Therapeutic elimination of amyloid deposits: is it possible?

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NHS Trust

Conflict of interest

- Inventor of granted and pending patents on use of CPHPC alone and in combination with anti-SAP antibodies for treatment of amyloidosis and amyloid-associated diseases

- Founder, Director and share holder in Pentraxin Therapeutics Ltd, UCL spin out company which owns these patents and has licensed them to GlaxoSmithKline for clinical development

Amyloidosis

- Disease caused by amyloid deposits: local or systemic
- Diagnosis usually late
- Treatment very challenging
- Major recent advances & better outcomes in specialist centres
- Still a major unmet medical need

Amyloidosis & amyloid-associated diseases

- Systemic amyloidosis: acquired or hereditary
- Local amyloidosis: acquired or hereditary

- Type 2 diabetes
- Alzheimer’s disease

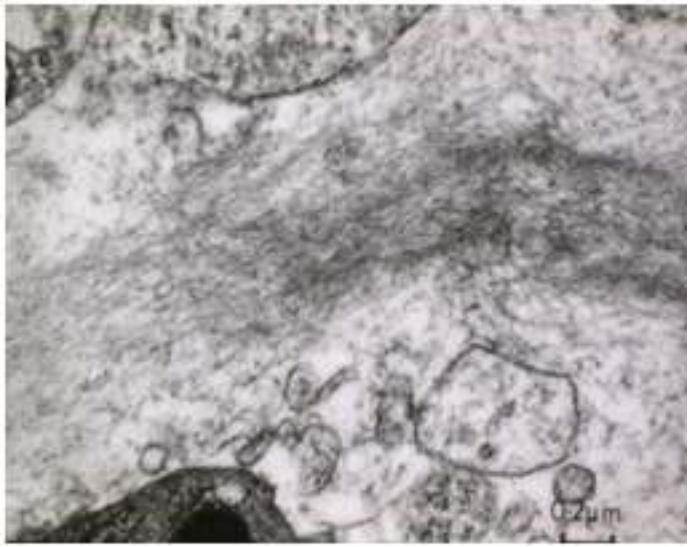
- Transmissible spongiform encephalopathies

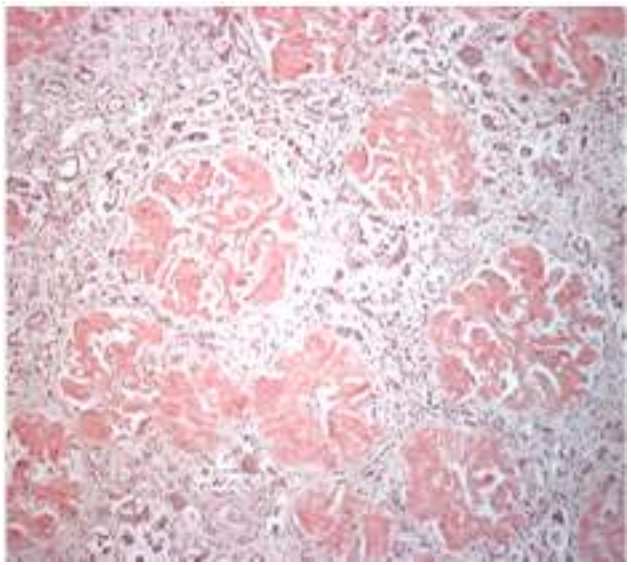
Progress in amyloidosis 1976-2010

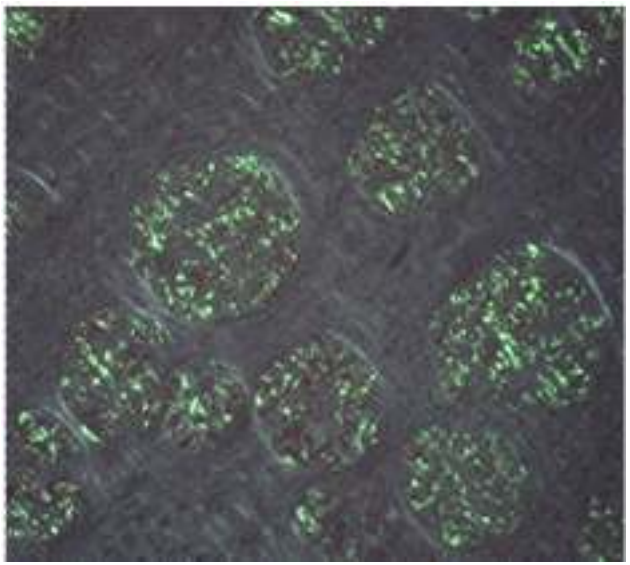
- Better diagnosis but usually still very late
- Better retention & replacement of organ function but often not sufficient
- Much better control of precursor protein abundance but often difficult & dangerous
- Better survival but systemic amyloidosis still usually fatal
- Important unmet medical need

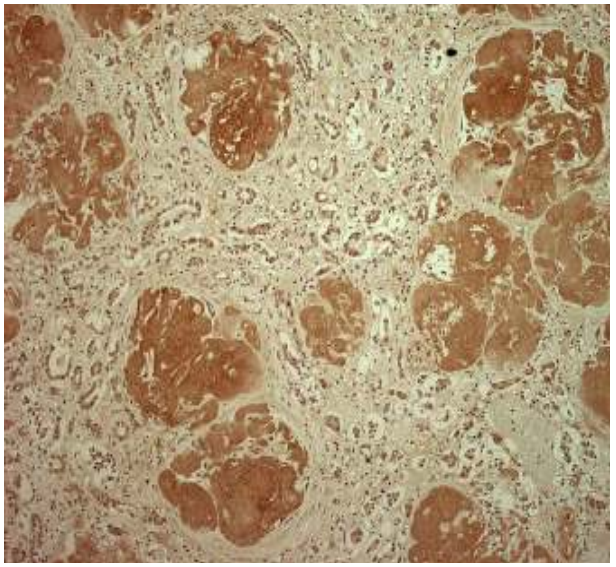
Amyloid deposits

- Amyloid fibrils
- Heparan/dermatan sulphate PGs
- Serum amyloid P component (SAP)









Amyloid fibrillogenesis *in vivo*

- Sustained high concentration of normal protein: SAA, β_2M, TTR
- Acquired production of abnormal protein: AL (myeloma, other plasma cell dyscrasias)
- Hereditary production of variant protein: TTR, fibrinogen, apoAI, lysozyme, gelsolin, etc

- Misfolding & aggregation with typical cross-β polypeptide core structure

The mystery of amyloid persistence

- Persistent production of fibril precursor proteins causes accumulation
- But why is amyloid not cleared?
- No local or systemic inflammatory reaction, no immunological response
- But macrophages & giant cells are sometimes present
- Amyloid deposits can regress

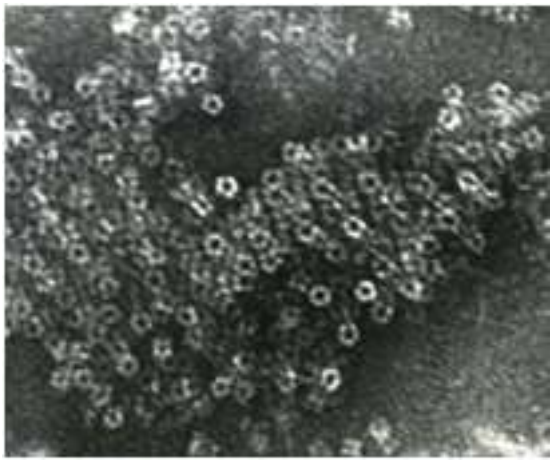
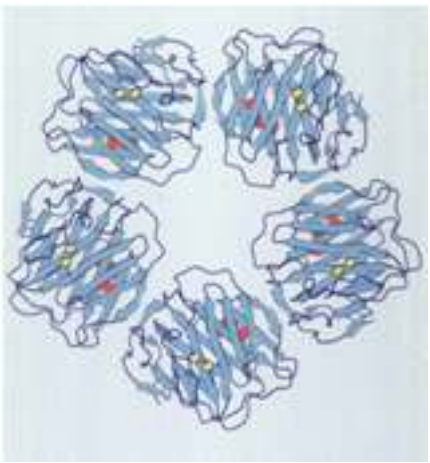
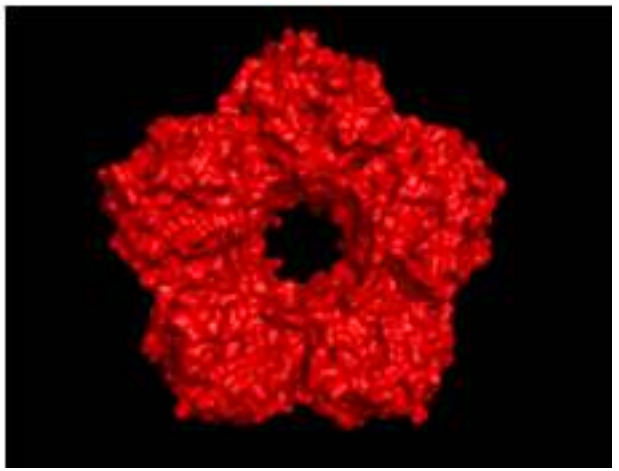
Treatment of amyloidosis

- No amyloid: no disease
  More amyloid: disease progression & death
  Amyloid regression: clinical benefit, survival
- Physical presence of amyloid is directly damaging to tissues and organ function

- Early diagnosis, maintain/replace organ function
- Control supply of fibril precursor

Serum amyloid P component (SAP)

- Highly conserved plasma glycoprotein
- Pentraxin protein family, with CRP

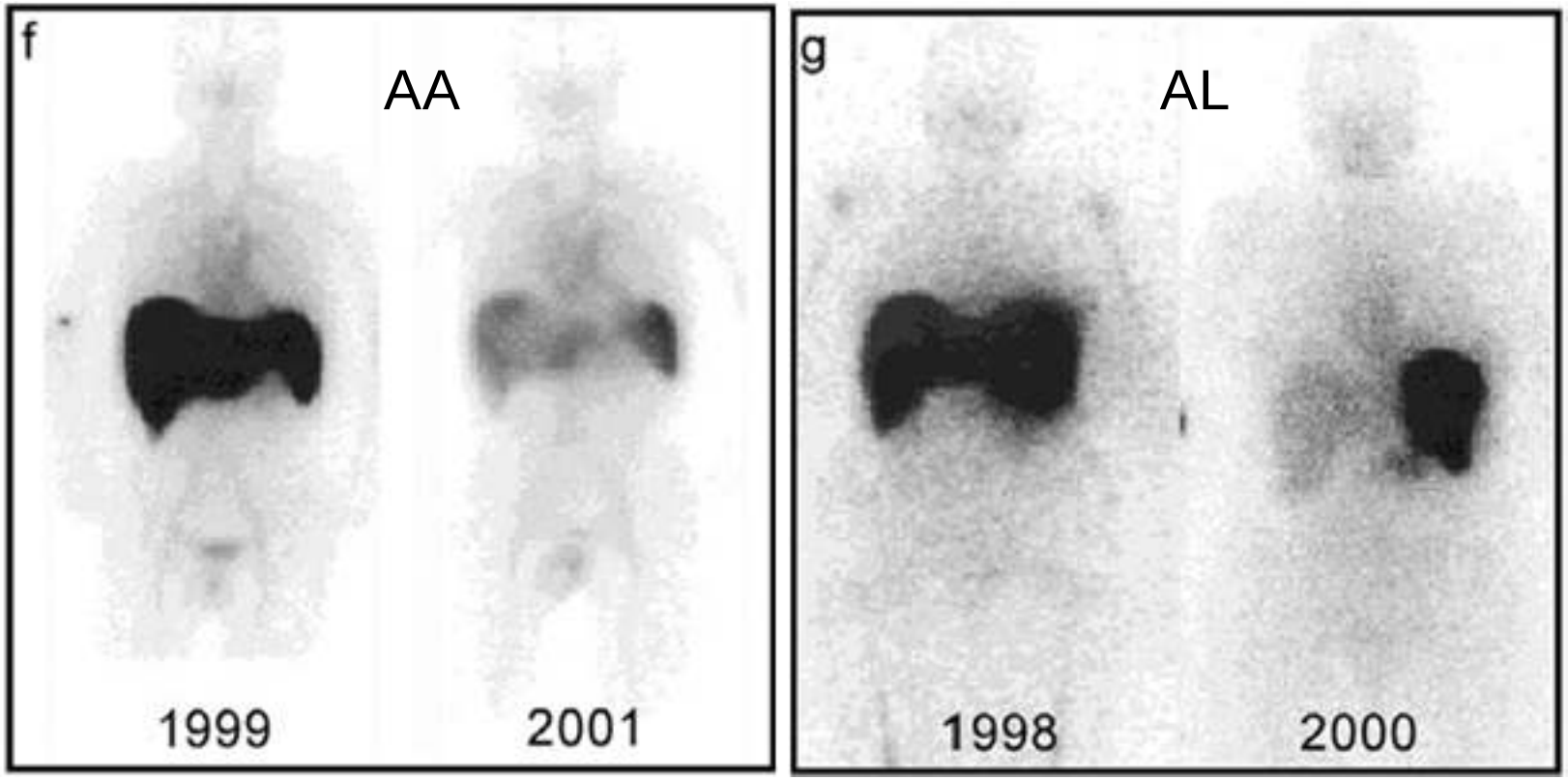




- Homopentamer, lectin fold, 20-40 mg/l in plasma, $t_{1/2}$ ~24 h, synthesized & catabolized only by hepatocytes

SAP and amyloid

- SAP binds to all amyloid fibrils (1979)
- Specifically concentrated in amyloid deposits
  in plasma - albumin : SAP ~2000 : 1
  in amyloid - albumin : SAP <1 : 10
- Equilibrium: SAP in amyloid & circulation
- Plasma and ECF SAP = ~100 mg
  Amyloid SAP = up to 20,000 mg
- Radiolabelled SAP, injected intravenously, localises specifically to amyloid (1988)

Regression of amyloid



Hawkins et al. 1993. SAP scintigraphy and turnover studies demonstrate regression of amyloidosis." *Nucl. Med. Commun.* **14**: 259-60; Scintigraphic quantification and serial monitoring of human visceral amyloid deposits provide evidence for turnover and regression. *Q.J. Med.* **86**: 365-74; Serum amyloid P component scintigraphy and turnover studies for diagnosis and quantitative monitoring of AA amyloidosis in juvenile rheumatoid arthritis. *Arthritis Rheum.* **36**: 842-51.

