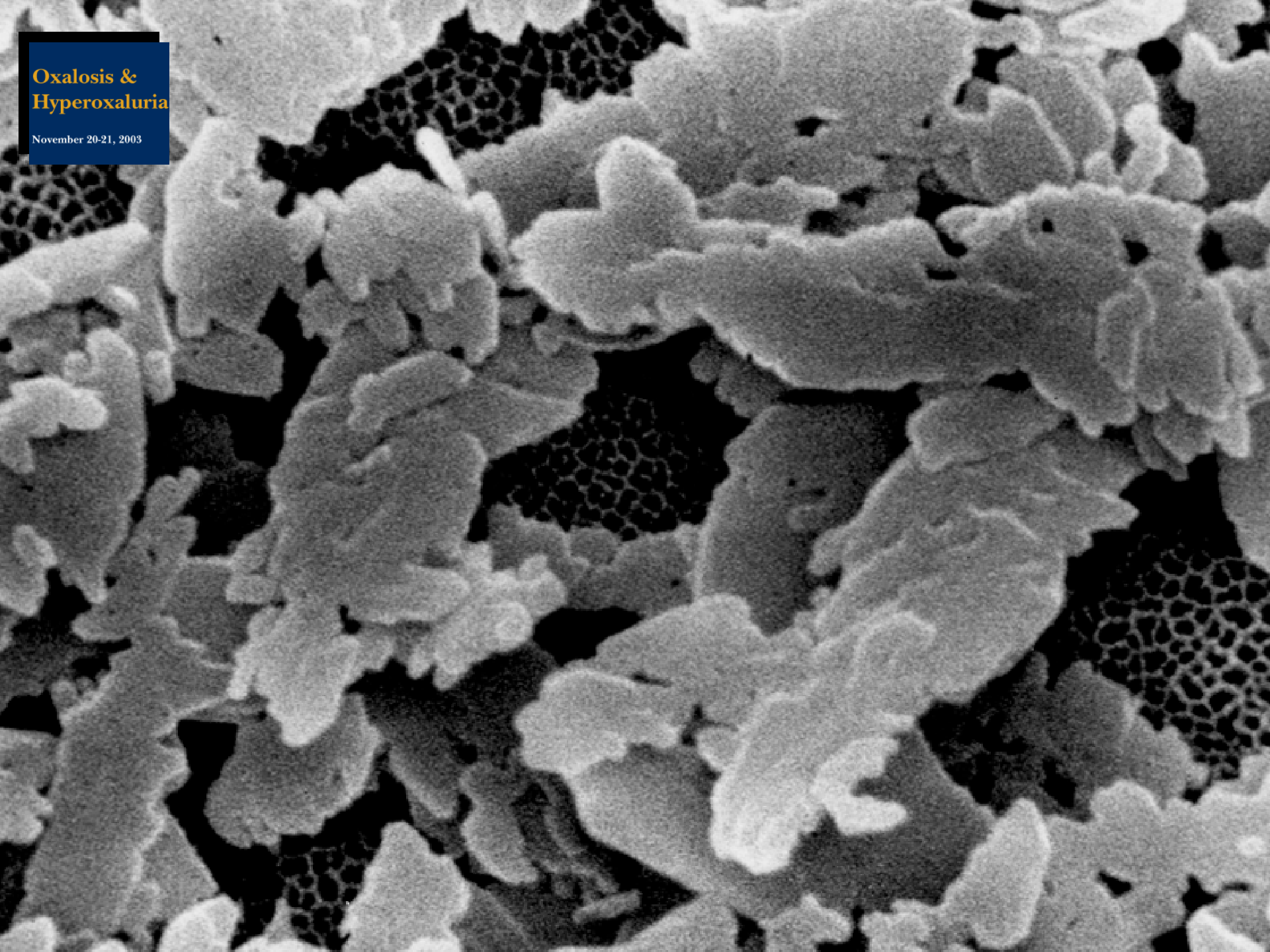


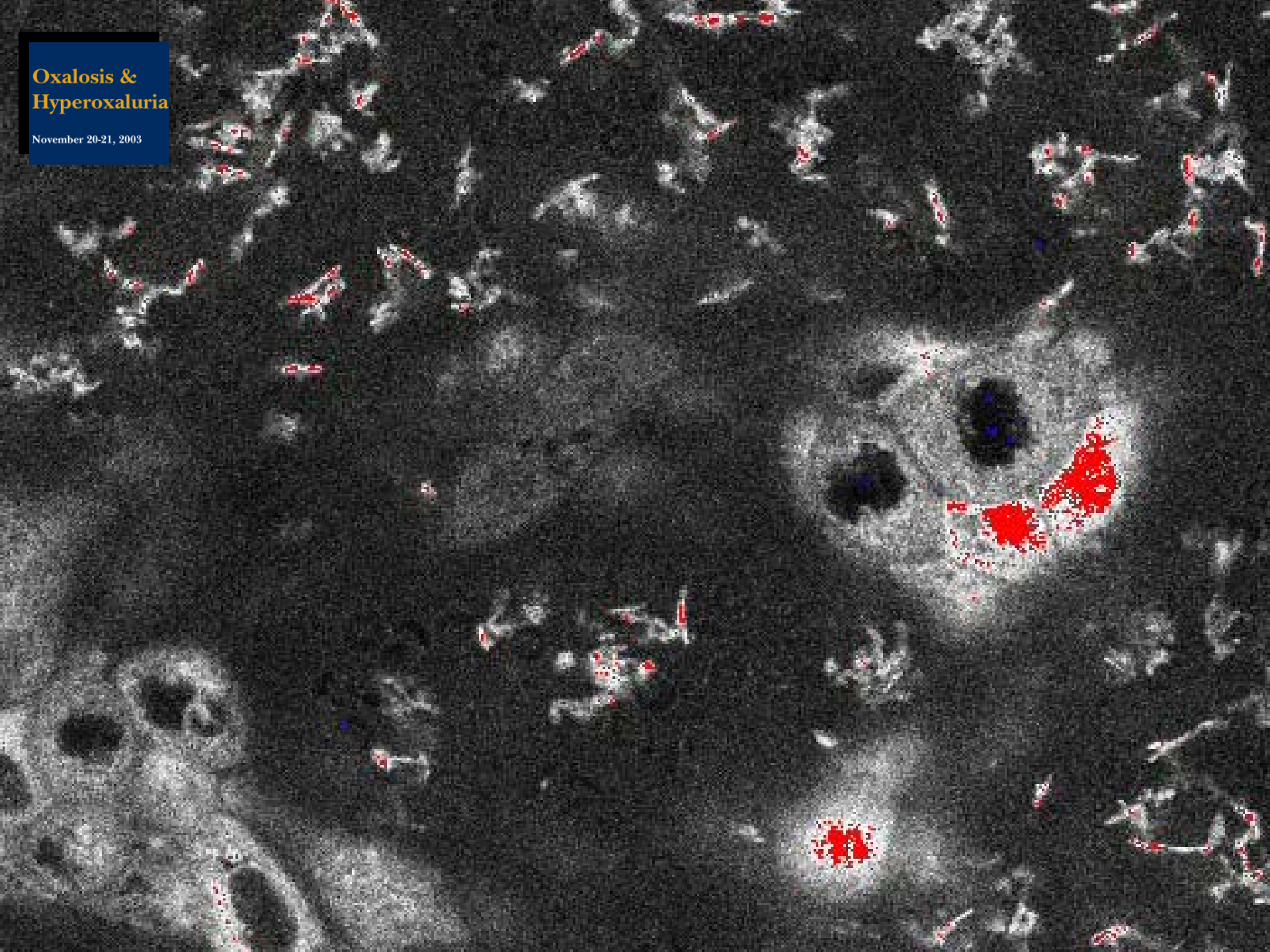
Oxalosis &
Hyperoxaluria

November 20-21, 2003




Oxalosis &
Hyperoxaluria
November 20-21, 2003


Oxalosis &
Hyperoxaluria
November 20-21, 2003

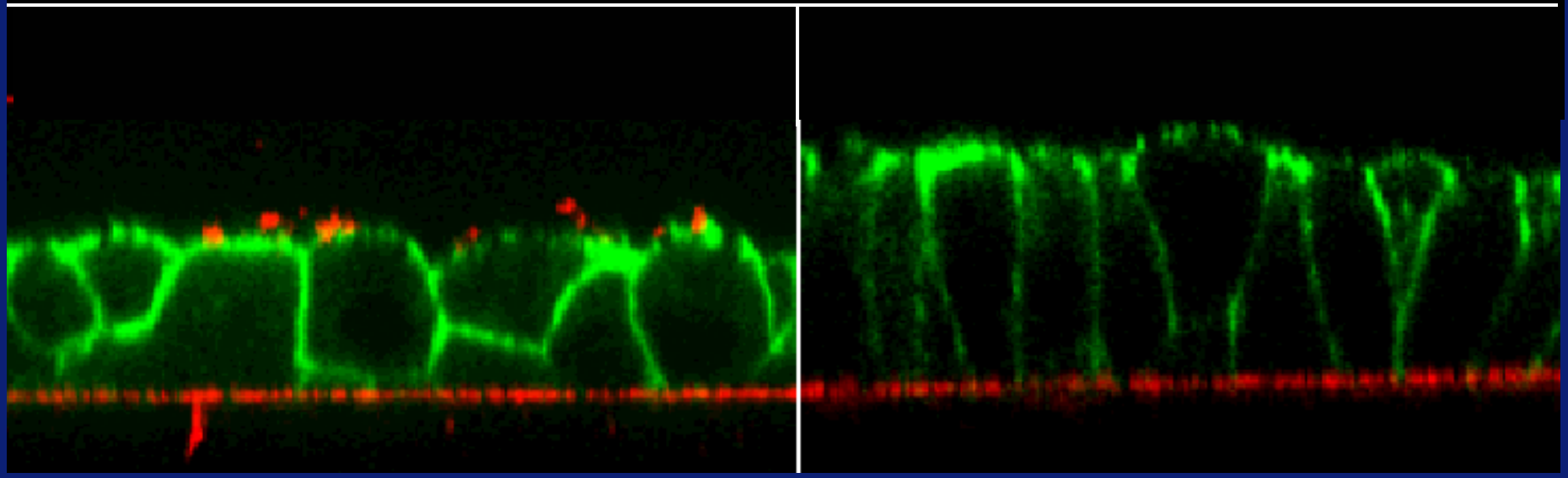

Oxalosis &
Hyperoxaluria
November 20-21, 2003

Crystal binding

phalloidin-FITC

calcium oxalate crystals

light reflection confocal laser scanning microscopy

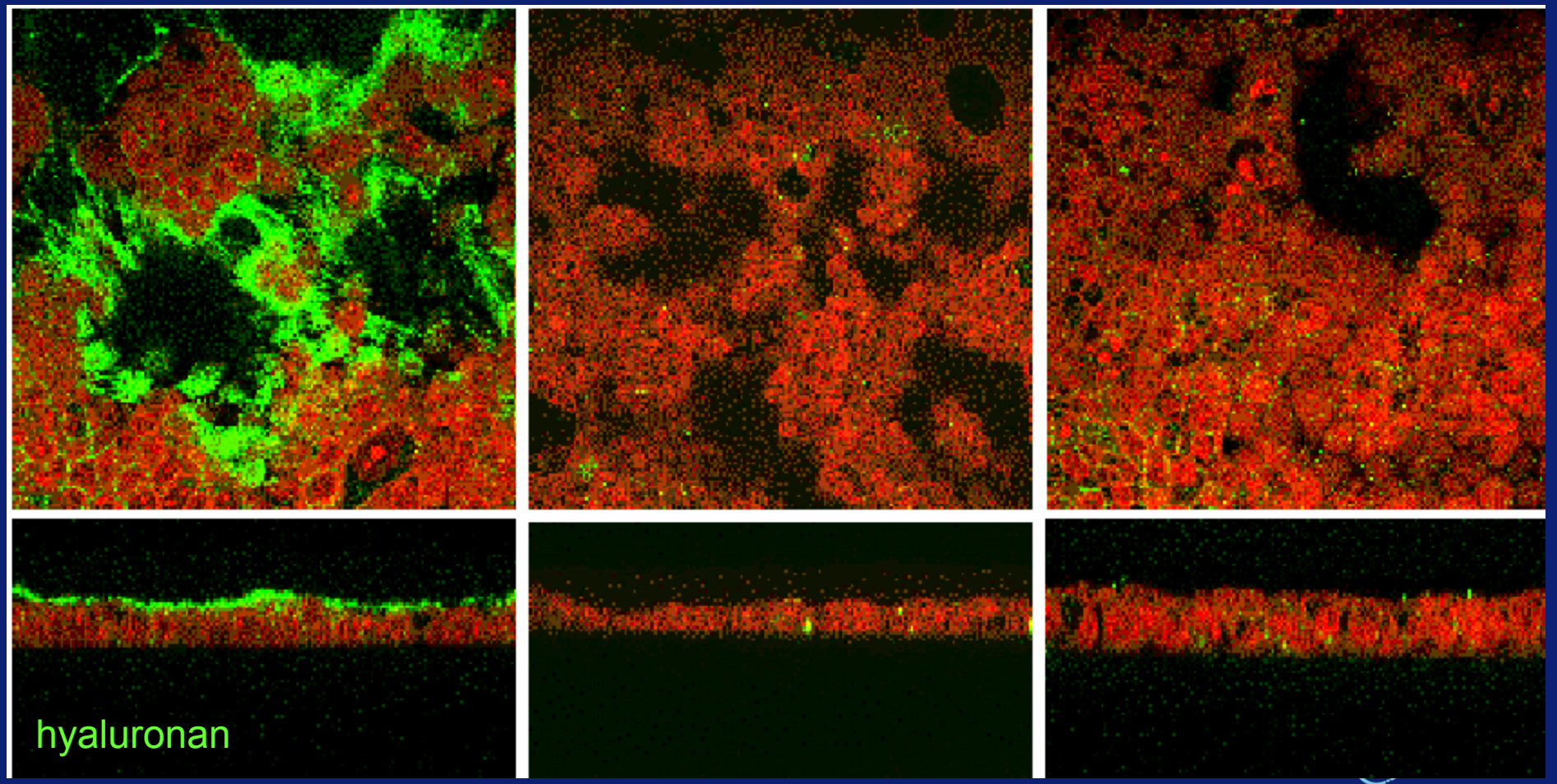


subconfluence

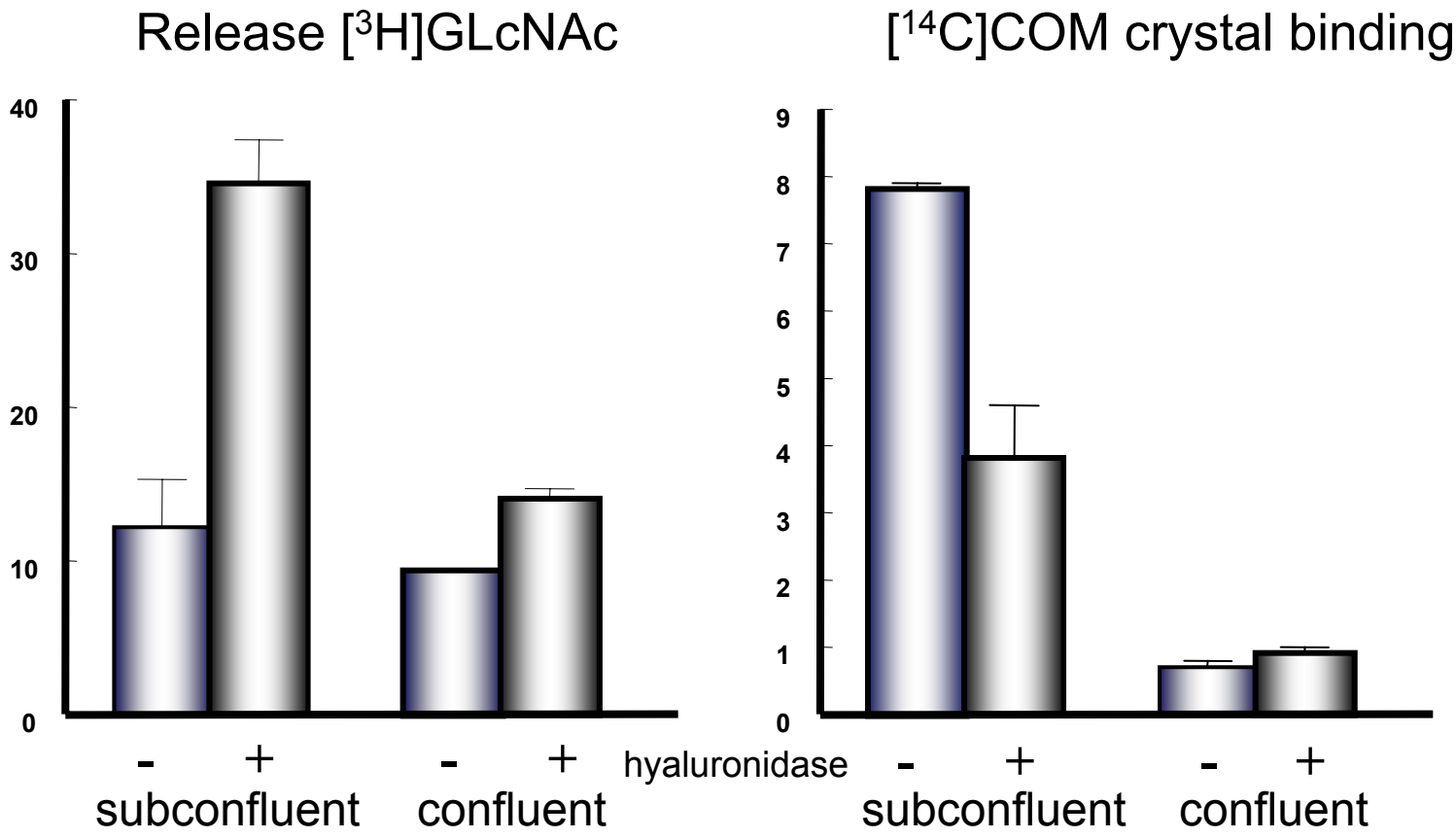
confluence

Verkoelen et al. Am J Physiol 274:F958-965, 1998

Hyaluronan staining



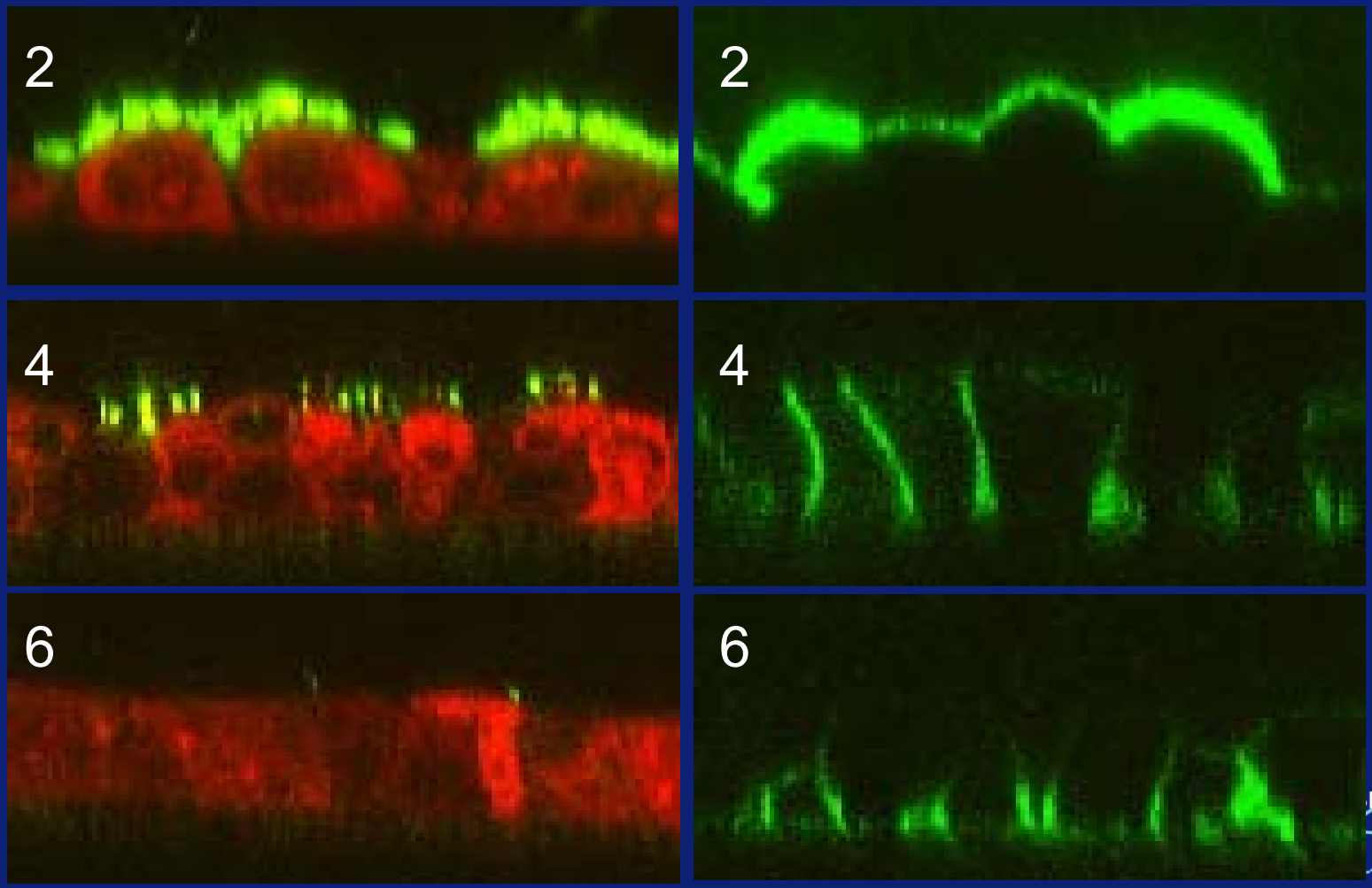
Effect hyaluronidase



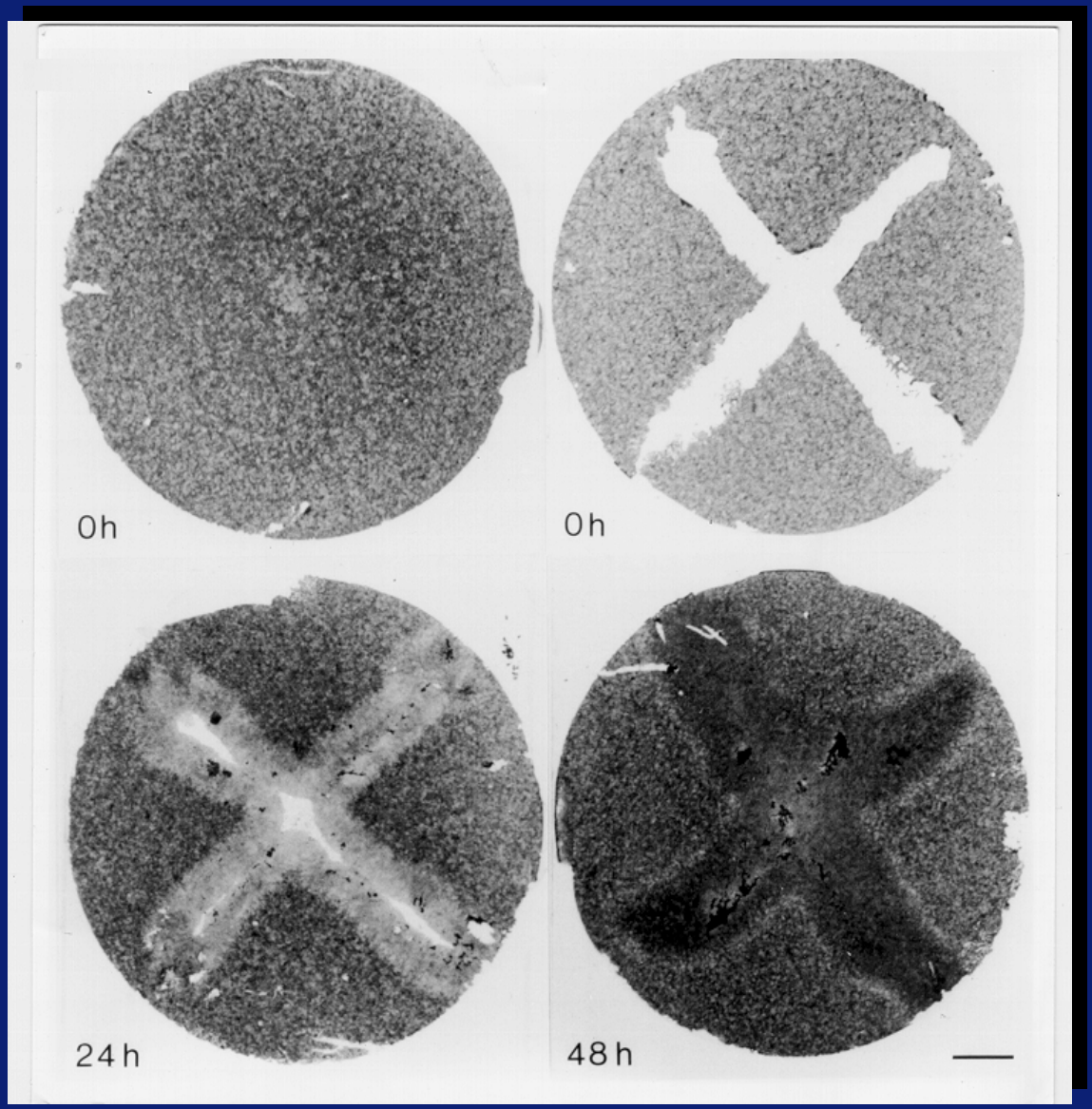
