AJS McFadzean Distinguished Lecture
Department of Medicine, The University of Hong Kong
23 November 2018

New treatments for amyloidosis and Alzheimer's disease

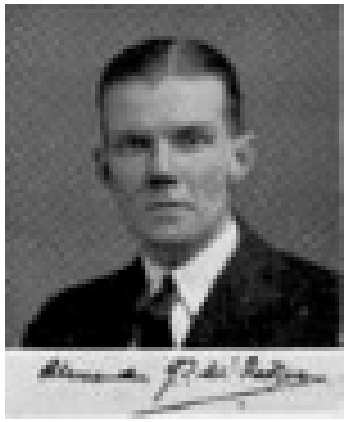
Professor Sir Mark Pepys FRS FMedSci
Wolfson Drug Discovery Unit & National Amyloidosis Centre
Centre for Amyloidosis and Acute Phase Proteins
Royal Free Campus, University College London & Royal Free Hospital

Emeritus Professor & Head of Medicine, Royal Free Campus, UCL

Founder & Director, Pentraxin Therapeutics Ltd

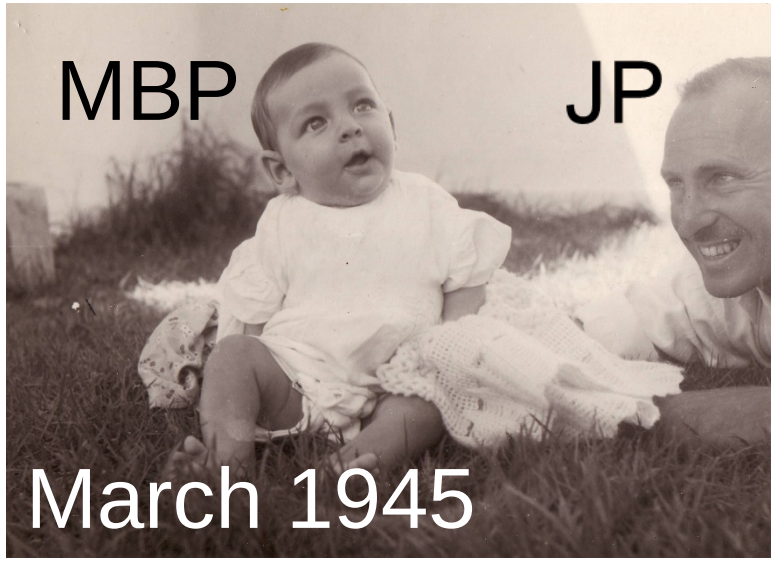
Professor AJS McFadzean 1914-1974

- Clinician
- Teacher
- Scientist
- Administrator
- Sportsman



Ancestors and teachers

- Professor Jack Pepys MD FRCP FRCPE FRCPath



- Rushton, Brindley, Iversen, Rosenheim, Dent, Coombs, Feinstein

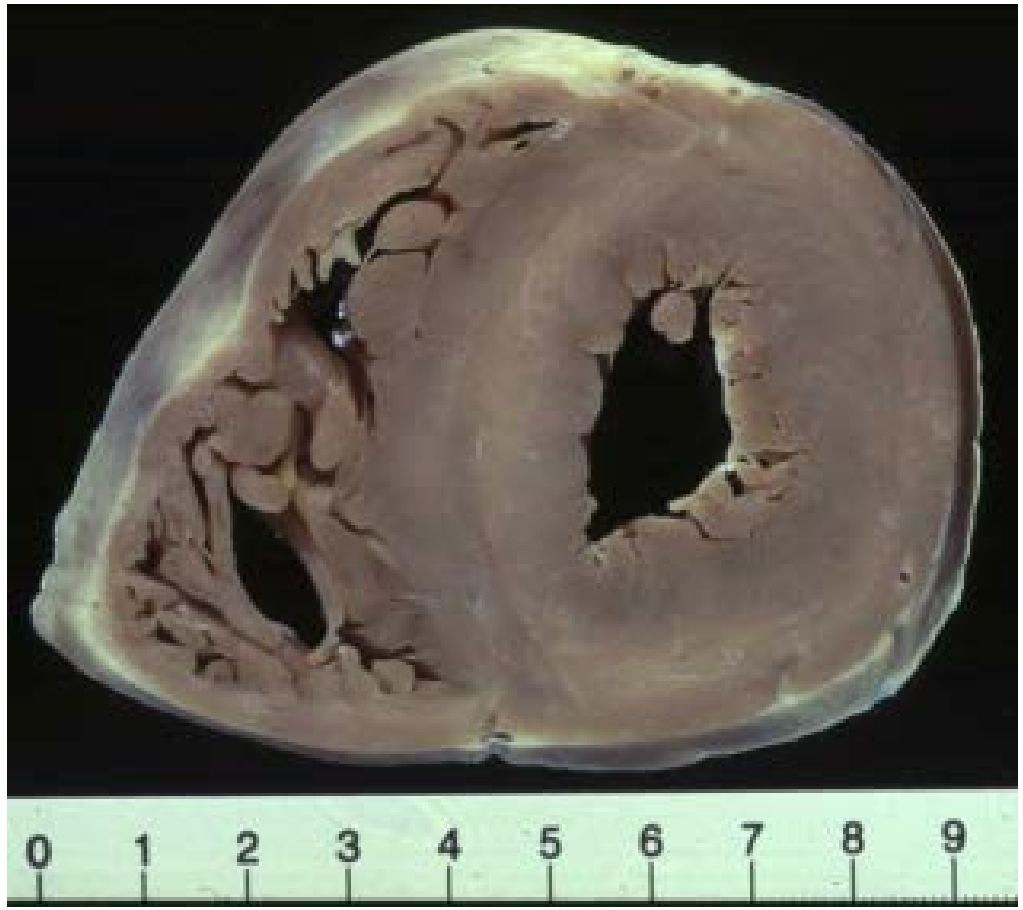
Amyloidosis

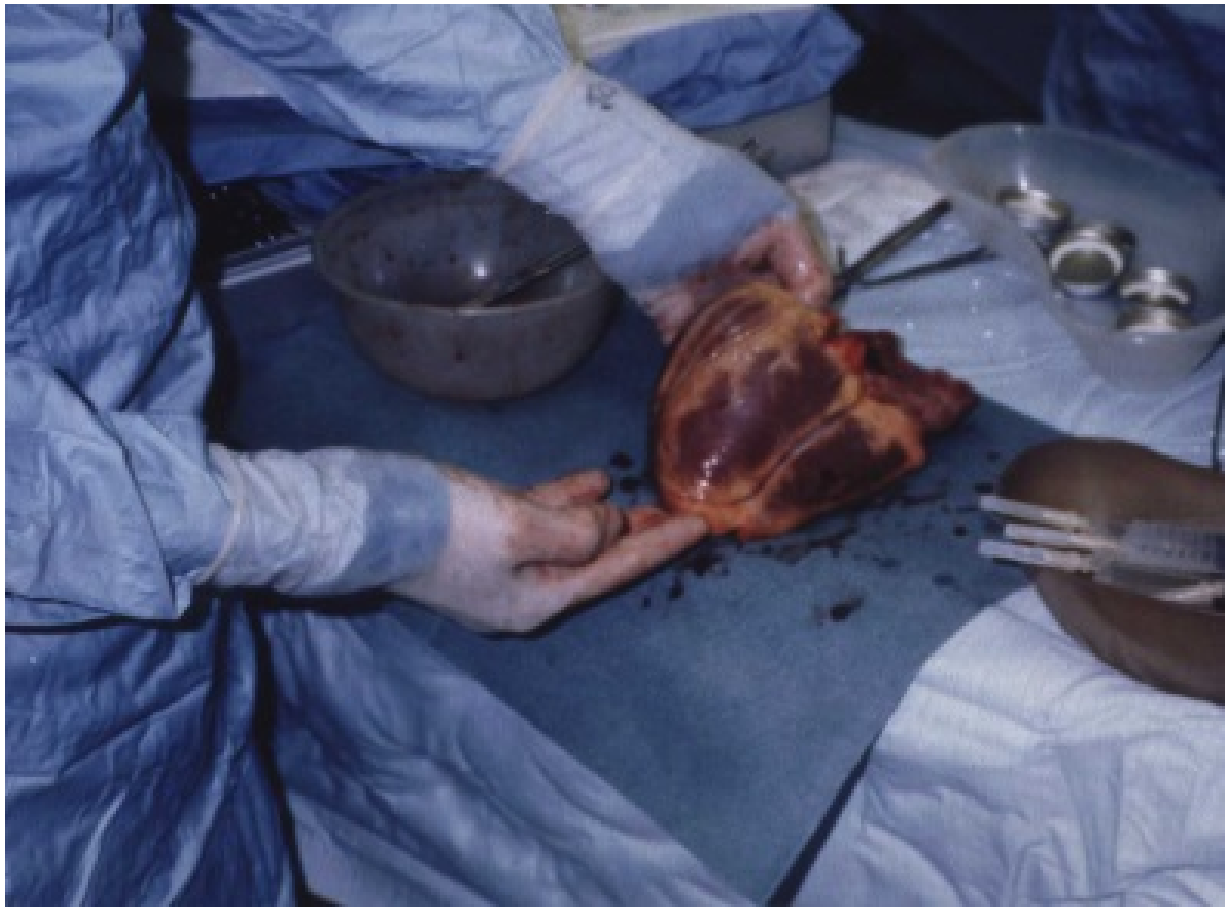
- Disease caused by amyloid deposits
- Localised or systemic
- Systemic amyloidosis: rare (0.4/100,000) but usually fatal
  ~1 per 1,000-1,500 deaths
- Diagnosis usually late
- Treatment very challenging
- Major recent advances & better outcomes in specialist centres
- Still an important unmet medical need

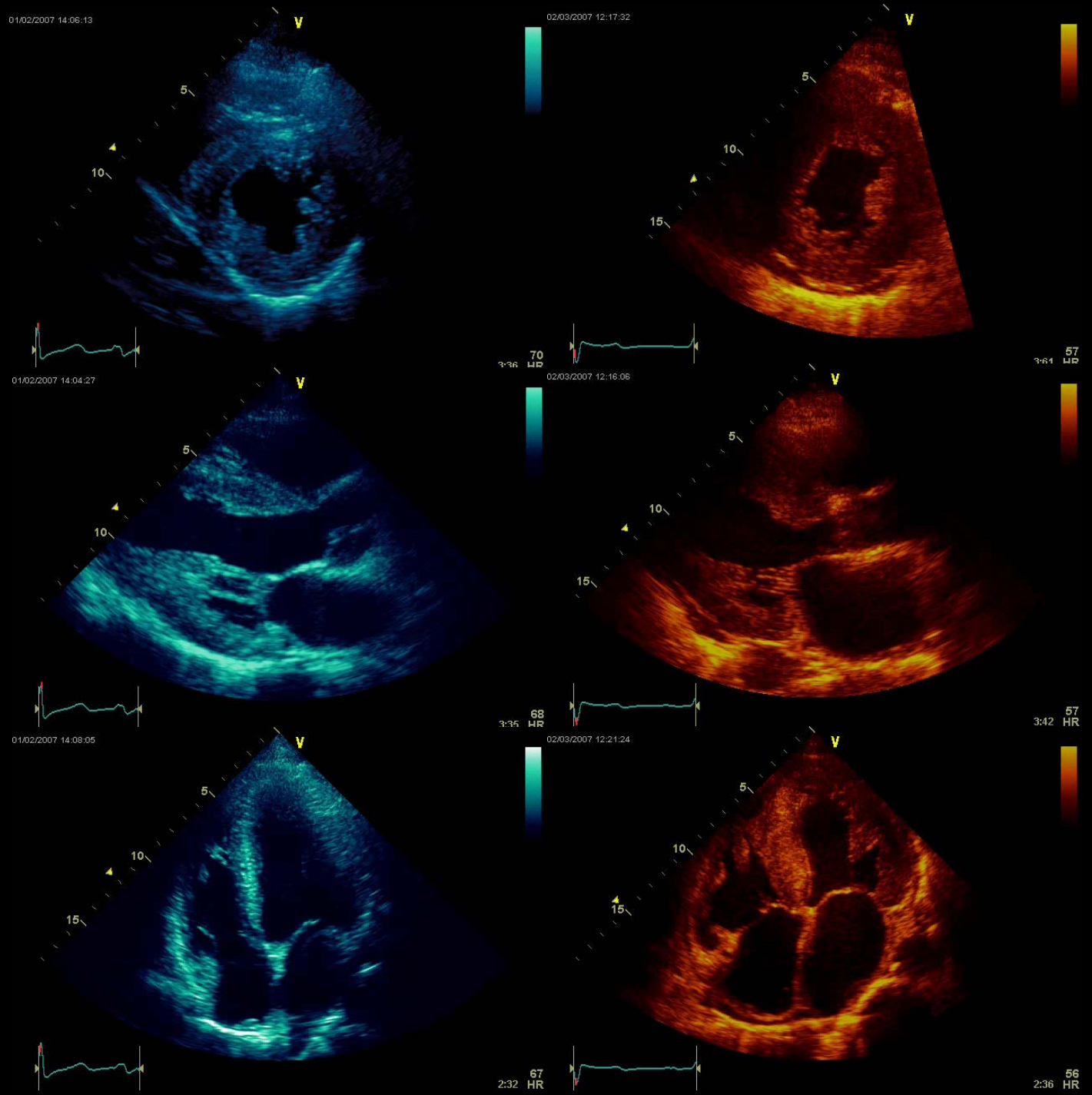
Current and developing treatment of systemic amyloidosis

