CPHPC plus anti-SAP antibody: a first in class small molecule/antibody combination to eliminate systemic amyloid deposits

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UCL Pentraxin Royal Free Hampstead NHS

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

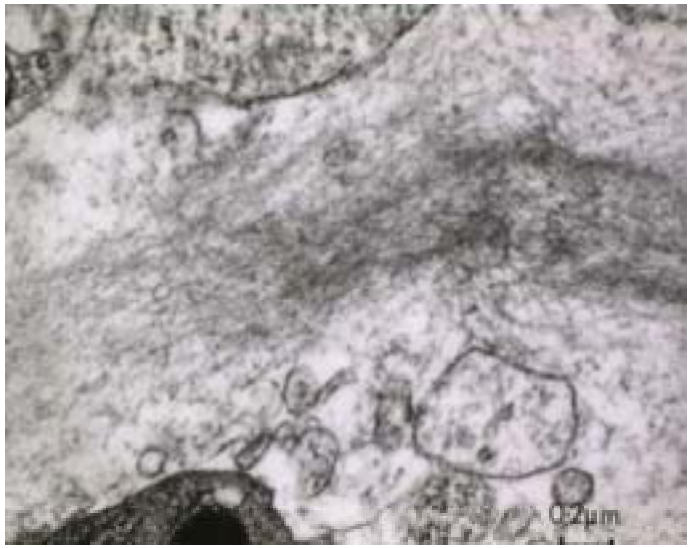
- Transmissible spongiform encephalopathies
- Other protein aggregation diseases (PD, HD, serpinopathies, etc): NOT amyloid

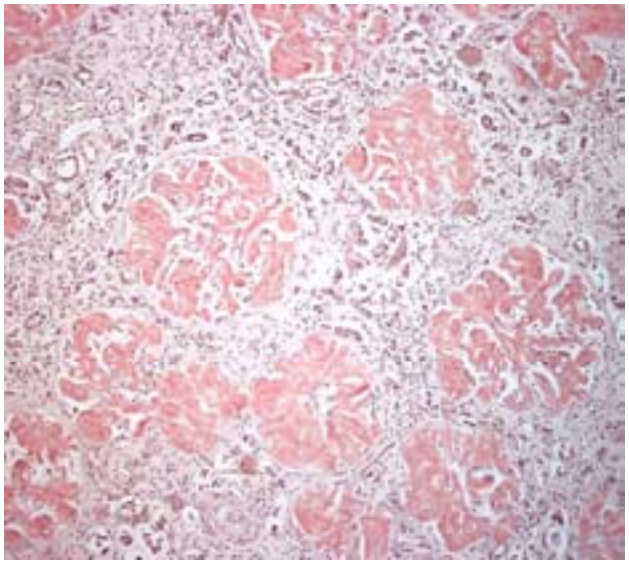
Progress in amyloidosis 1976-2011

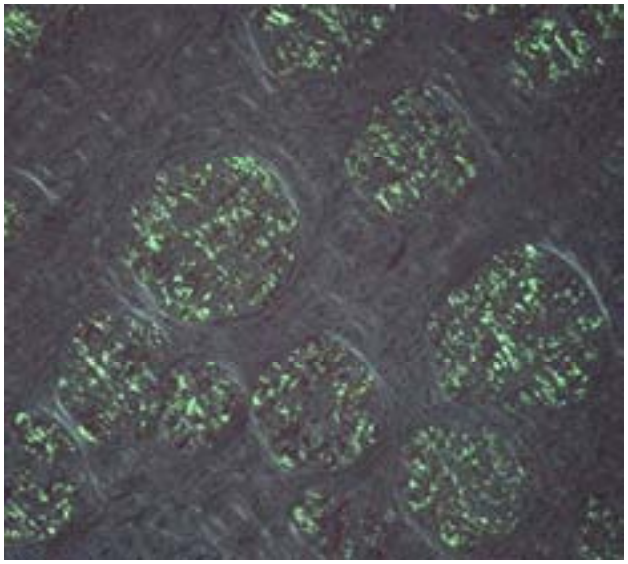
- Better diagnosis but usually still very late
- Better retention & replacement of organ function but often not sufficient
- Much better control of precursor protein abundance but often difficult & dangerous
- Better survival but systemic amyloidosis still usually fatal

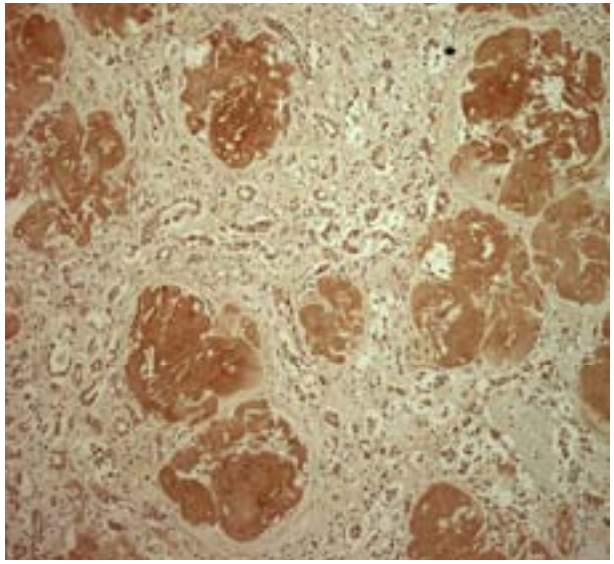
Amyloid deposits

- 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

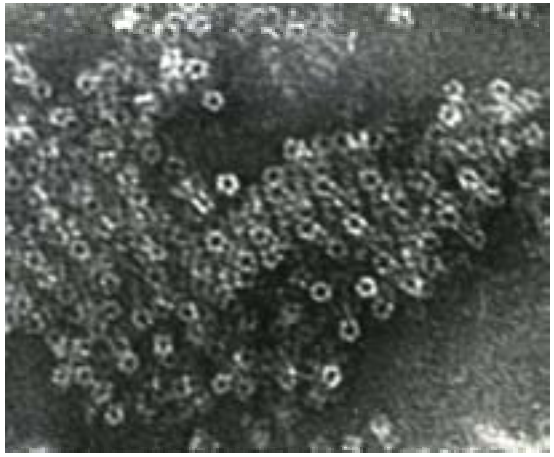
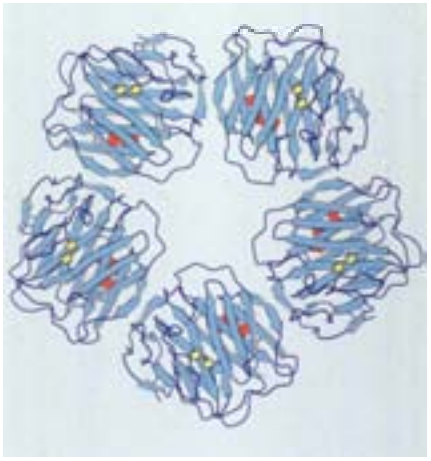
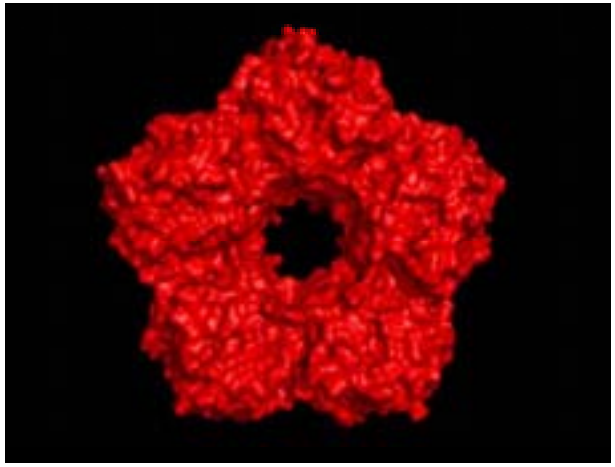
- Persistent production of fibril precursor proteins causes accumulation
- But why is amyloid not cleared?
- Usually no local or systemic inflammatory reaction. No immunological response
- Rare macrophage & giant cell infiltration
- Amyloid deposits can regress

Pathogenesis & 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

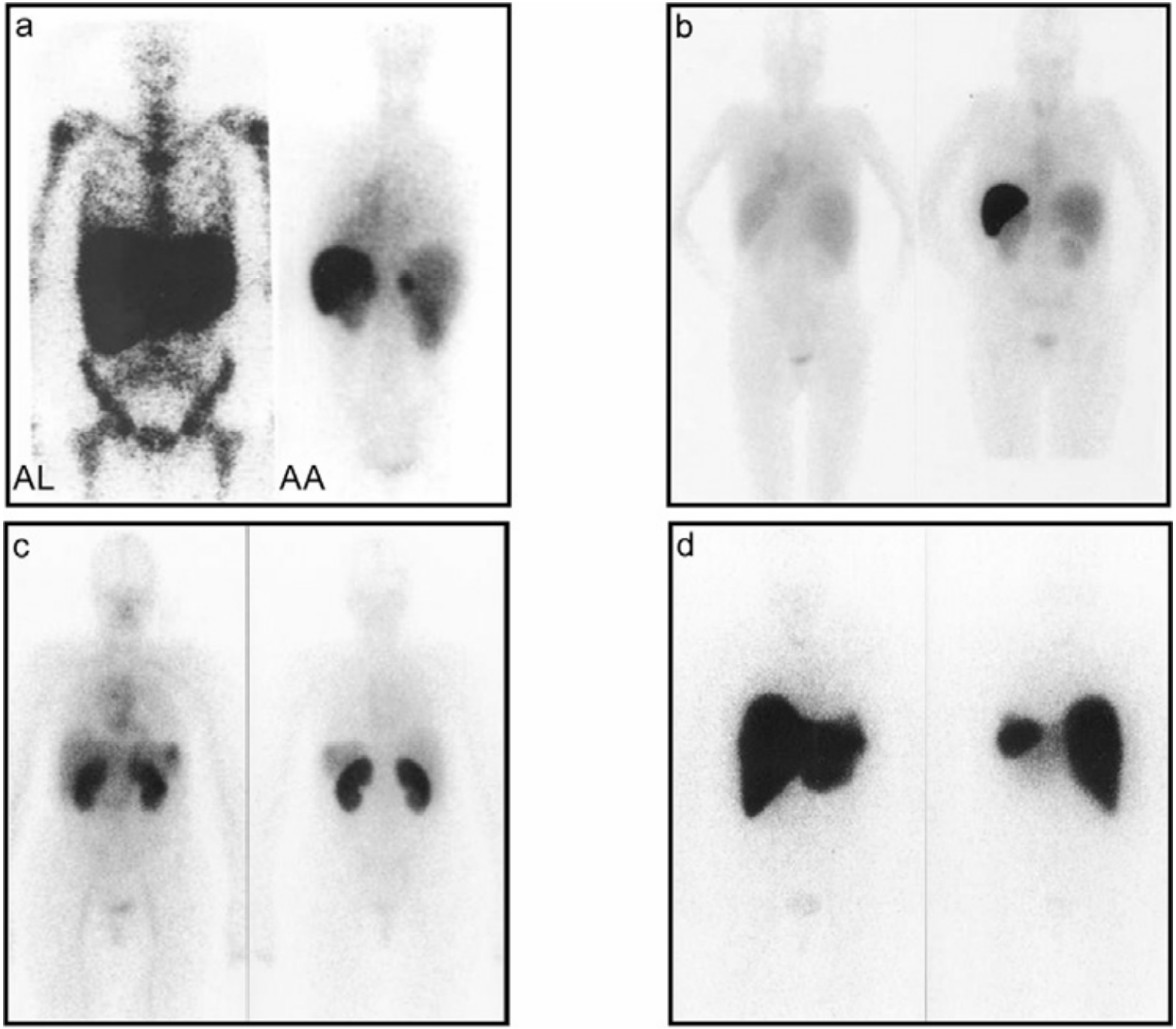
- Homopentamer, lectin fold, 20-40 mg/l in plasma, $t_{1/2}$ ~24 h, synthesized & catabolized only by hepatocytes