Development of polarized monolayers

Hyaluronan

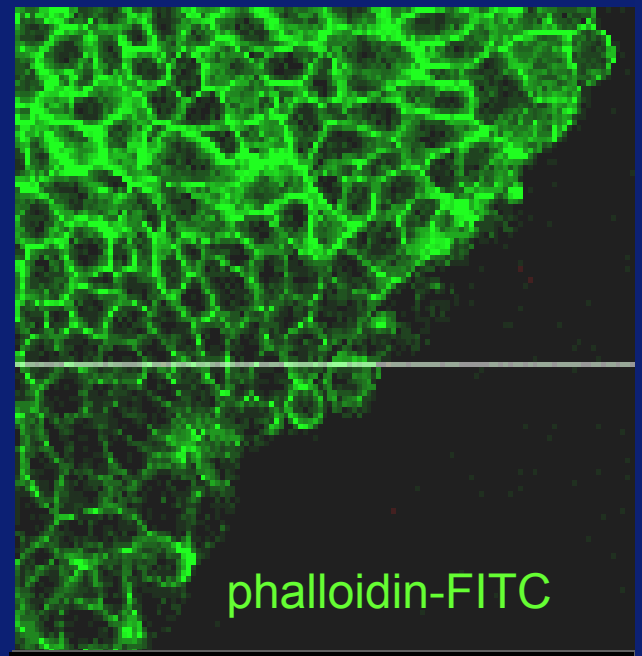
Hyaluronan receptor, CD44



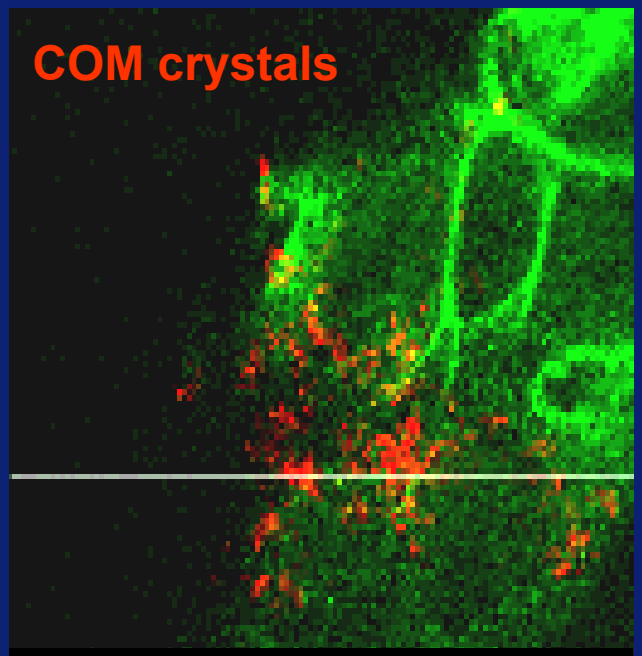
Mechanical damage



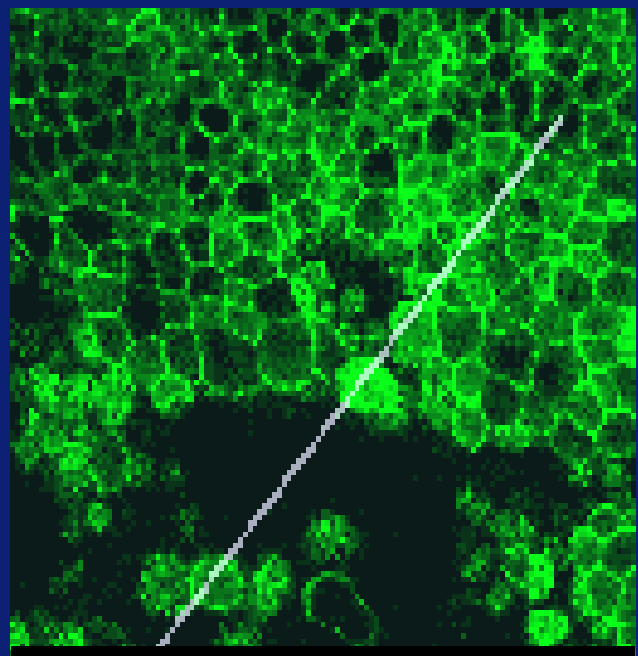
Crystal binding during wound healing



directly after scrape-damage

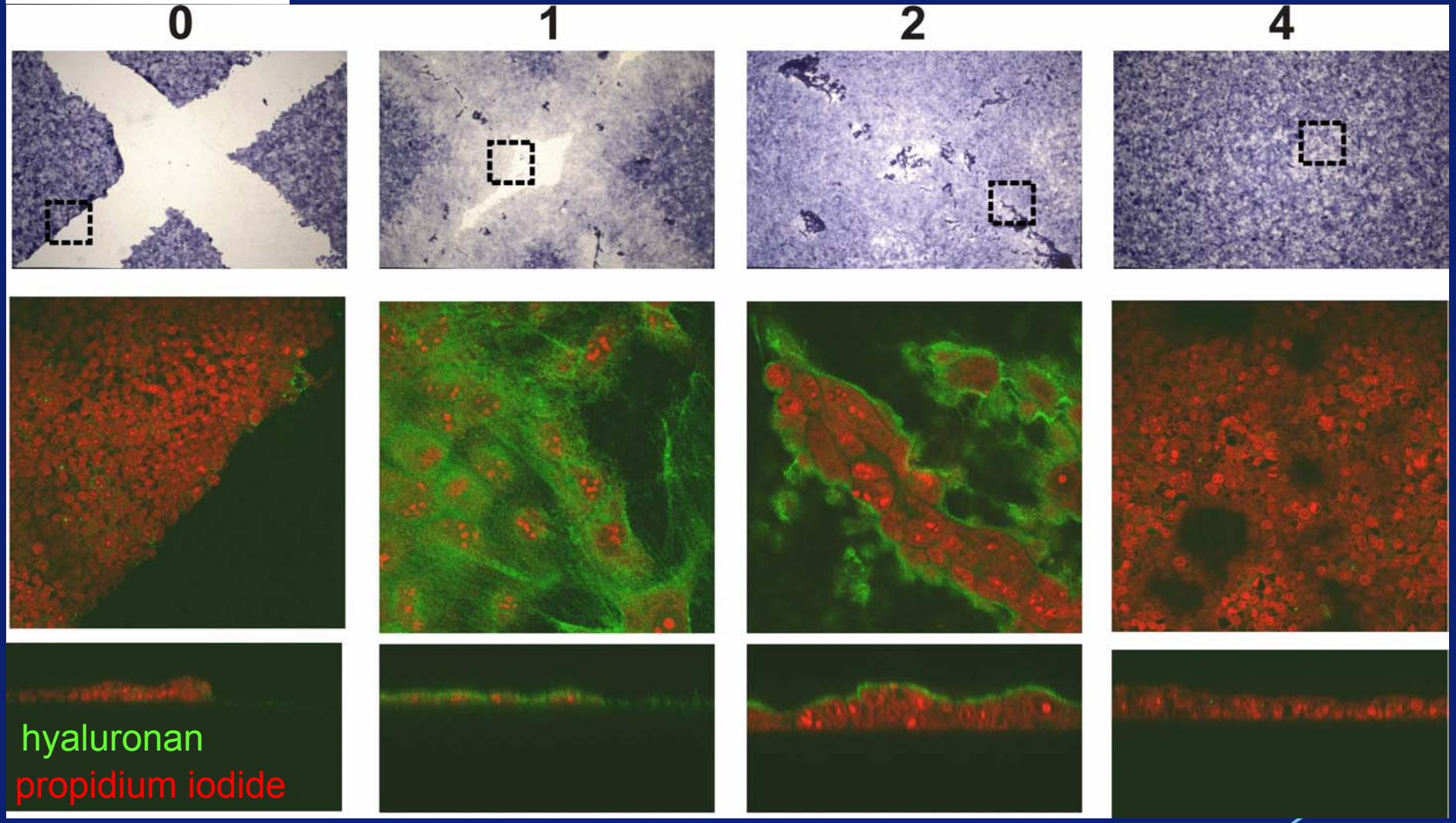


during repair



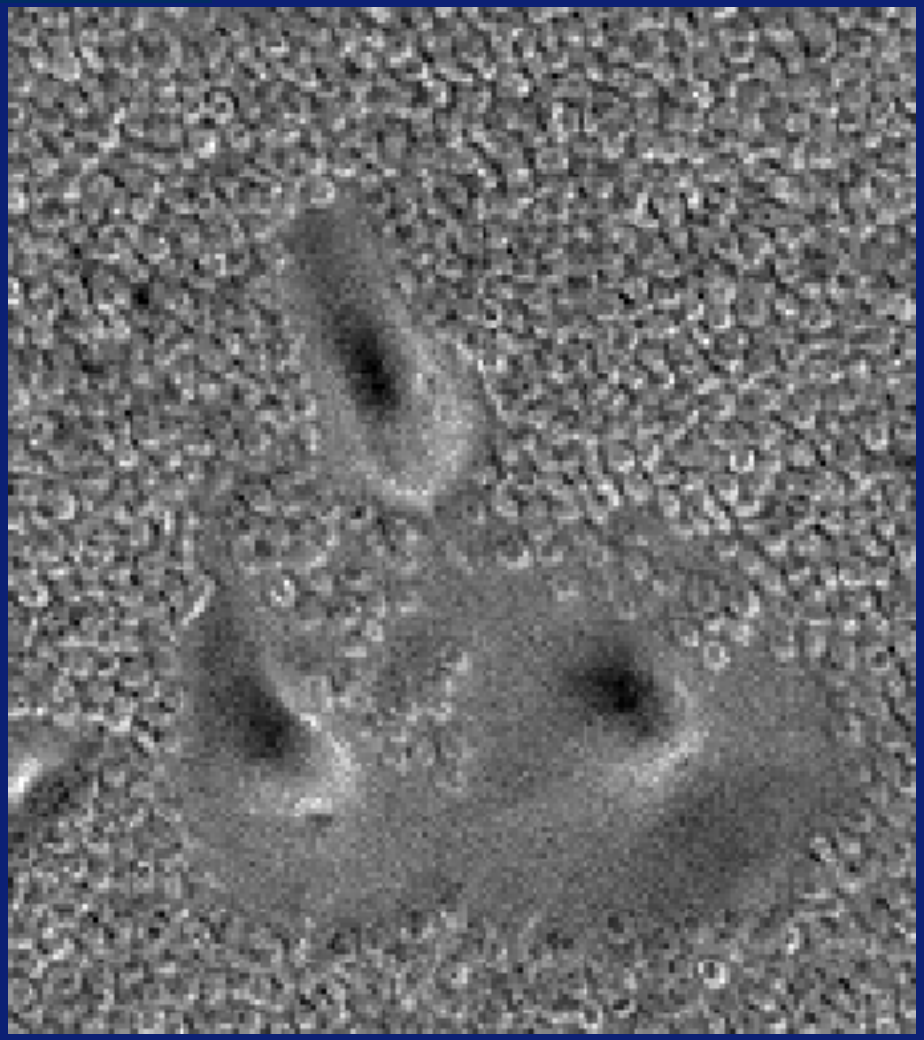
after wound healing

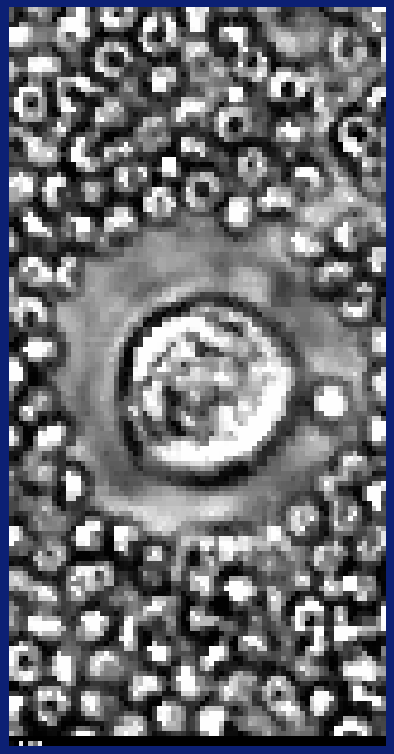
Hyaluronan staining



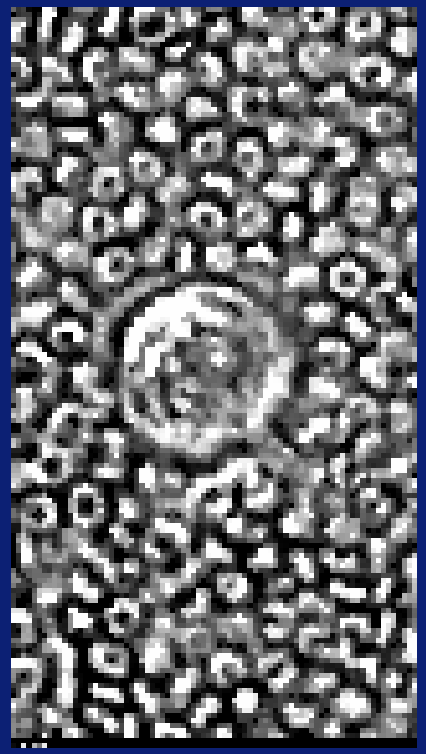
Verkoelen et al. Kidney Int 58:1045-1054, 2000

Pericellular matrices





control



streptomyces
hyaluronidase

Oxalosis & Hyperoxaluria
November 20-21, 2003