- Supportive – maintain and replace function of failing organs if possible
- Reduce production of fibril precursor proteins to stop amyloid formation & allow regression
- Inhibit misfolding of precursors and amyloid fibrillogenesis
- **BUT REMOVAL OF AMYLOID FROM THE TISSUES IS CLEARLY DESIRABLE**

Cardiac amyloid



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01/02/2007 14:08:05
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70
57
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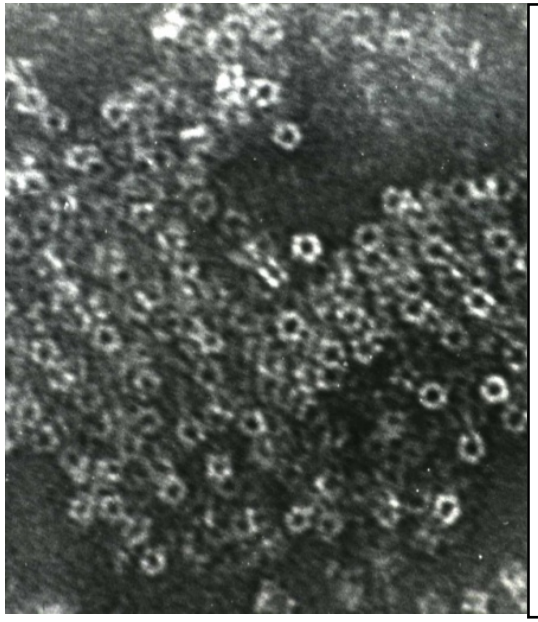
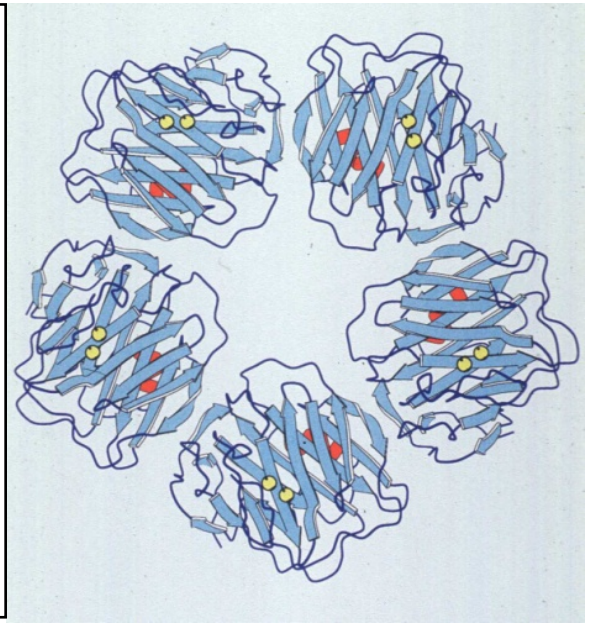
67
56

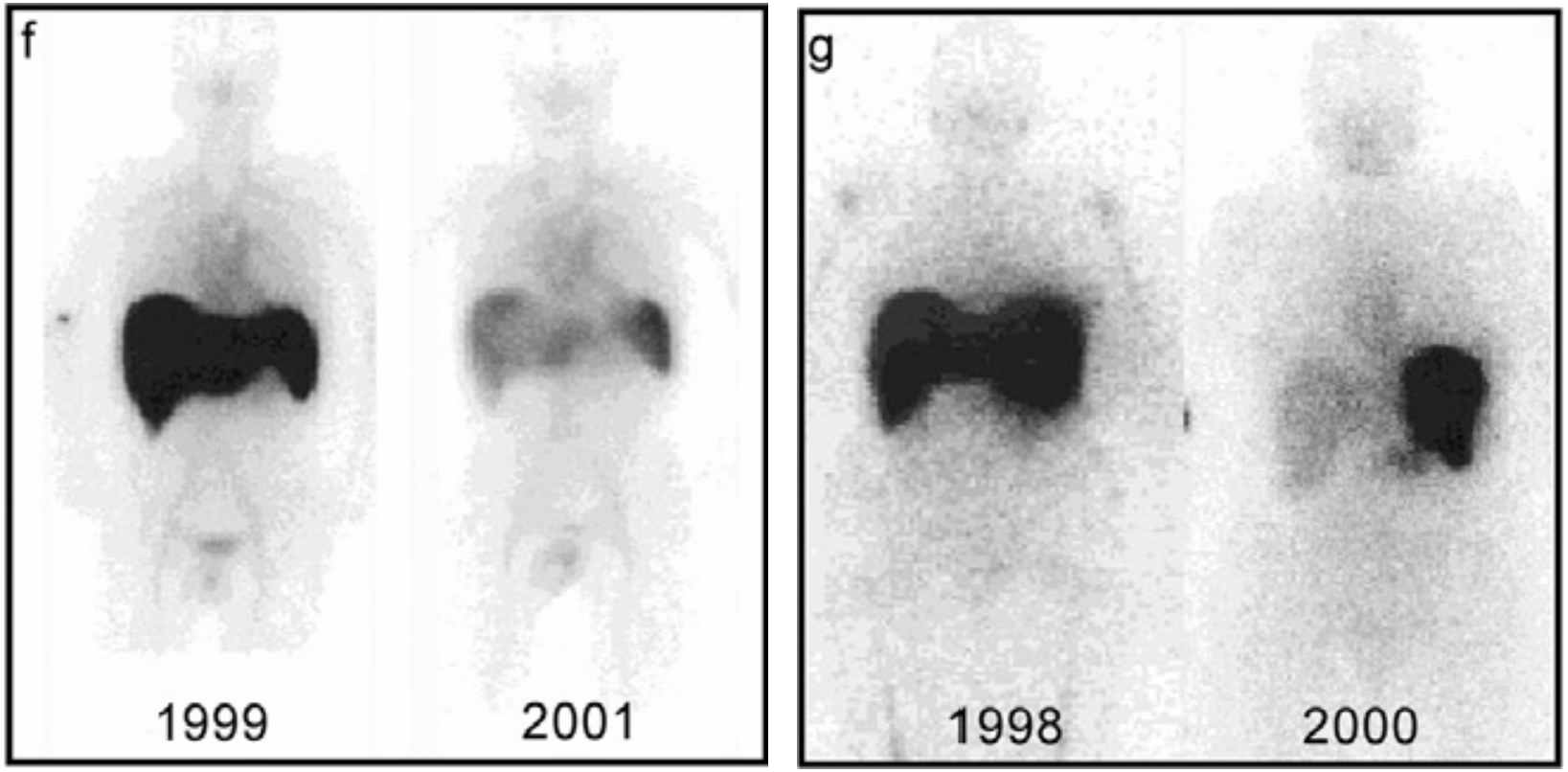
Serum amyloid P component (SAP)

Normal plasma pentraxin protein; universal minor constituent of amyloid deposits; contributes to amyloid formation & persistence





Whole body scintigraphy with ^{123}I-labelled SAP



SAP in amyloid formation & persistence

- SAP is universal in amyloid deposits (1965)
- SAP binds to all amyloid fibril types (1977)
- SAP in amyloid is not degraded (1994)
- SAP is protease resistant & binding to amyloid fibrils stabilises & protects them from degradation (1995)
- SAP promotes amyloid fibrillogenesis (1995)
- SAP knockout mice show retarded, reduced systemic amyloid deposition (1997)

Targeting SAP

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*

* *Centre for Amyloidosis and Acute Phase Proteins, Department of Medicine, Royal Free and University College Medical School, London NW3 2PF, UK*
† *Preclinical CNS Research, Pharmaceutical Division, F Hoffmann-La Roche Ltd, CH-4070 Basel, Switzerland*
§ *Institute of Molecular Embryology and Genetics, and Center for Animal Resources and Development, Kumamoto University, Japan*
|| *Division of Medicine, Imperial College School of Medicine, London W12 0NN, UK*
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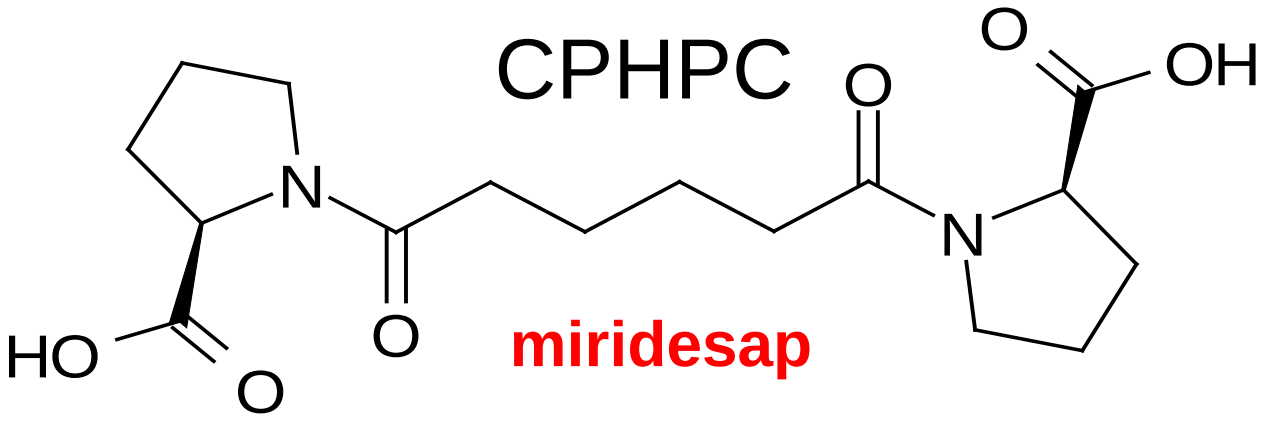
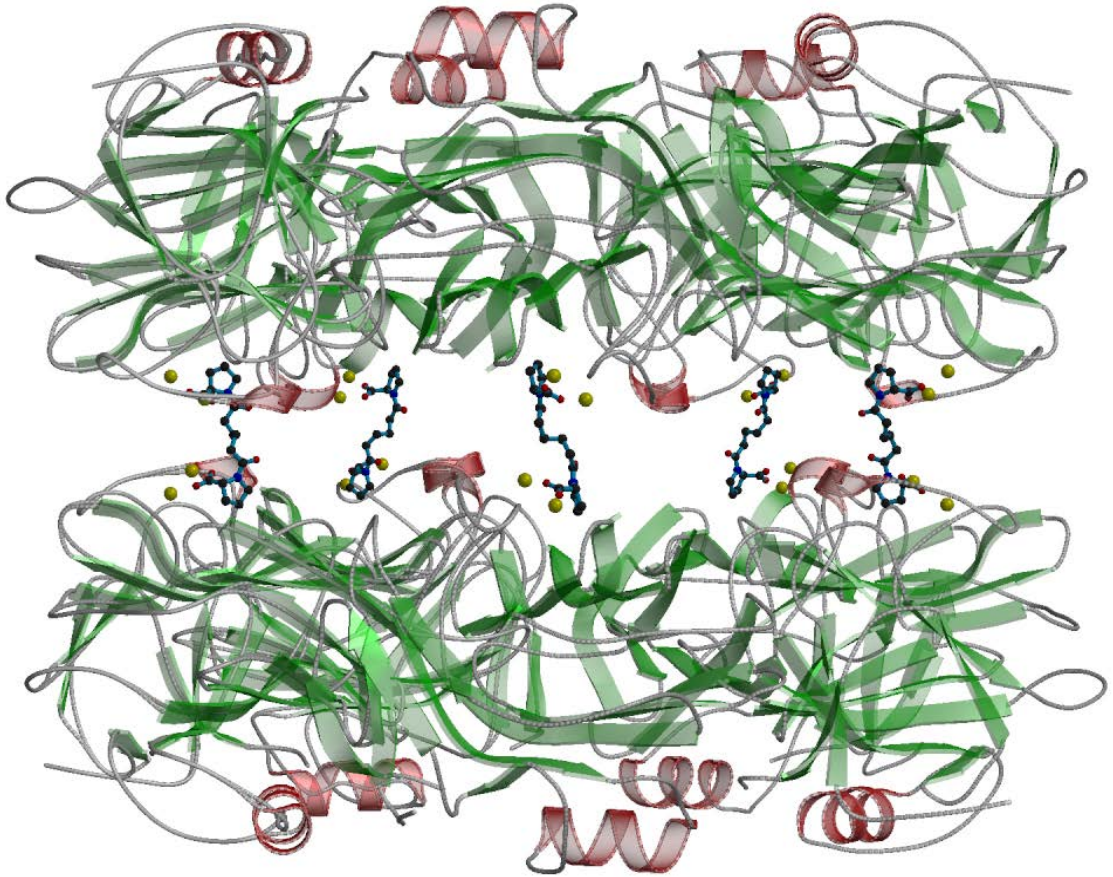
The normal plasma protein serum amyloid P component (SAP) binds to fibrils in all types of amyloid deposits, and contributes to the pathogenesis of amyloidosis. In order to intervene in this process we have developed a drug, *R*-1-[6-[*R*-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid, that is a competitive inhibitor of SAP binding to amyloid fibrils. This palindromic compound also crosslinks and dimerizes SAP molecules, leading to their very rapid clearance by the liver, and thus produces a marked depletion of circulating human SAP. This mechanism of drug action potently removes SAP from human amyloid deposits in the tissues and may provide a new therapeutic approach to both systemic amyloidosis and diseases associated with local amyloid, including Alzheimer's disease and type 2 diabetes.