New treatments for amyloidosis?

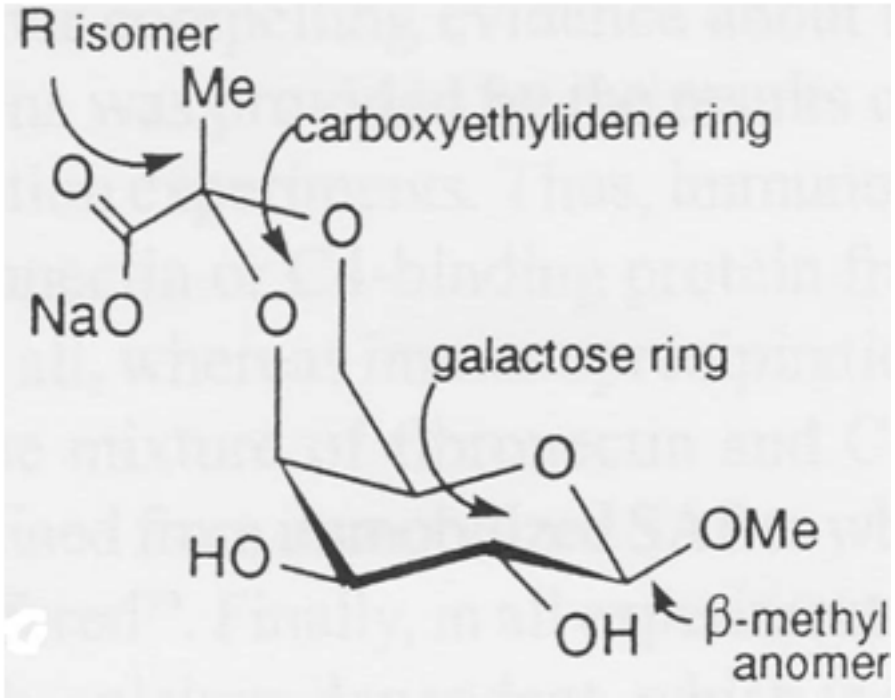
- Inhibition of fibrillogenesis
  small molecules, antibodies
  stabilisation of precursor native fold
  inhibition of precursor synthesis
  by siRNA, ASO, etc

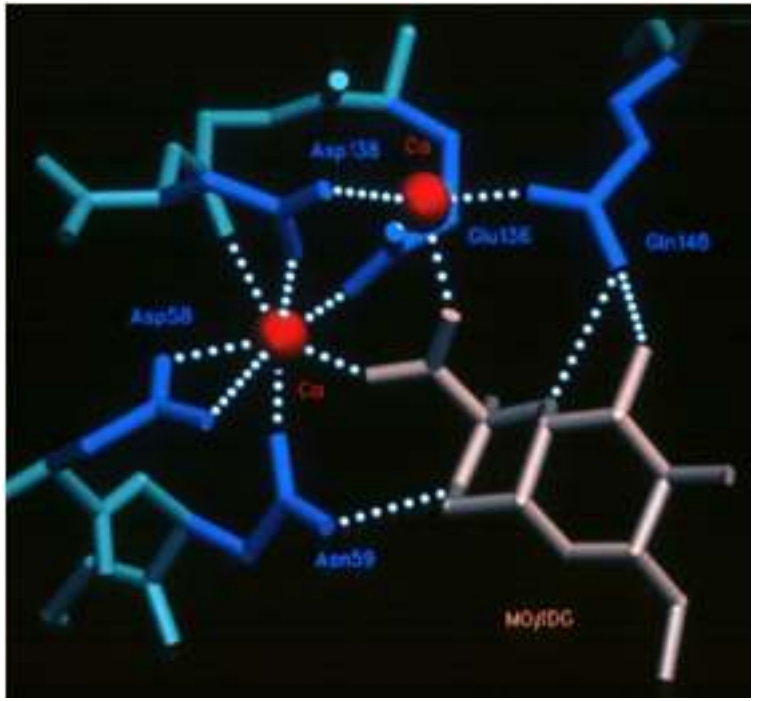
- Enhancement of amyloid regression
  antibodies to fibril proteins
  disaggregating peptides
  targeting SAP

SAP & amyloidogenesis

- SAP is universal in amyloid deposits
- SAP production correlates with amyloid deposition in mice and hamsters
- SAP in amyloid deposits is not degraded
- SAP binding stabilises amyloid fibrils *in vitro*
- SAP is an anti-opsonin
- SAP promotes fibrillogenesis *in vitro*
- Amyloid deposition reduced in SAP knockouts

1984: SAP ligand as a drug?

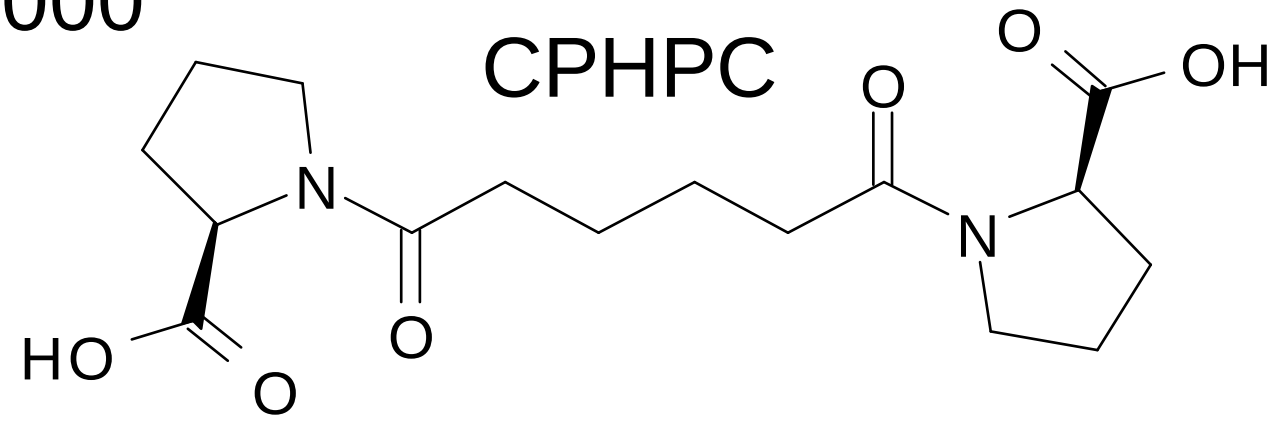




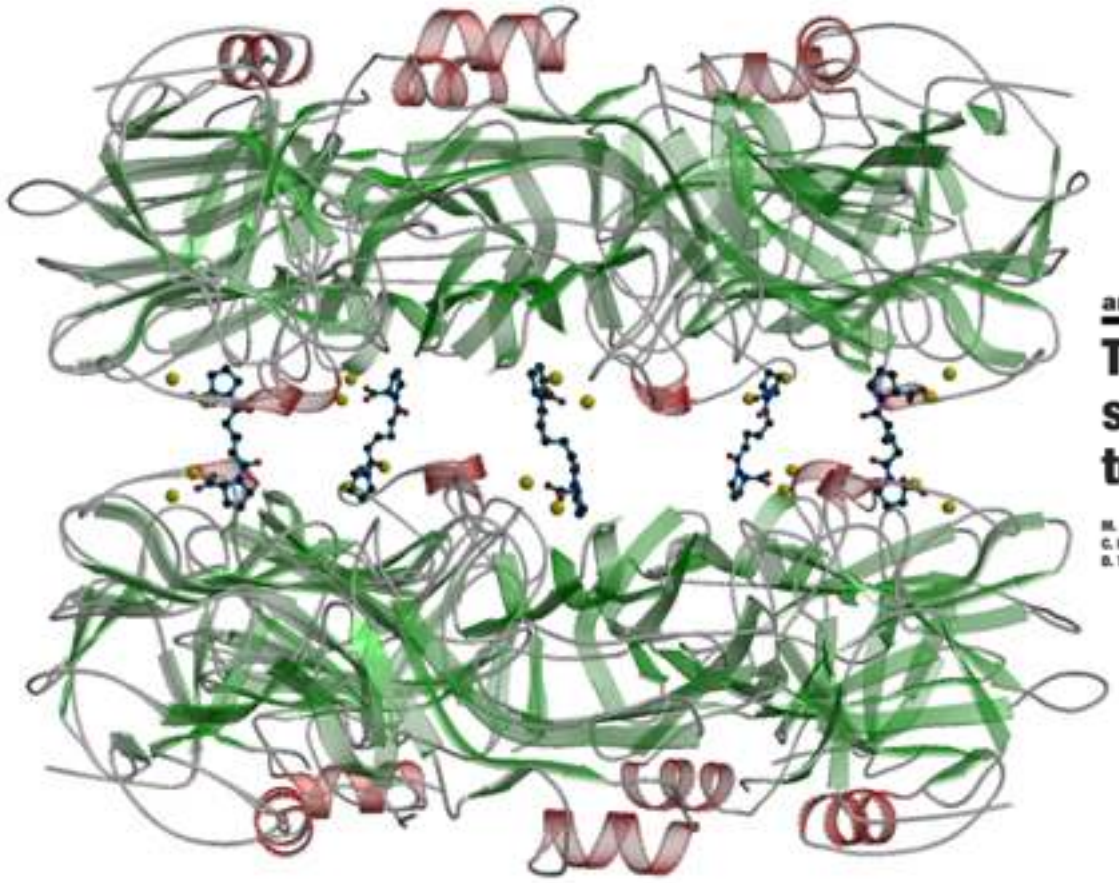
Hind *et al,* Specific chemical dissociation of fibrillar and non-fibrillar components of amyloid deposits. *Lancet*, 1984, **2**(8399):376-8