Primary cultures of human renal tubular cells

Verhulst A, Persy VP, Van Rompay AR, Verstrepen WA, Helbert MF, De Broe ME.
J Am Soc Nephrol 13:1210-1218, 2002
Osteopontin synthesis and localization along the human nephron.

Verhulst A, Asselman M, Persy V, Schepers M, Helbert MF, Verkoelen CF, De Broe ME.
J Am Soc Nephrol 14:107-115, 2003
Crystal retention capacity of cells in the human nephron: involvement of CD44 and its ligands hyaluronic acid and osteopontin in the transition of a crystal binding- into a nonadherent epithelium.

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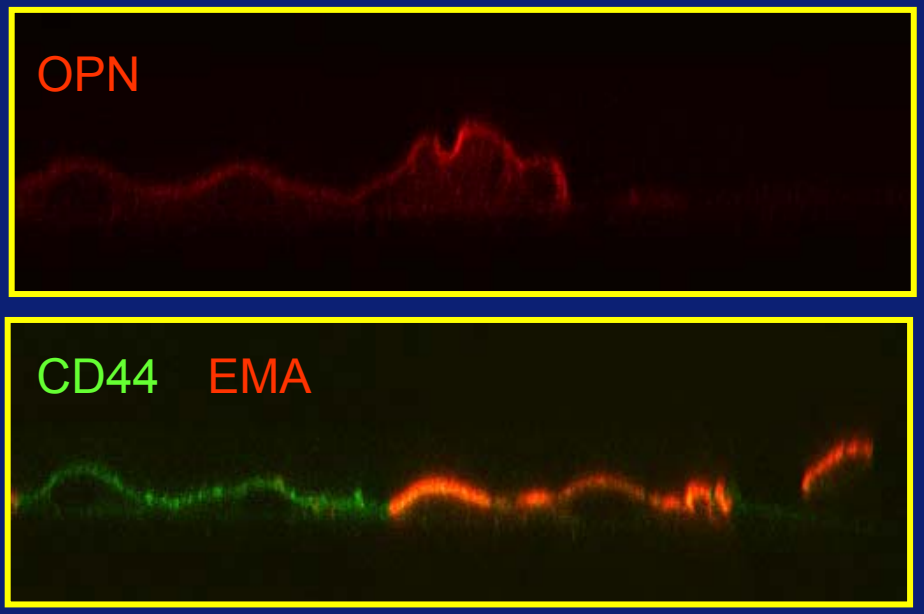
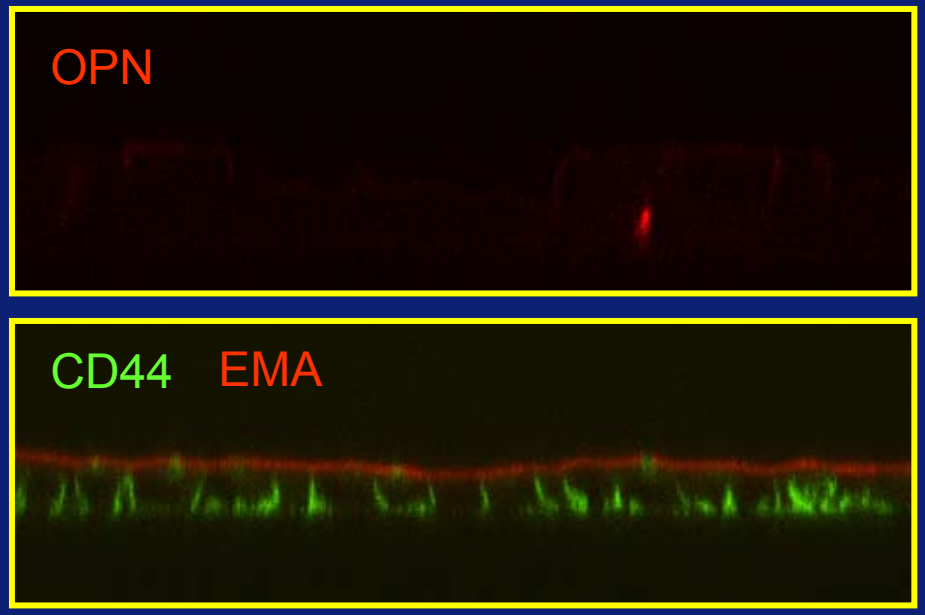
Primary cultures of human renal tubular cells