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

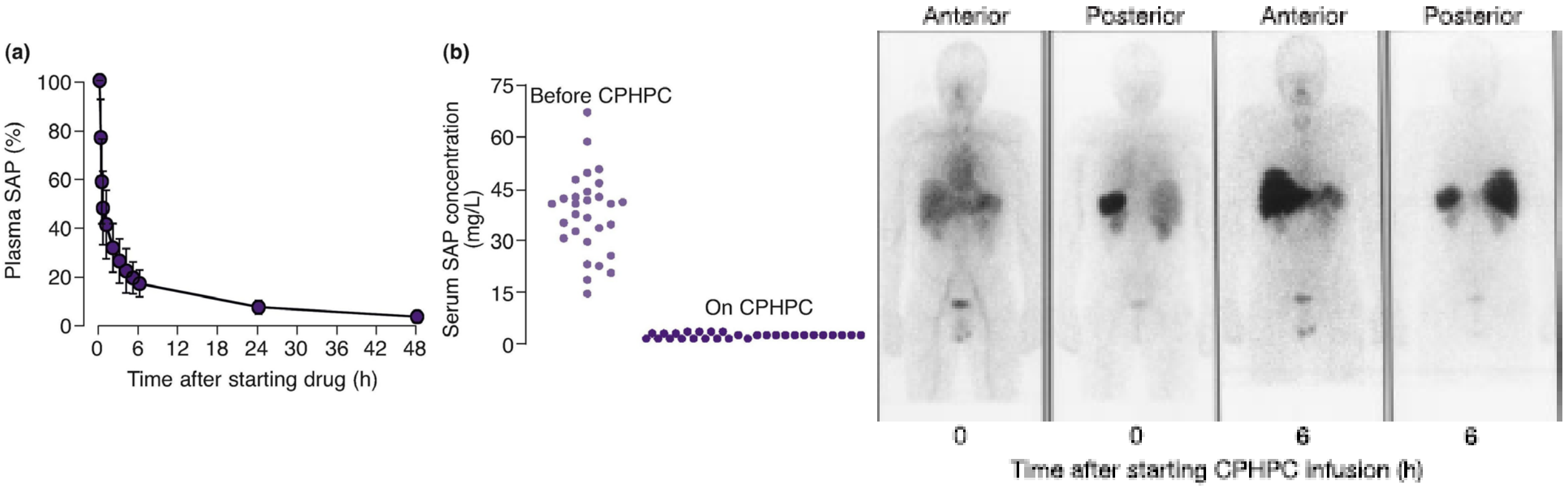


miridesap

K_d 10 nM



Effect of miridesap on plasma SAP



Pepys *et al* (2002) Targeted pharmacological depletion of serum amyloid P component for treatment of human amyloidosis. *Nature* **417**: 254-259.

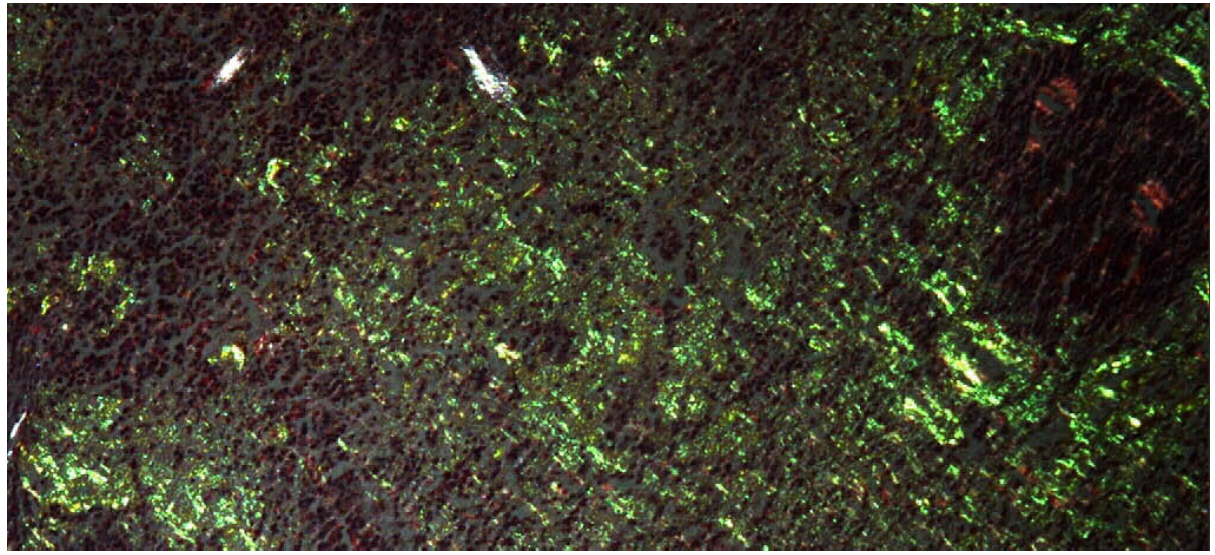
Miridesap in systemic amyloidosis patients

- No adverse clinical effects
- No laboratory test or organ function abnormalities attributable to miridesap or SAP depletion
- Plasma SAP depleted throughout; but avid SAP binding to amyloid means that only ~90% of SAP removed from amyloid
- Most patients remain stable but no amyloid regression

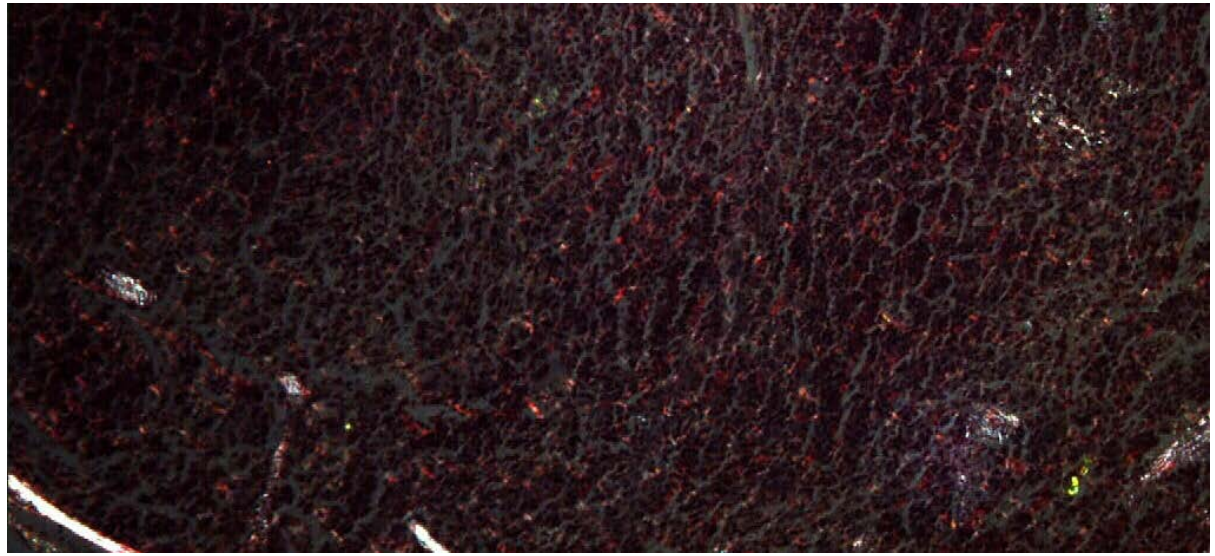
Elimination of amyloid deposits 2005

- Miridesap depletes circulating SAP but leaves some SAP in amyloid deposits
- Anti-SAP antibodies can then be safely given and remain available to target deposits
- Antibody binding triggers complement activation and macrophage dependent clearance of amyloid