SAP and amyloid

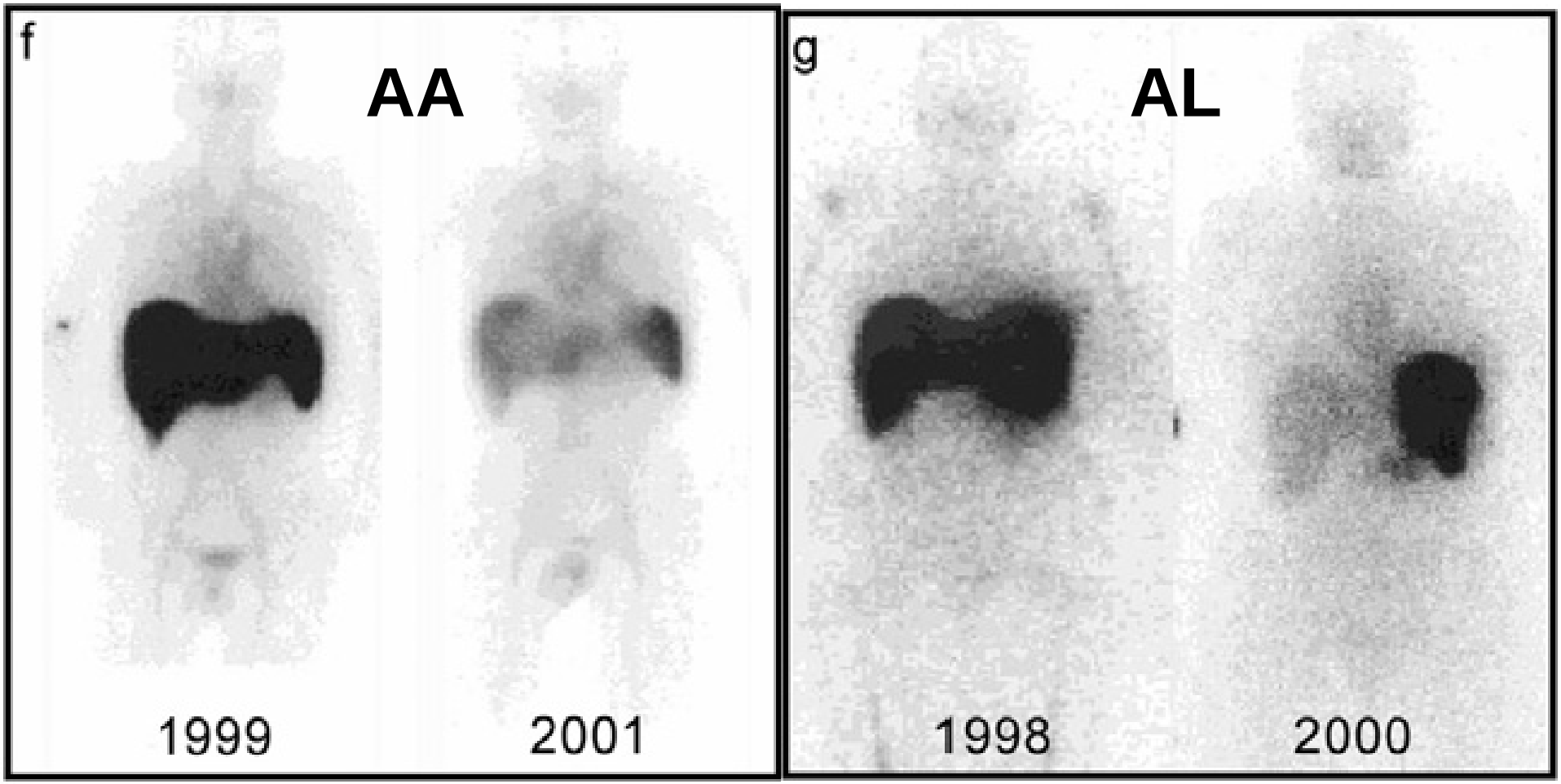
- SAP binds to all amyloid fibrils (1979)
- Specifically concentrated in amyloid deposits
  in plasma - albumin : SAP ~2000 : 1
  in amyloid - albumin : SAP <1 : 10
- Equilibrium: SAP in amyloid & circulation
- Plasma and ECF SAP = ~100 mg
  Amyloid SAP = up to 20,000 mg
- Radiolabelled SAP, injected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

UK NHS National Amyloidosis Centre

- Diagnosis/management of >2000 patients/year
- Clinical director: Professor Philip Hawkins
- Unparalleled experience of amyloidosis & FPF
- SAP scintigraphy is essential
- Only centre doing routine SAP scintigraphy
- ~1000 SAP scintigraphy scans per year
- UK Dept of Health funding ~£4.5 million/year


a
AL
AA
b
c
d

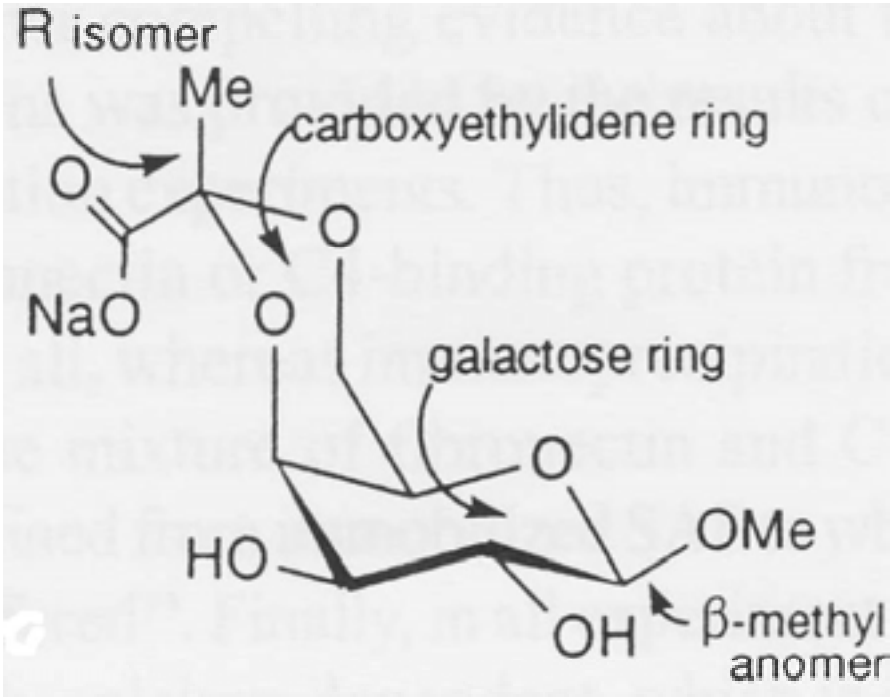
Regression of amyloid

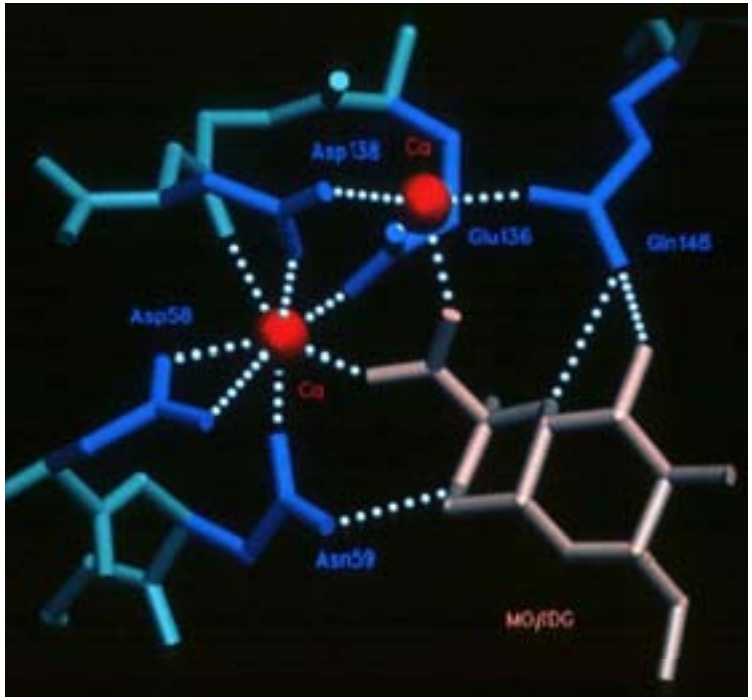


SAP & amyloidogenesis

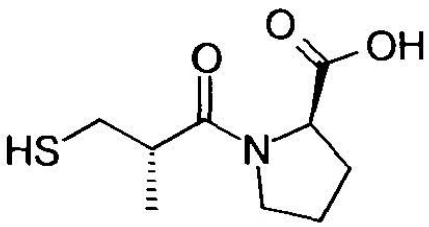
- SAP is universal in amyloid deposits
- SAP production correlates with amyloid deposition in mice and hamsters
- SAP in amyloid deposits is not degraded
- SAP binding stabilises amyloid fibrils *in vitro*
- SAP is an anti-opsonin
- SAP promotes fibrillogenesis *in vitro*
- Amyloid deposition reduced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

1984: SAP ligand as a drug?

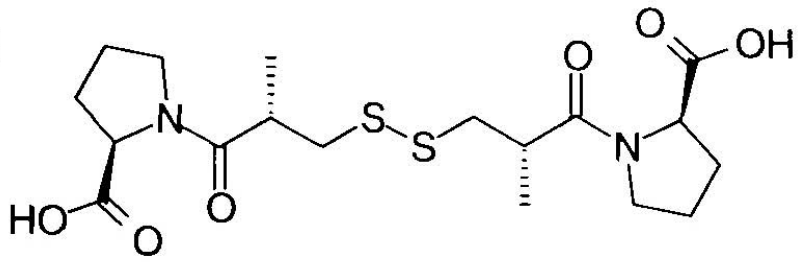




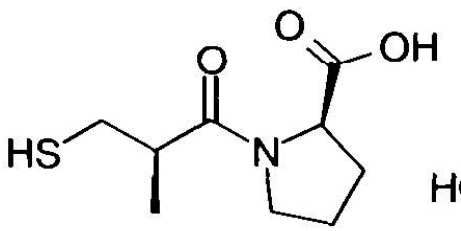
Hind *et al,* Specific chemical dissociation of fibrillar and non-fibrillar components of amyloid deposits. *Lancet*, 1984, **2**(8399):376-8