1995-2000

CPHPC



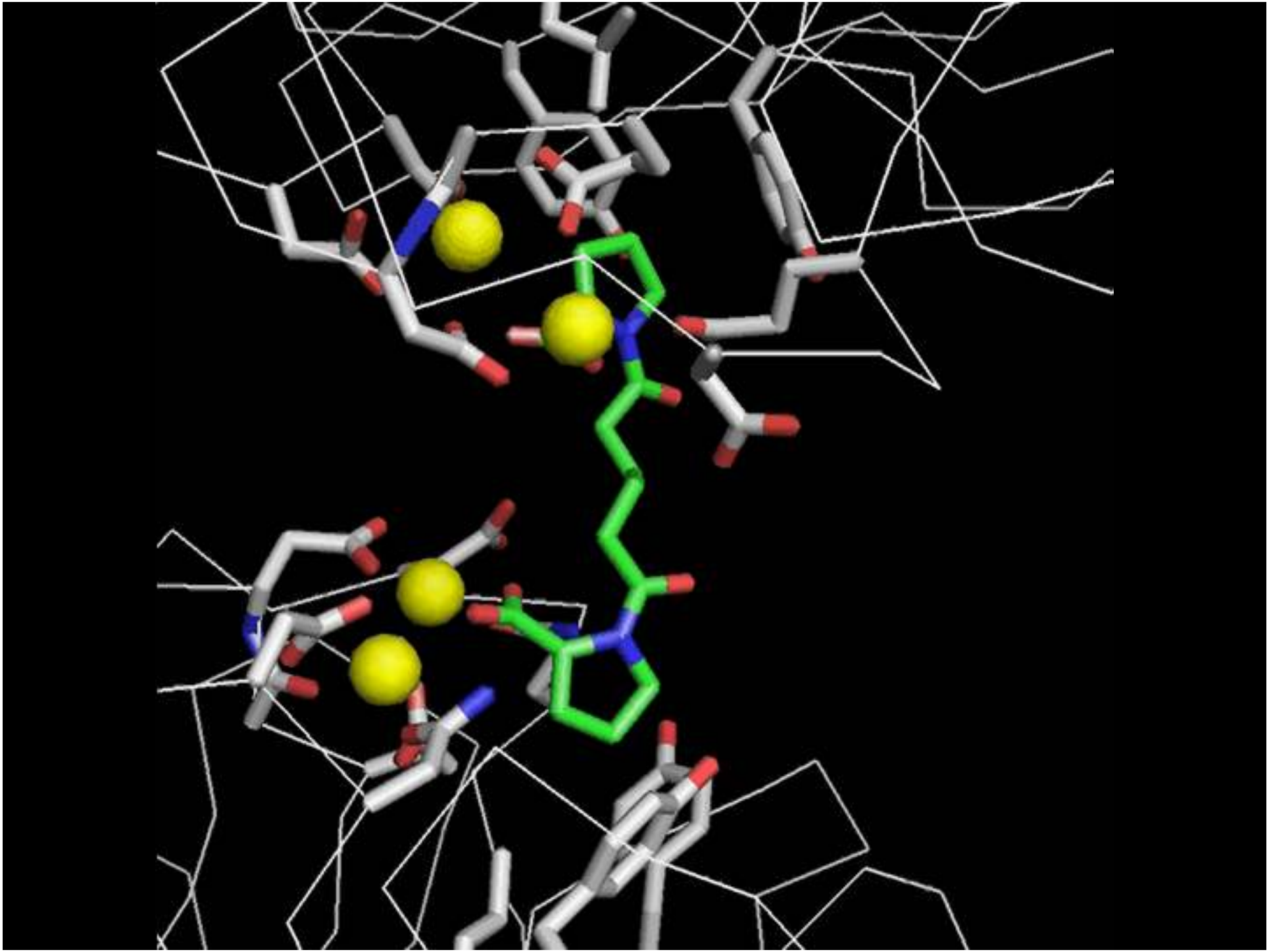
K_d 10 nM



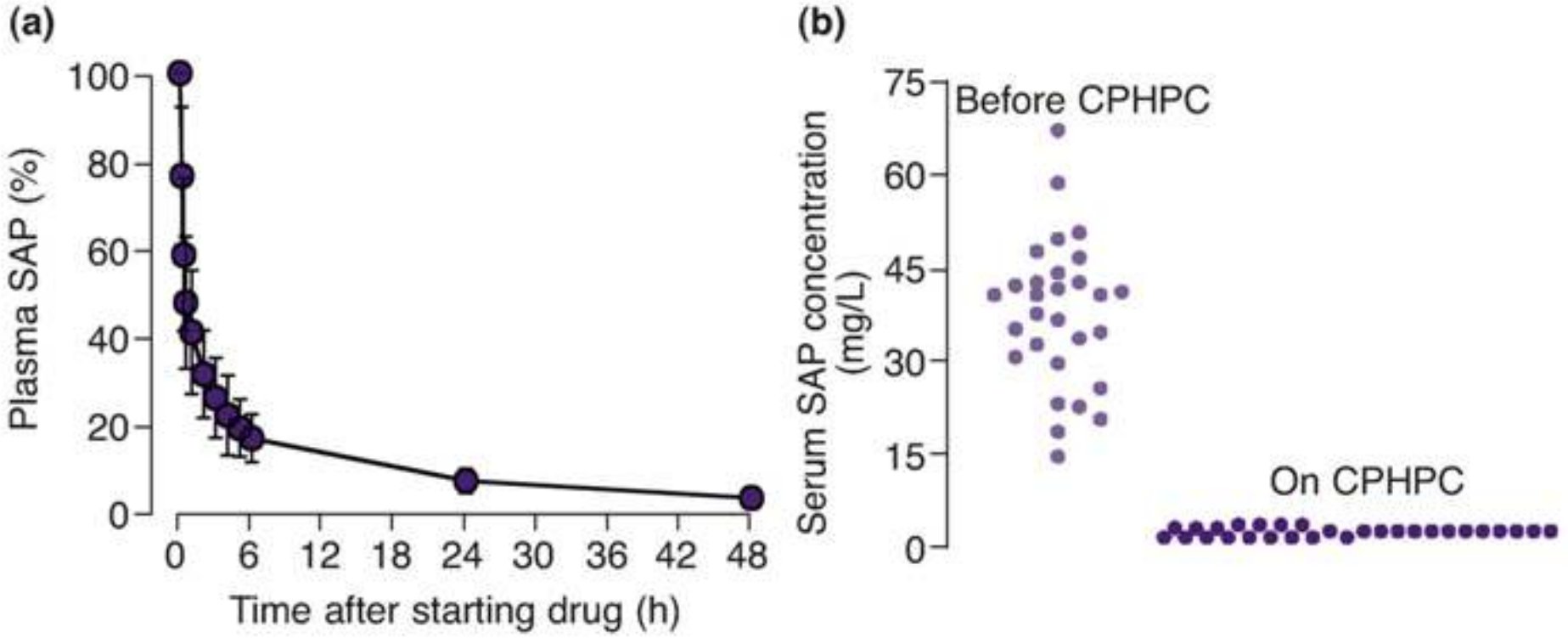
articles

Targeted pharmacological depletion of serum amyloid P component for treatment of human amyloidosis

M. B. Pepys*, J. Herbert*, W. L. Hutchinson*, G. A. Tennent*, H. J. Lachmann*, J. R. Gallimore*, L. B. Lovat*, T. Bartfai*†, A. Alanine†, C. Hertel†, T. Hoffmann*, R. Jakob-Roetne†, R. D. Norcross†, J. A. Kemp†, K. Yamamura†, M. Suzuki†, G. W. Taylor†, S. Murray†, D. Thompson†, A. Purvis†, S. Kolstoe†, S. P. Wood†‡ & P. N. Hawkins*



Effect of CPHPC on plasma SAP



Clinical study of CPHPC in systemic amyloidosis (2001-4)

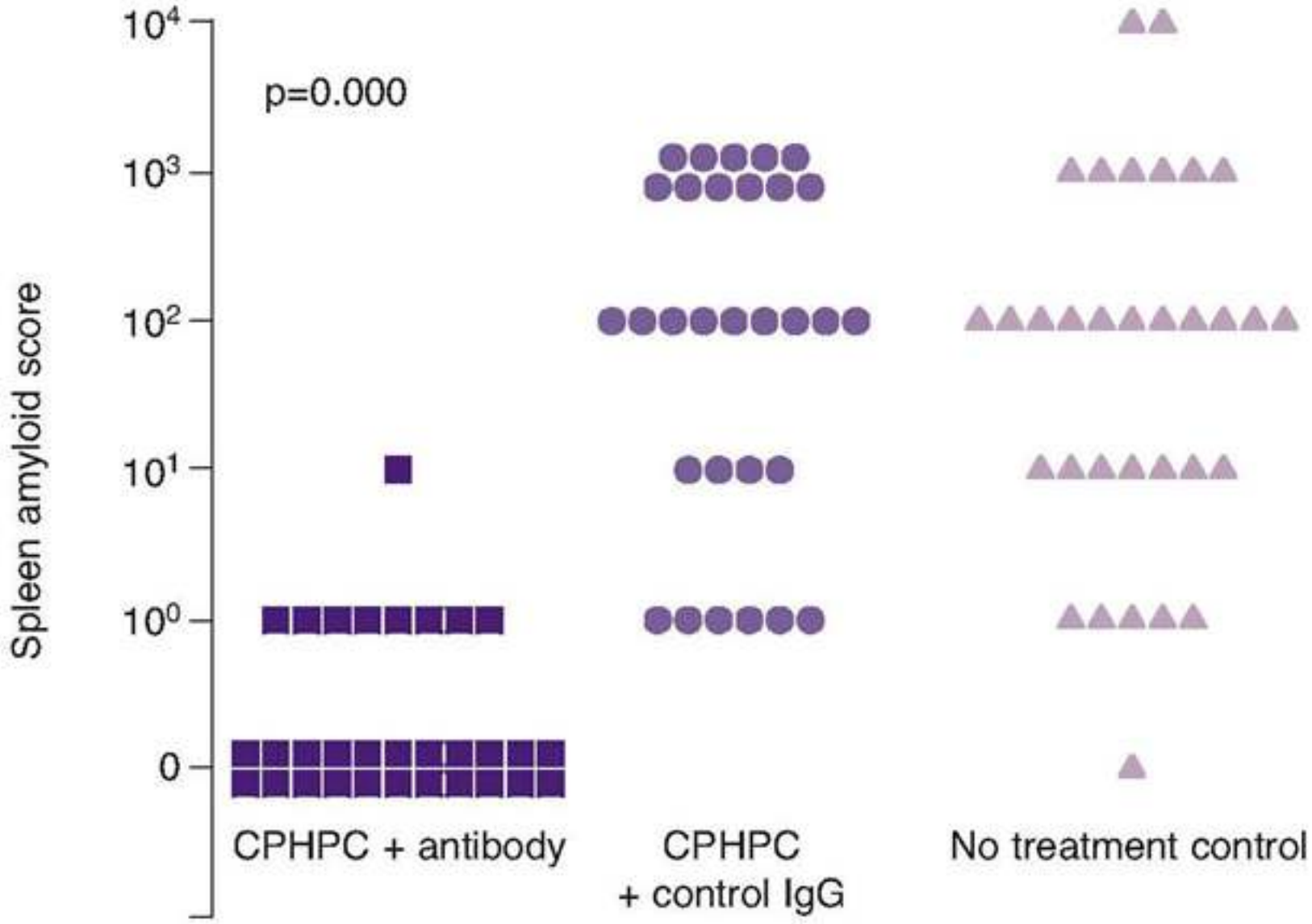
- No adverse clinical effects in 31 patients, >45 patient years
- Plasma SAP depleted throughout; ~90% of SAP removed from amyloid
- No laboratory test or organ function abnormalities attributable to CPHPC or persistent SAP depletion in >5 yrs
- No new amyloid accumulation, most patients remain stable but no amyloid regression

Gillmore *et al. Br. J. Haematol*, 2010, **148**: 760-767

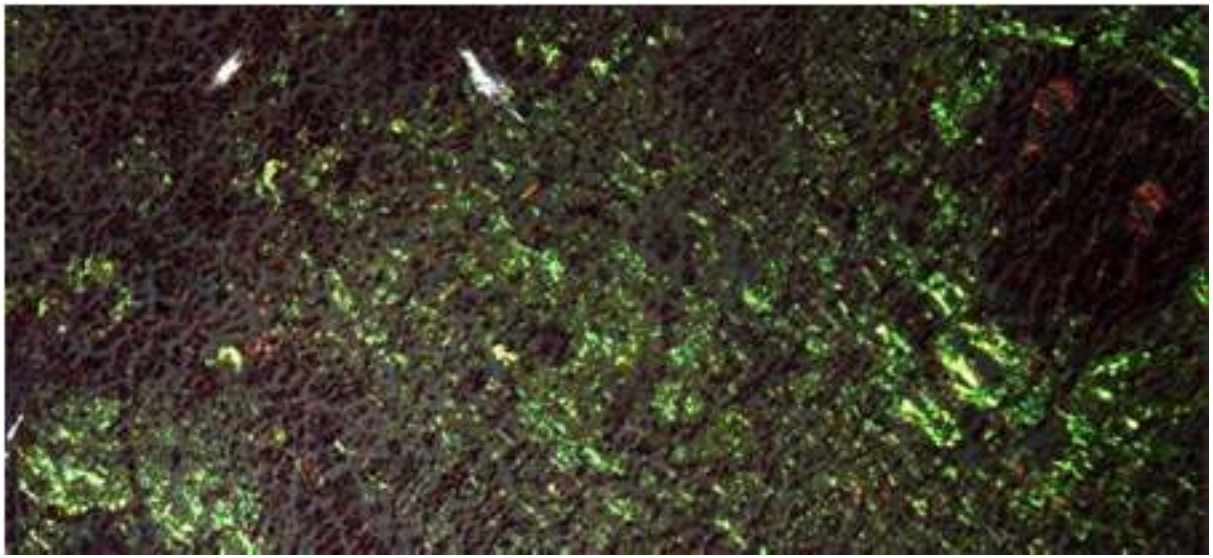
Curing amyloidosis in mice (2005-8)

- Human SAP transgenic C57BL/6 mice with AA amyloidosis
- CPHPC clears SAP from plasma but leaves some SAP in amyloid
- Antibodies to SAP can reach the amyloid
- Amyloid deposits disappear!