Amyloidotic spleen day 28 post antibody



Control IgG



Anti-SAP antibody

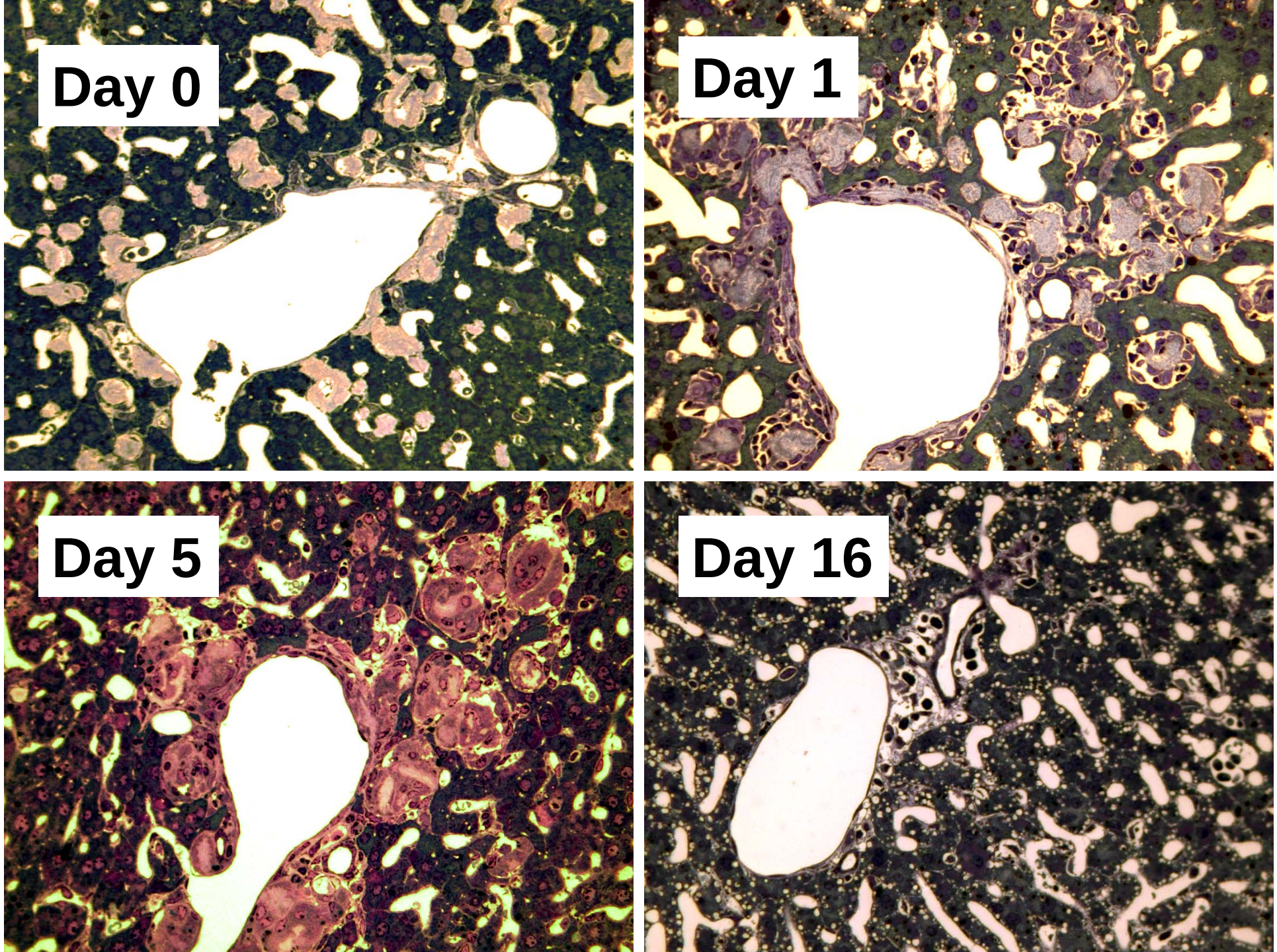
Elimination of amyloid deposits

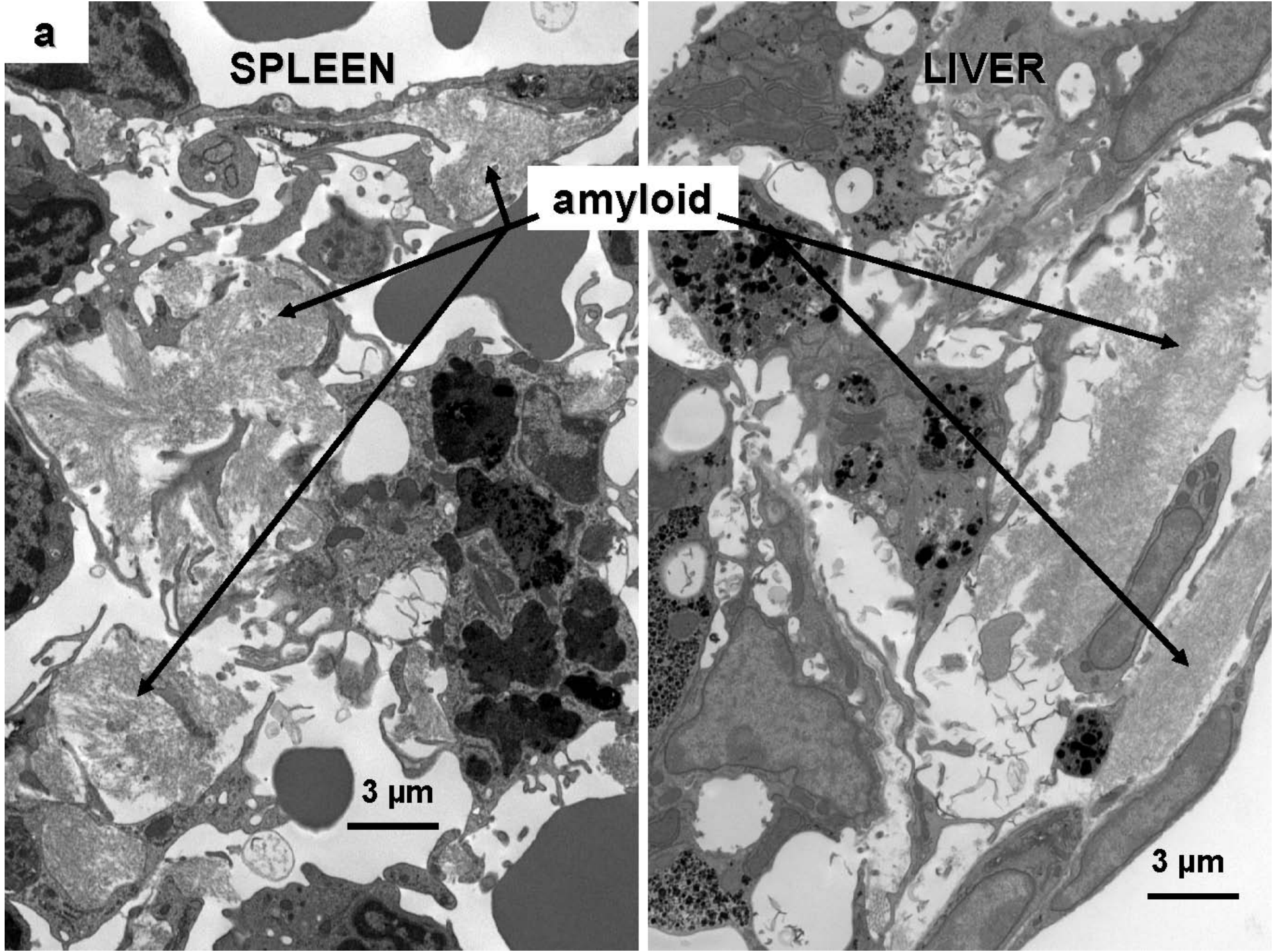
4 NOVEMBER 2010 | VOL 468 | NATURE | 93

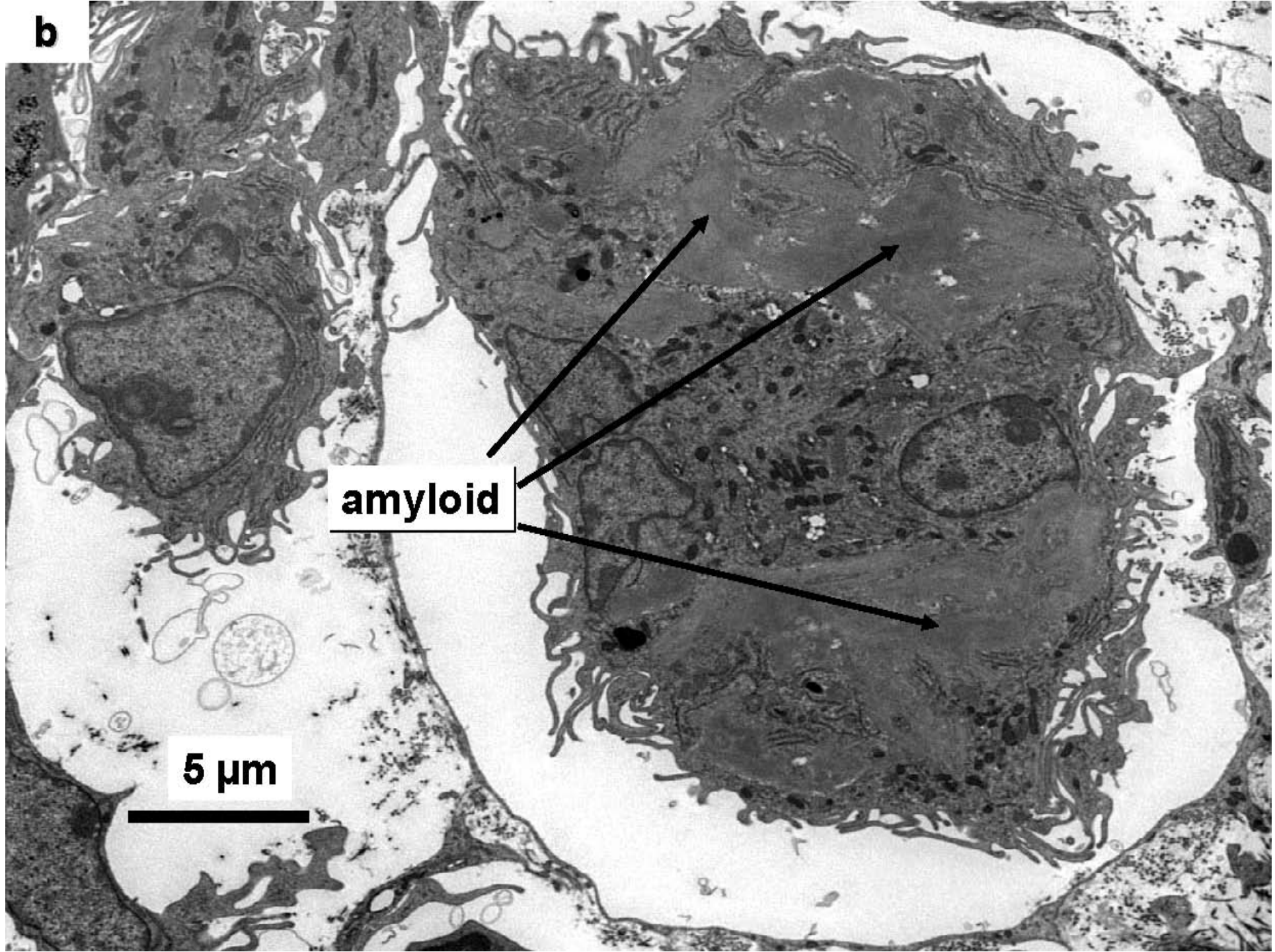
doi:10.1038/nature09494

Antibodies to human serum amyloid P component eliminate visceral amyloid deposits

Karl Bodin[1]*, Stephan Ellmerich[1]*, Melvyn C. Kahan[1], Glenys A. Tennent[1], Andrzej Loesch[1], Janet A. Gilbertson[1], Winston L. Hutchinson[1], Palma P. Mangione[1,2], J. Ruth Gallimore[1], David J. Millar[1], Shane Minogue[3], Amar P. Dhillon[4], Graham W. Taylor[1], Arthur R. Bradwell[5,6], Aviva Petrie[7], Julian D. Gillmore[1], Vittorio Bellotti[1,2], Marina Botto[8], Philip N. Hawkins[1] & Mark B. Pepys[1]


Day 0
Day 1
Day 5
Day 16


a
SPLEEN
LIVER
amyloid
3 µm
3 µm


b
amyloid
5 µm

Multinucleated giant cells *in vitro*

- Derived by macrophage fusion
- Abundant ‘extra’ plasma membrane forming membrane ruffles
- Pre-activated C3 receptors, down regulated Fc receptors
- Surround and internalise large complement opsonised objects

Milde *et al* (2015) Multinucleated giant cells are specialized for complement-mediated phagocytosis and large target destruction *Cell Reports*, **13**: 1937-48.