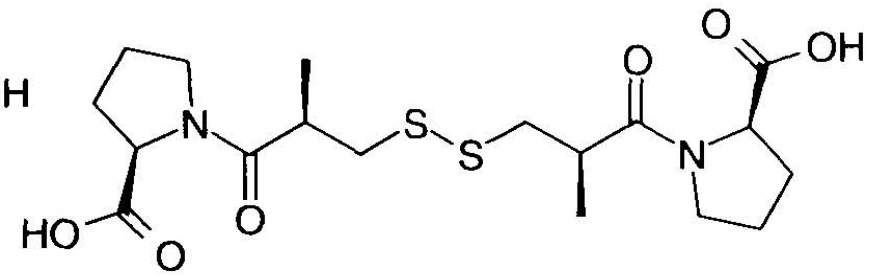
Ro 15-3479
IC_{50} = 100 μM



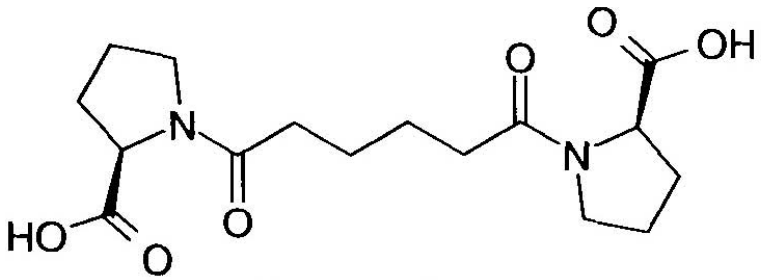
Ro 63-3300
IC_{50} = 5 μM



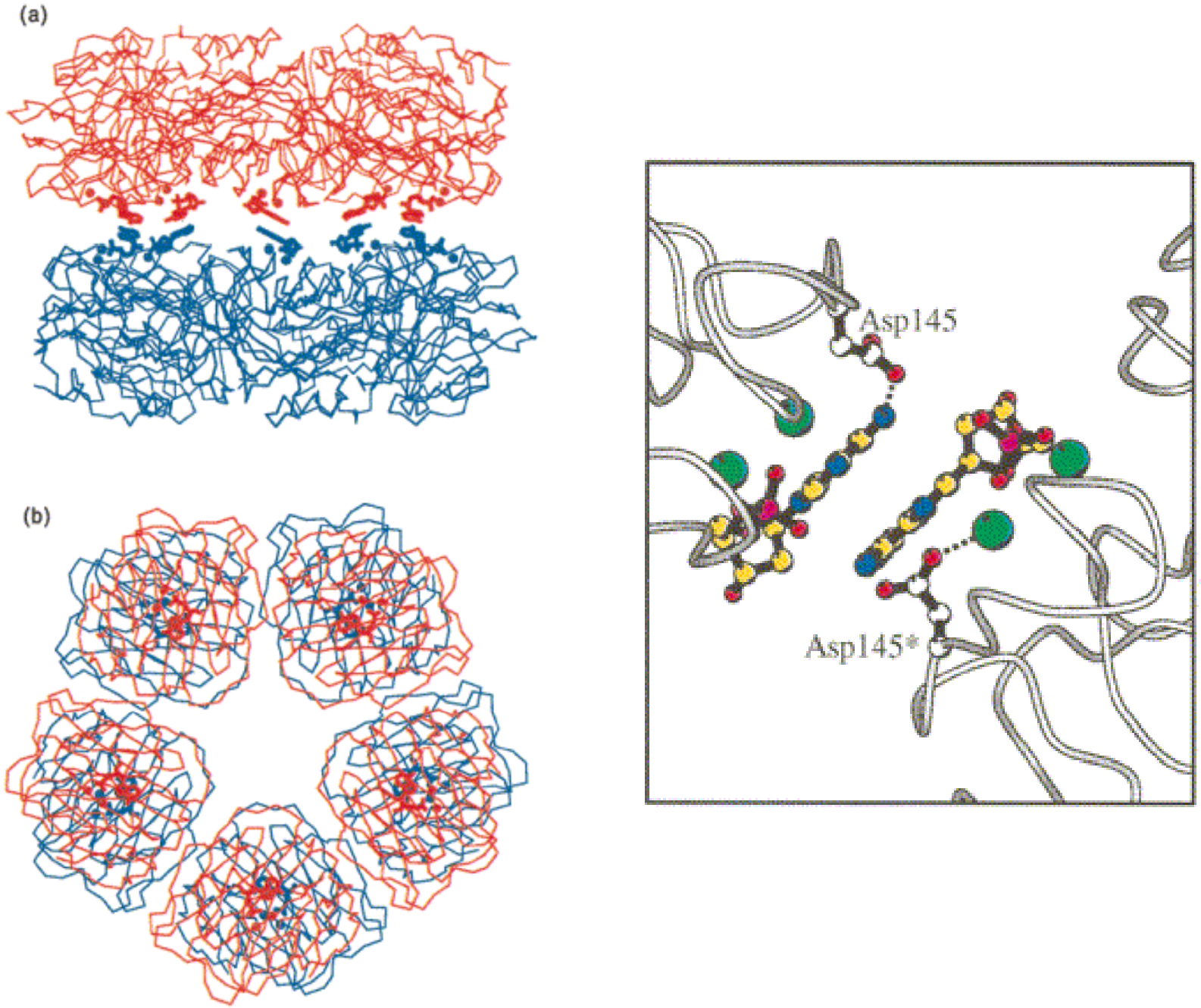
Ro 15-3743
IC_{50} > 100 μM



Ro 63-2346
IC_{50} = 50 μM

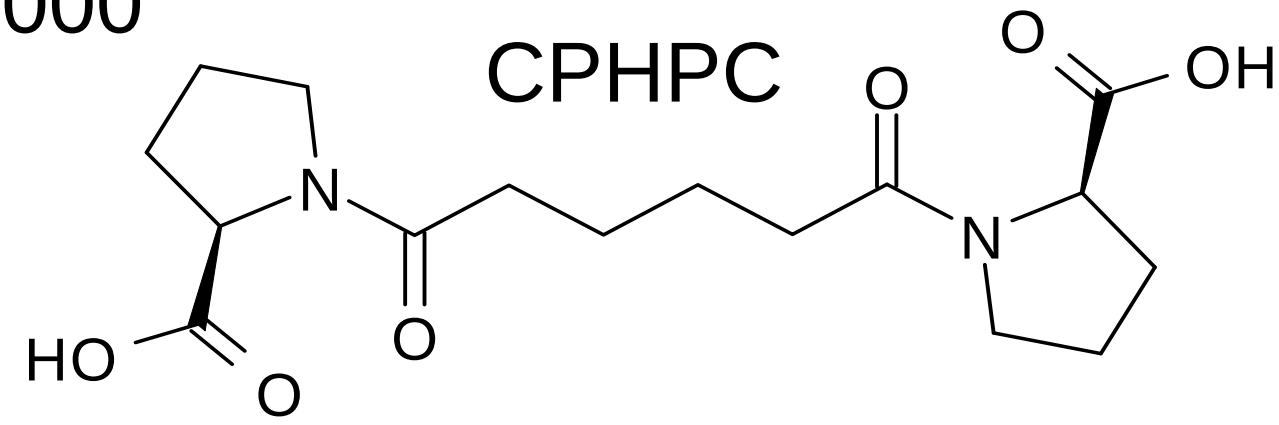


Ro 63-8695
IC_{50} = 0.9 μM

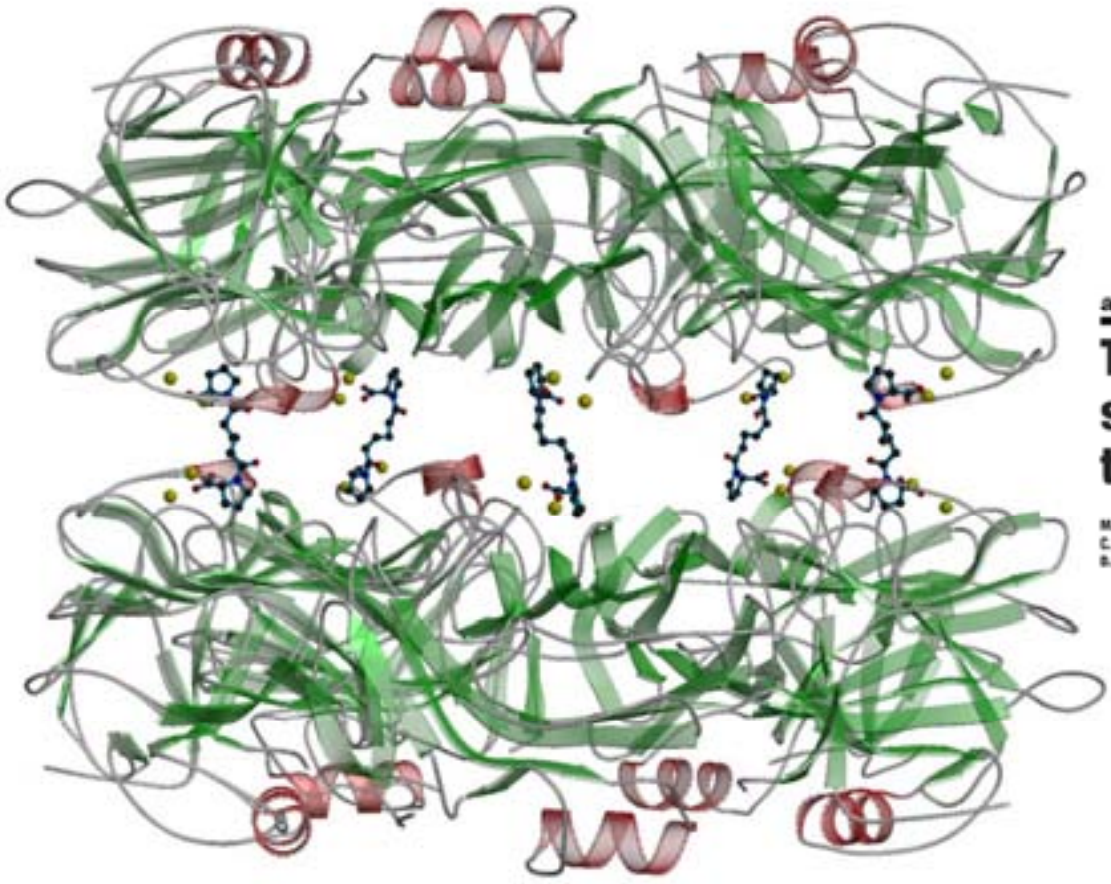

(a)
(b)
Asp145
Asp145*

1995-2000

CPHPC



K_d 10 nM

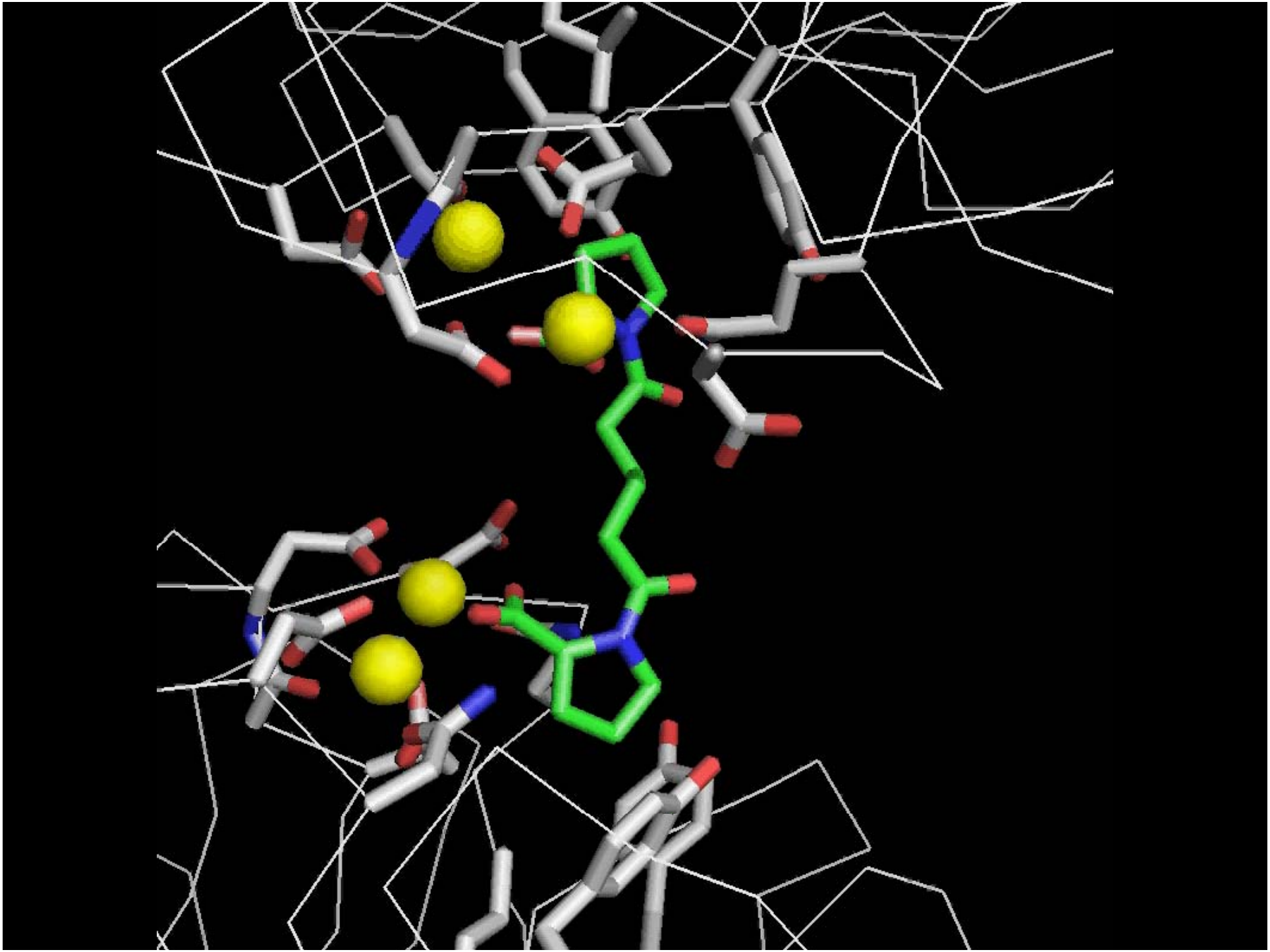


articles

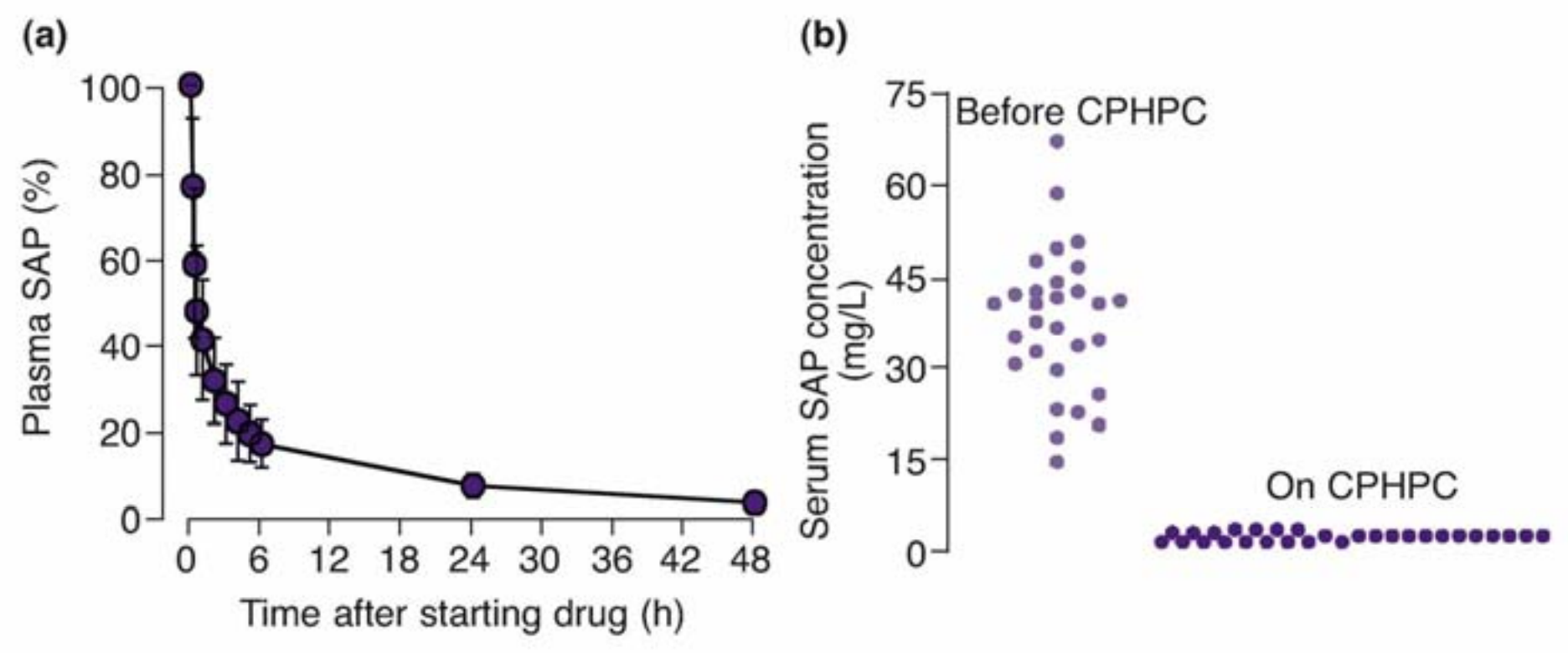
Targeted pharmacological depletion of serum amyloid P component for treatment of human amyloidosis