Osteopontin and CD44



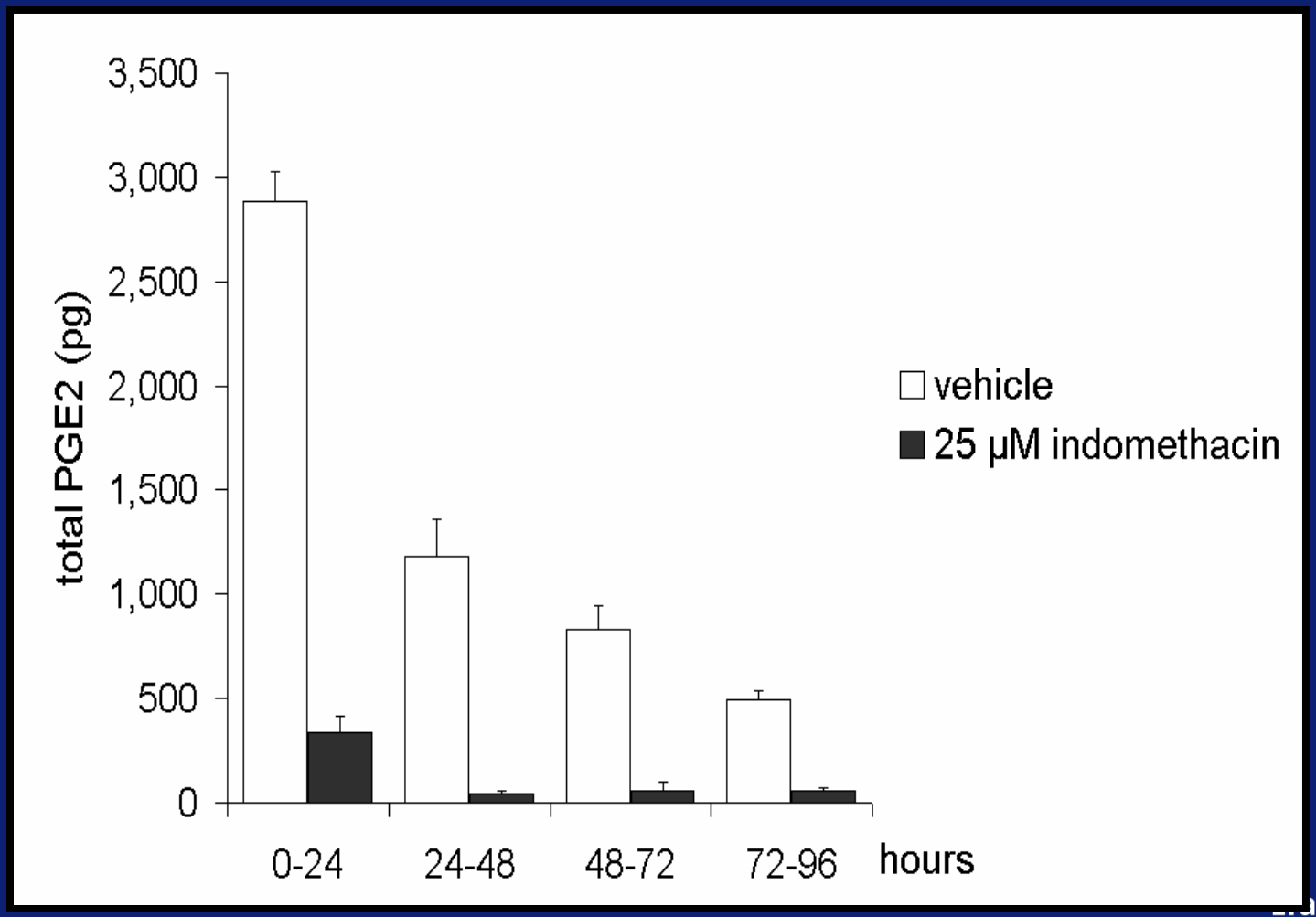
subconfluence



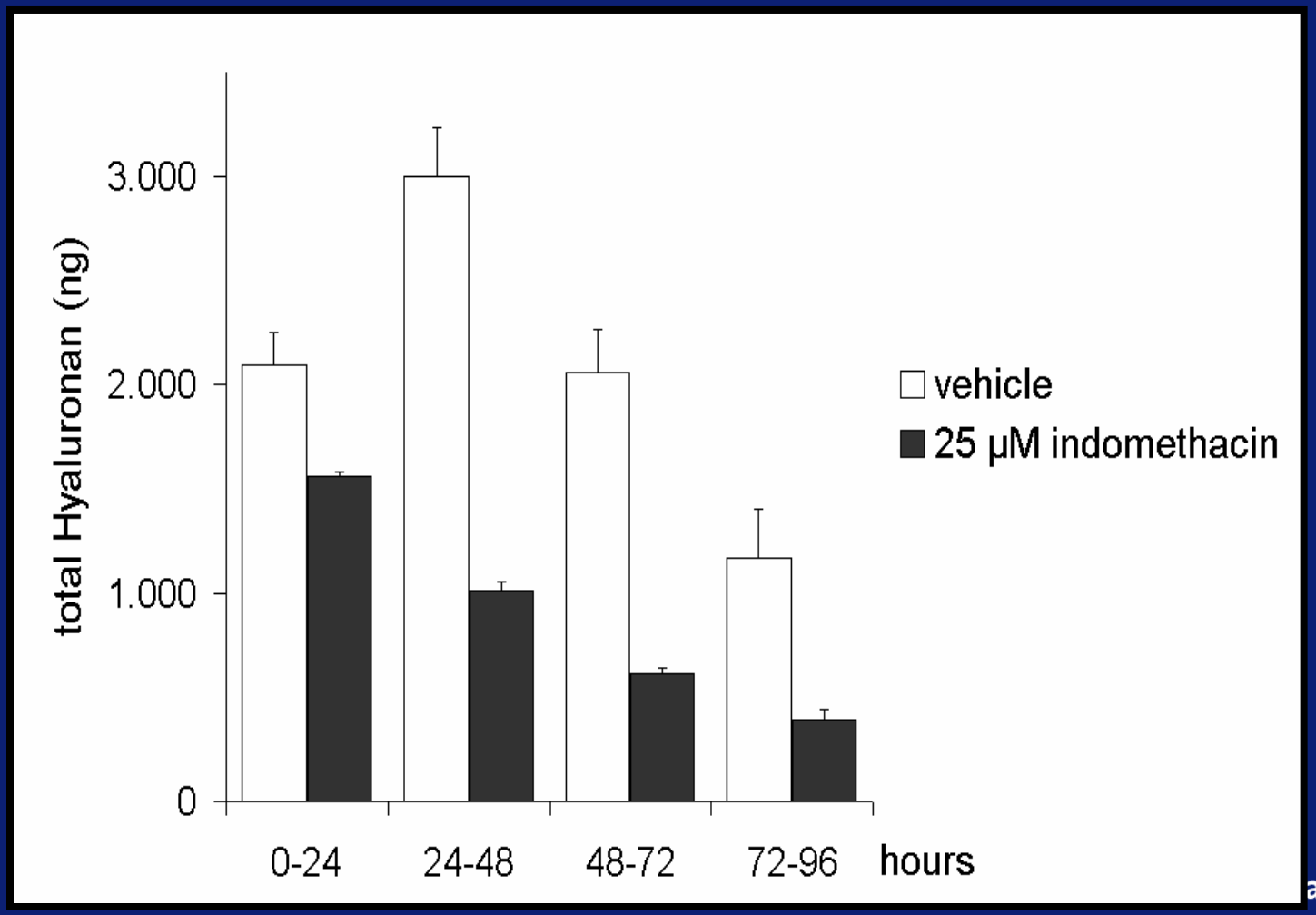
confluence

Treatment

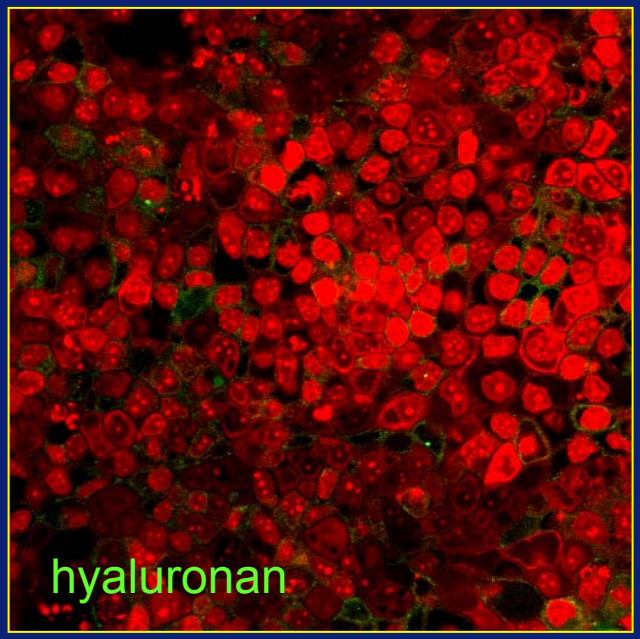
Effect indomethacin on PGE2 synthesis during wound healing



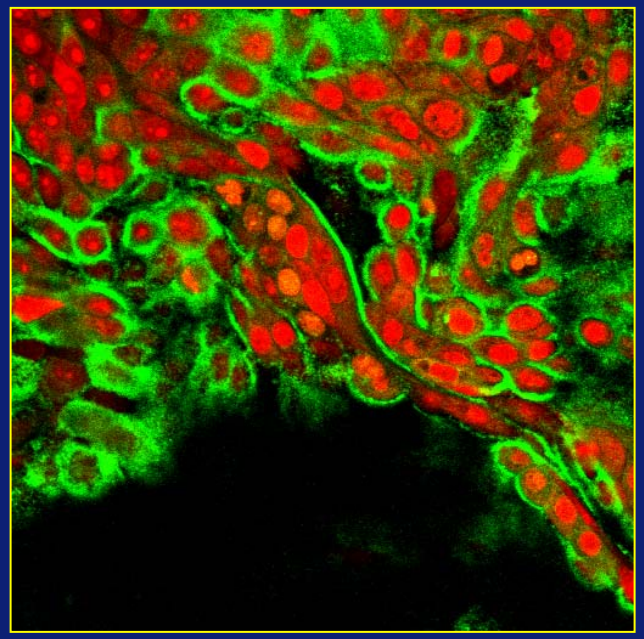
Effect indomethacin on hyaluronan synthesis during wound healing



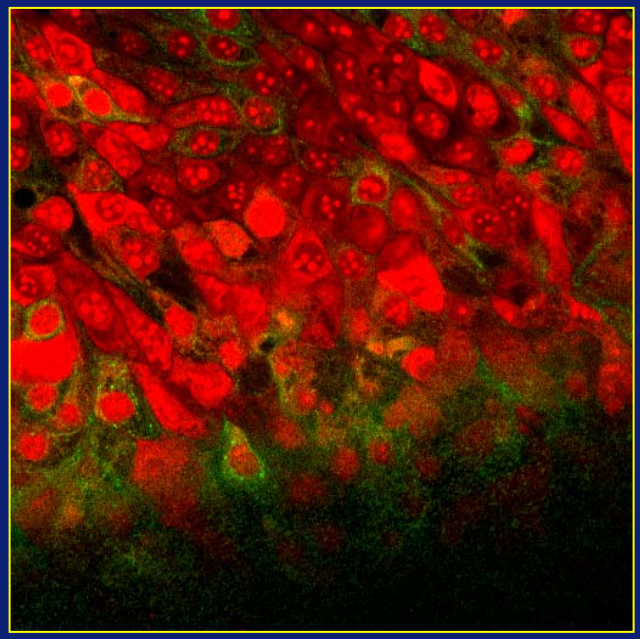
Effect indomethacin on hyaluronan expression during wound healing



Undamaged control

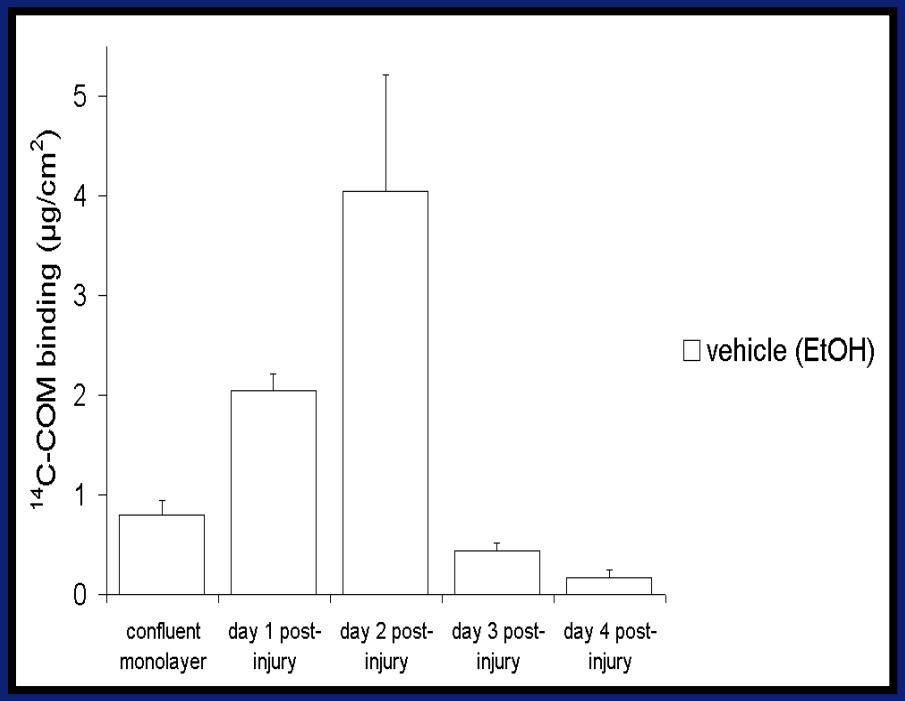


Wound healing

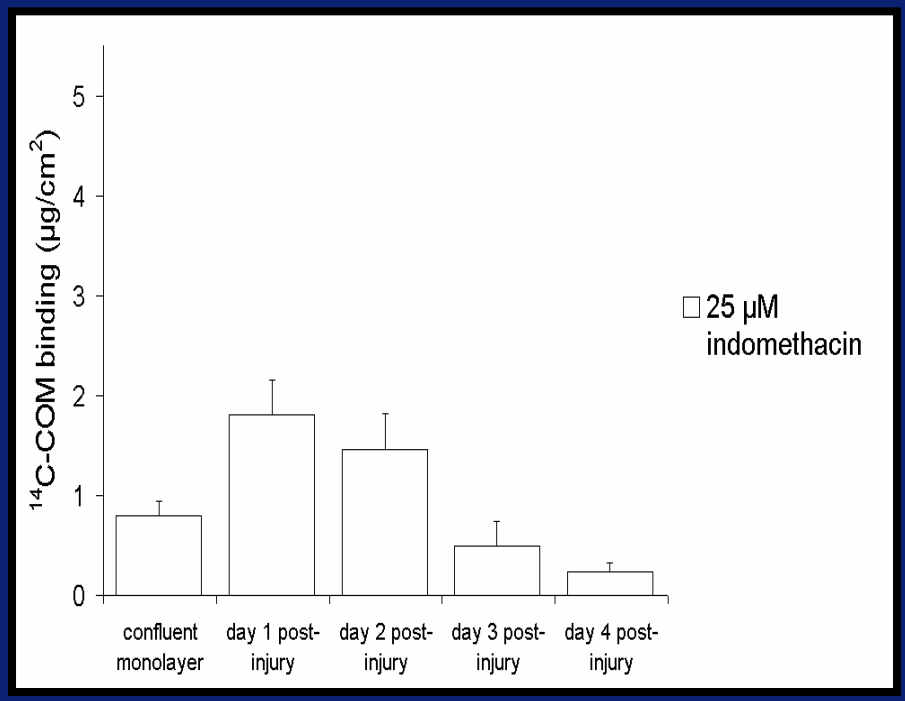


Wound healing
+25 µM indomethacin

Effect indomethacin on crystal binding during wound healing



Wound healing



Wound healing + indomethacin

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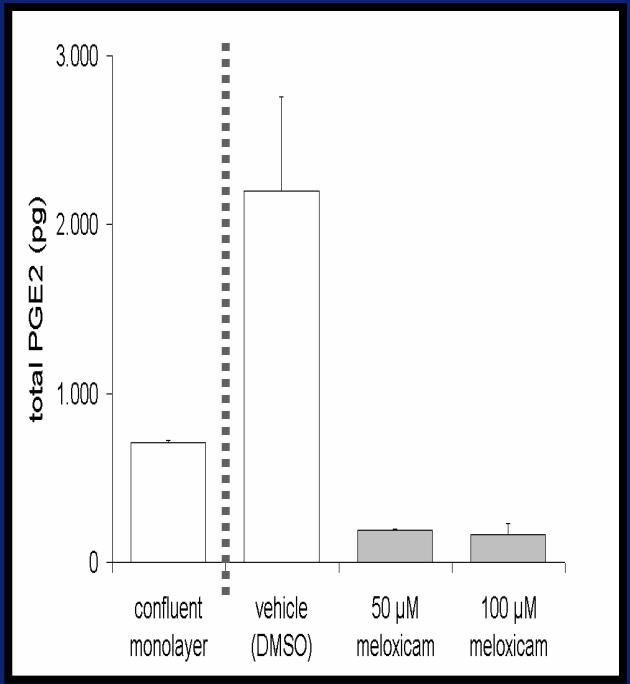
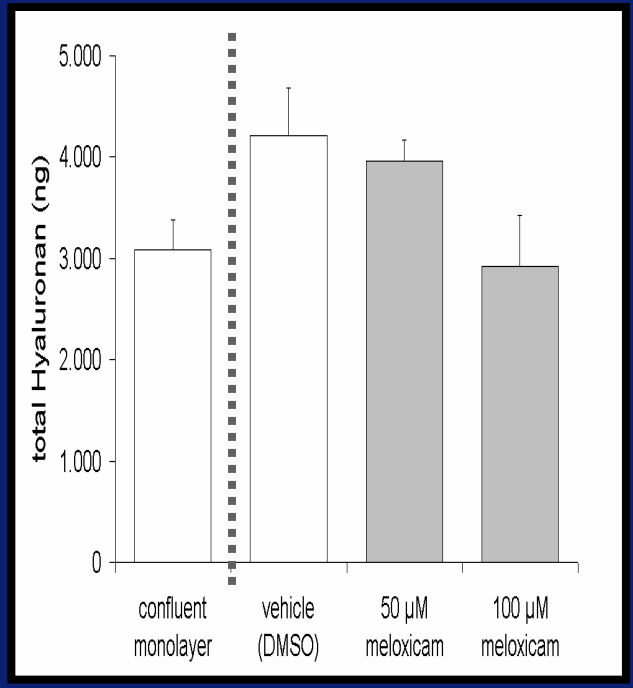
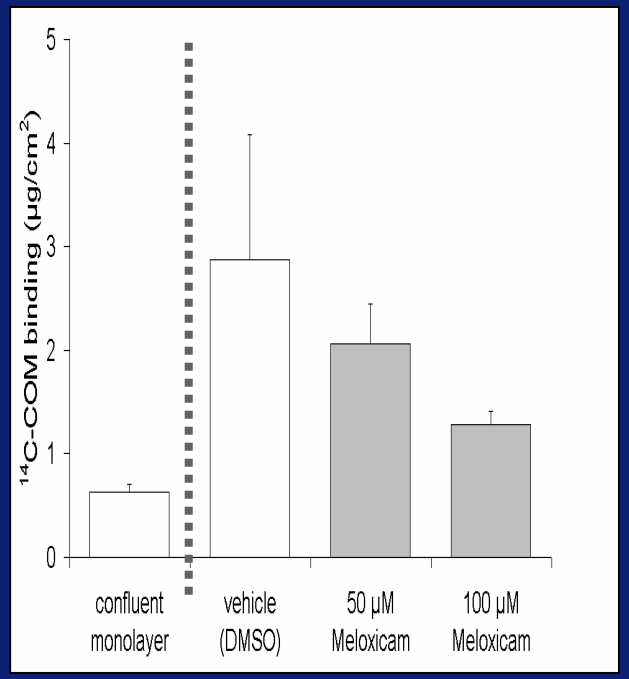
Effect meloxicam (COX-2-specific NSAID)