Obligate therapeutic partnership

- Miridesap alone does not promote amyloid regression
- Anti-SAP antibody (dezamizumab) cannot be administered without prior and continuing depletion of circulating SAP by miridesap
- Miridesap uniquely enables anti-SAP antibodies to safely trigger complement mediated removal of amyloid deposits by macrophage derived multinucleated giant cells

Drug development – the good news

- Anti-SAP mAb fully humanised for therapy (dezamizumab)
- Phase 1 study of miridesap alone & followed by dezamizumab
- Generally well tolerated in patients
- Unequivocal evidence of amyloid removal
- Improved liver function
- Encouraging cardiac safety

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Therapeutic Clearance of Amyloid by Antibodies to Serum Amyloid P Component

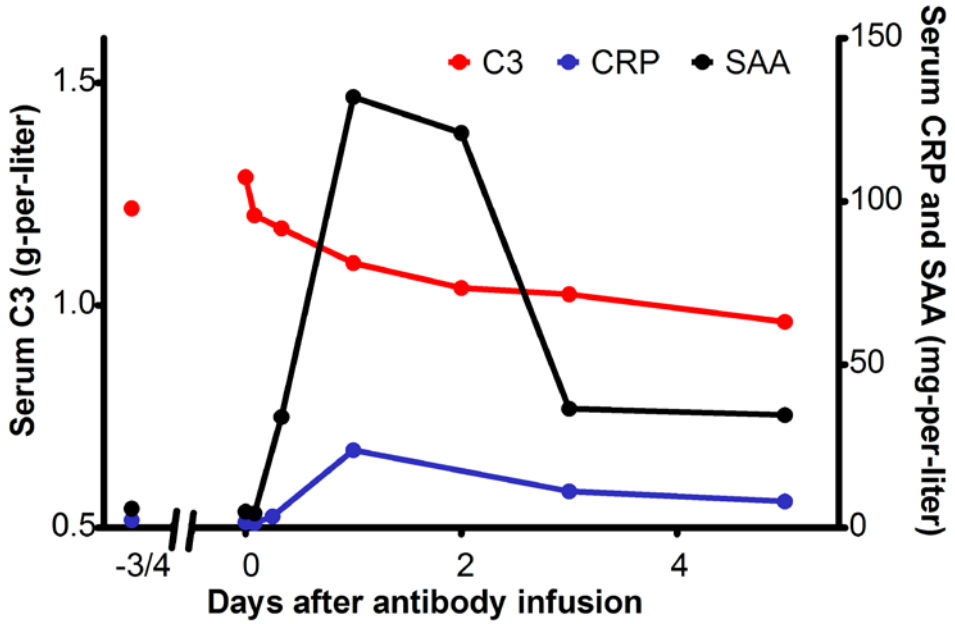
Duncan B. Richards, D.M., Louise M. Cookson, B.Sc.,
Alienor C. Berges, Pharm.D., Sharon V. Barton, M.Sc.,
Thirusha Lane, R.N., M.Sc., James M. Ritter, D.Phil., F.Med.Sci.,
Marianna Fontana, M.D., James C. Moon, M.D., Massimo Pinzani, M.D., Ph.D.,
Julian D. Gillmore, M.D., Ph.D., Philip N. Hawkins, Ph.D., F.Med.Sci.,
and Mark B. Pepys, Ph.D., F.R.S.

N Engl J Med 2015;373:1106-14.

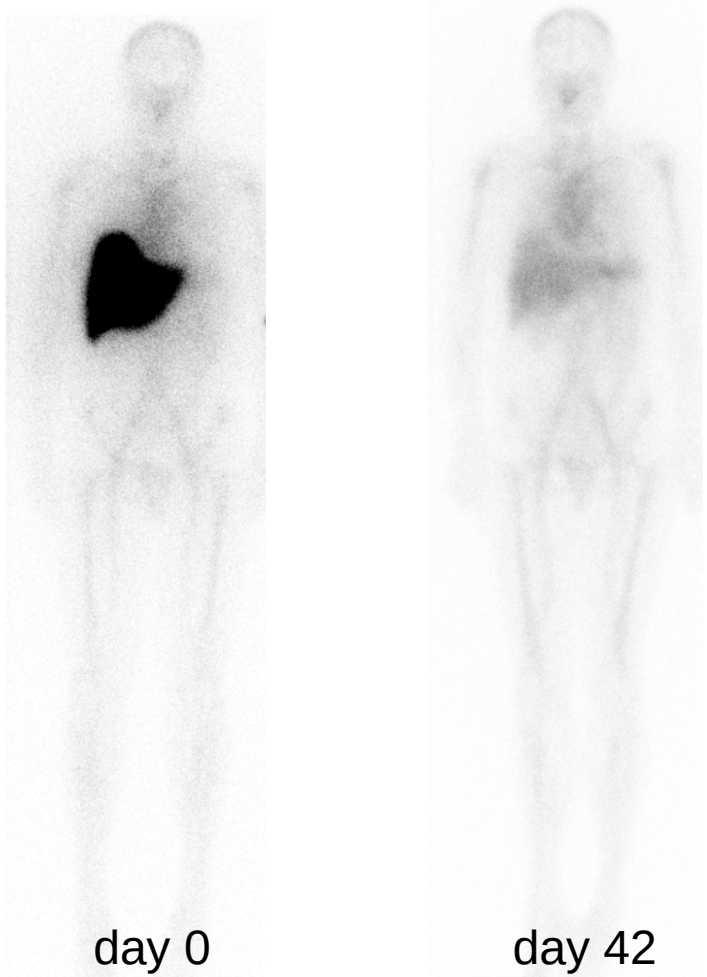
NEJM 2015, **373**:1106-14. Subject 13

AL amyloidosis: large liver, moderate spleen, small kidney, bone marrow, amyloidotic lymph node.
650 mg dezamizumab (10.2 mg/kg)

Complement depletion & acute phase response



^{123}I-SAP scintigraphy



	day 0 pre-dose	day 42 post-dose
^{123}I-SAP retention in liver (% injected dose)	61.1%	17.4%
Liver ECV (median normal 29%)	36%	29%
Liver Stiffness (median normal 5.3 kPa)	5.7 kPa	2.8 kPa

SCIENCE TRANSLATIONAL MEDICINE | REPORT

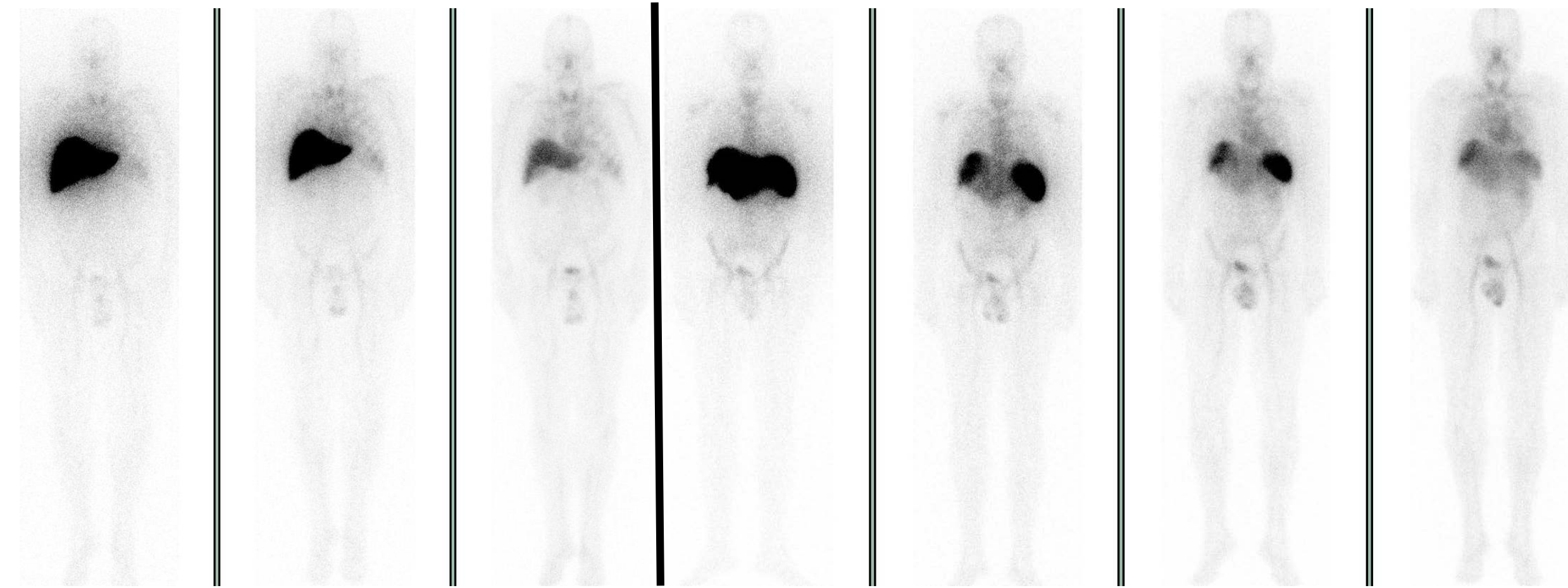
SYSTEMIC AMYLOIDOSIS

Repeat doses of antibody to serum amyloid P component clear amyloid deposits in patients with systemic amyloidosis

Duncan B. Richards,[1] Louise M. Cookson,[1] Sharon V. Barton,[1] Lia Liefaard,[1] Thirusha Lane,[2] David F. Hutt,[2] James M. Ritter,[3] Marianna Fontana,[2] James C. Moon,[4] Julian D. Gillmore,[2] Ashutosh Wechalekar,[2] Philip N. Hawkins,[2] Mark B. Pepys[2,5]*

Sci. Transl. Med. **10**, eaan3128 (2018) 3 January 2018

Progressive amyloid removal



Before dosing

Post 1st dose

Post 2nd dose

Before dosing

Post 1st dose

Before 2nd dose

Post 2nd dose

Key changes in hepatic amyloidosis patients

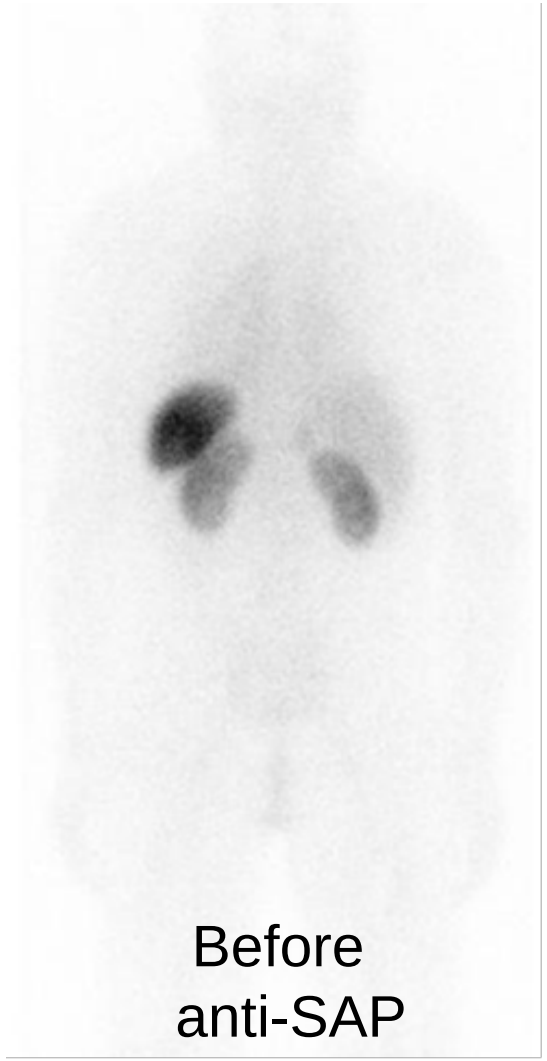
Case	mAb dose (mg)	Amyloid type	Amyloid load by SAP scan	Baseline liver ECV	Day 42 liver ECV	Baseline liver stiffness	Day 42 liver stiffness	Pre-dose GGT	Day 42 GGT
F	152	AL	No change	**0.45**	0.50	**10.4**	9.8	**93**	96
	600		No change	0.40	0.43	8.4	5.9	74	79
	2000		Liver and spleen reduced	0.40	**0.37**	6.3	**4.9**	66	**67**
G	246	AL	Liver reduced	**0.37**	0.33	**14.4**	8.9	**135**	98
	592		Spleen reduced	0.30	**0.24**	5.7	**8.9**	44	**43**
H	637	ApoAI	Liver reduced	**0.48**	0.42	**24.2**	11.9	**714**	331
	1000		No change	0.46	0.44	17.8	8.9	264	278
	2000		Liver and spleen reduced	0.40	**0.40**	12.5	**6.6**	283	**211**
I	400	AL	No change	0.58	0.61	**46.5**	25.7	**181**	158
	1200		No change	0.61	0.66	48.0	28.0	166	125
	2000		Liver better	0.53	0.56	27.3	**16.9**	129	**88**
J	650	AL	Liver reduced	0.54	0.53	27.0	15.7	466	411
	1000		No change	0.58	0.63	28.0	23.9	401	465
	2000		No change	0.65	0.63	35.3	27.0	526	751
L	650	AL	Liver reduced	0.36	0.29	**5.7**	2.8	20	16
	600		Kidney reduced	0.33	0.35	3.3	**3.7**	14	18
			Adrenal reduced						
M	600	AL	Liver reduced	**0.35**	0.34	**8.9**	4.4	**148**	96
	1000		Liver reduced	0.34	0.32	4.3	7.5	60	44
	500		Liver worse	0.31	**0.32**	4.8	**4.8**	32	**33**
N	600	AL	No change	**0.42**	0.38	4.9	5.2	27	19
	2000		Spleen reduced	0.43	**0.37**	6.3	4.2	24	18
O	600	AL	No change	**0.45**	0.43	**27.7**	27.0	**274**	240
	1998		No change	0.43	0.40	35.3	17.3	161	126
	1998		Liver reduced	0.36	**0.33**	14.8	**13.3**	106	**77**
R	1998	AL	No change	0.42	0.43	26.6	32.0	69	70