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*

Nature 2002, **417**: 254-9



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

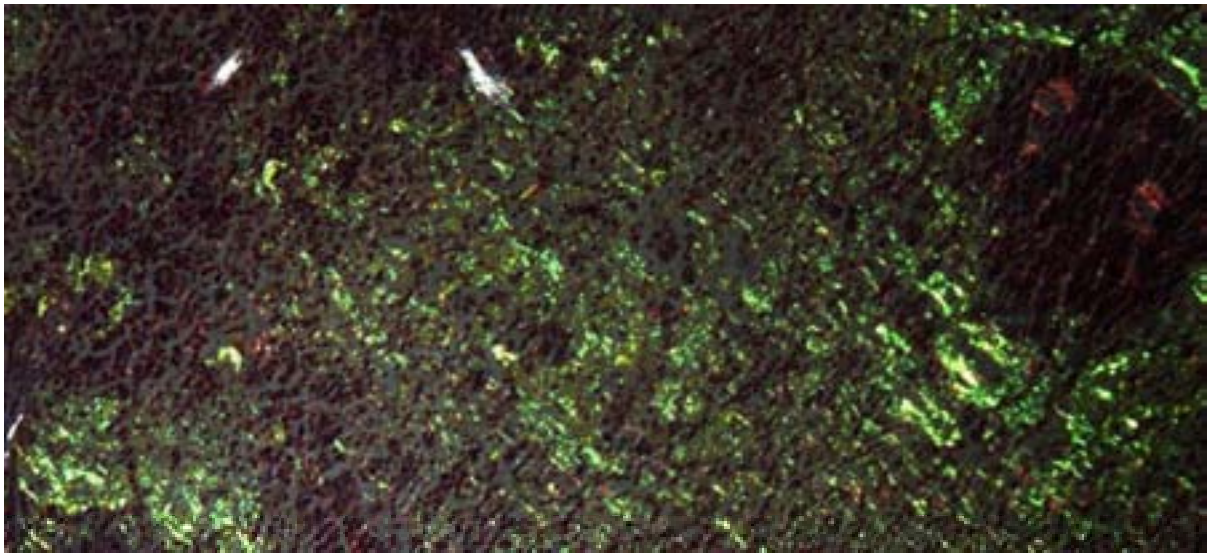
Gillmore *et al. Br. J. Haematol*, 2010, **148**: 760-767

‘Curing’ amyloidosis in mice (2005-8)

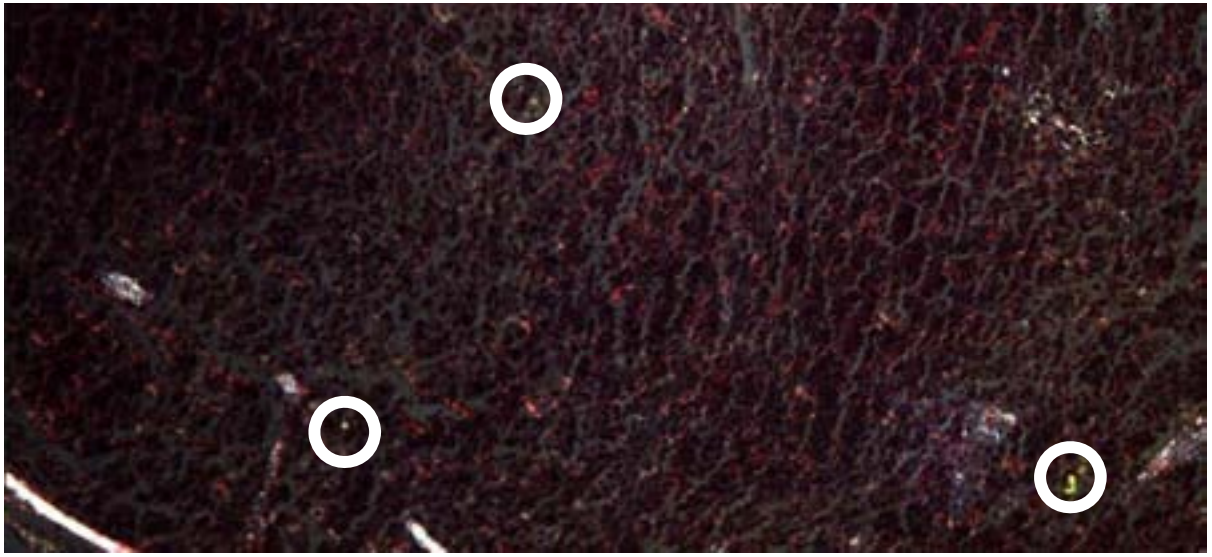
- Human SAP transgenic C57BL/6 mice with AA amyloidosis
- CPHPC clears SAP from plasma but leaves some SAP in amyloid
- Antibodies to SAP can reach the amyloid
- Amyloid deposits disappear!