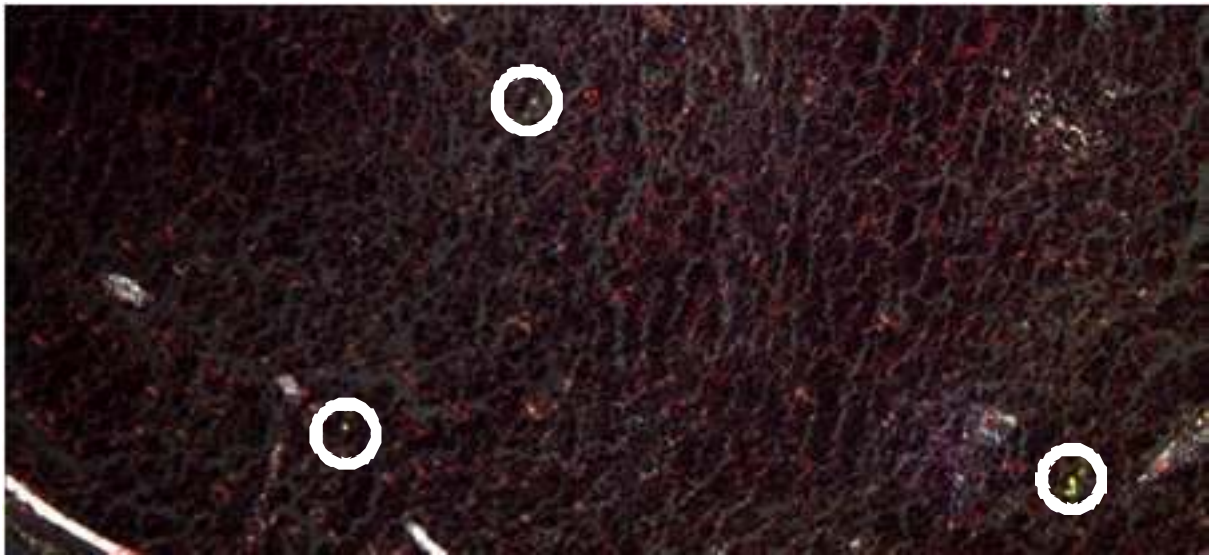
Bodin *et al*. *Nature* 2010, **468**: 93-97


Spleen amyloid score
10^4
10^3
10^2
10^1
10^0
0
p=0.000
CPHPC + antibody
CPHPC
+ control IgG
No treatment control