PGE_2



hyaluronan



COM crystal binding

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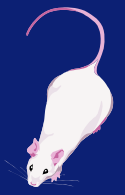
Rat studies

Asselman M, et al. J Am Soc Nephrol 14 (12) 2003, in press

Oxalosis & Hyperoxaluria

November 20-21, 2003

Ethylene glycol (EG)



alcohol dehydrogenase

glycoaldehyde

aldehyde oxidase

glycolate

LDH or glycolate oxidase (GO)

glycolate reductase (GR)

glyoxylate

alanine:glyoxylate aminotransferase (AGT)

LDH or glycolate oxidase (GO)

glycine

oxalate

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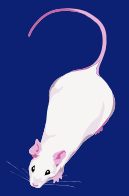
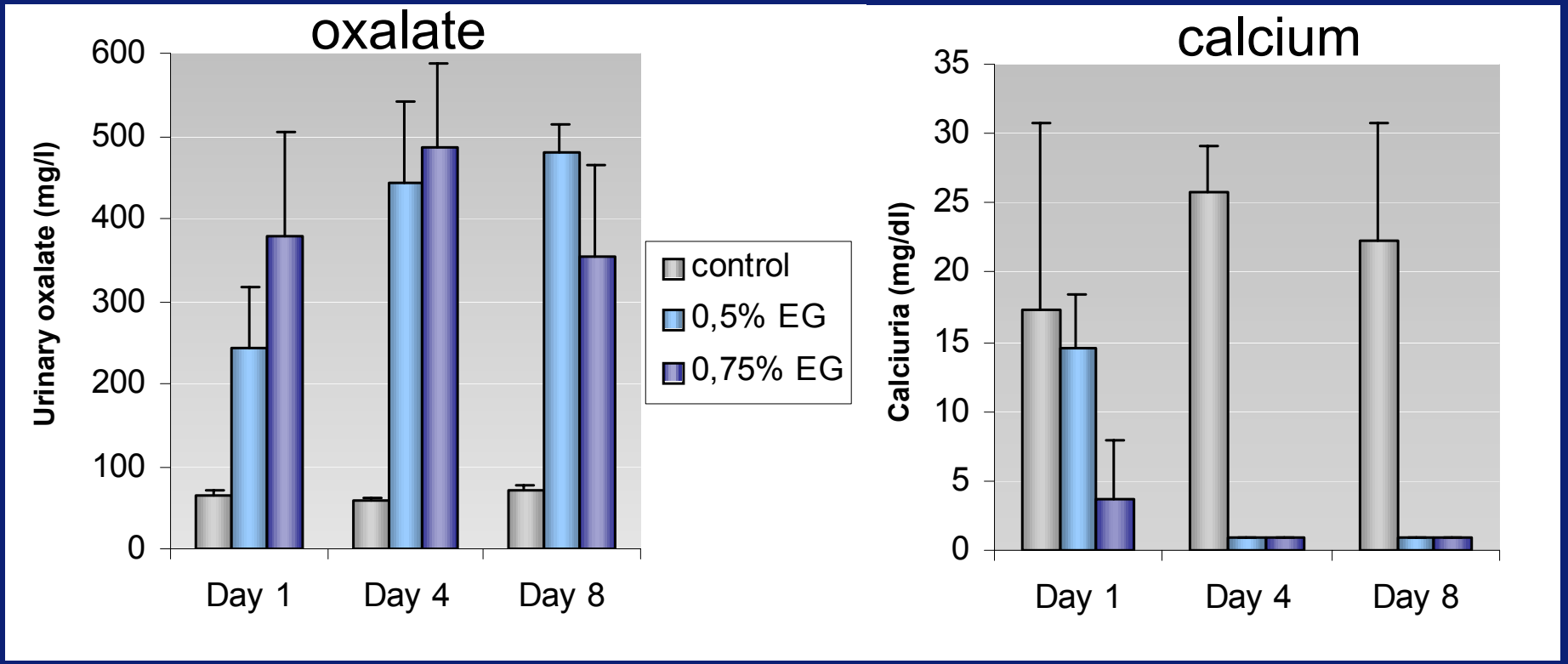
Oxalosis & Hyperoxaluria

November 20-21, 2003

Effect ethylene glycol on urinary oxalate and calcium excretion





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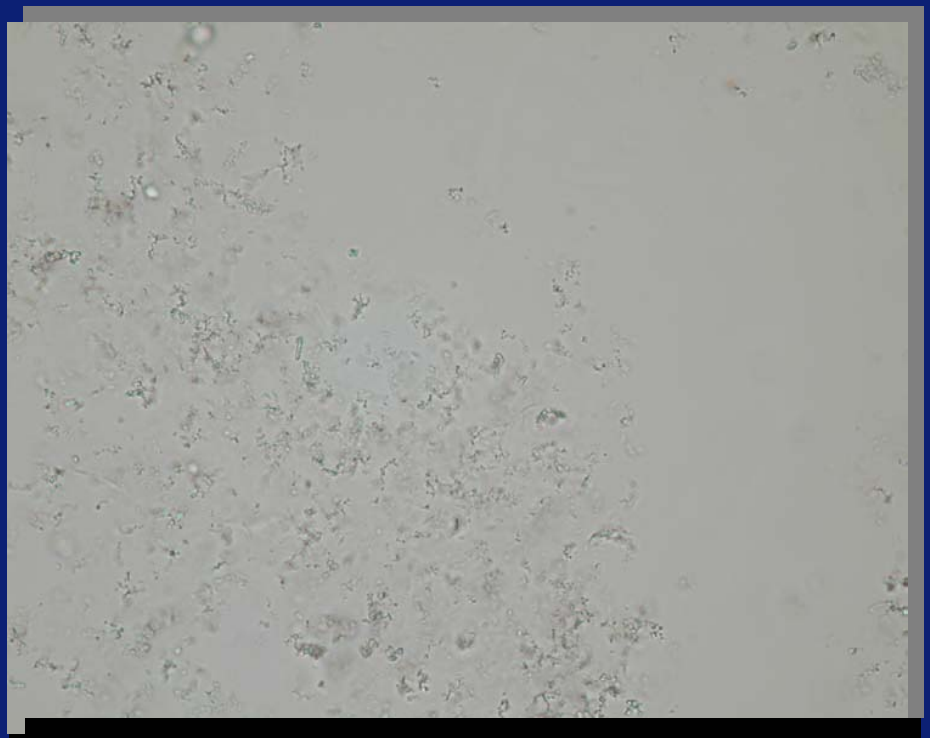
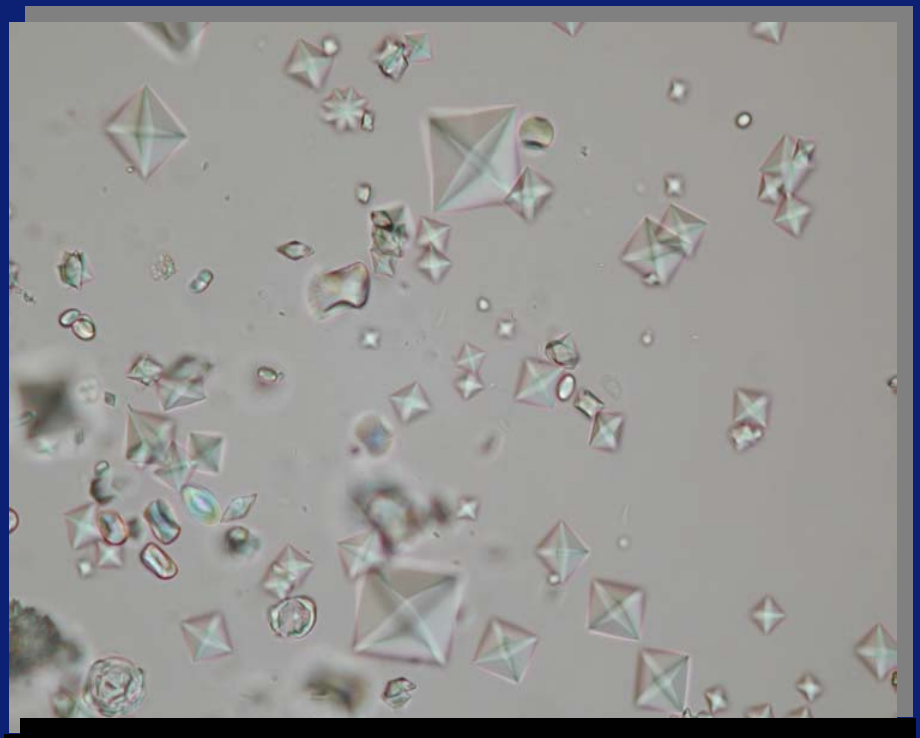
crystalluria after 24 h ethylene glycol

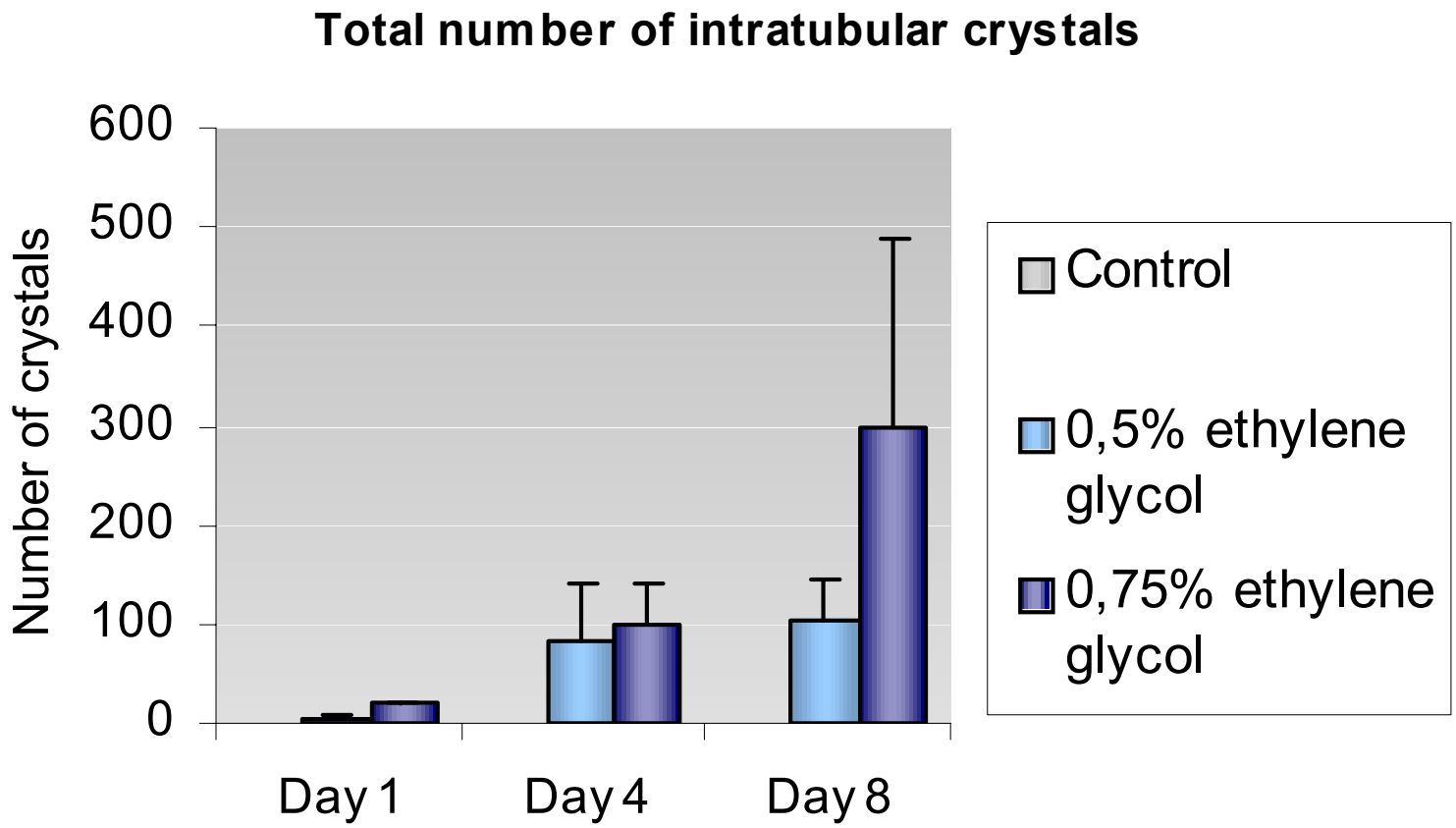


untreated control



ethylene glycol (0.5%)