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

Day 28 post antibody

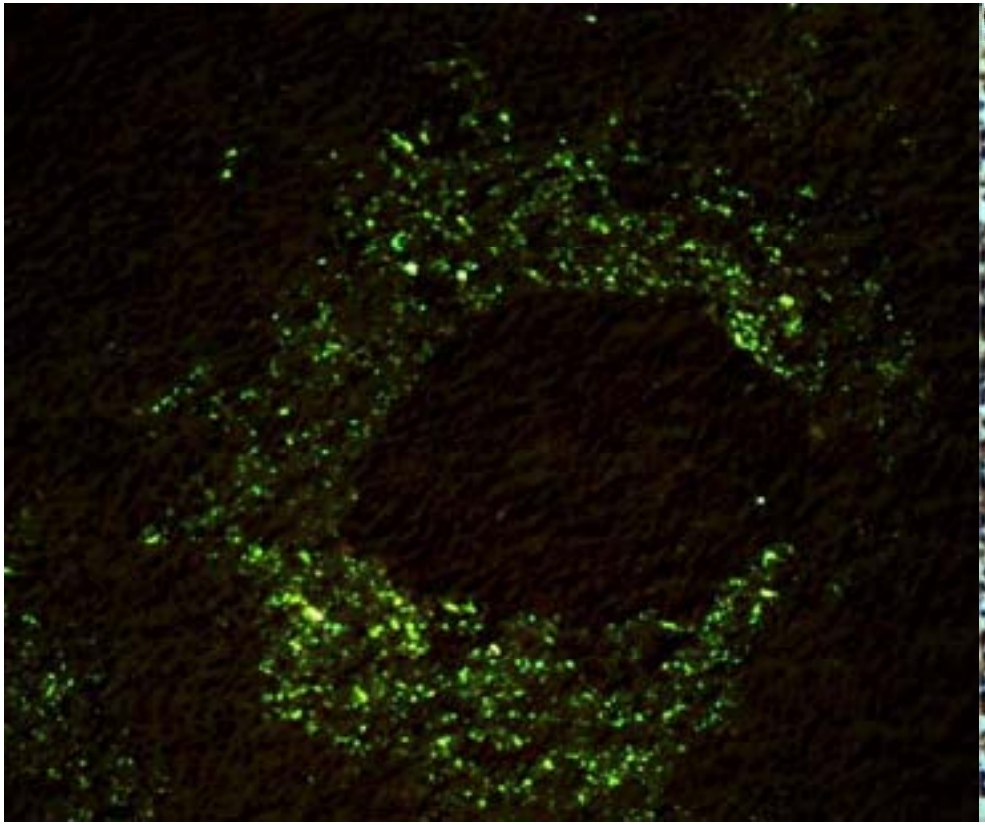


Control IgG

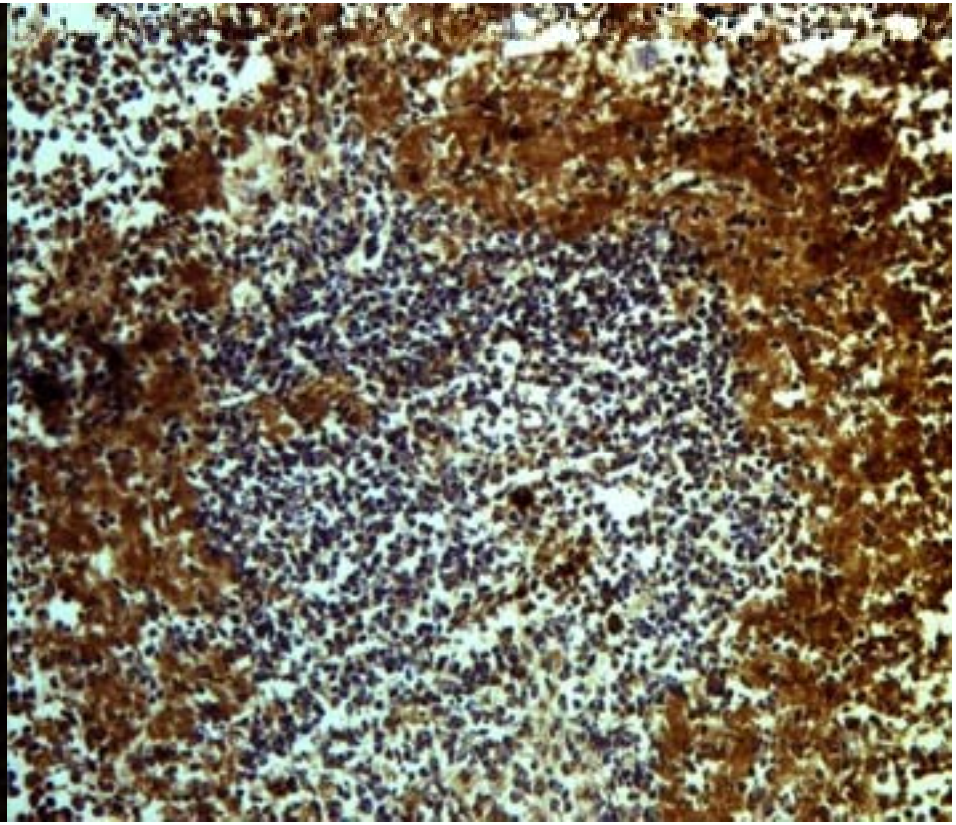


Anti-SAP antibody

Day 1 post antibody

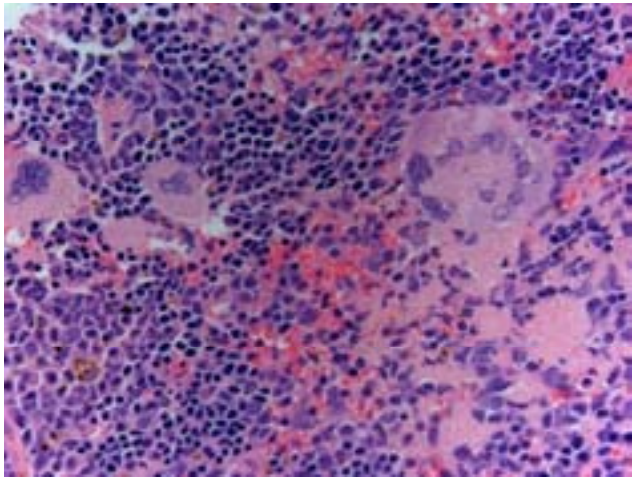


Congo red

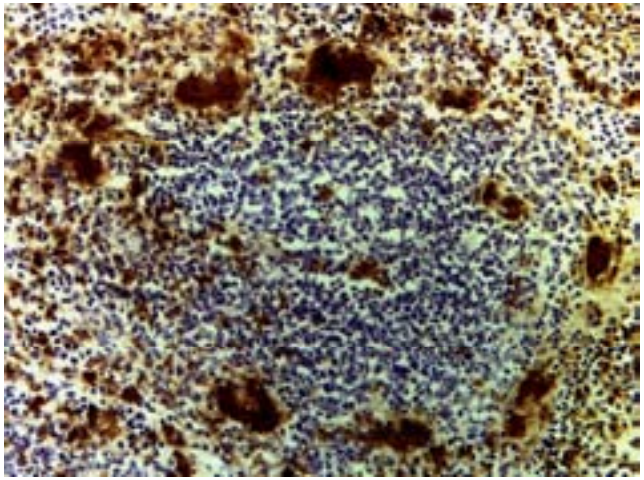


F4/80

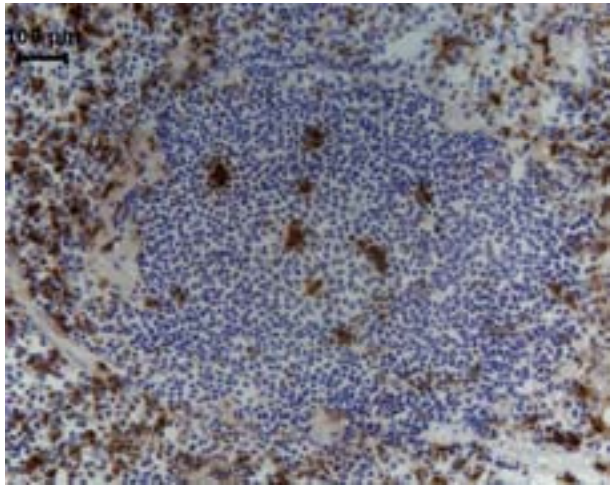
Day 4 post antibody



H & E

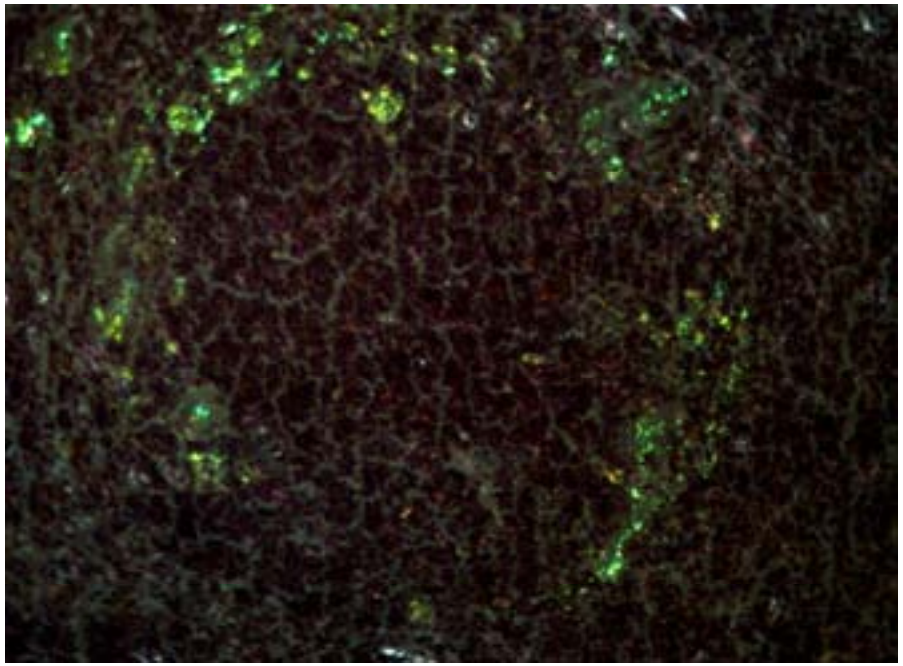


CD68