Day 28 post antibody

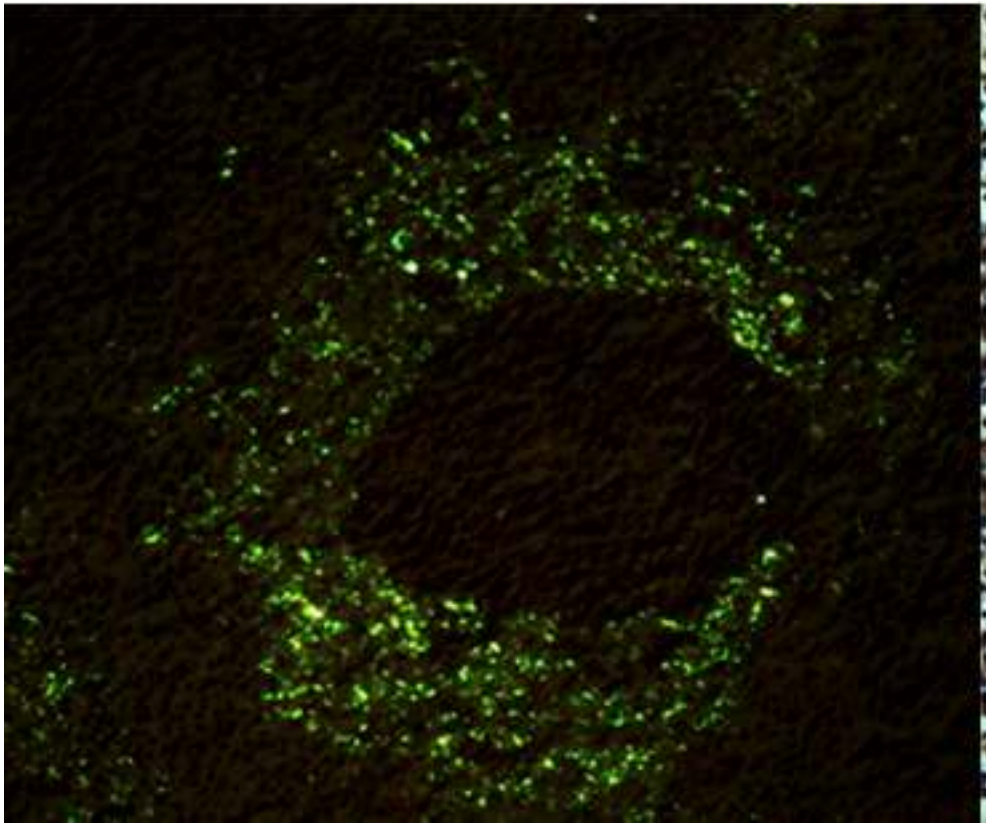


Control IgG

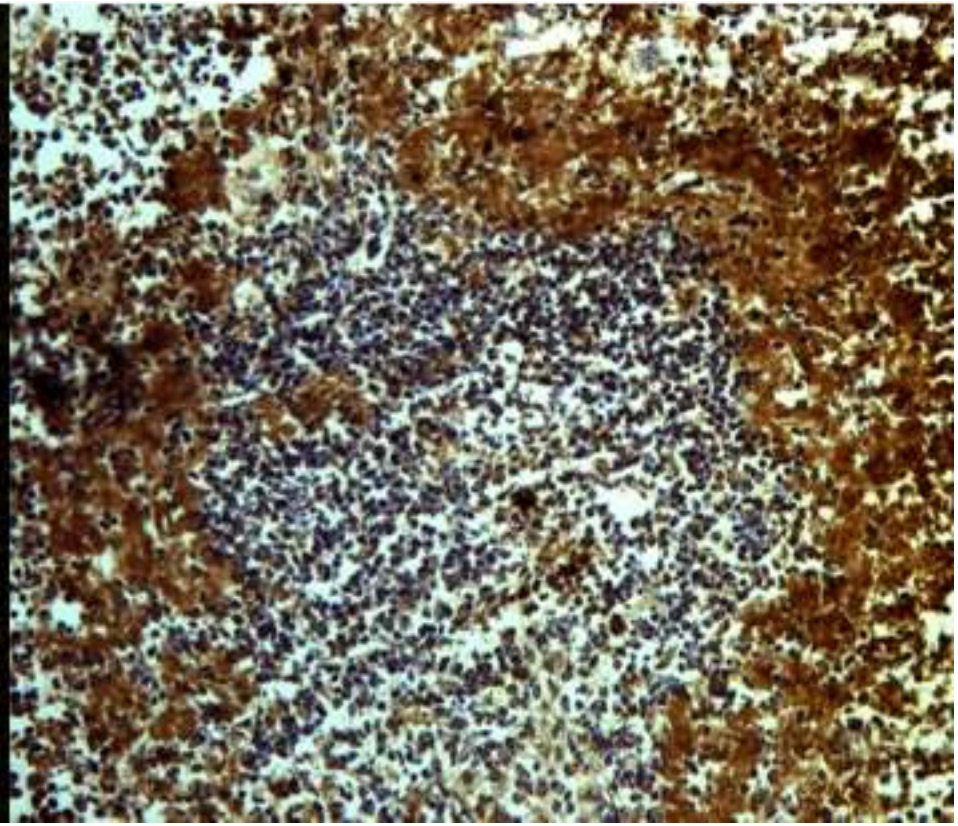


Anti-SAP antibody

Day 1 post antibody

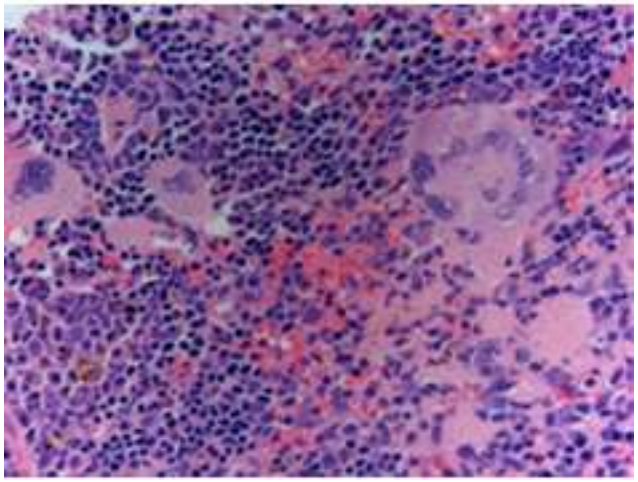


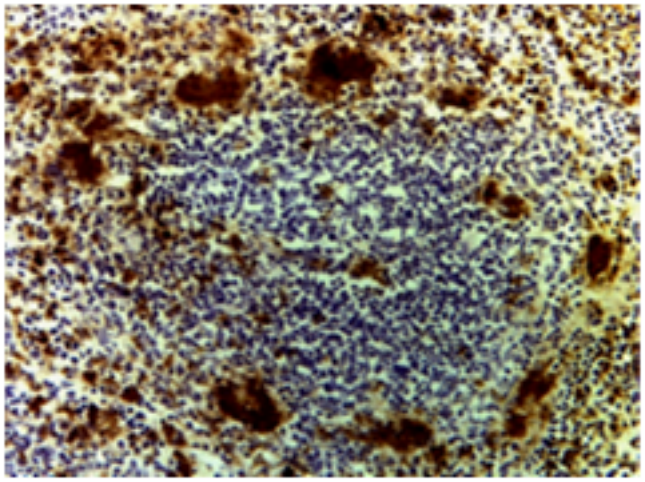
Congo red

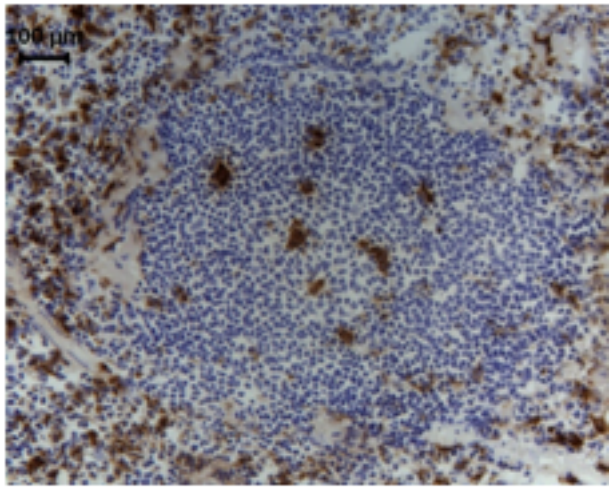


F4/80

Day 4 post antibody





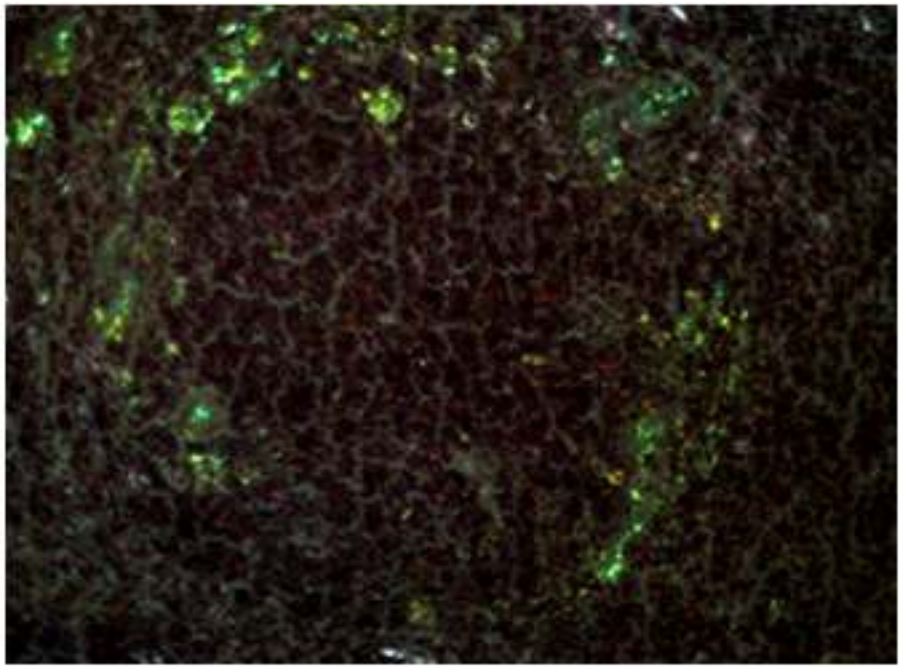


H & E

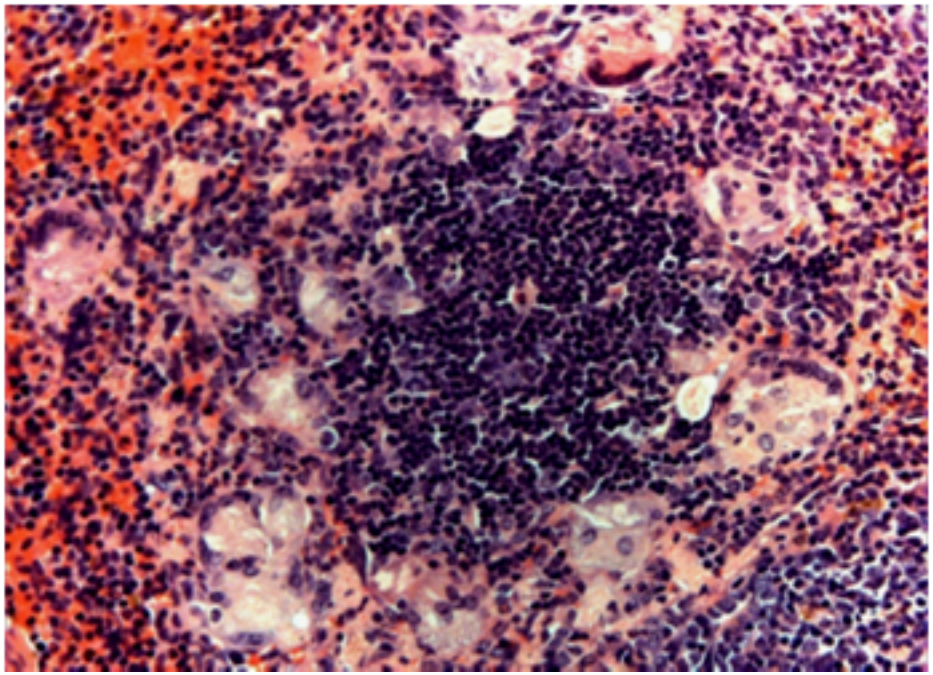
CD68

control CD68

Day 4 post antibody

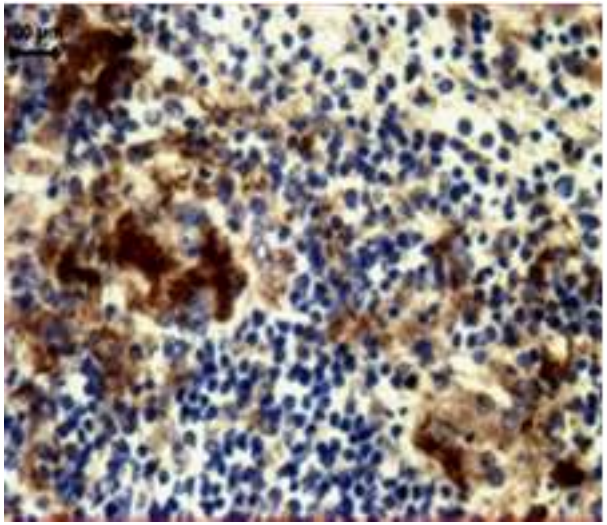


Congo red

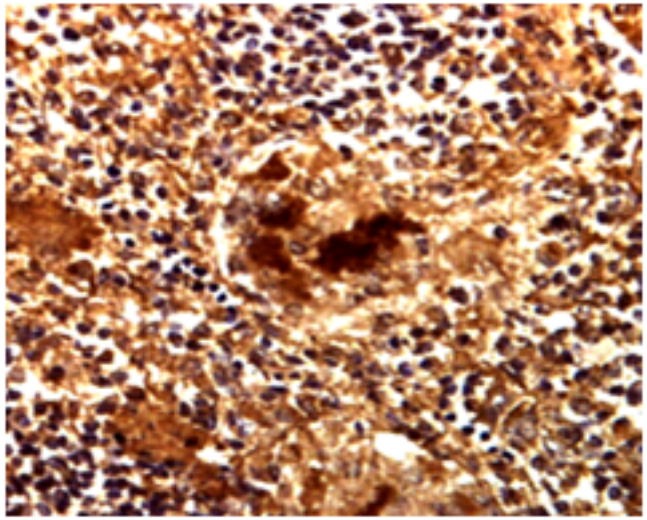