Crystal retention in the renal tubules



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Oxalosis & Hyperoxaluria

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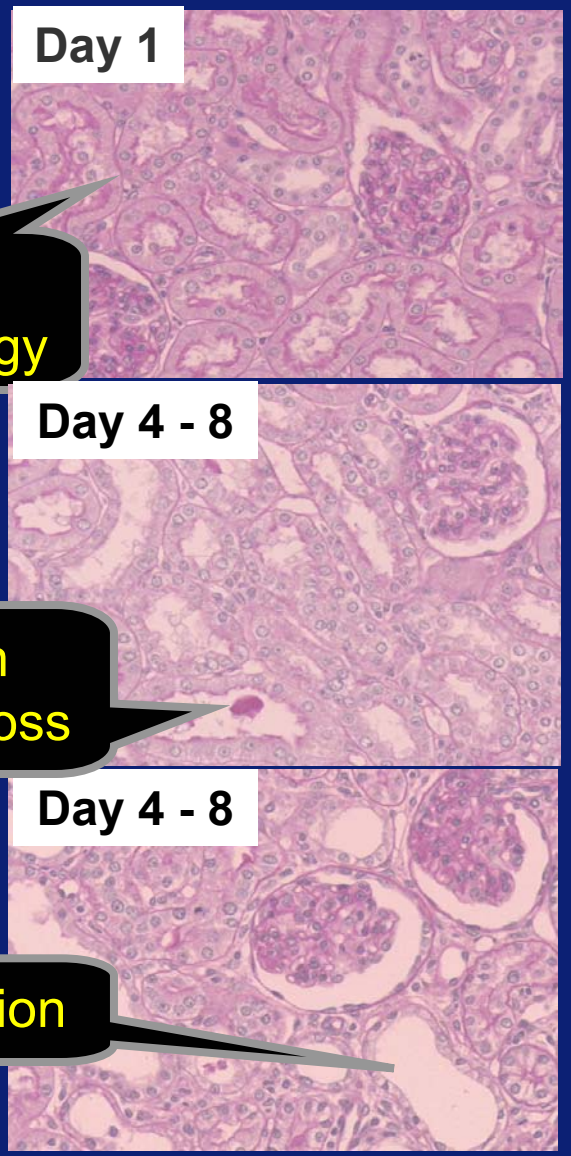
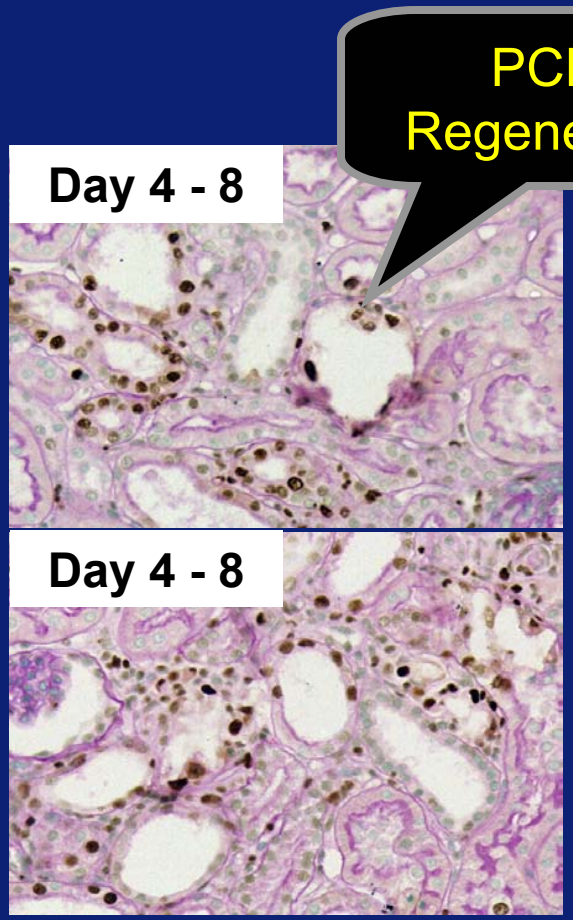
Ethylene glycol-induced renal tubular damage





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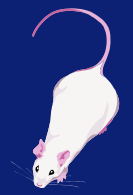
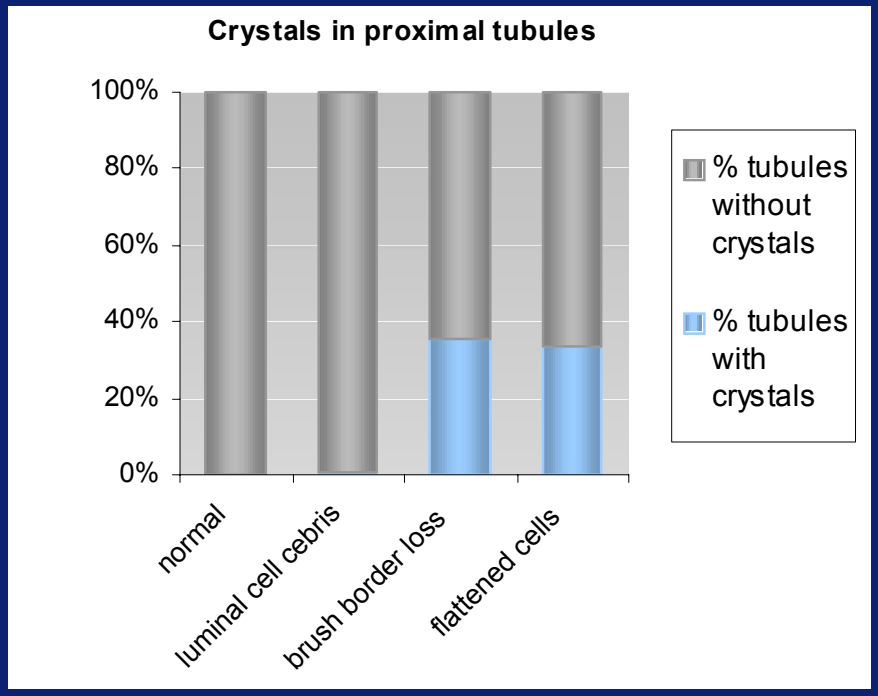
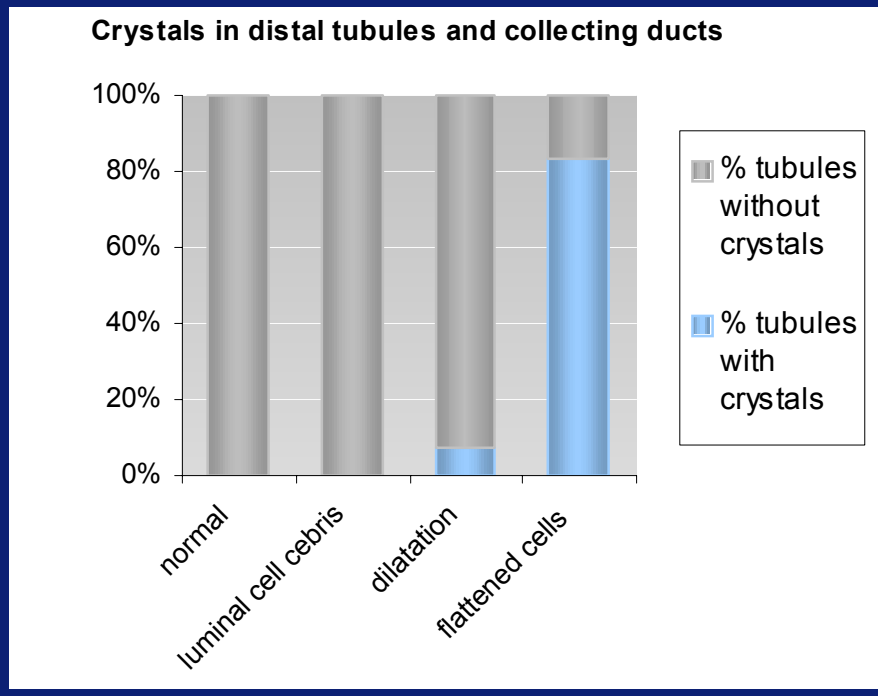


Crystals are selectively retained in damaged tubules





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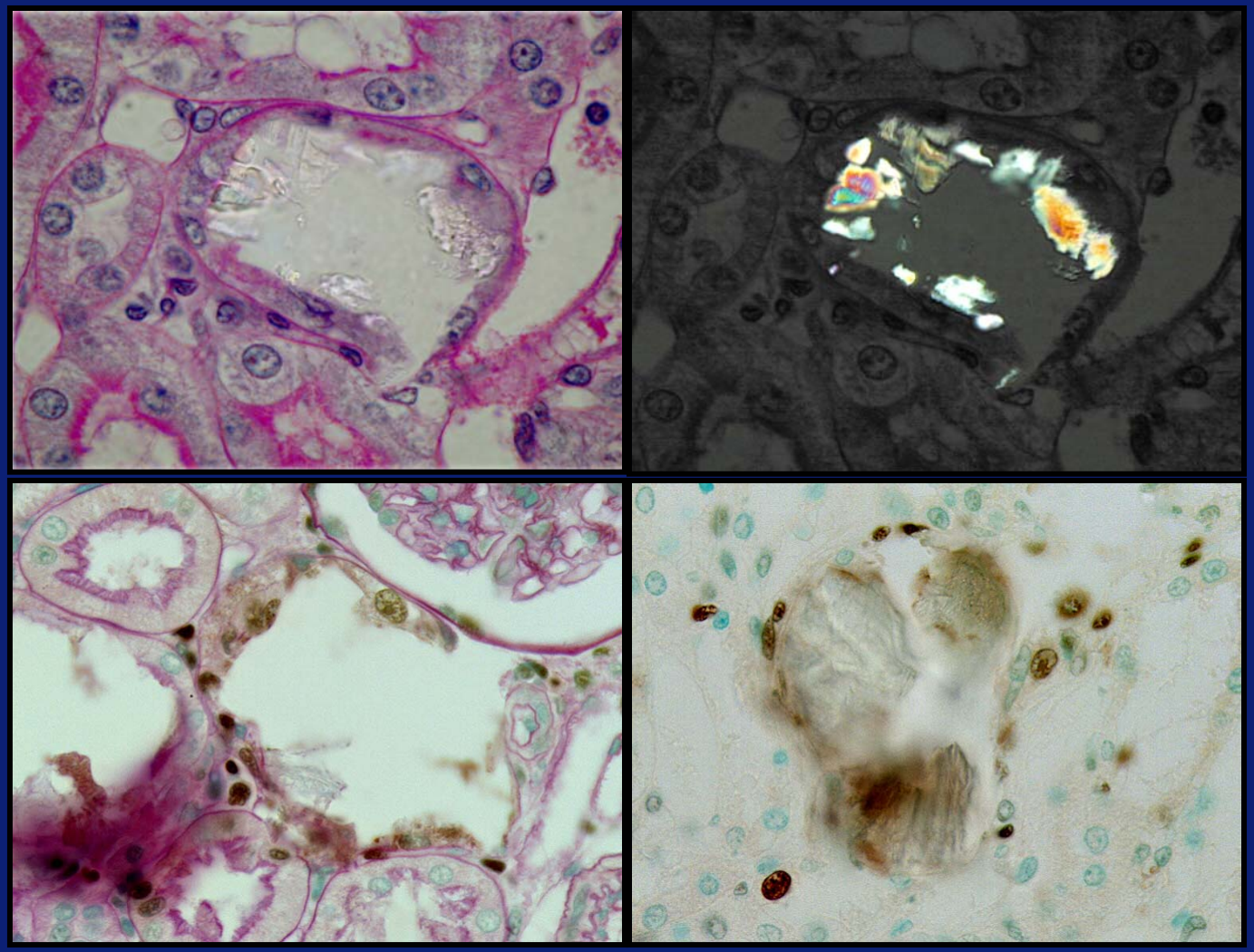
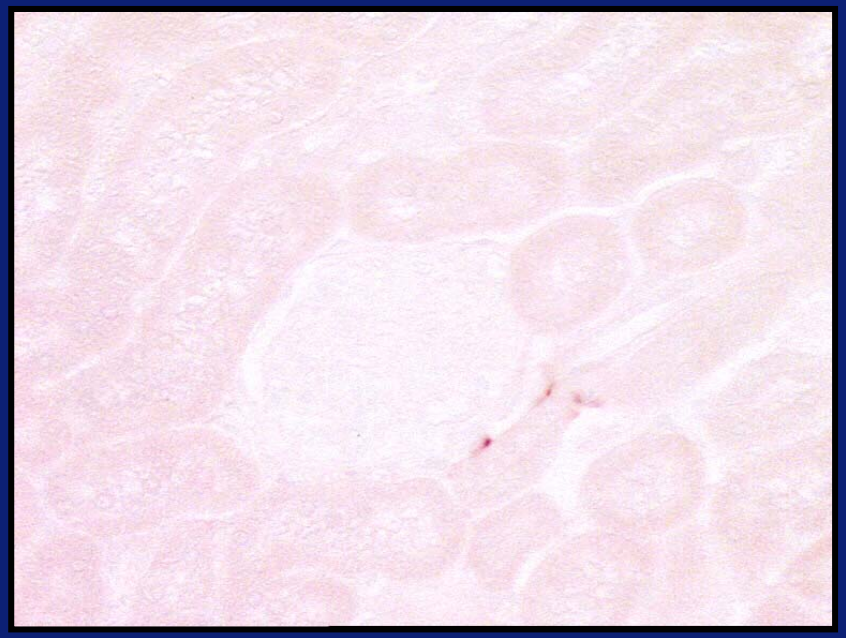
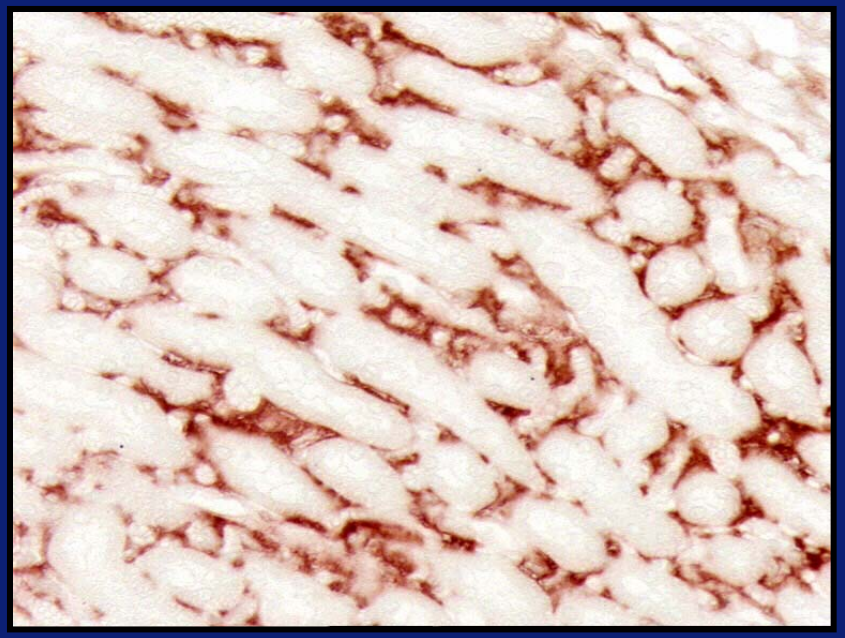
Crystals predominantly bind to regenerating cells