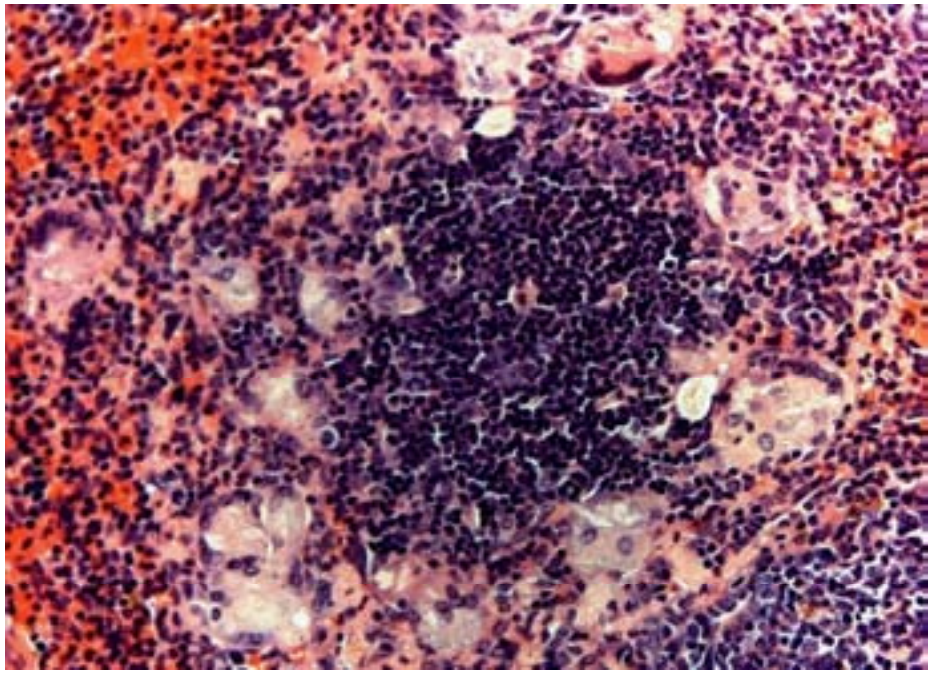


control CD68

Day 4 post antibody

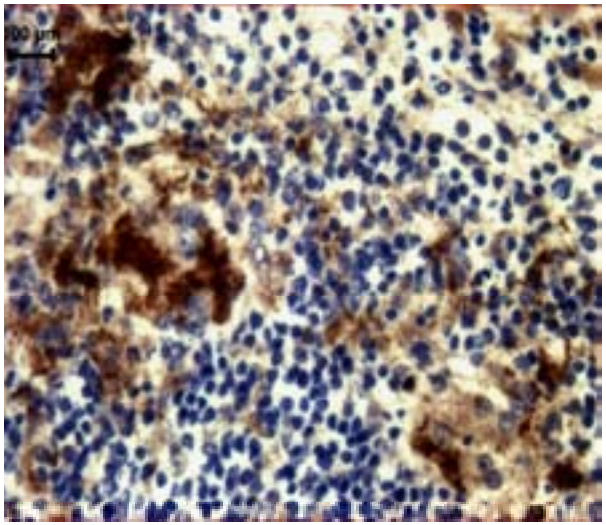


Congo red

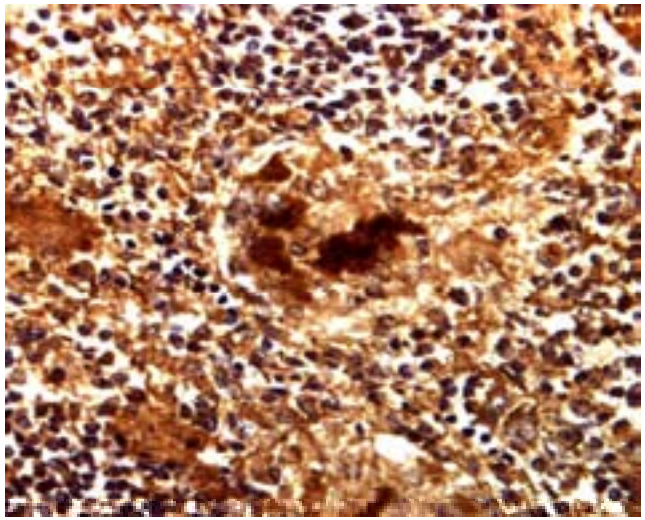


H & E

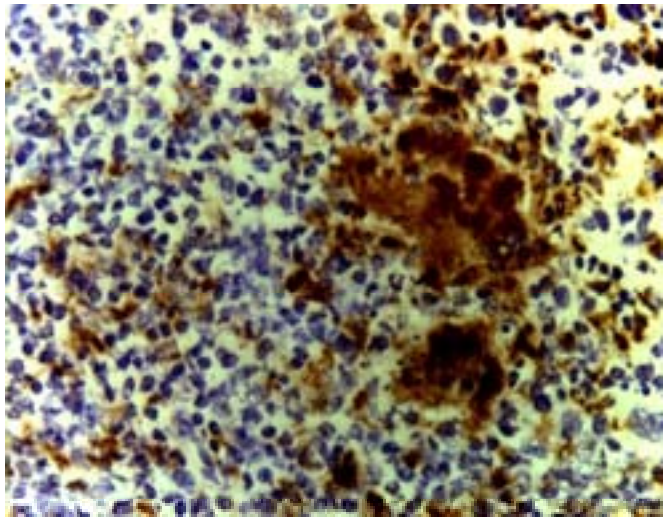
Day 4 post antibody



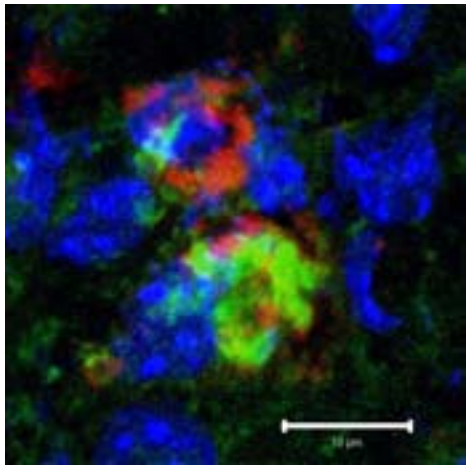
SAA



C3

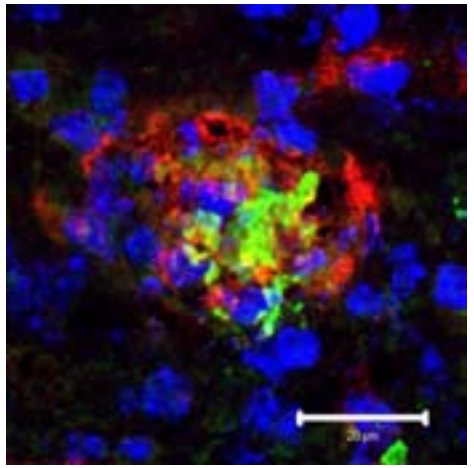


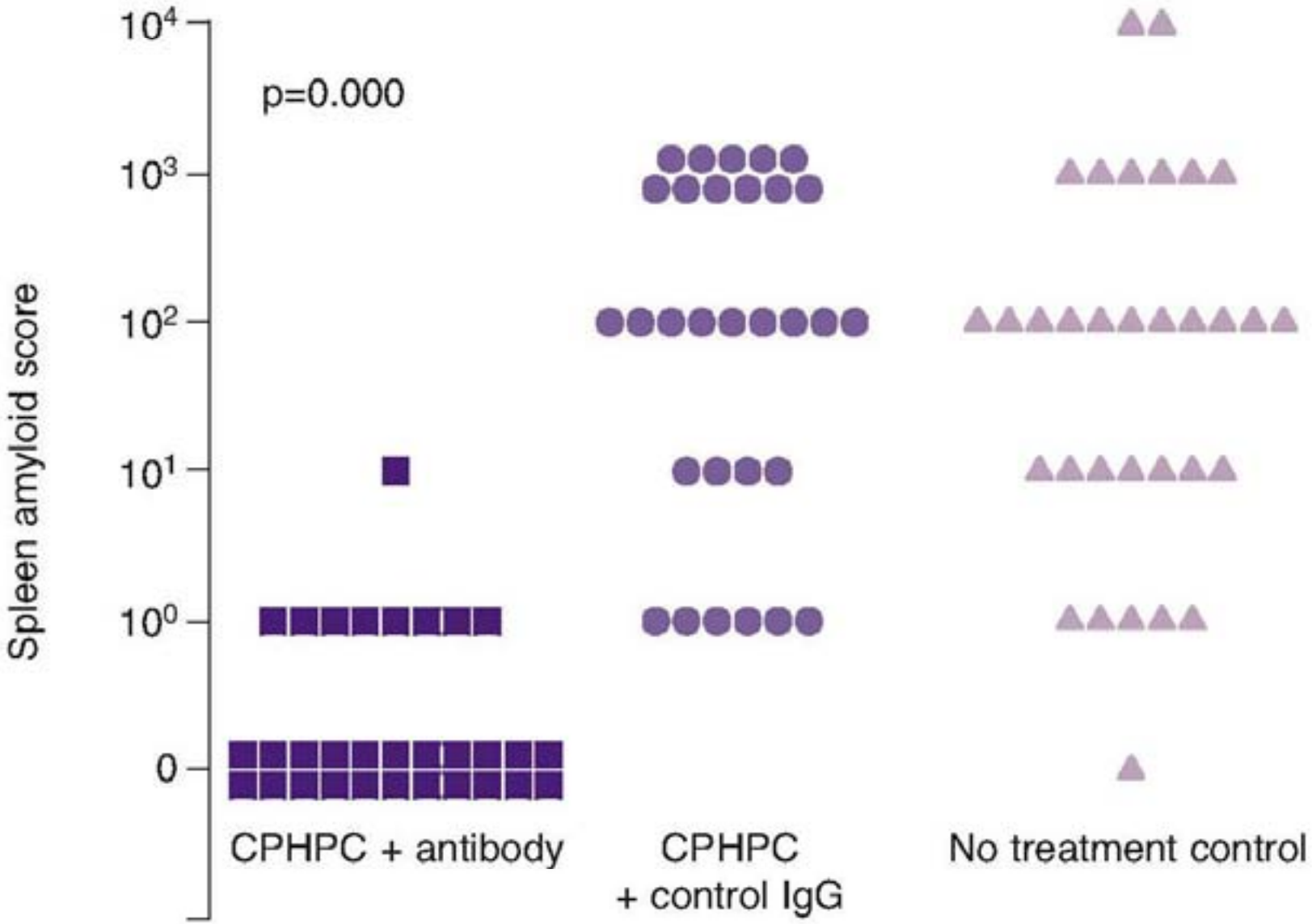
CD68

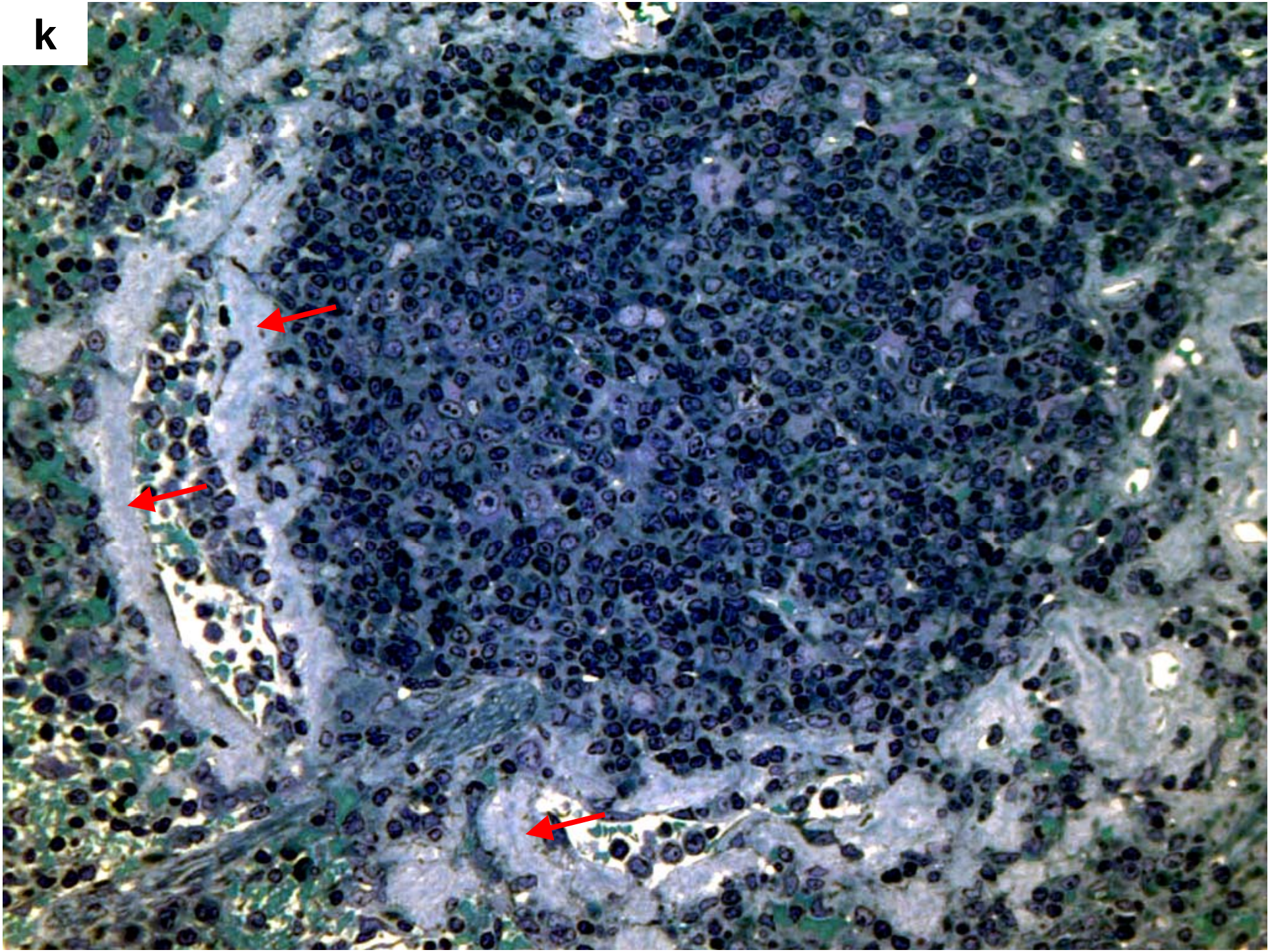


SAA green