H & E

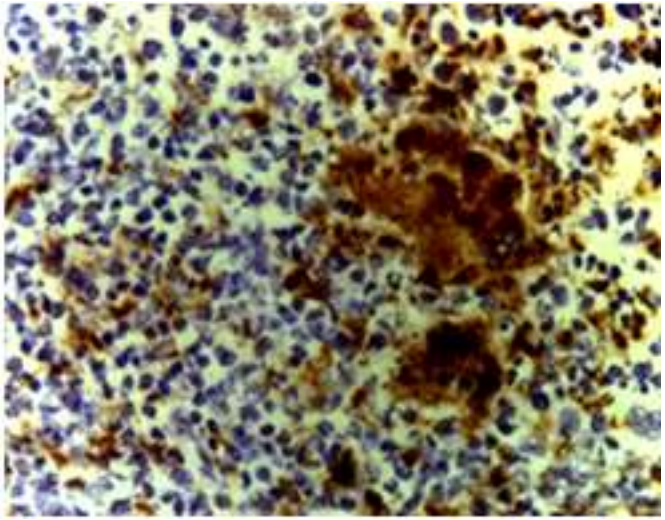
Day 4 post antibody



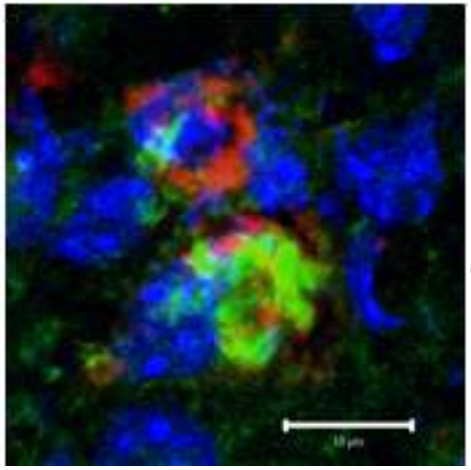
SAA



C3

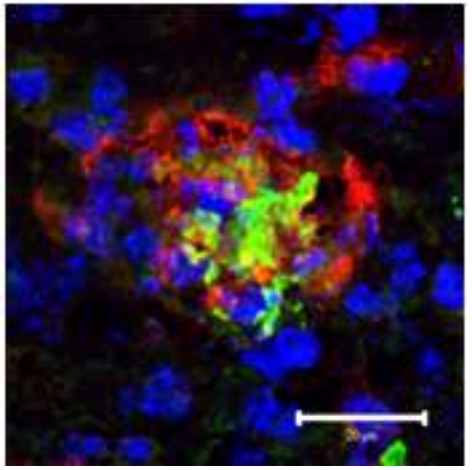


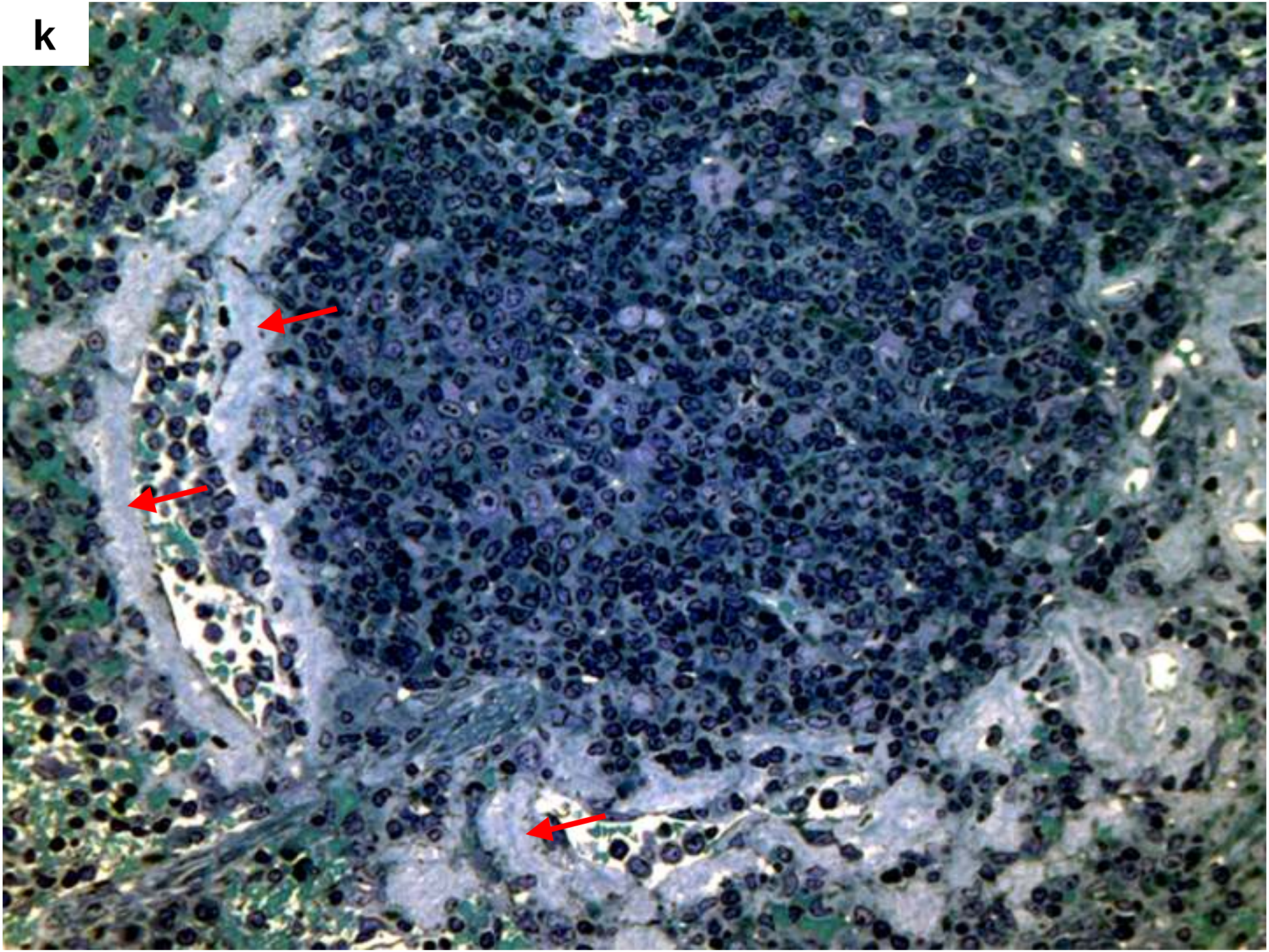
CD68



SAA green

CD68 red

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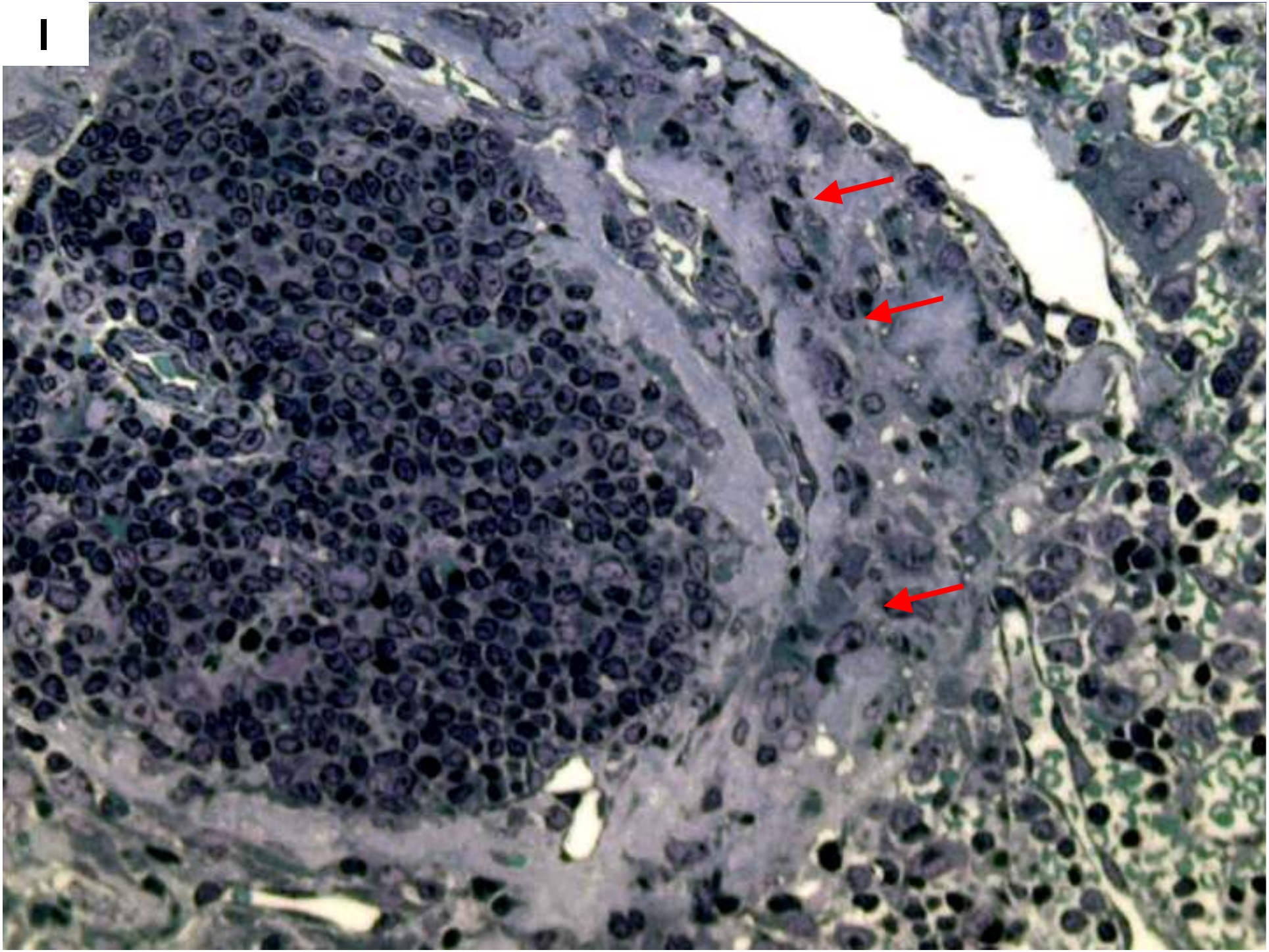

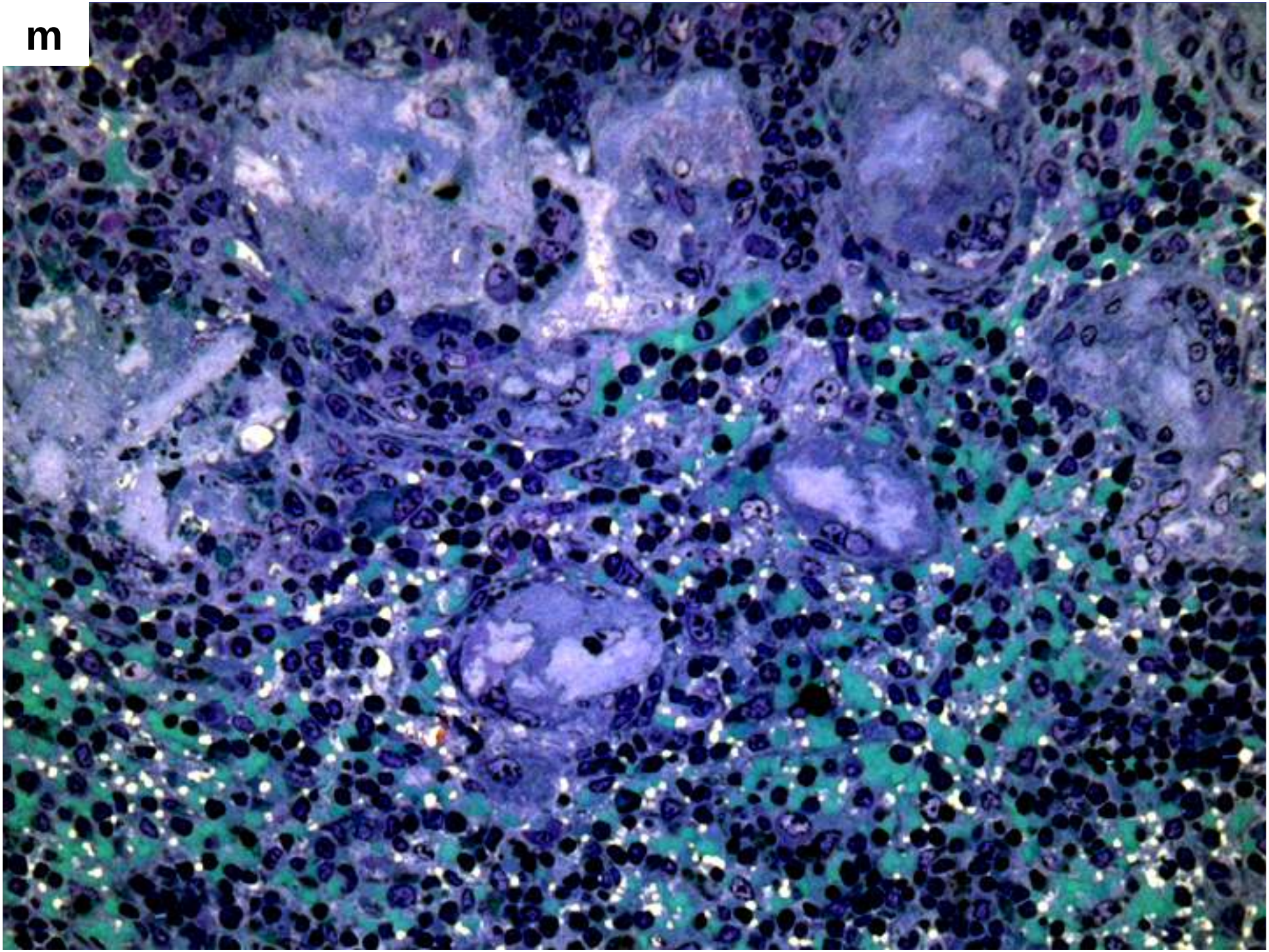
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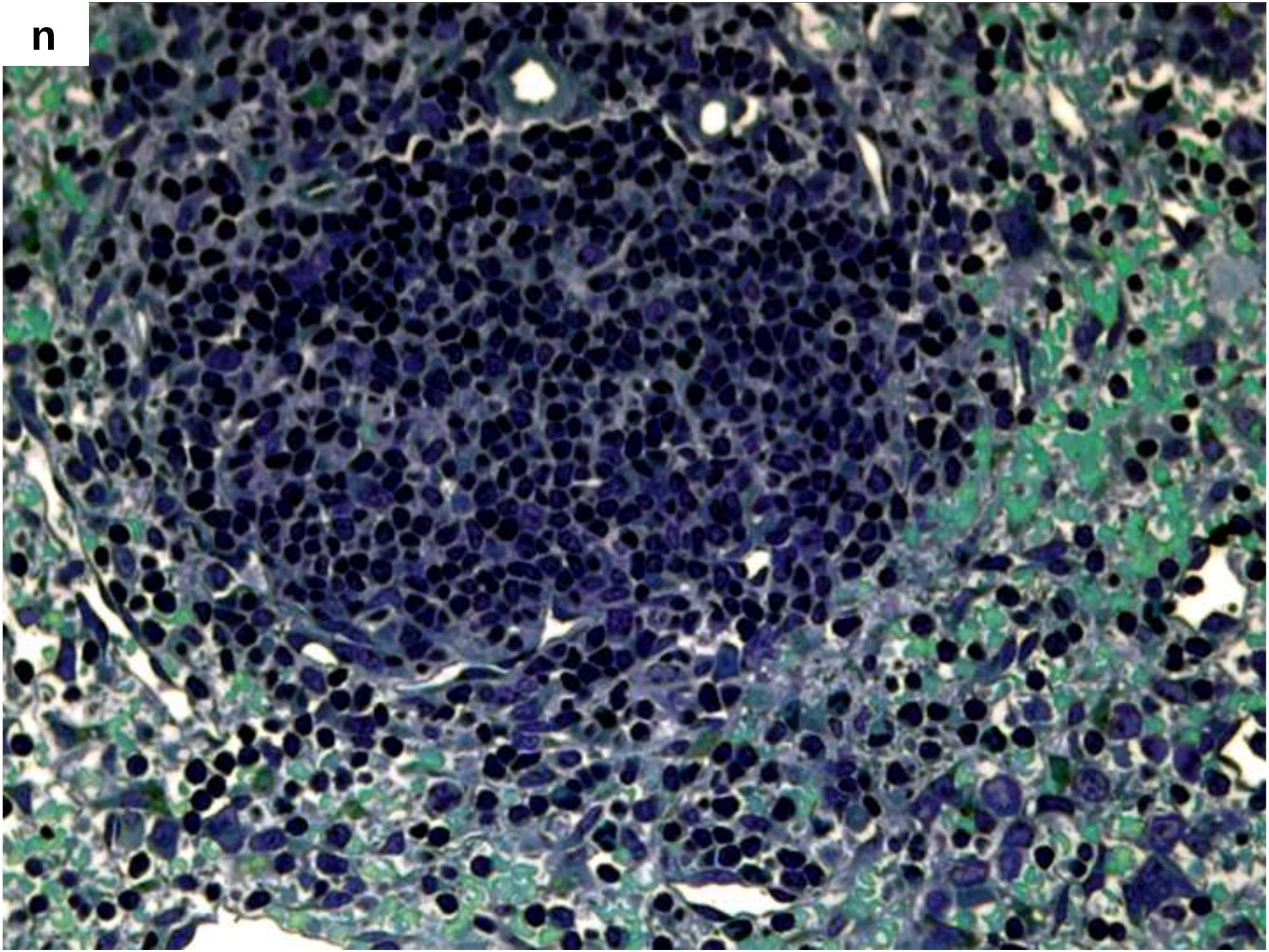
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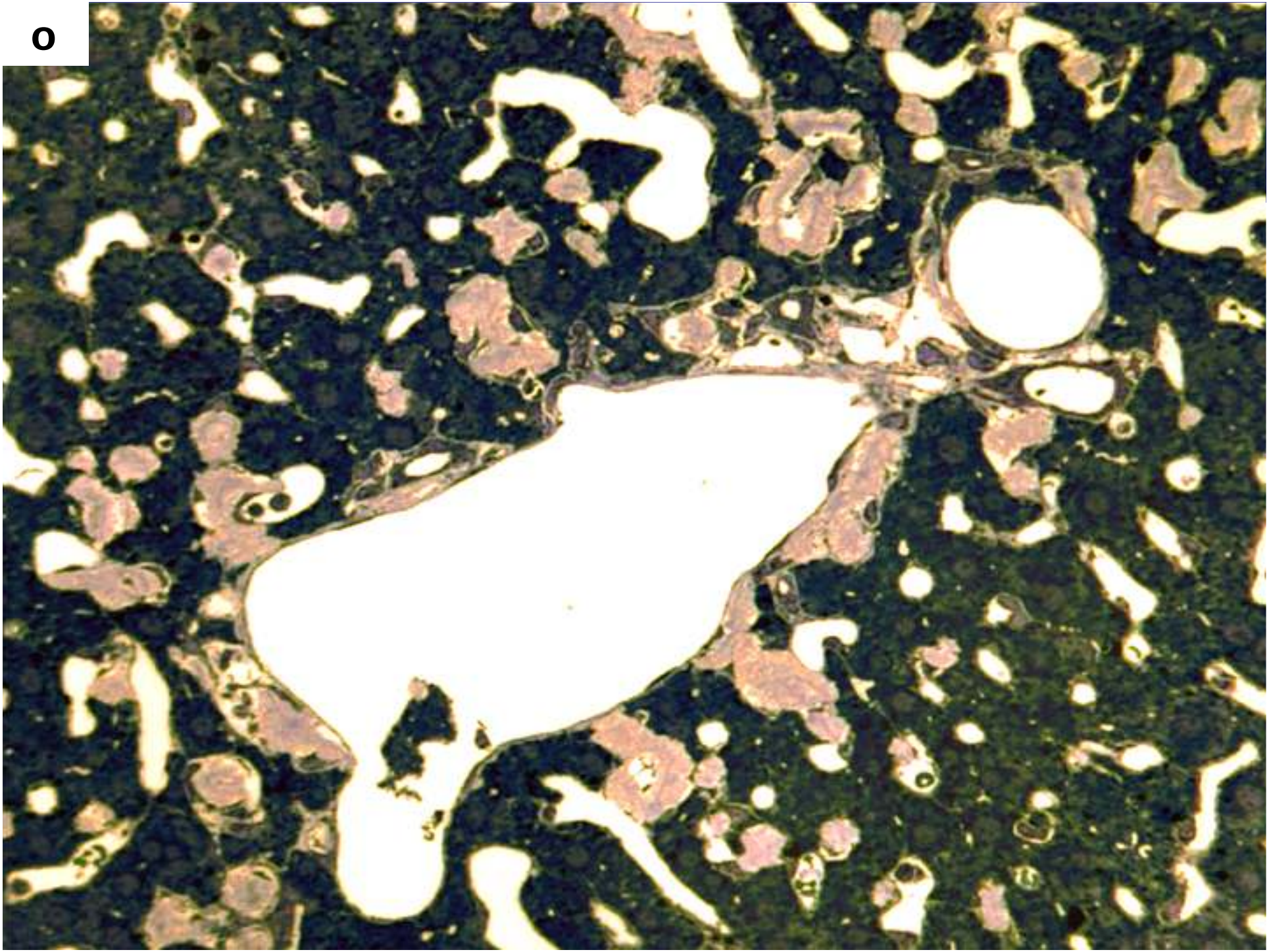