Hyaluronan expression in the normal kidney

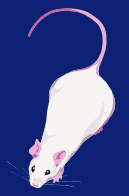


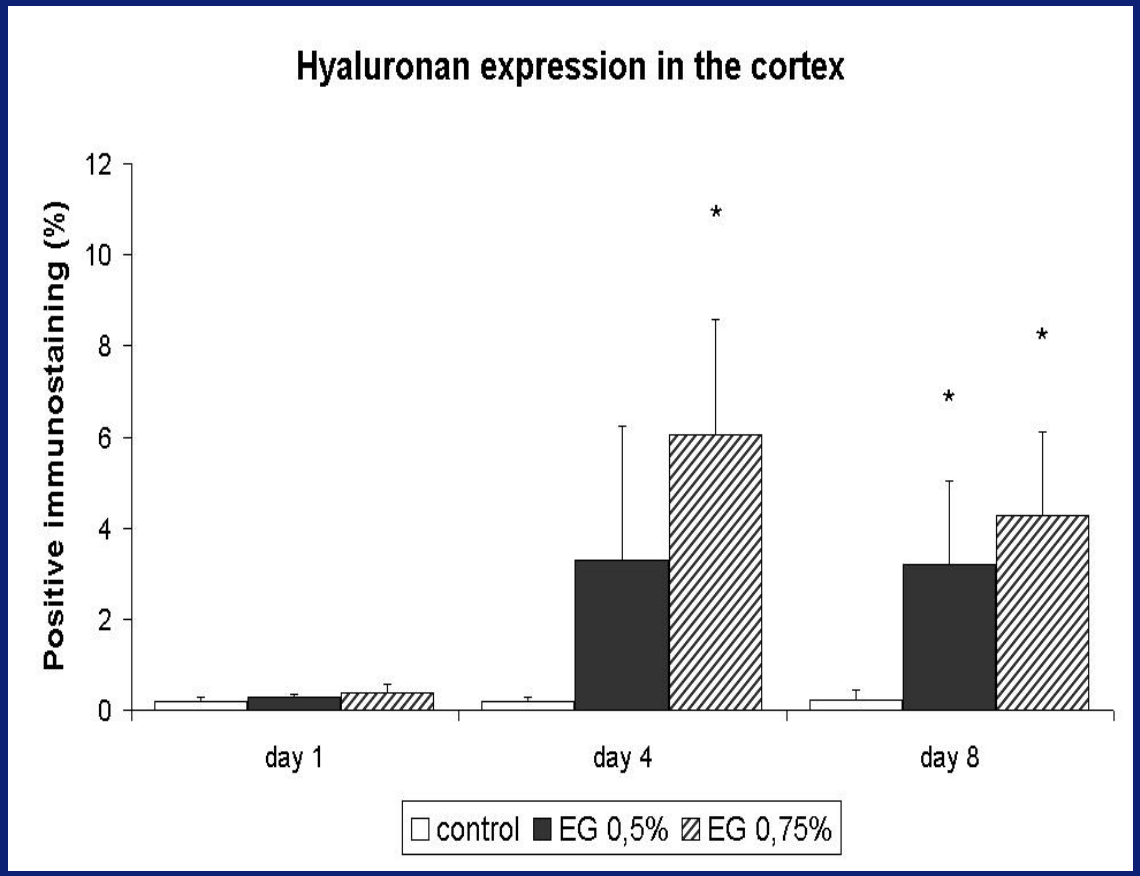
cortex

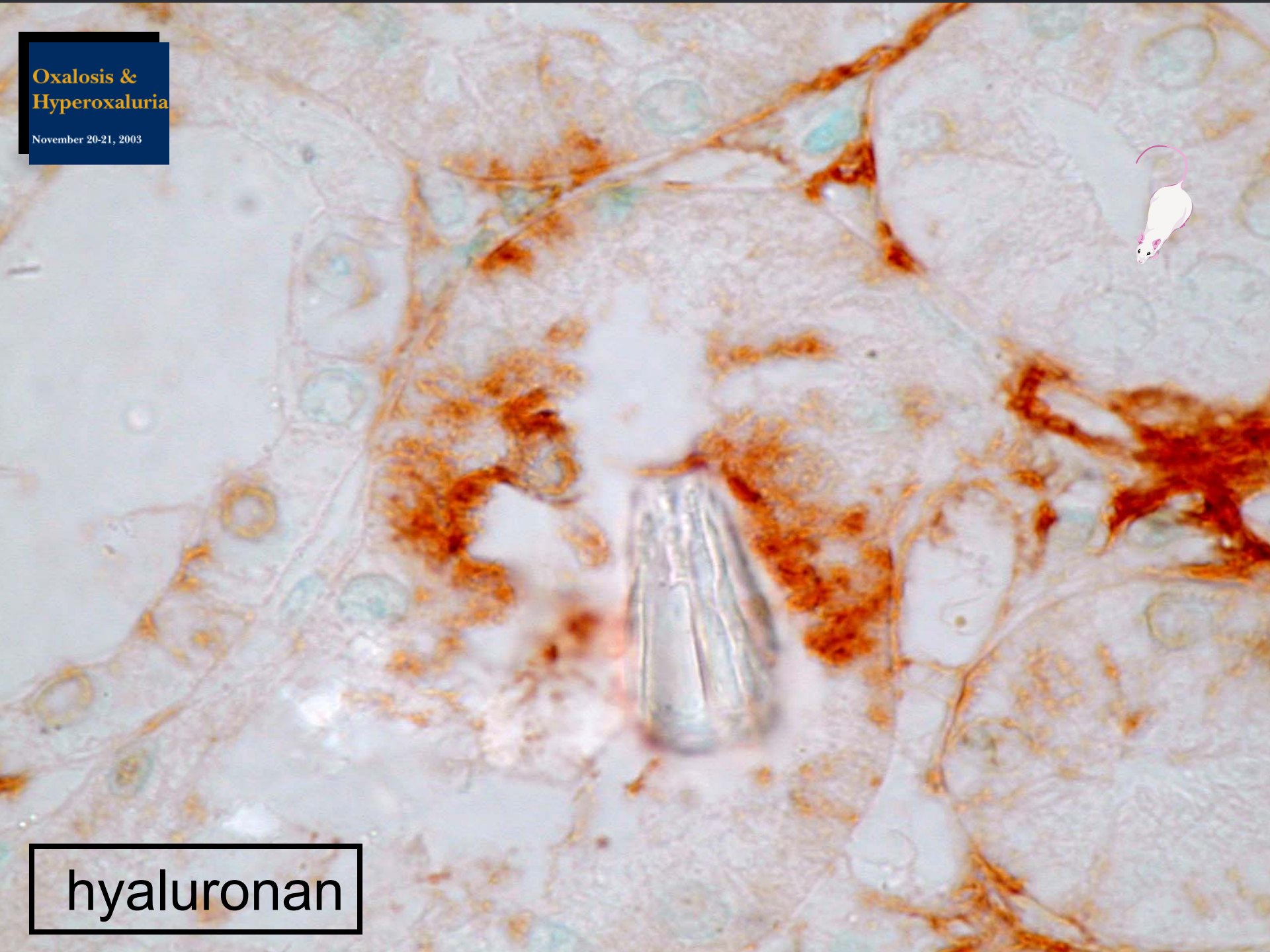


medulla

Ethylene glycol-induced up-regulated expression of hyaluronan (OPN and CD44)






Oxalosis &
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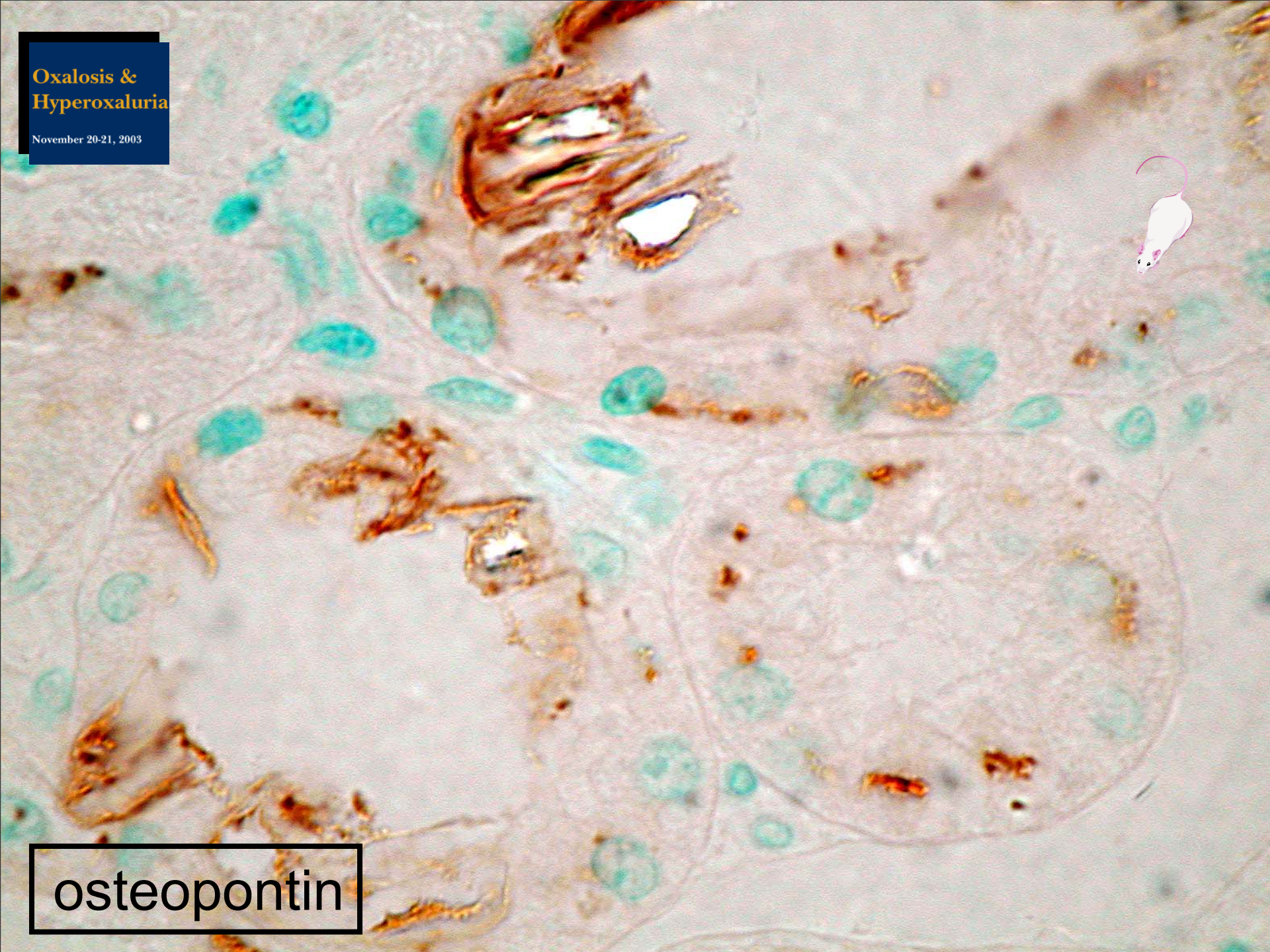
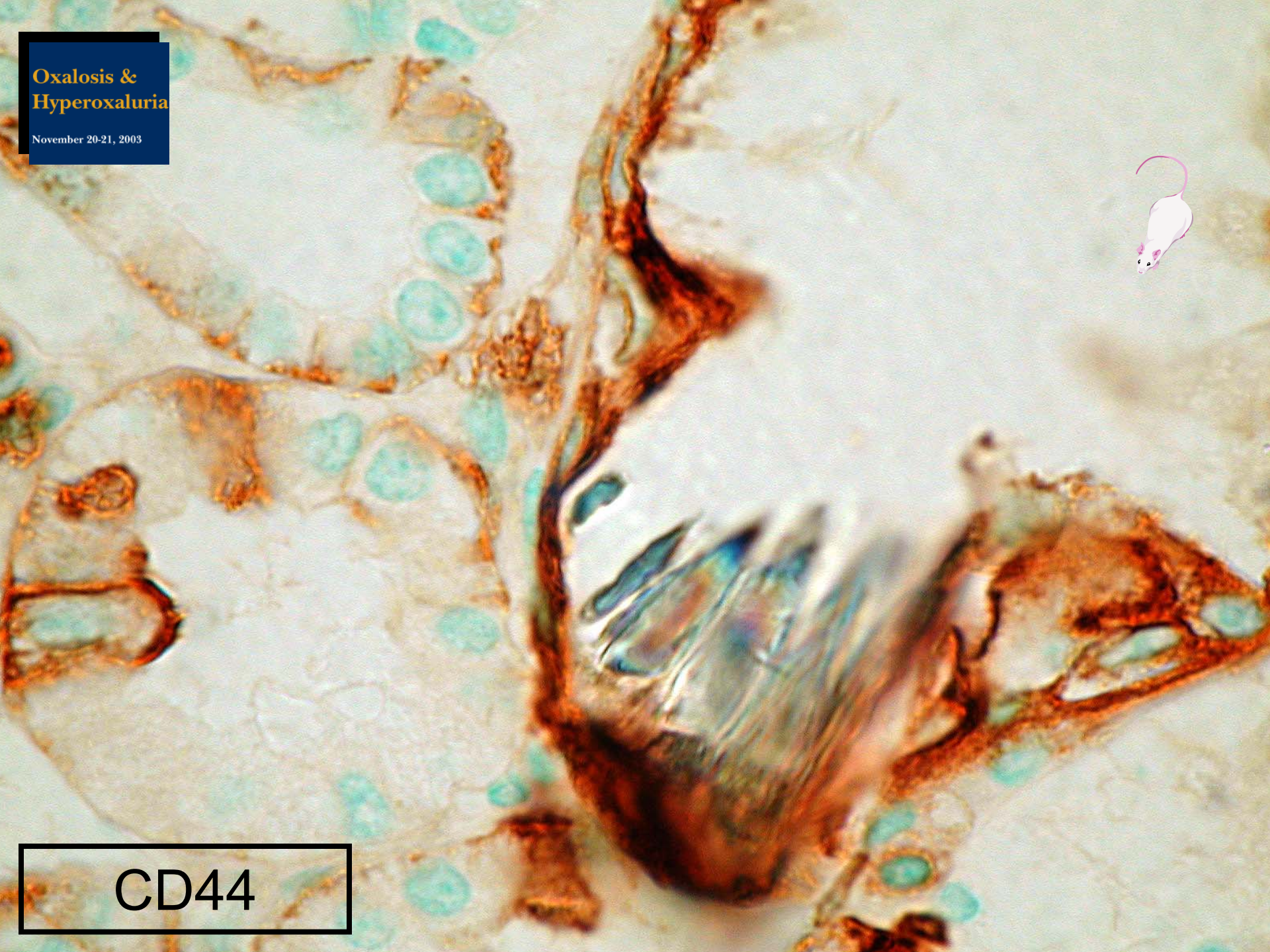
hyaluronan