CD68 red




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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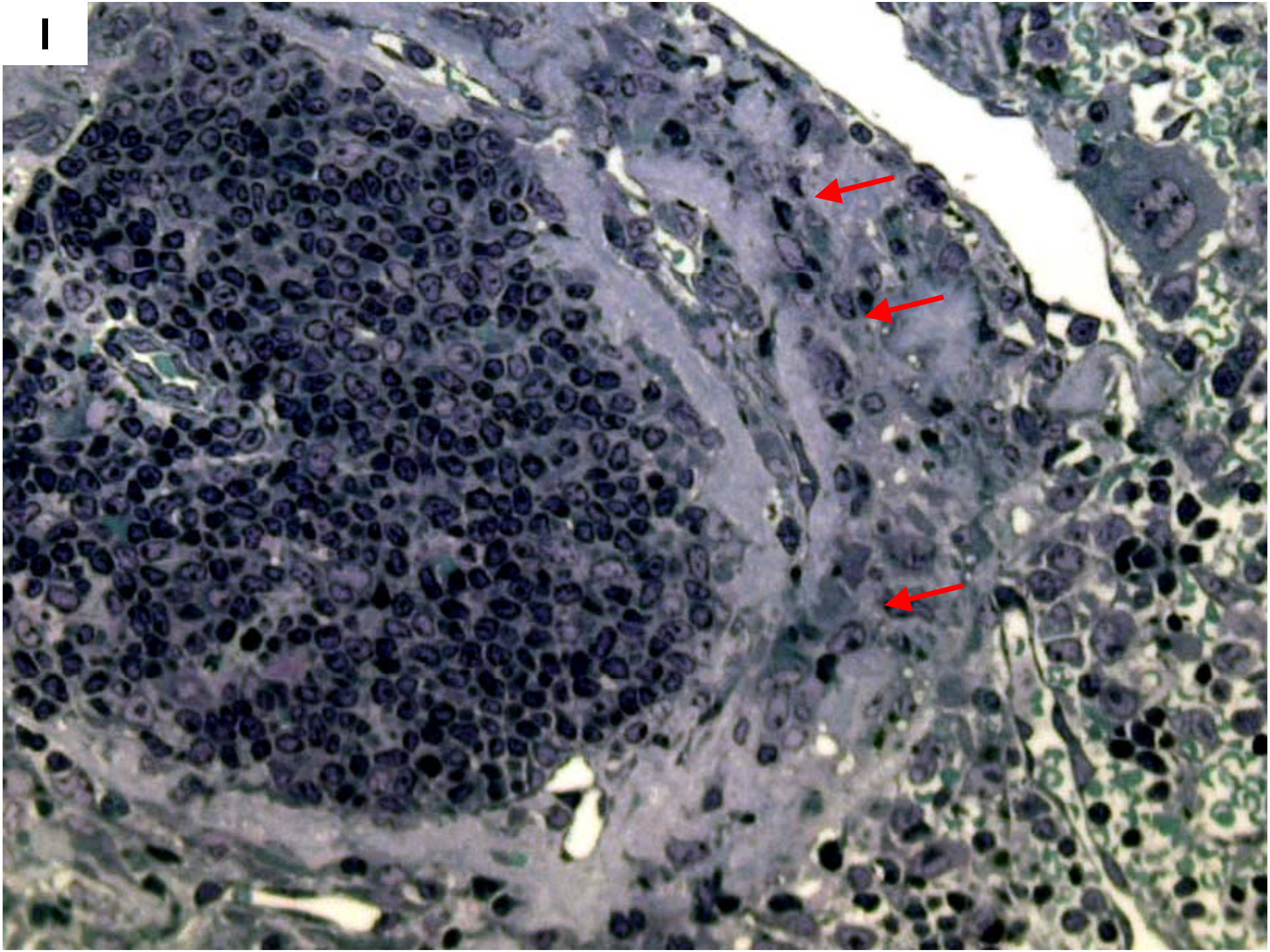
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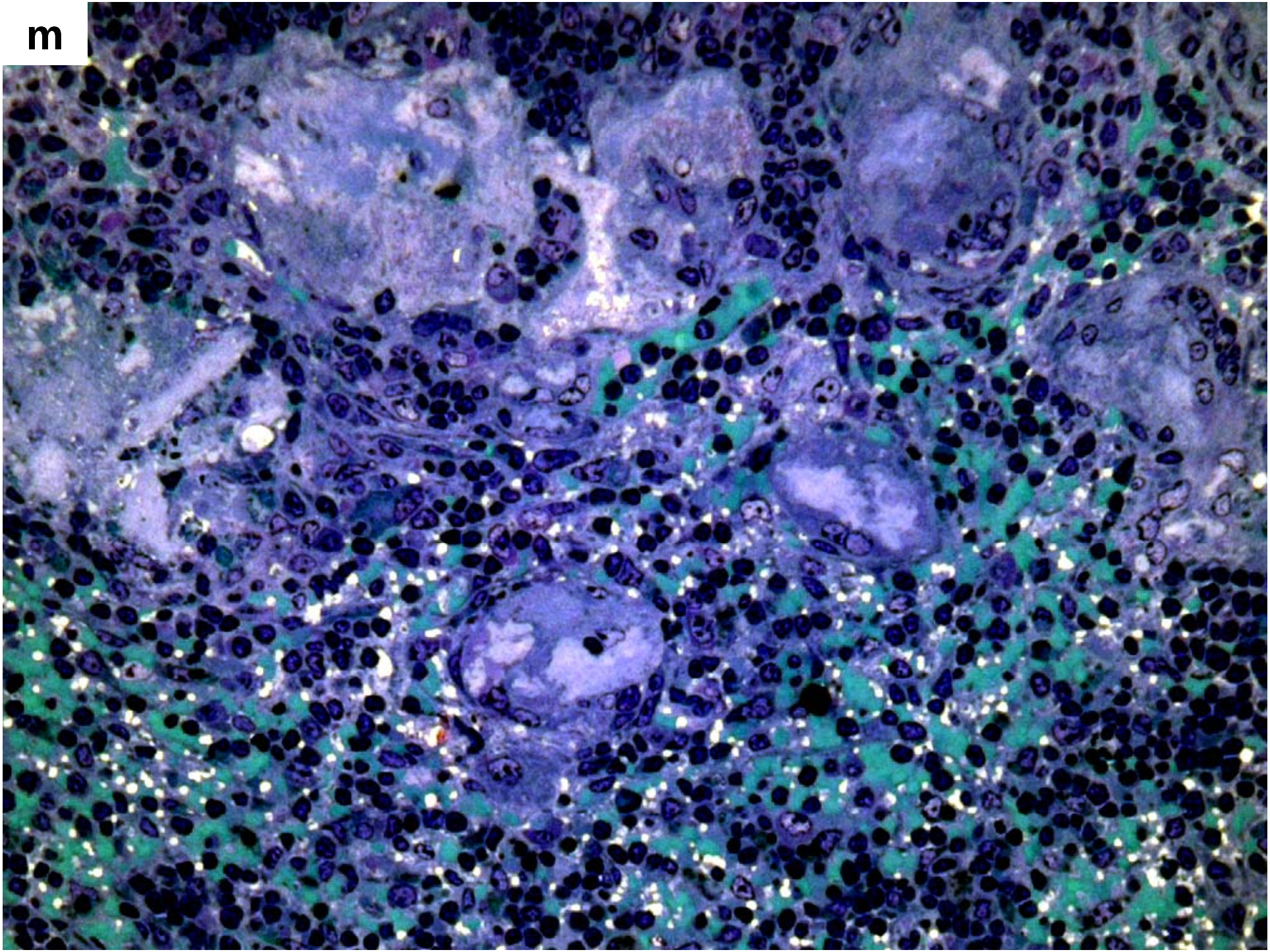
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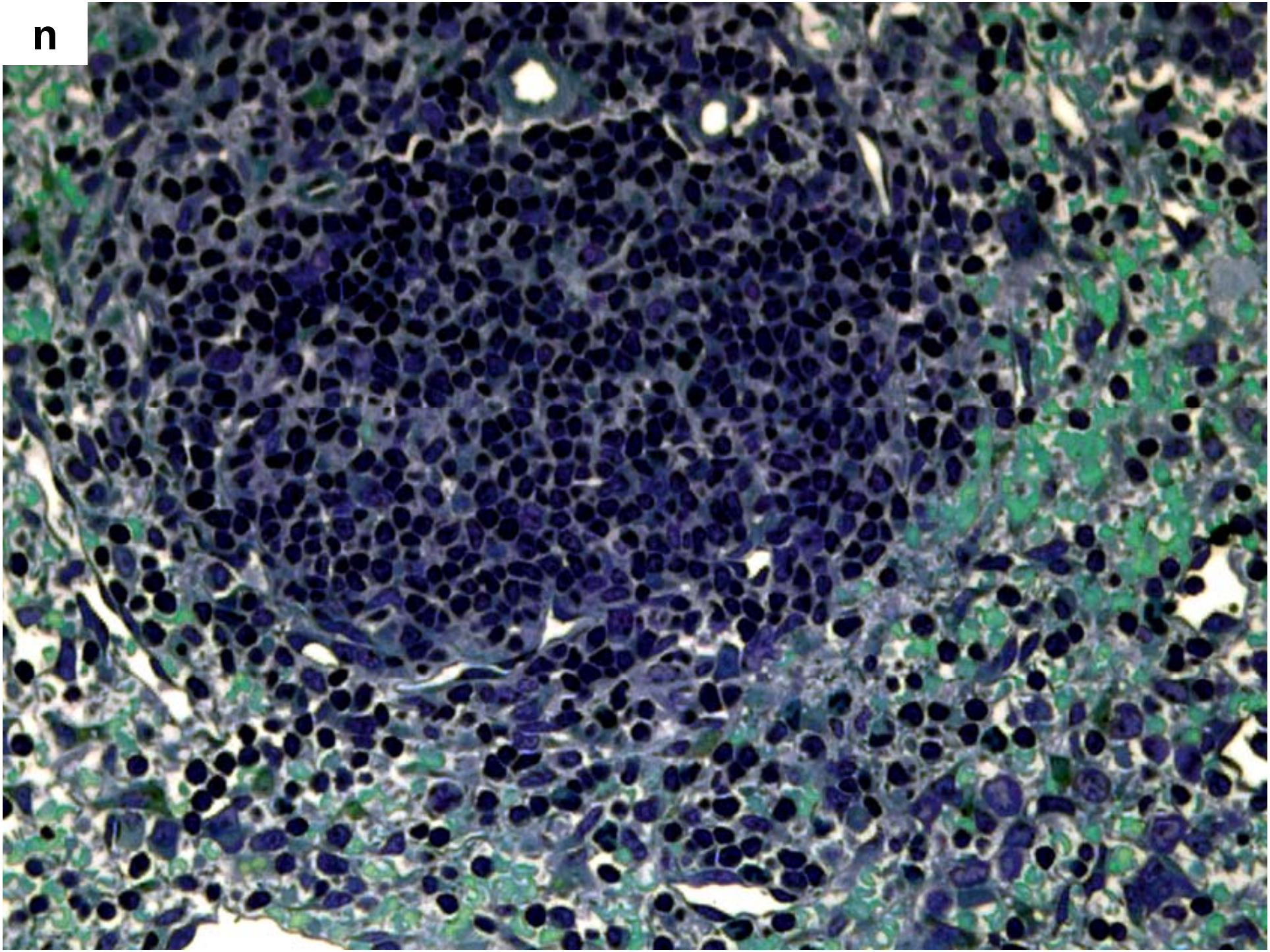
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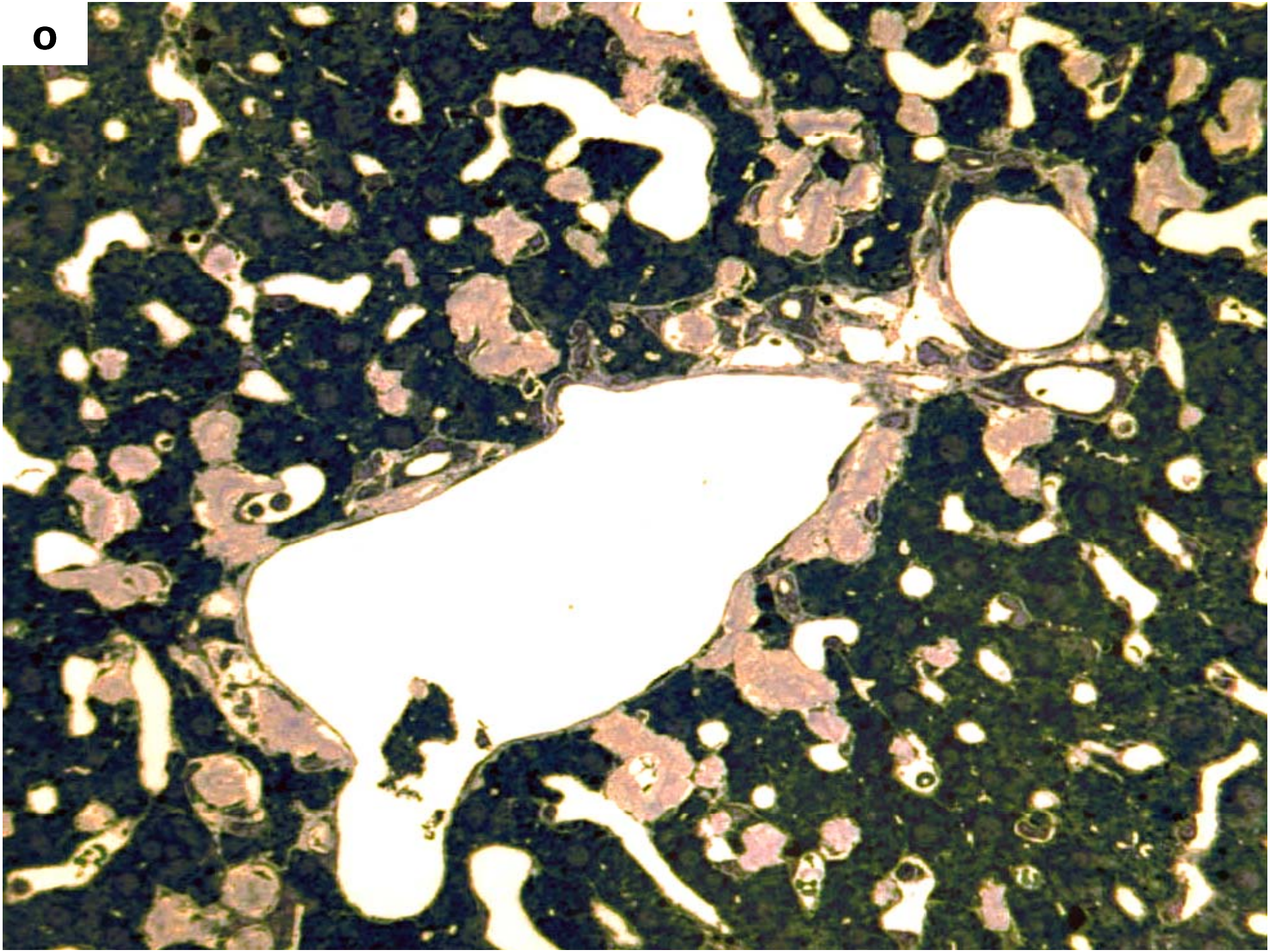