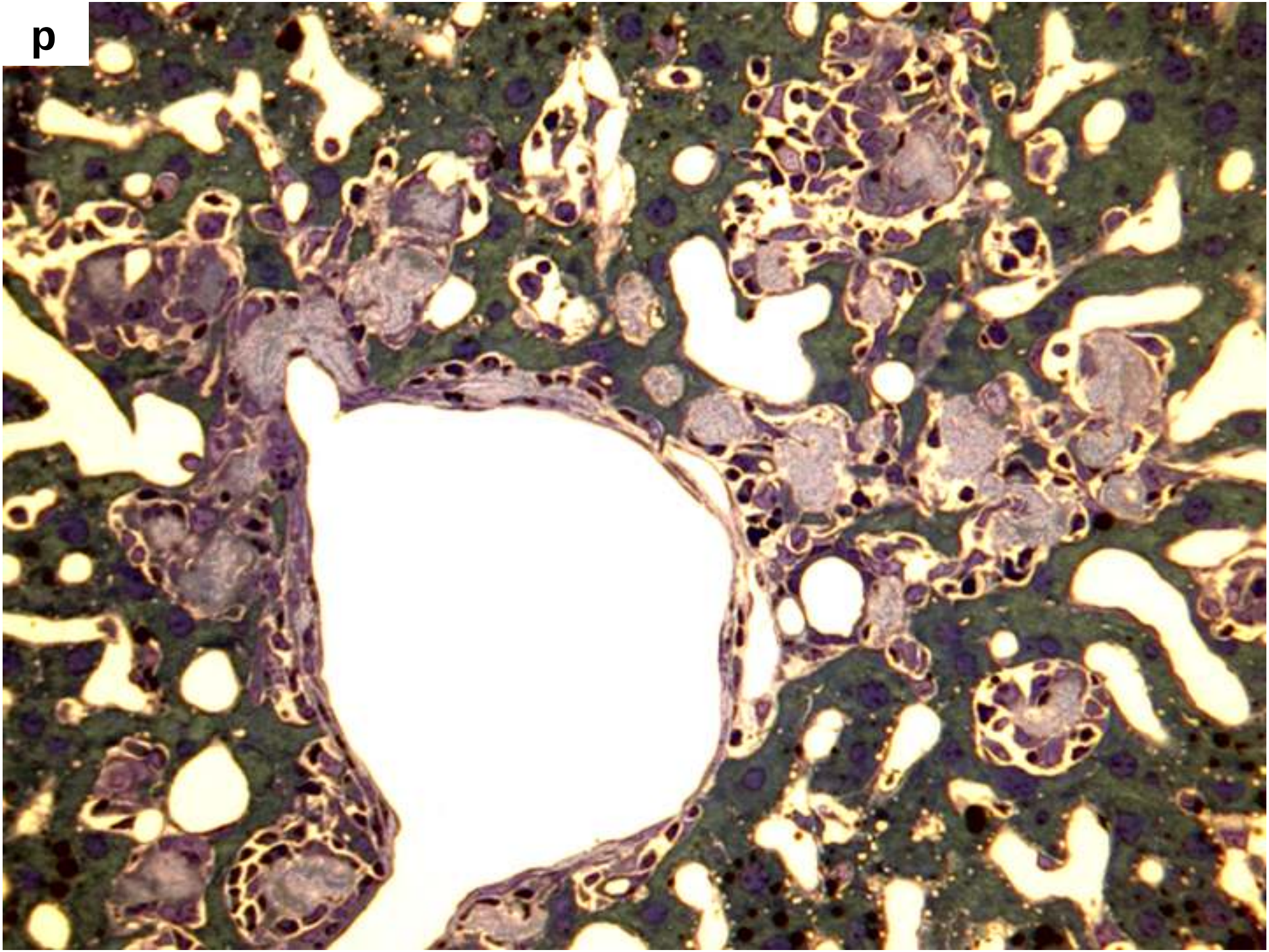
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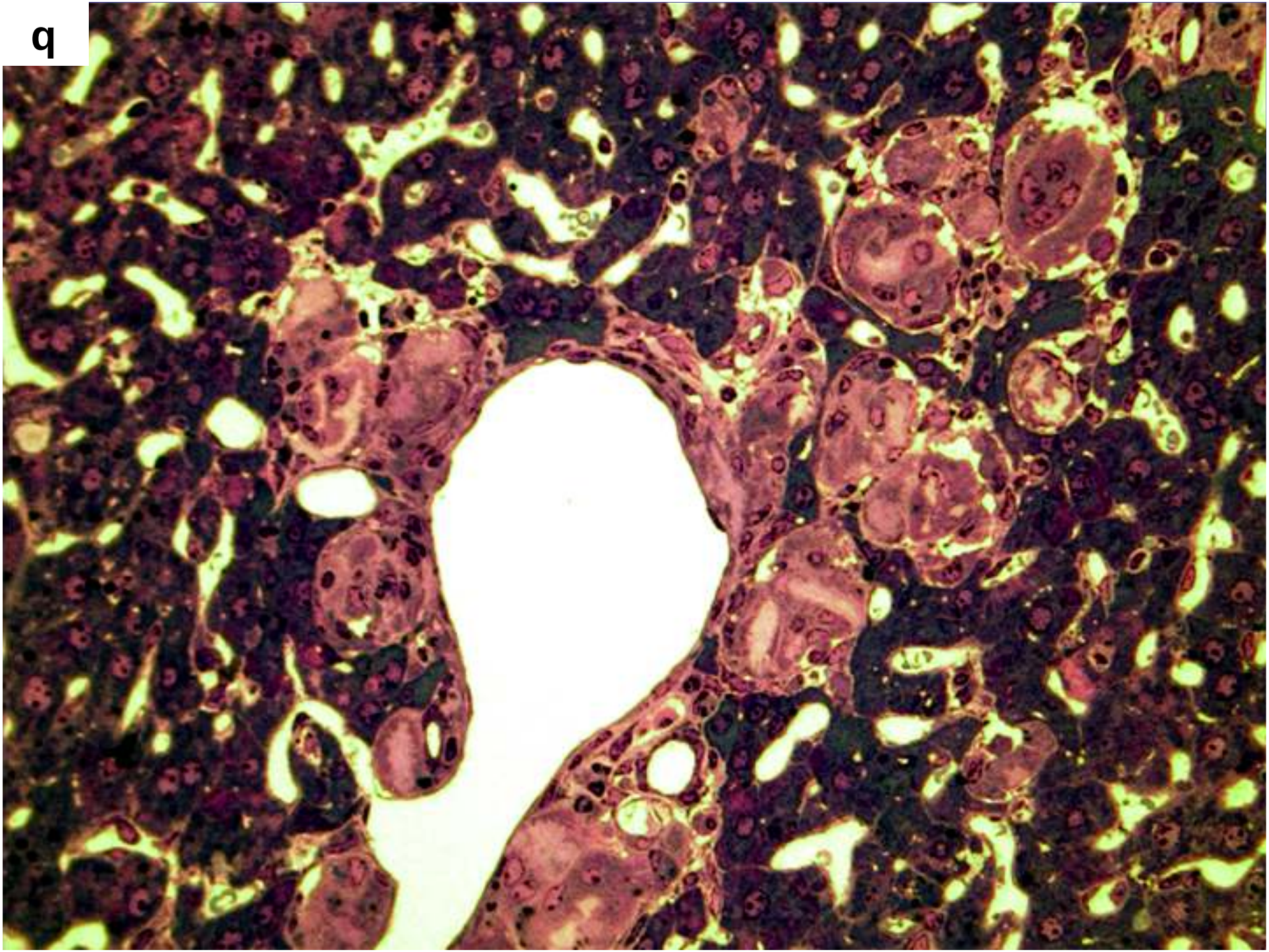