Median normal ECV, 0.29; liver stiffness, 5.3 kPa (90% <7.0); GGT, 5-45 IU/L

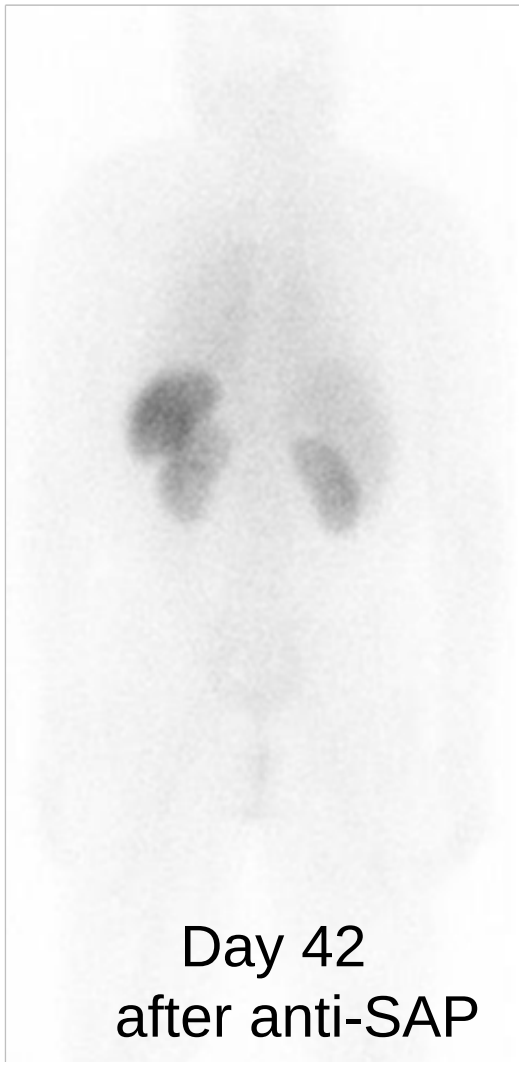
Subject J entered clonal relapse after first dosing session. Subject M developed rash in session 3 and received only half the planned 1000 mg dose. They also entered clonal relapse in session 2.

Reduction of renal and spleen AFib amyloid

^{123}I-SAP retention
before & after treatment:
spleen, 5.3% & 3.8%;
kidneys, 8.2% & 5.7%



Before
anti-SAP



Day 42
after anti-SAP

Conclusions

- Anti-SAP immunotherapy, with miridesap and dezamizumab, is applicable to all forms of systemic amyloidosis
- Removal of amyloid will improve clinical status
- Should increase efficacy of interventions to reduce amyloid formation
- Encouraging potential to improve outcomes and prolong survival

Drug development – the bad news

- Suboptimal phase 2 cardiac amyloidosis clinical trial design
- July 2018, GSK assessment of initial results: unfavourable risk-benefit profile
- September 2018, GSK divests its whole rare diseases portfolio
- October 2018, GSK terminates development of miridesap and dezamizumab for systemic amyloidosis
- Unlikely to be developed further by others

Immunotherapy for amyloidosis?

- Proof of concept rigorously established
- Unprecedented clinical efficacy of anti-SAP approach
- Safety acceptable to amyloidosis specialist physicians
- Alternative, novel antibody therapy exists
- Effective in experimental models
- No reason why it won’t be effective clinically
- BUT funding and prolongation of the inventor’s life span badly needed!

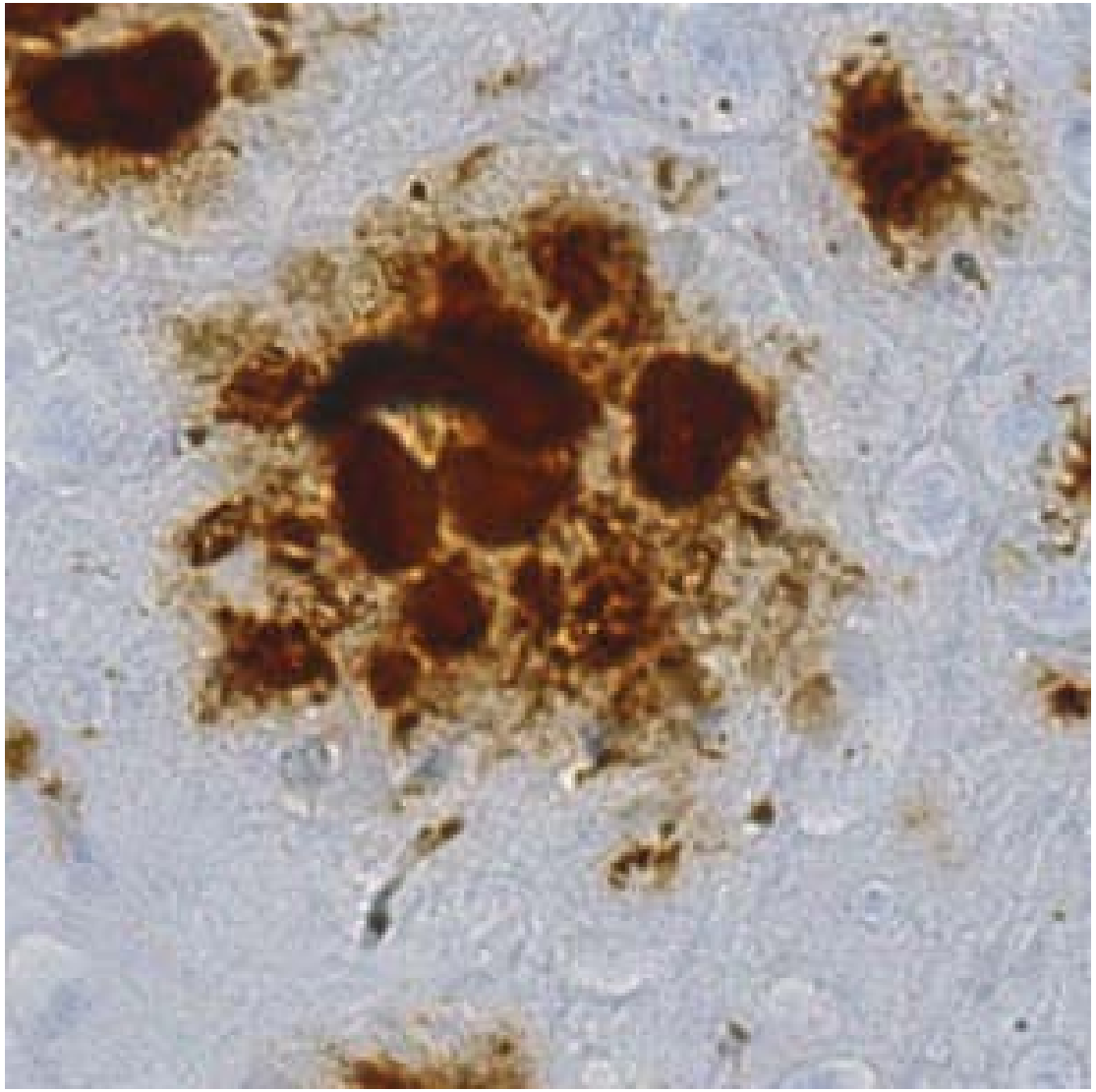
Dementia & Alzheimer's disease

- >35 million affected worldwide, doubling every 20 years
- G8 2013 'Declaration on Dementia'
  "cure or disease modifying treatment by 2025!"
- Worldwide cost of dementia care >US$400 billion
- Alzheimer's disease is the most common cause of dementia
- Large scale clinical trials, US$billions: no effective treatments
- Focus on APP/Aβ pathway, cerebral amyloid plaques and NFT
- Actual cause of neurodegeneration unknown

Amyloid, SAP & Alzheimer's

- Neuropathology of AD: cerebral Aβ amyloid plaques, cerebrovascular Aβ amyloidosis, neurofibrillary tangles (NFT), neurodegeneration
- SAP present on all amyloid deposits, extracellular NFT and most intracellular NFT; brain SAP content increased in dementia
- SAP enhances Aβ amyloid fibril formation and persistence
- SAP itself is directly neurotoxic for some cerebral neurones

Human SAP in Aβ amyloid plaque



SAP on Aβ plaques and tau NFT in AD brain

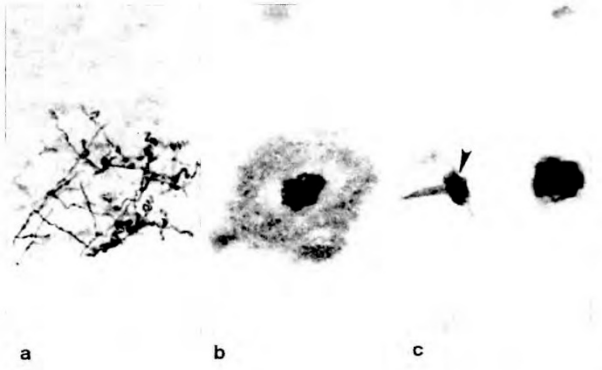


Fig. 1 a–c. Senile plaques (SP) labeled by amyloid P component (AP) antisera. **a** Neocortical SP containing only dystrophic neurites, ×360. **b** SP with amyloid fibrils and core, ×630. **c** SP displaying core only. Note adjacent AP-labeled neurofibrillary tangle (NFT; *arrowhead*), ×630