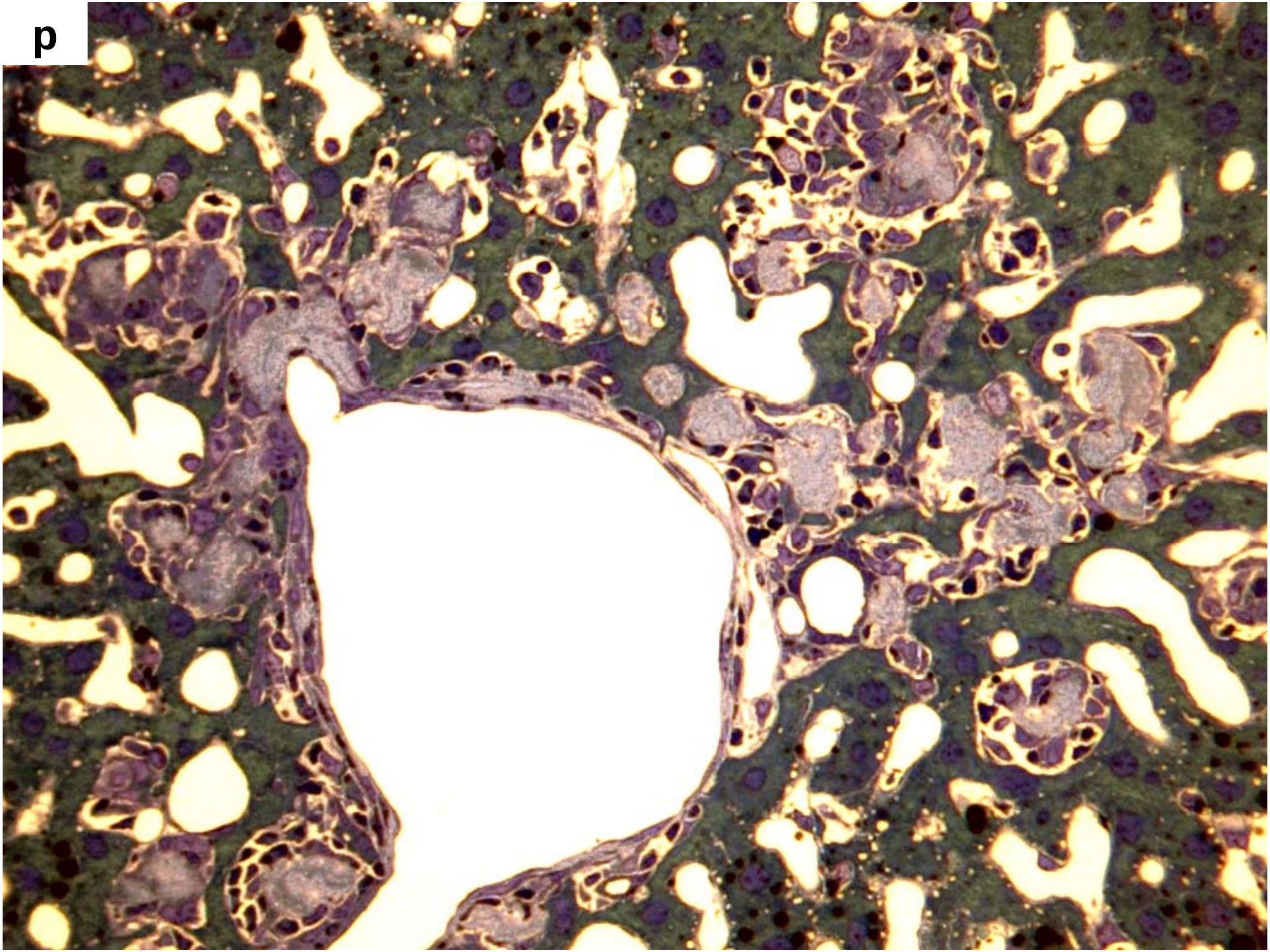
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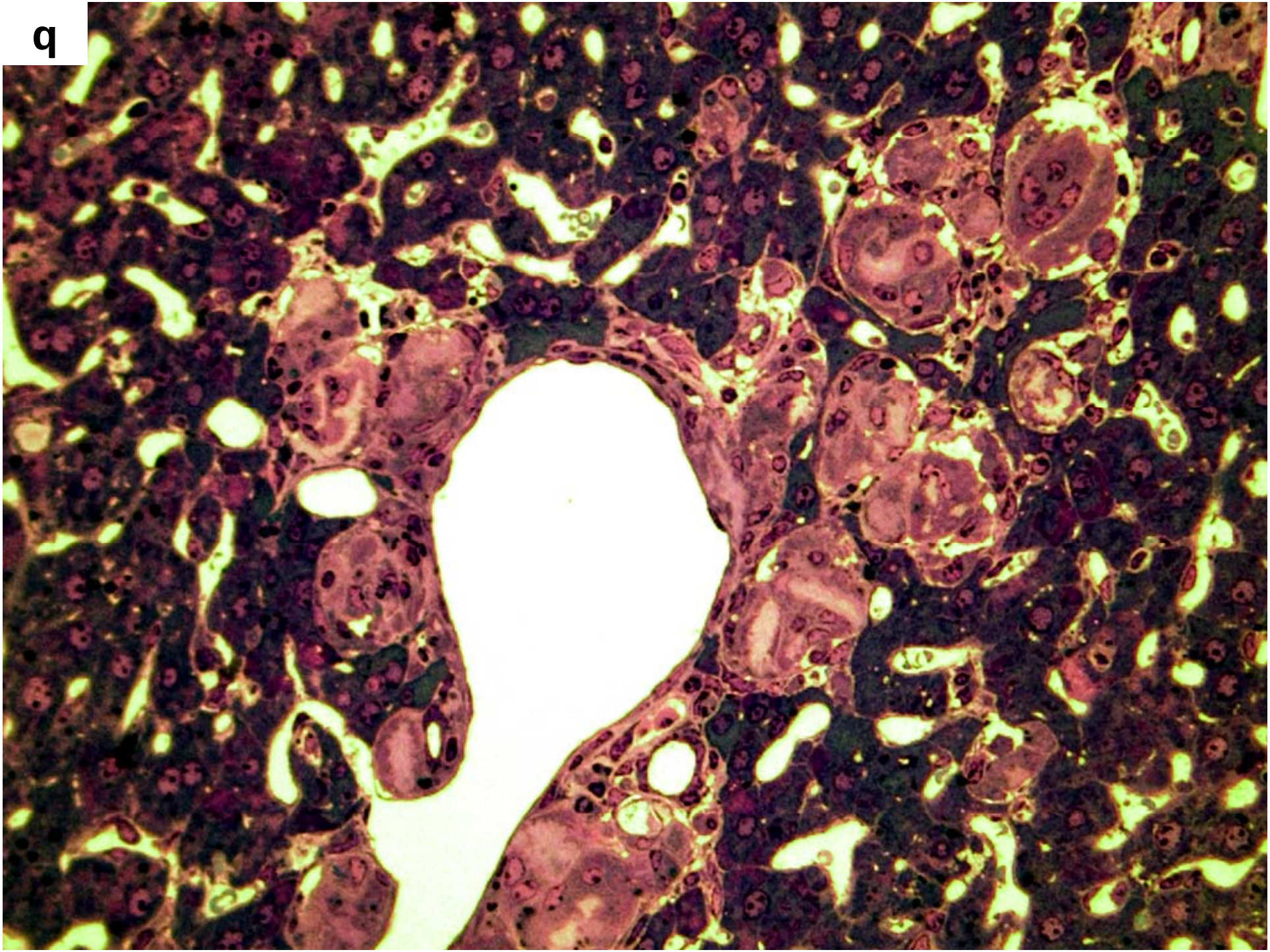
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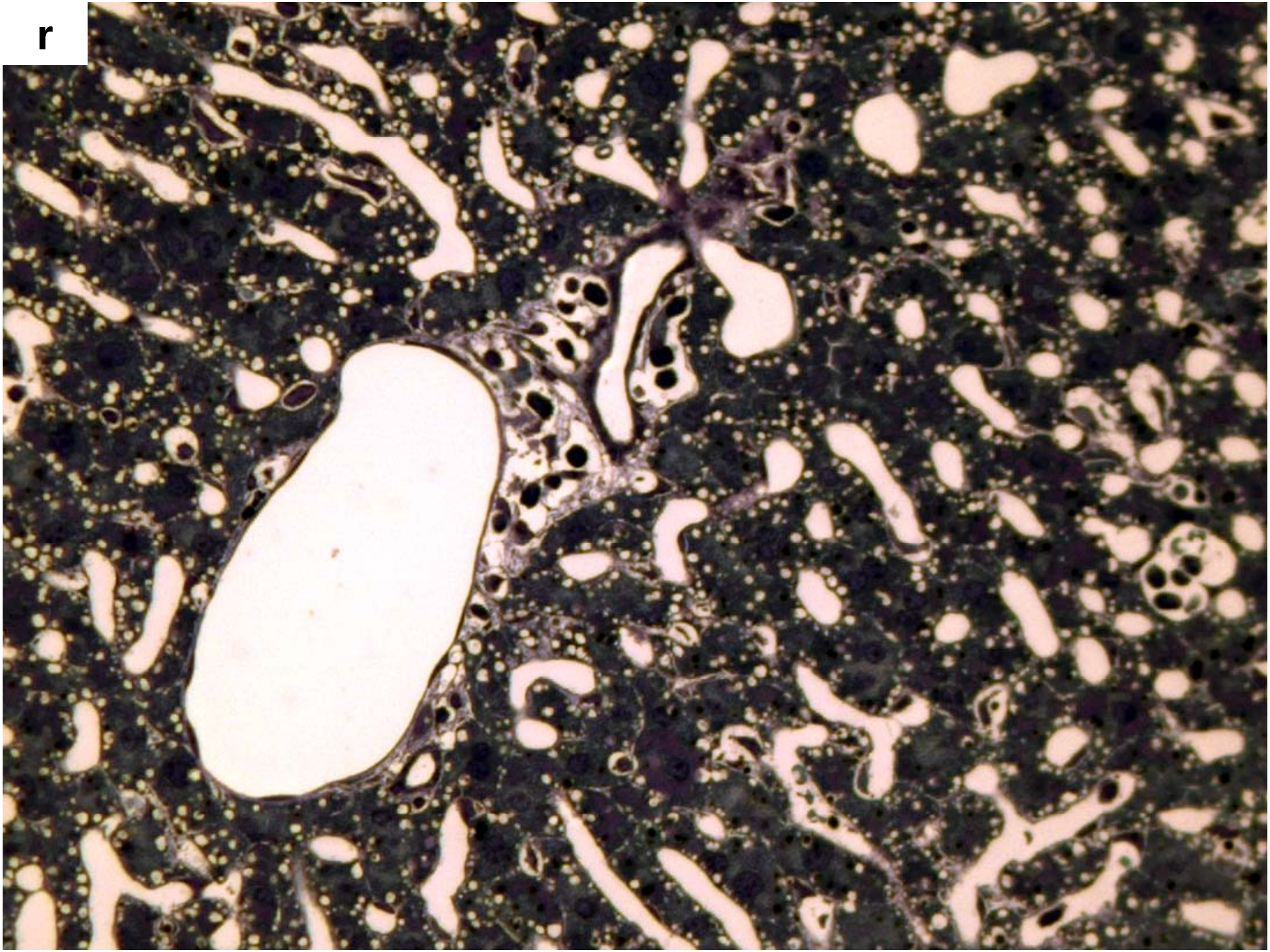
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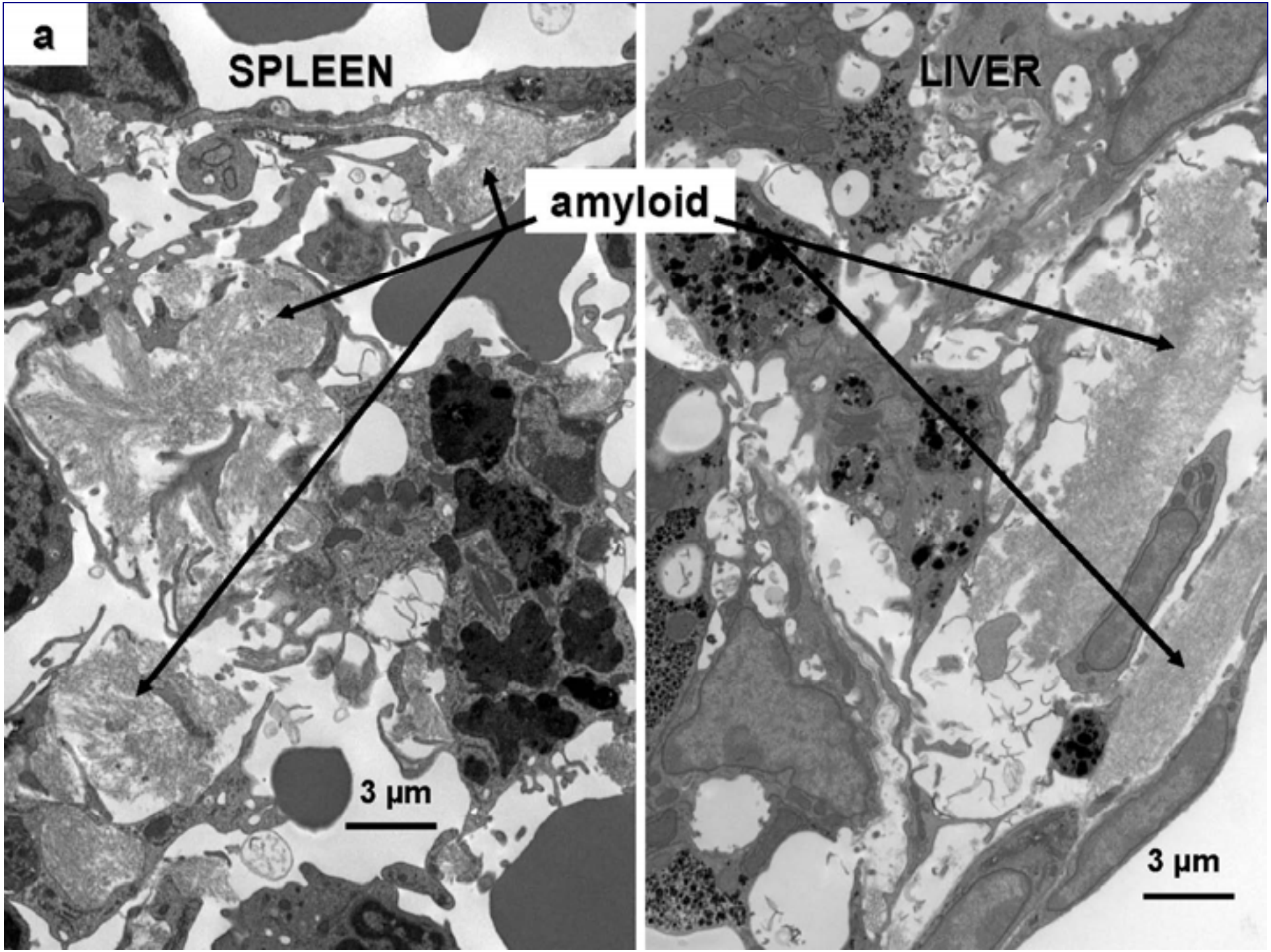
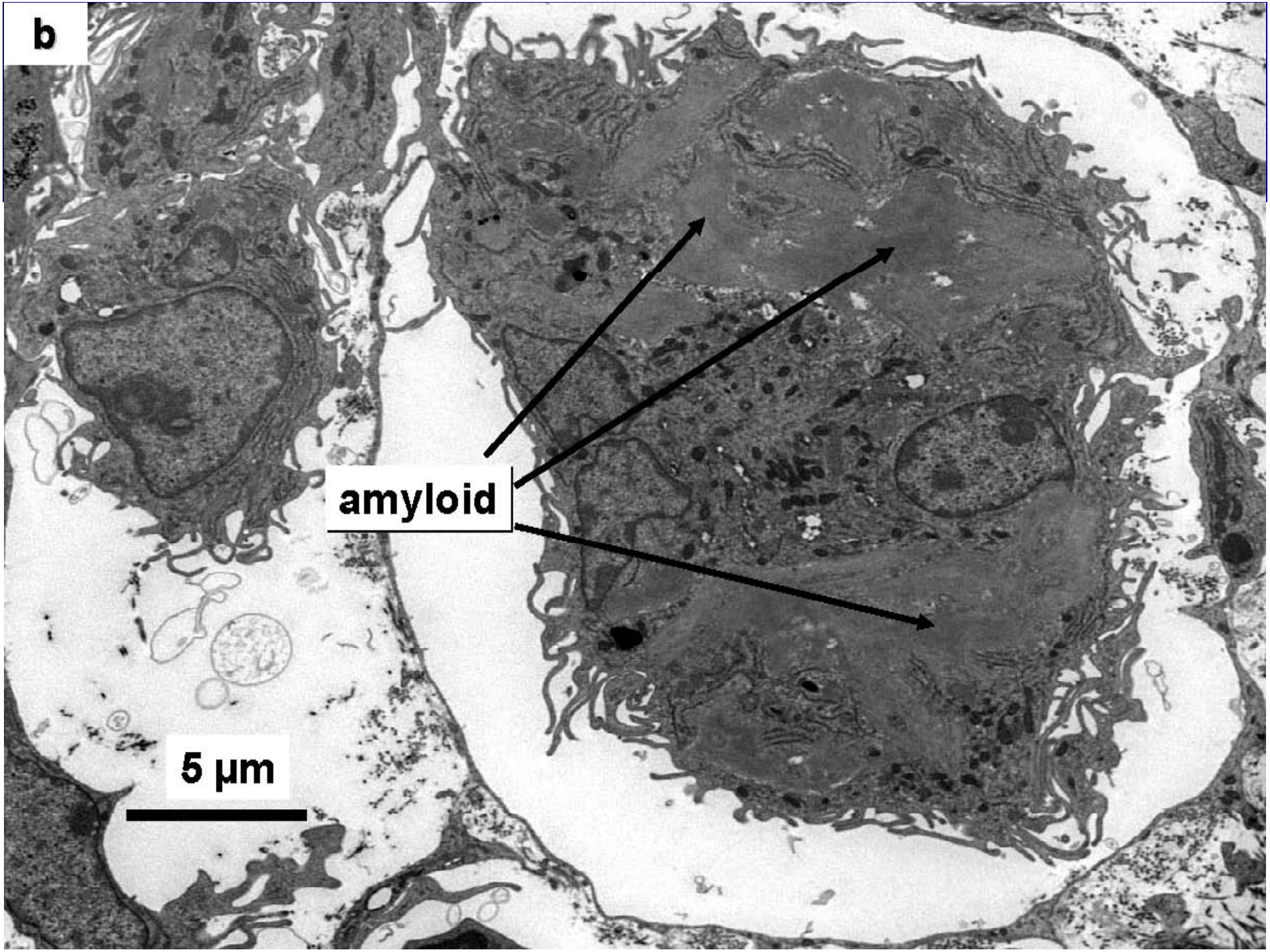
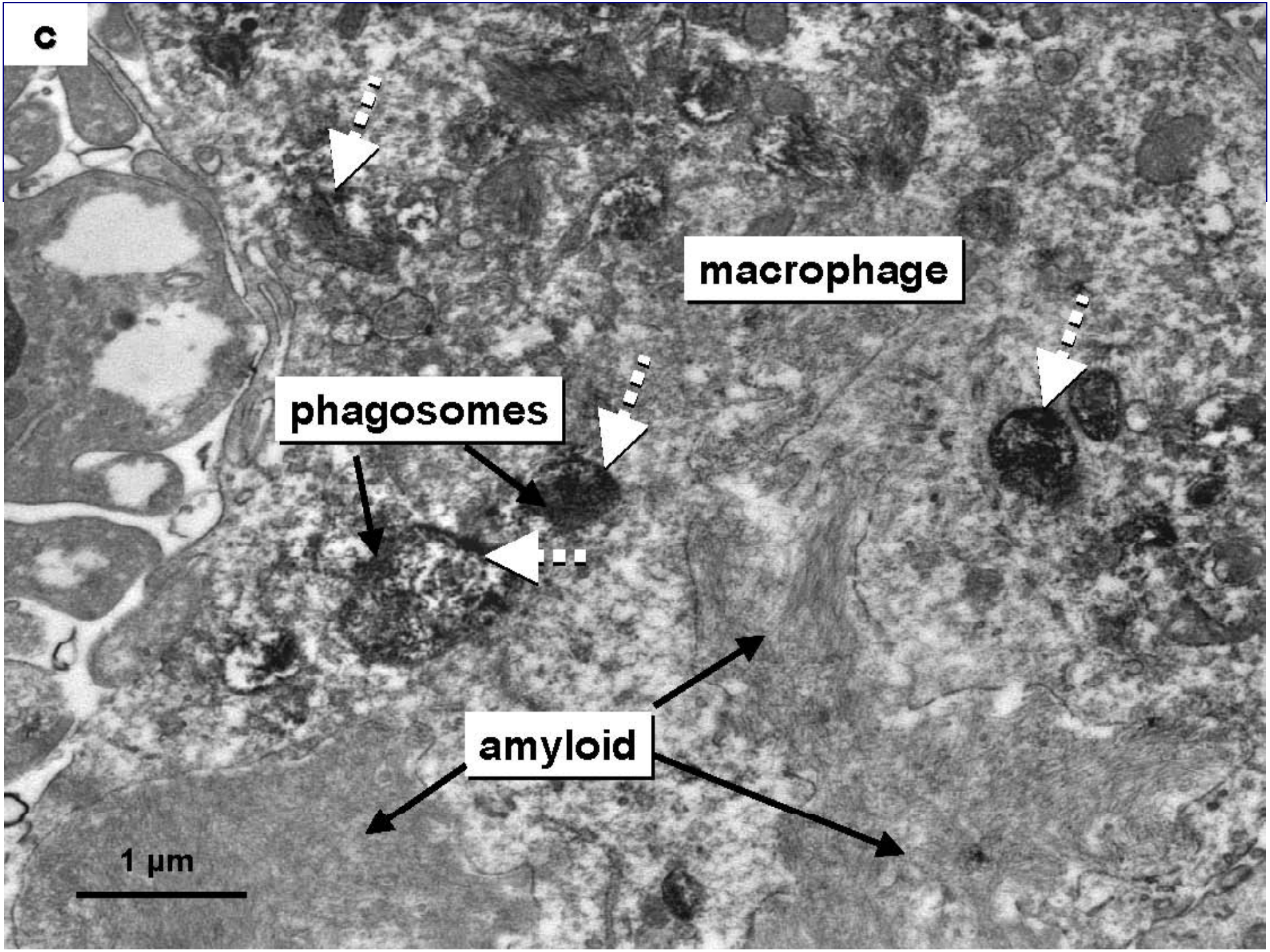

a
SPLEEN
LIVER
amyloid
3 µm
3 µm


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 other amyloid-associated diseases

Drug discovery & development: slow, hard, expensive & painful!

- 1984 to 2011 – 27 years and counting!
- MRC grants 1969-2013; Programme Grant 1979-2010; Research grant 2010-13
- CPHPC developed with Roche 1995-1999
- Divested to UCL spinout, Pentraxin Therapeutics Ltd 2008
- CPHPC + anti-SAP licensed to GSK Feb 2009