Oxalosis &
Hyperoxaluria
November 20-21, 2003
osteopontin


Oxalosis &
Hyperoxaluria
November 20-21, 2003
CD44

Human studies

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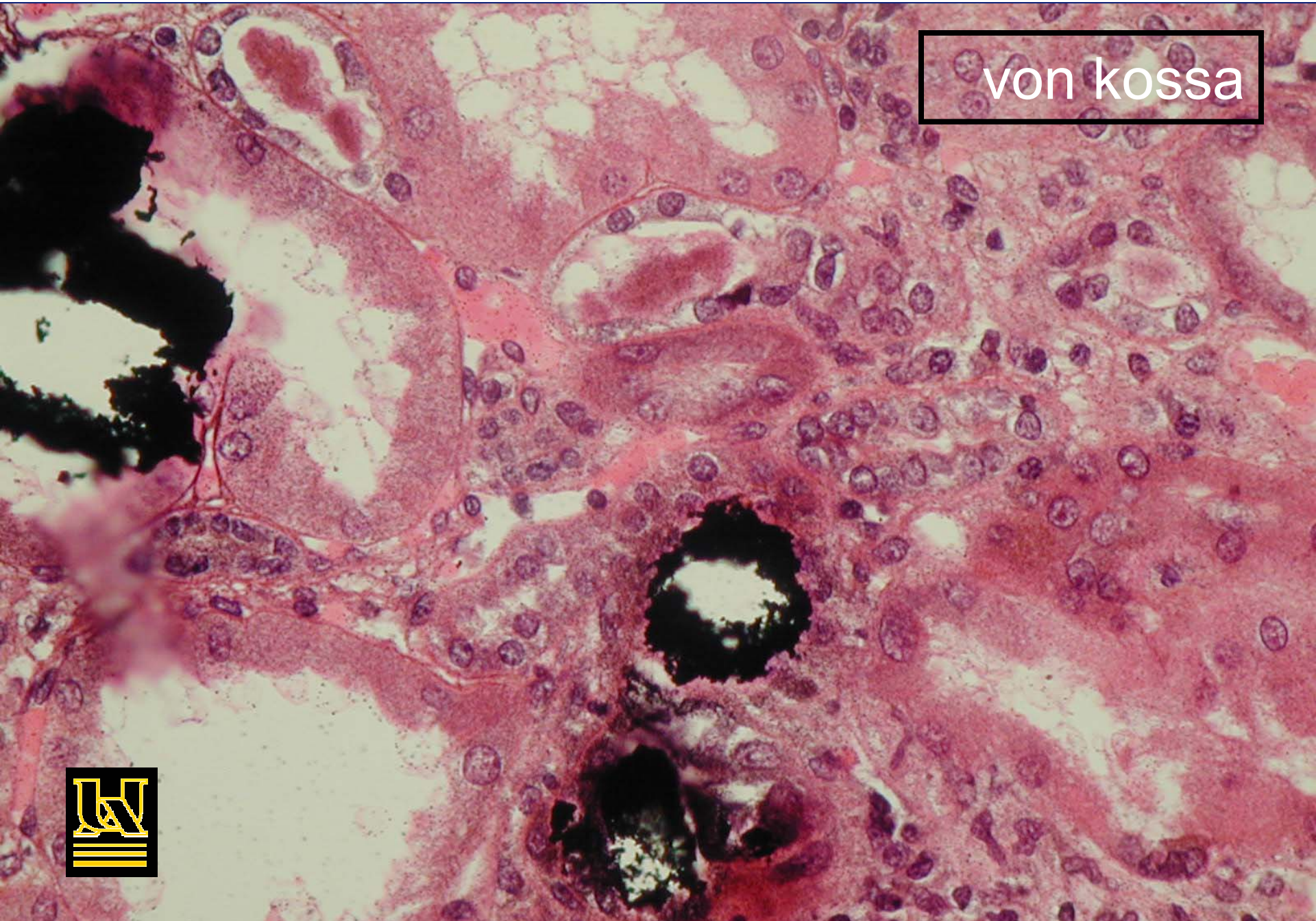
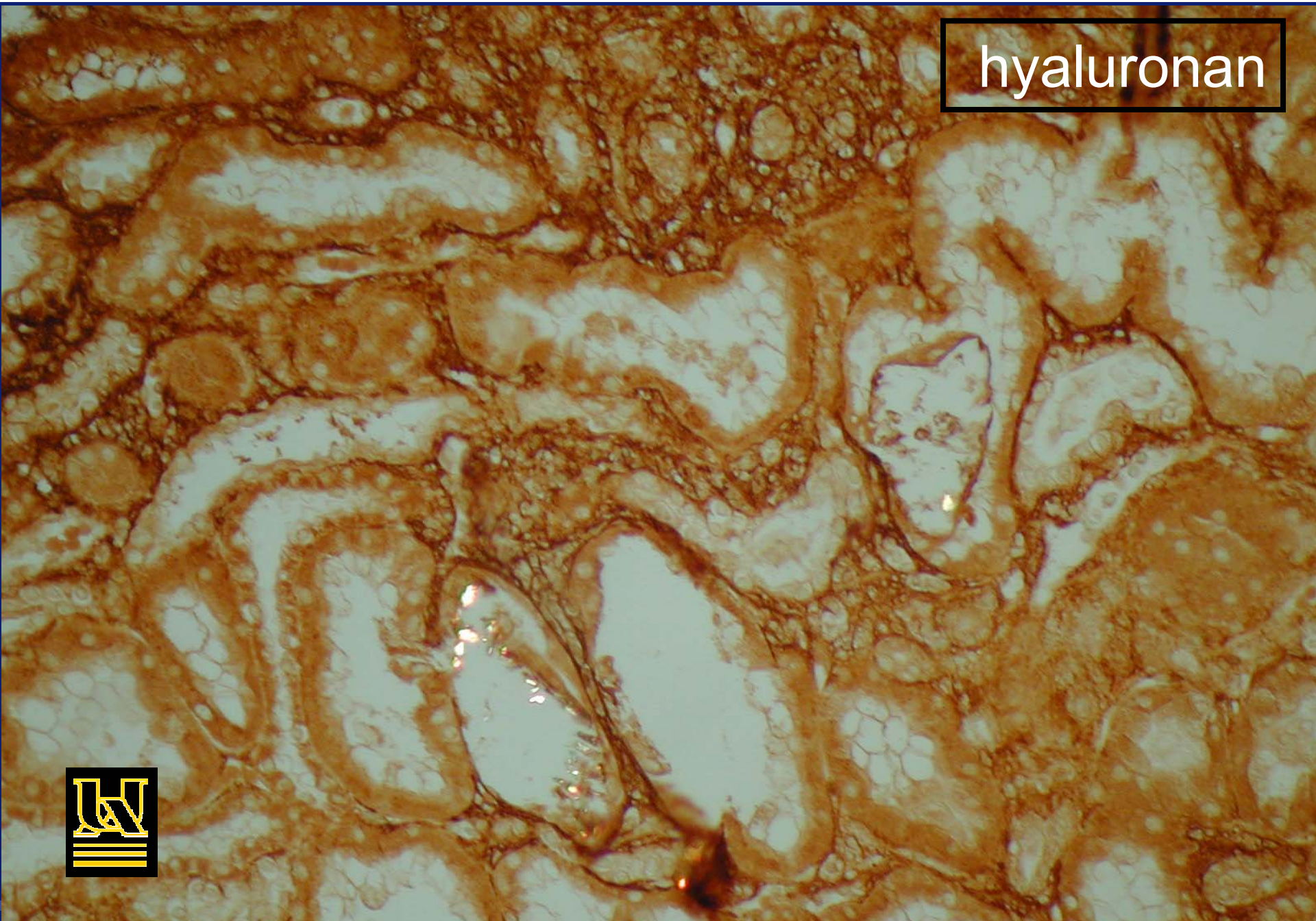
acute renal failure/tubular necrosis

hyaluronan

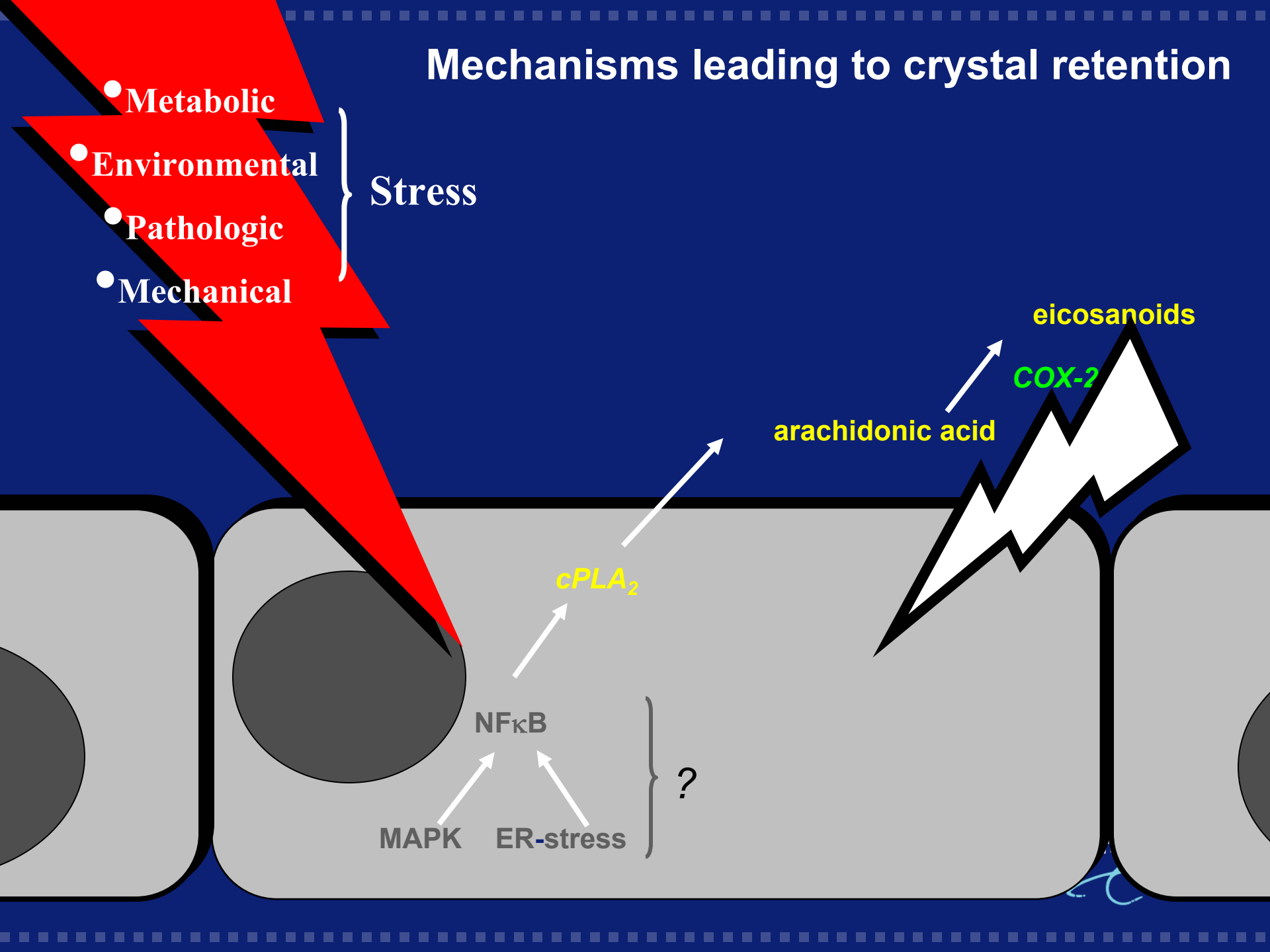
Transplanted kidney in patient with primary hyperoxaluria type I

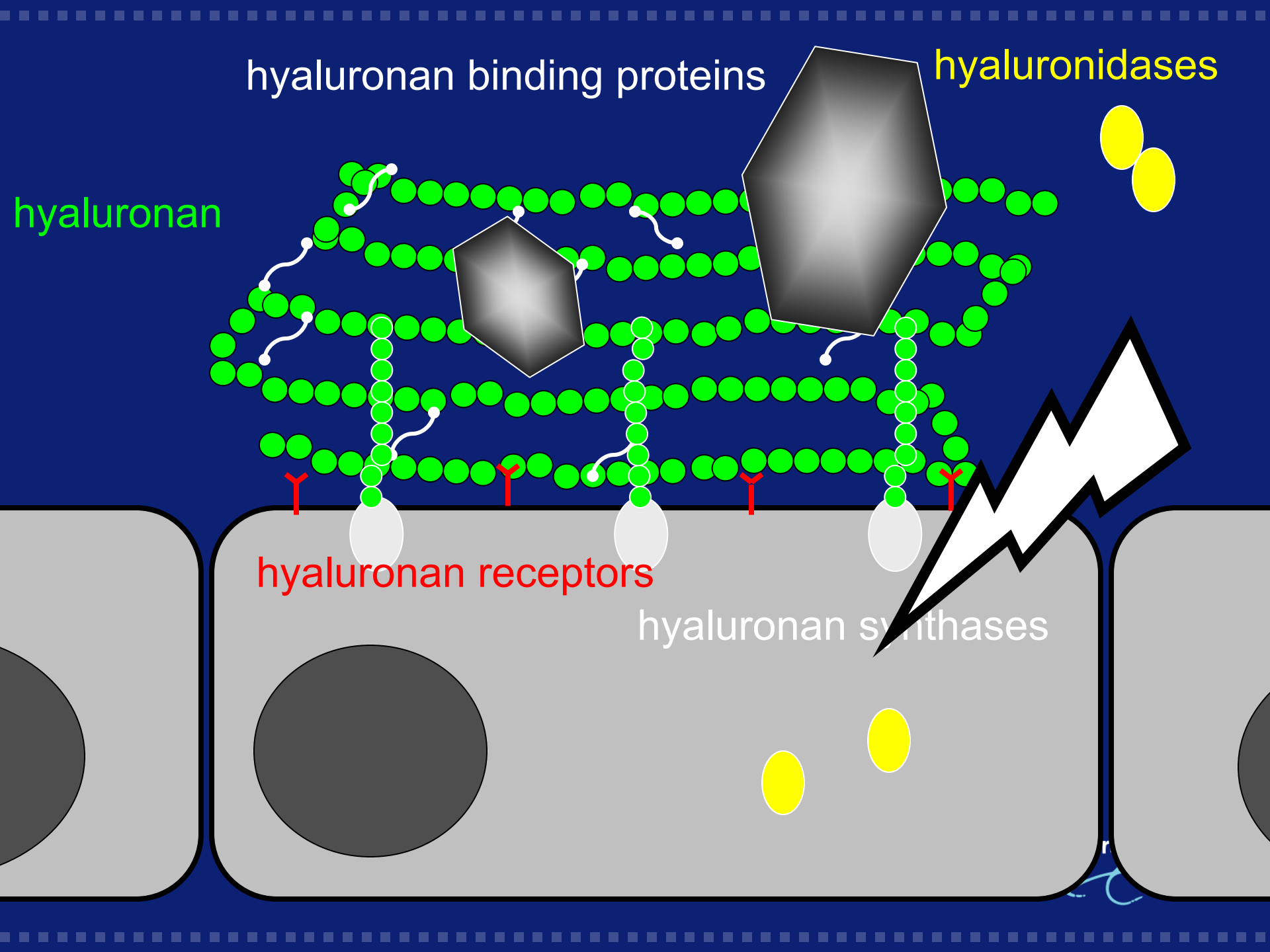


Transplanted kidney in patient with primary hyperoxaluria type I



Mechanisms leading to crystal retention




hyaluronan binding proteins
hyaluronidases
hyaluronan
hyaluronan receptors
hyaluronan synthases

Conclusion

Recurrent renal stone formation is an inflammation-mediated disease

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Eddy van Ballegooijen
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Patric D'Haese
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Veerle Persy
Benjamin Vervaet
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SUWO

Stichting Urologisch Wetenschappelijk Onderzoek

OHF

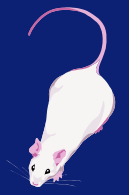
Oxalosis and Hyperoxaluria Foundation

NIERSTICHTING

Dutch Kidney Foundation

Ethylene glycol (EG)

anti-freeze



alcohol dehydrogenase

glycoaldehyde

aldehyde oxidase

glycolate

LDH or glycolate ox e (GO)

glycolate reductase (GR)

glyoxylate

alanine:glyoxylate aminotransferase (AGT)

LDH or glycolate oxidase (GO)

glycine

oxalate

Erasmus MC

Primary Hyperoxaluria type 1

glycolate

LDH or glycolate oxidase (GO)

glyoxylate reductase (GR)

glyoxylate

alanine:glyoxylate aminotransferase (AGT)

LDH or glycolate oxidase (GO)

glycine

oxalate

Erasmus MC

Primary hyperoxaluria type 1

metabolic

membrane phospholipids

Phospholipase A_2 (PLA_2)

arachidonic acid

fish-oil

Cyclooxygenases (COX-1, COX-2)

prostaglandins

NSAIDs

Hyaluronan synthases (HAS-1, HAS-2,

hyaluronan

crystal retention

Inhibitors

nephrocalcinosis/nephrolithiasis

tubular obstruction

loss of renal function → hyperoxalemia → oxalosis

Endoplasmic reticulum (ER) stress

mitogen-activated protein kinase (MAPK)

glycine

Erasmus MC