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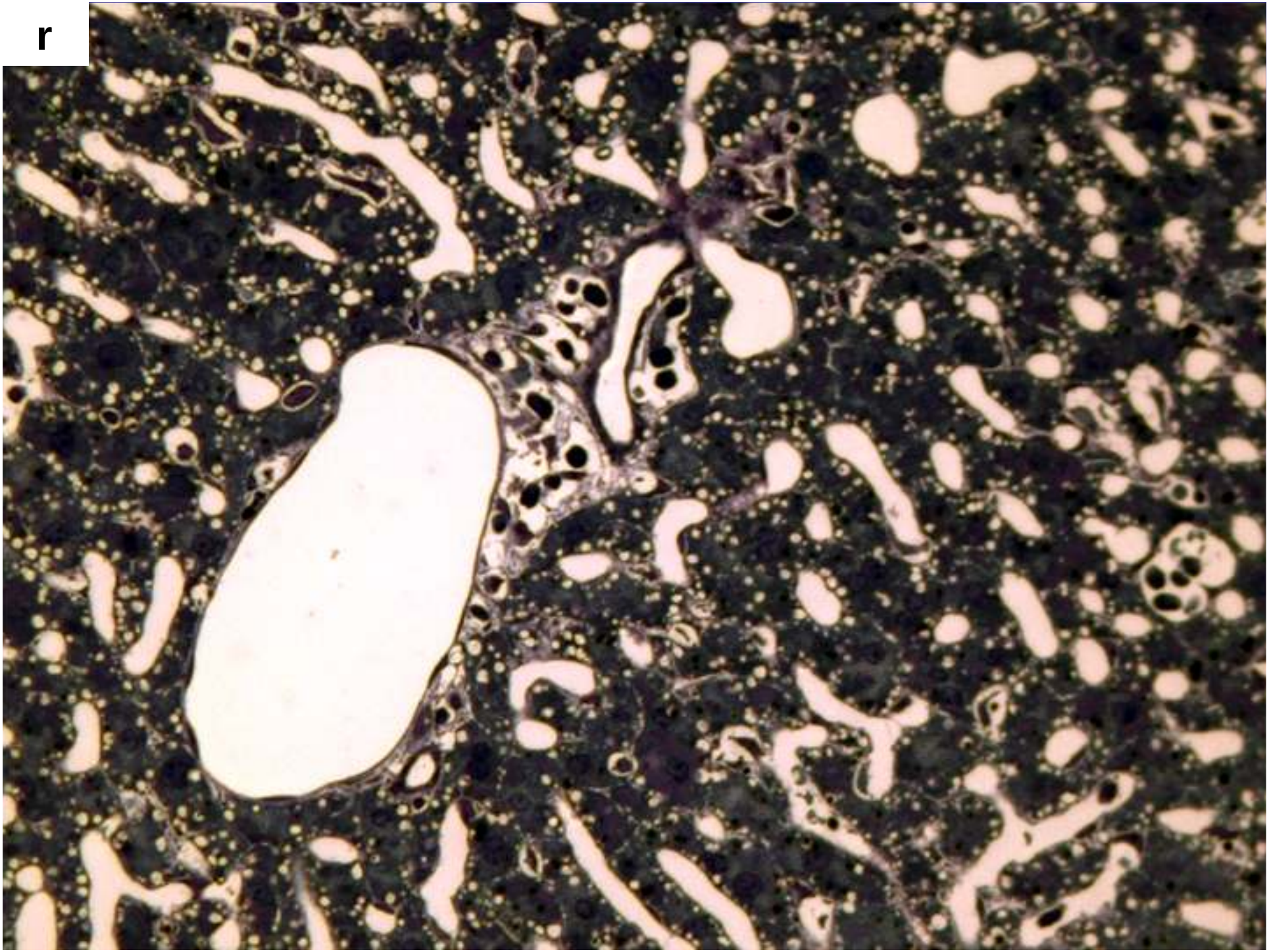
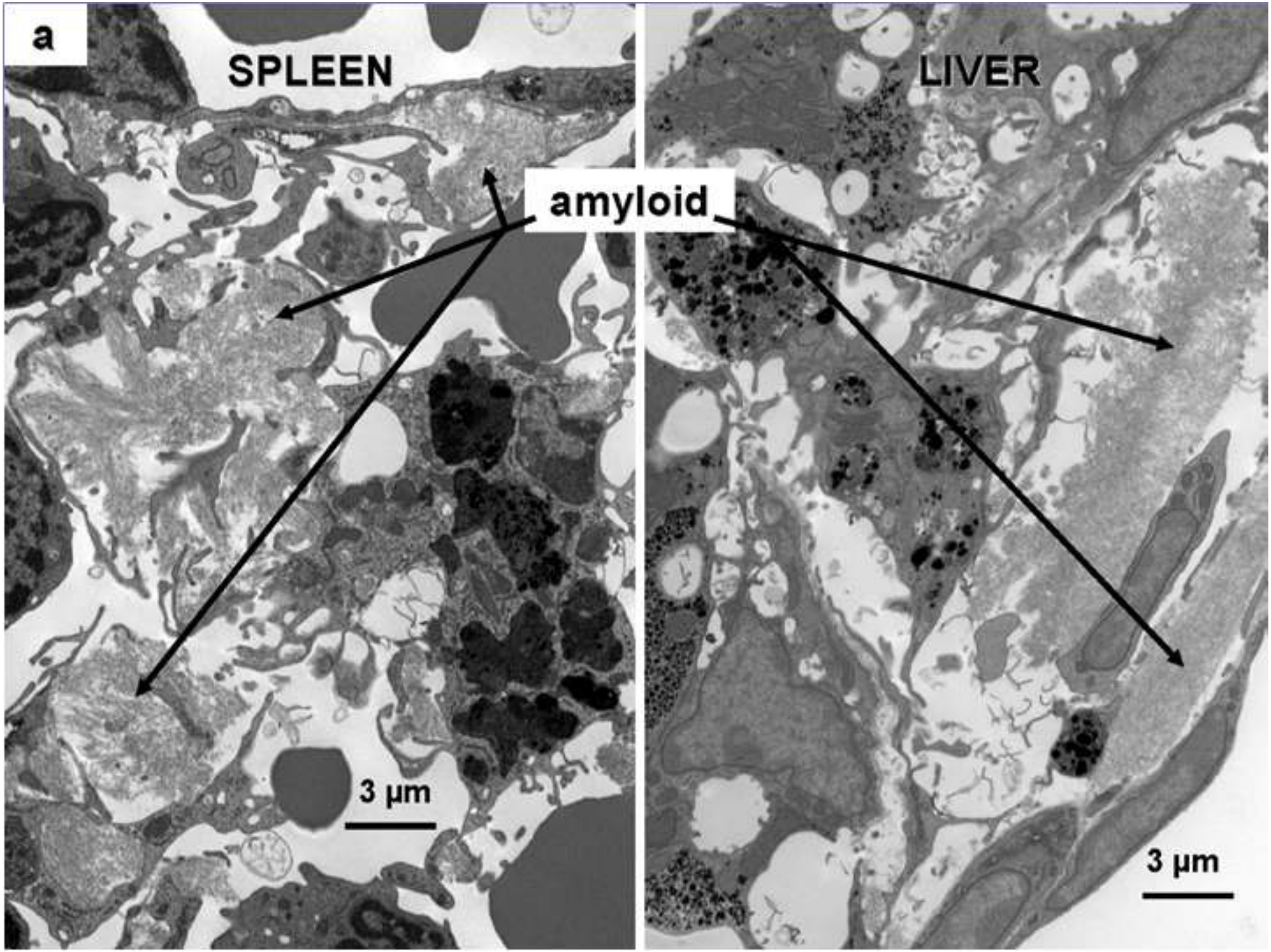
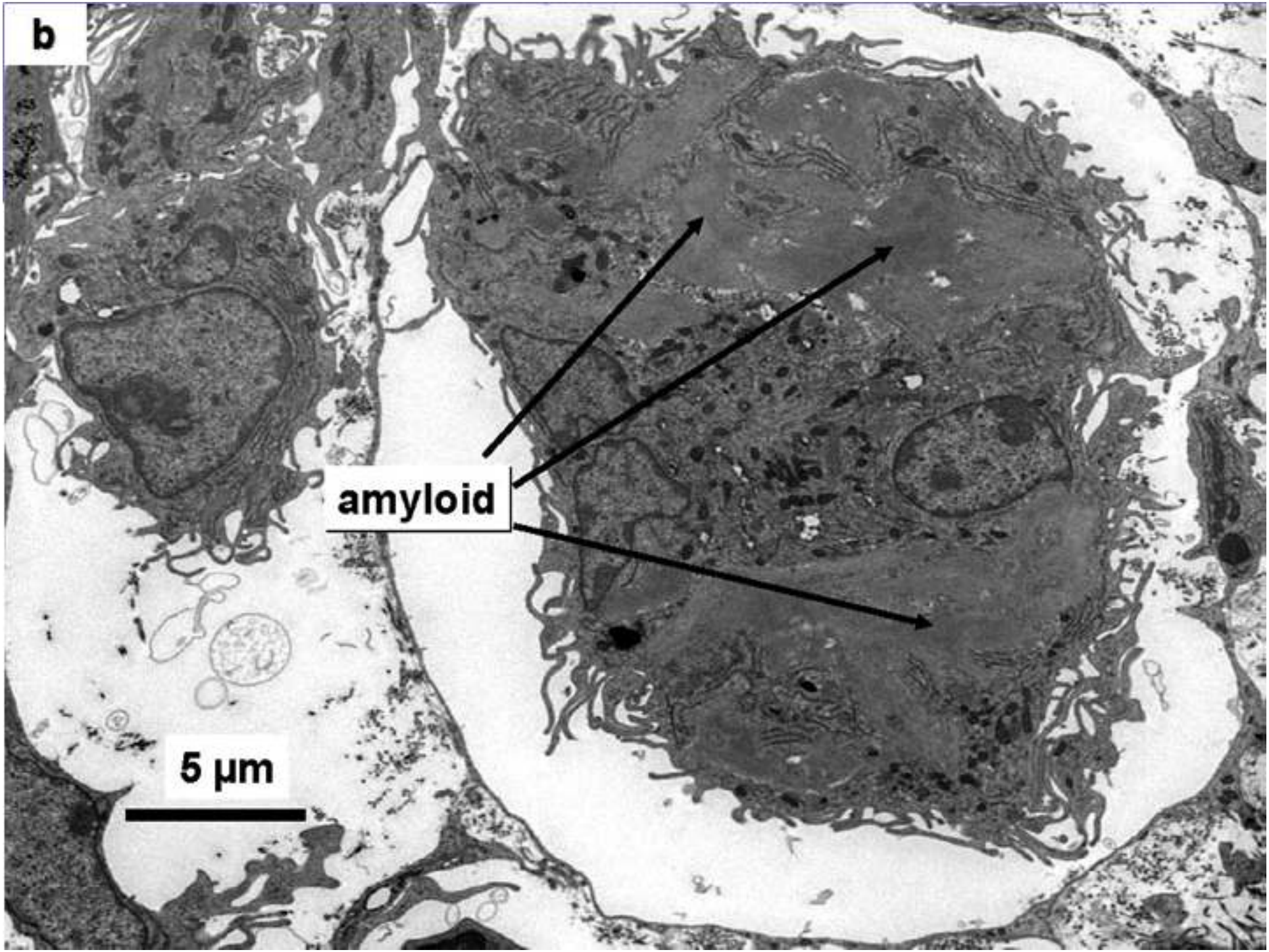
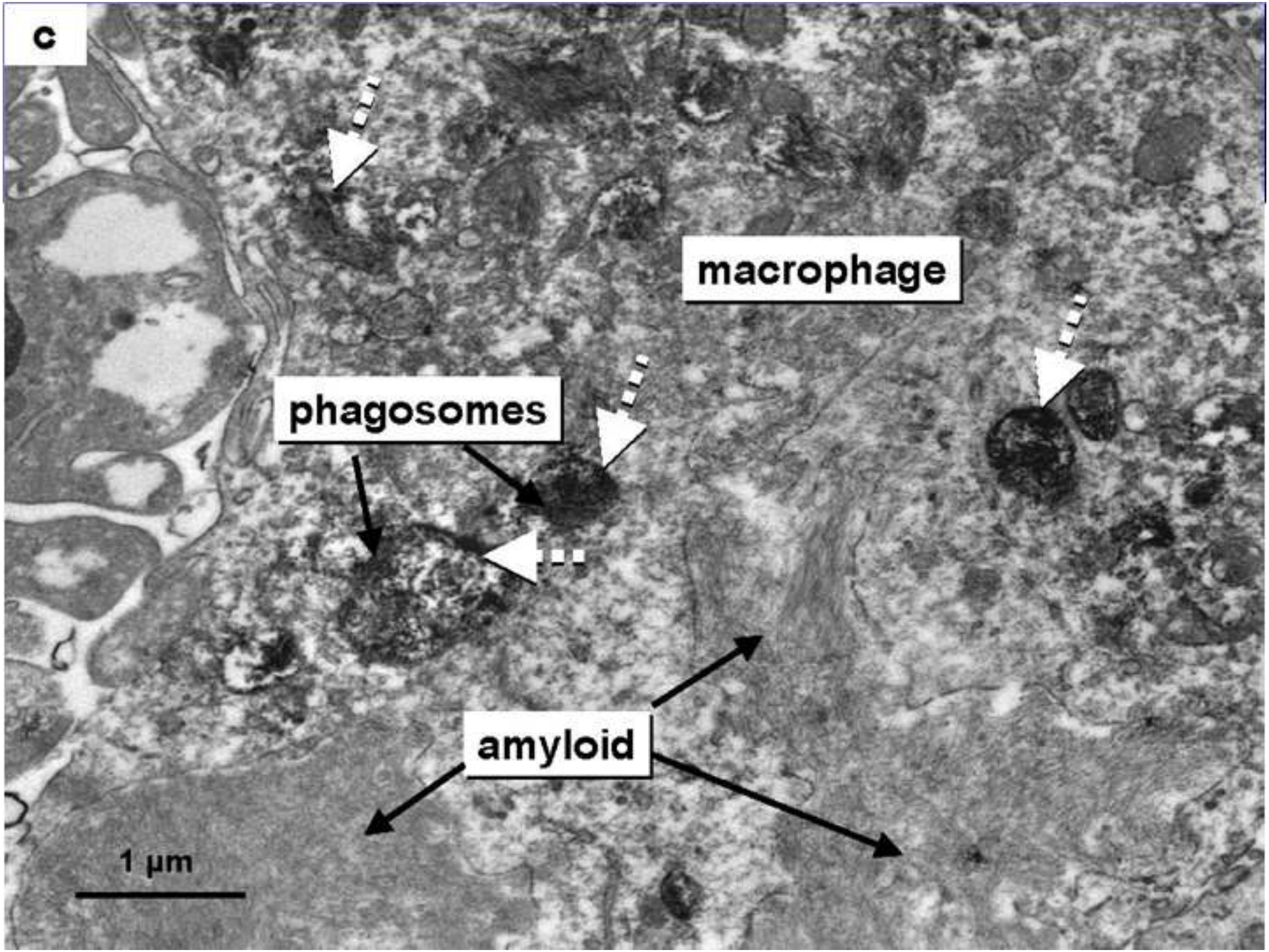



a
SPLEEN
LIVER
amyloid
3 µm
3 µm


b
amyloid
5 µm


c
macrophage
phagosomes
amyloid
1 µm

Elimination of amyloid deposits

- CPHPC depletes circulating SAP but leaves some SAP in amyloid
- Anti-SAP abs then safely target deposits
- Antibody binding triggers complement and macrophage dependent clearance of amyloid
- Clinical development with GSK for FITH trials in systemic amyloidosis
- Potential use in all amyloid-associated diseases

Therapeutic elimination of amyloid deposits is possible

- In mice with AA amyloidosis so far
- Fully humanised monoclonal anti-SAP antibody
- First human studies are coming

- Acknowledgements: Patients and NHS NAC, colleagues and collaborators, UK Medical Research Council, The Wolfson Foundation, The Wellcome Trust, UCL Amyloidosis Research Fund, GlaxoSmithKline