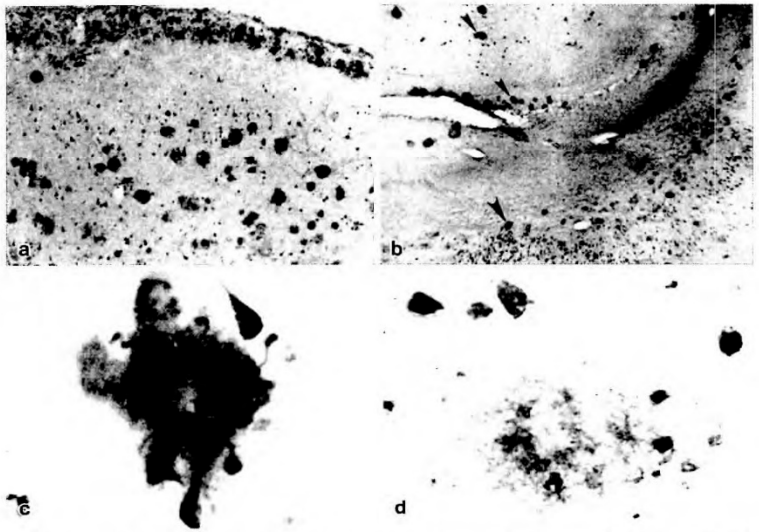
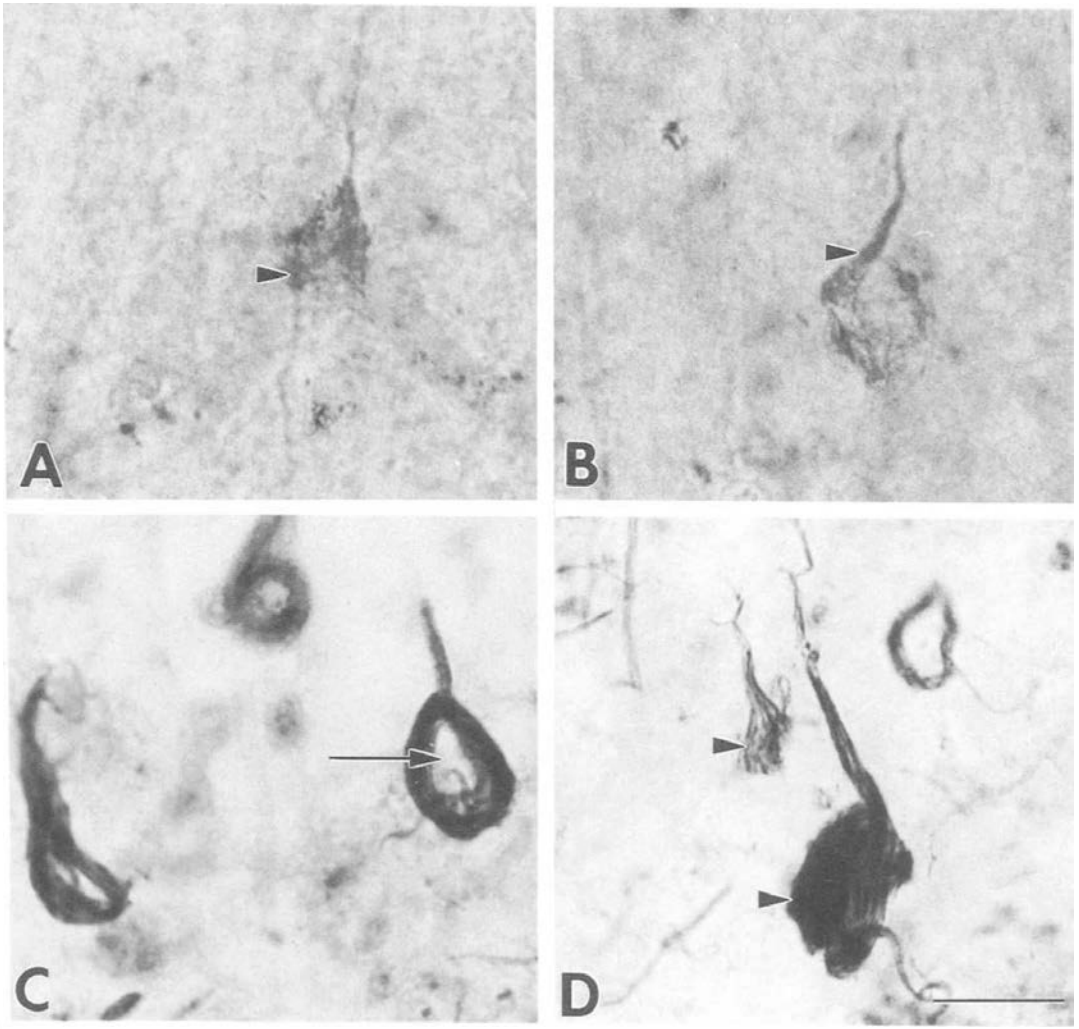


Fig. 2. **a** AP labeled neocortex. Note distribution of immunoreactive SP in cortical layers, ×40. **b** AP-labeled hippocampal formation. Note SP in subiculum, area dentata and CA4 (*arrowheads*), ×22. **c** SP in cortical layer III with labeled NFT, ×660. **d** AP-labeled SP in CA4 of hippocampus, ×288



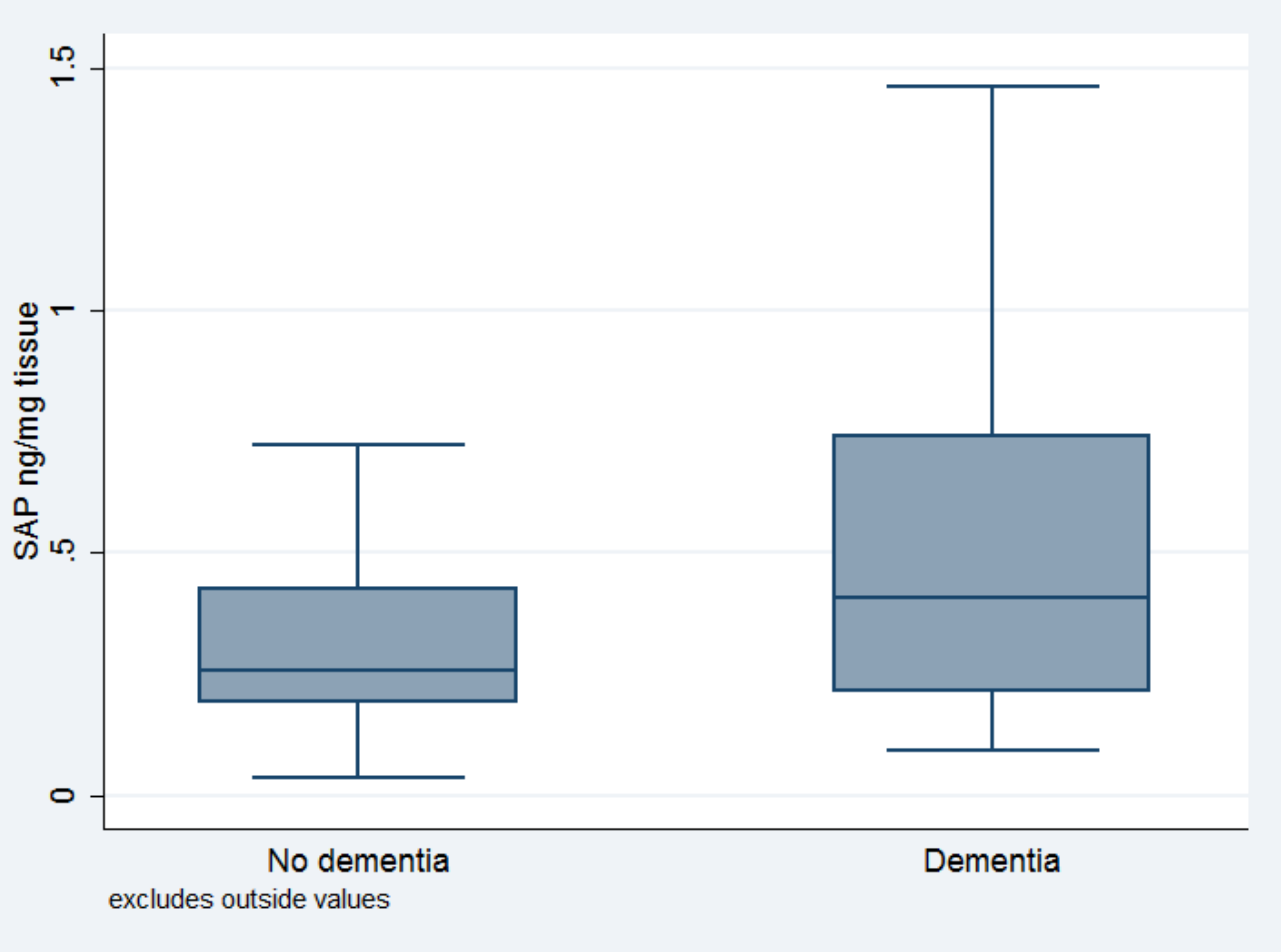
Human SAP & neurodegeneration

- Human CSF:plasma SAP concentration = 1:1,000
- SAP penetrates BBB very poorly *cf* other plasma proteins &/or is actively removed
- Conditions predisposing to/causing dementia increase brain exposure to SAP:
  - old age
  - AD, CAA, other cerebral amyloid & NFT neuropathology
  - non-penetrating head injury & traumatic brain injury
  - cerebral haemorrhage

Increased brain exposure to SAP & risk of dementia

- Age: normal cognitive decline; risk of Alzheimer's disease
- Cerebral amyloid & NFT: SAP concentrated at sites of neurodegeneration
- NFT loaded SAP in frontotemporal dementia
- Non-penetrating head injury: boxers, soldiers, NFL football and rugby players
- Traumatic brain injury: chronic traumatic encephalopathy, Aβ amyloid deposition, dementia
- Cerebral haemorrhage/stroke

Cognition at death & brain SAP content



SAP content in temporal cortex in 136 subjects in the Cognitive Function in Ageing Study

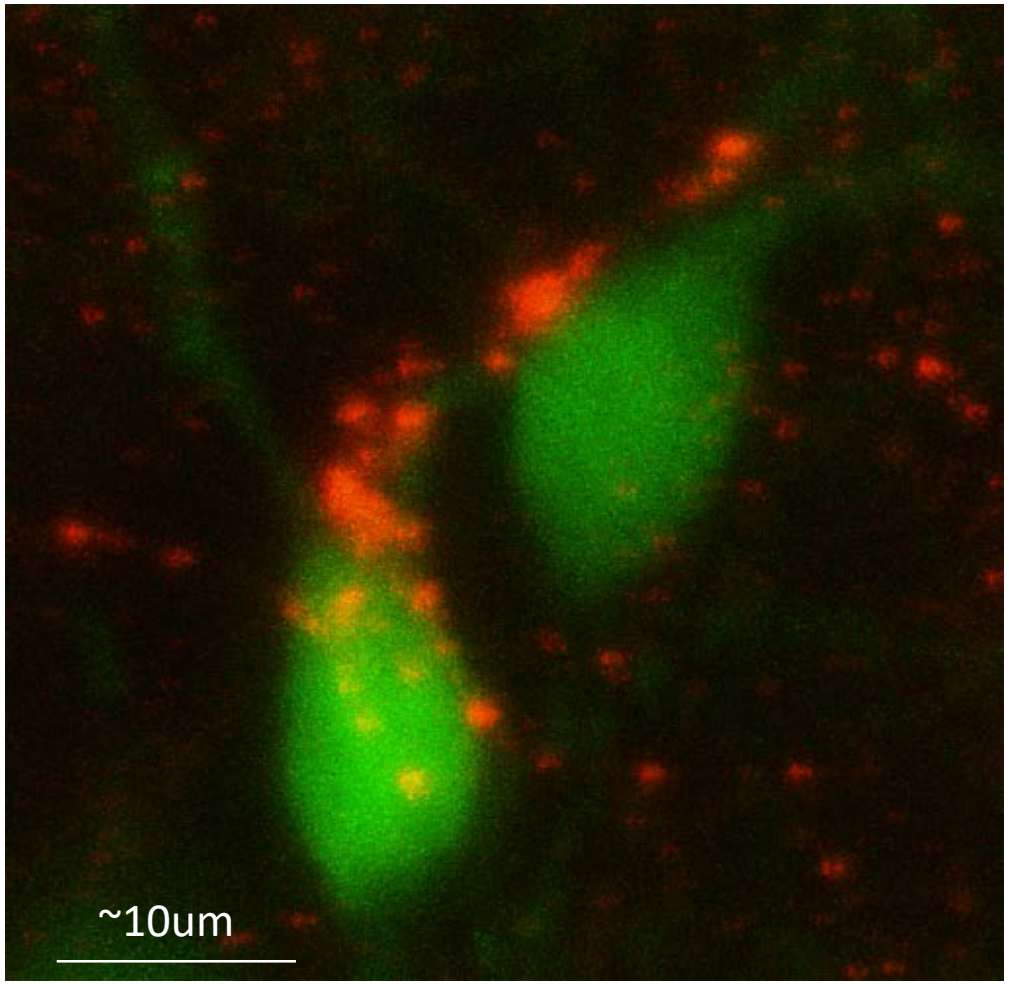
	Dementia status	Mean	SD	Median	Interquartile range
SAP ng/mg tissue	Normal	0.31	0.17	0.26	(0.19; 0.43)
	Dementia	0.58	0.64	0.41	(0.21; 0.74)

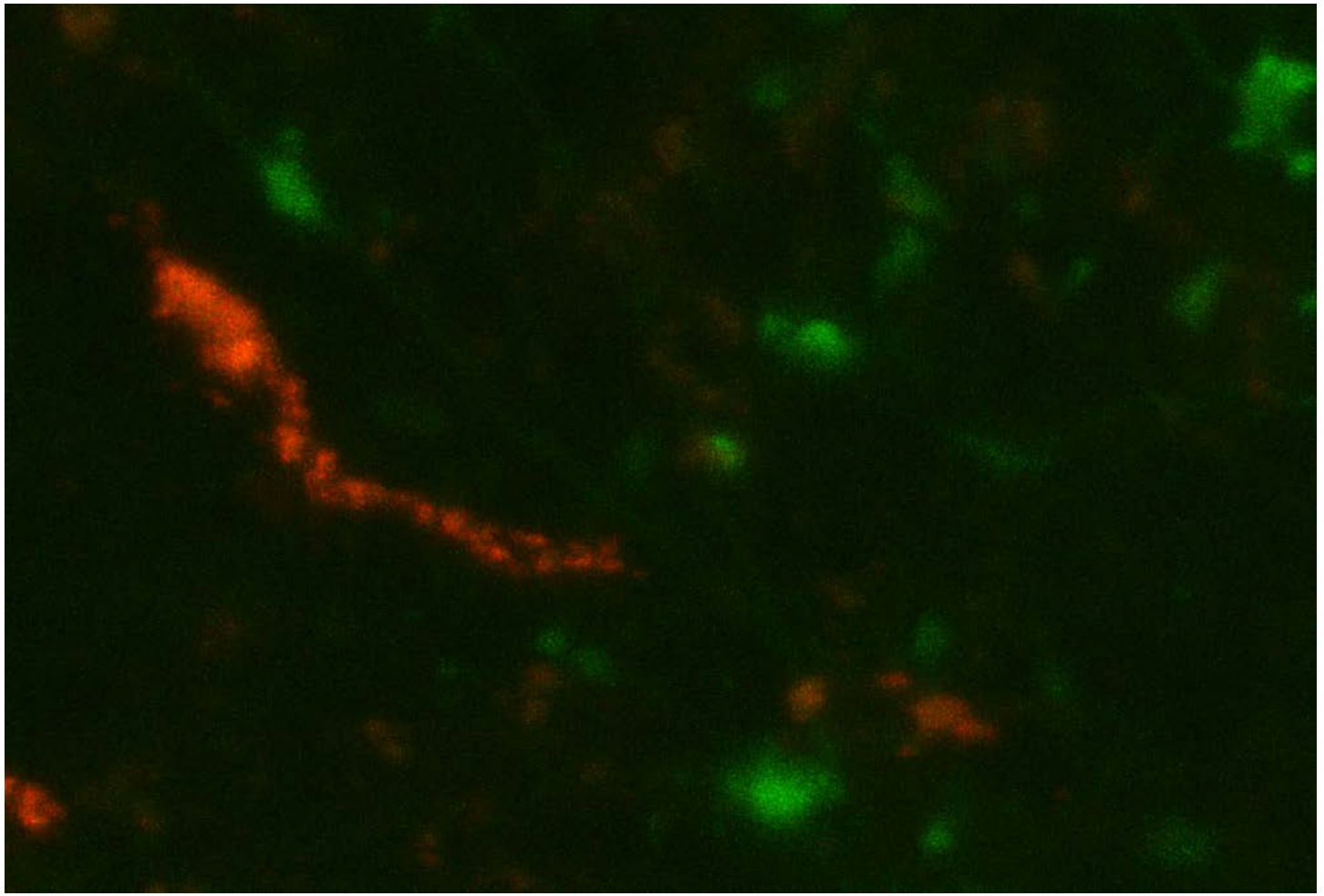
Logistic regression analysis

	OR	95%CI (OR)	p
SAP ng/mg tissue	14.08	(2.83; 70.07)	0.001

n (no dementia: dementia) 58:78

Binding & internalisation of human SAP in cerebral neurones



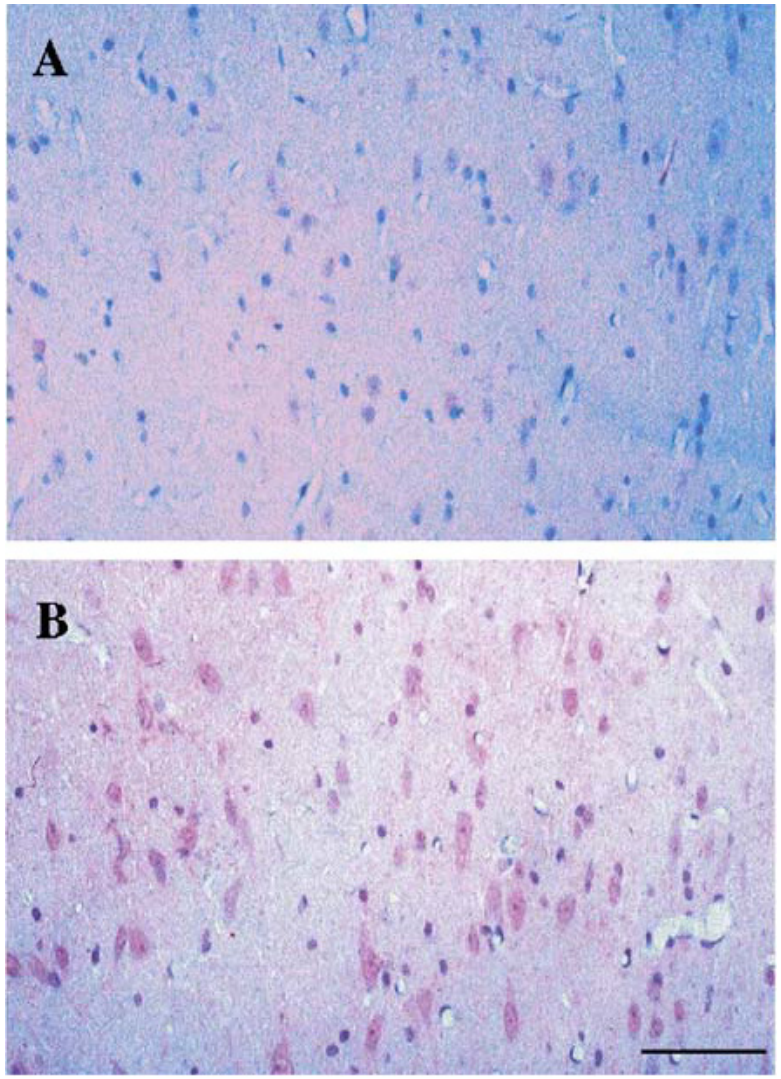


Human SAP enters neurones *in vivo* causing apoptosis

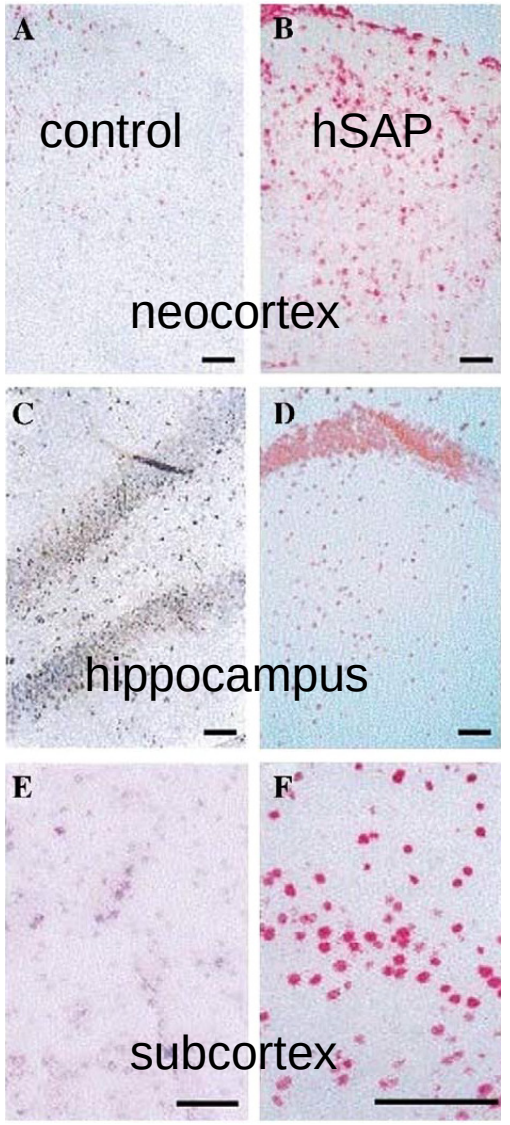
Immunostaining for human SAP after intrahippocampal injection in rat

Control injection

Human SAP



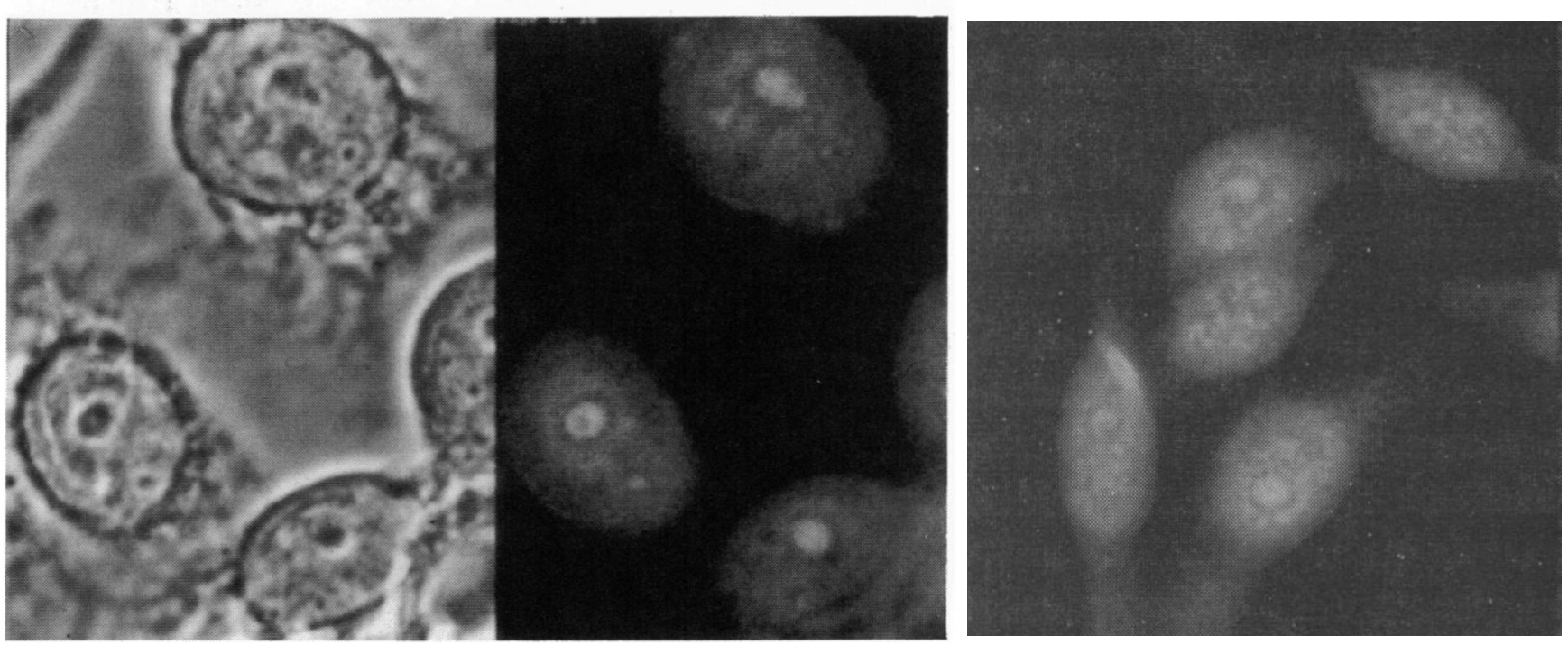
TUNEL-+ve nuclei



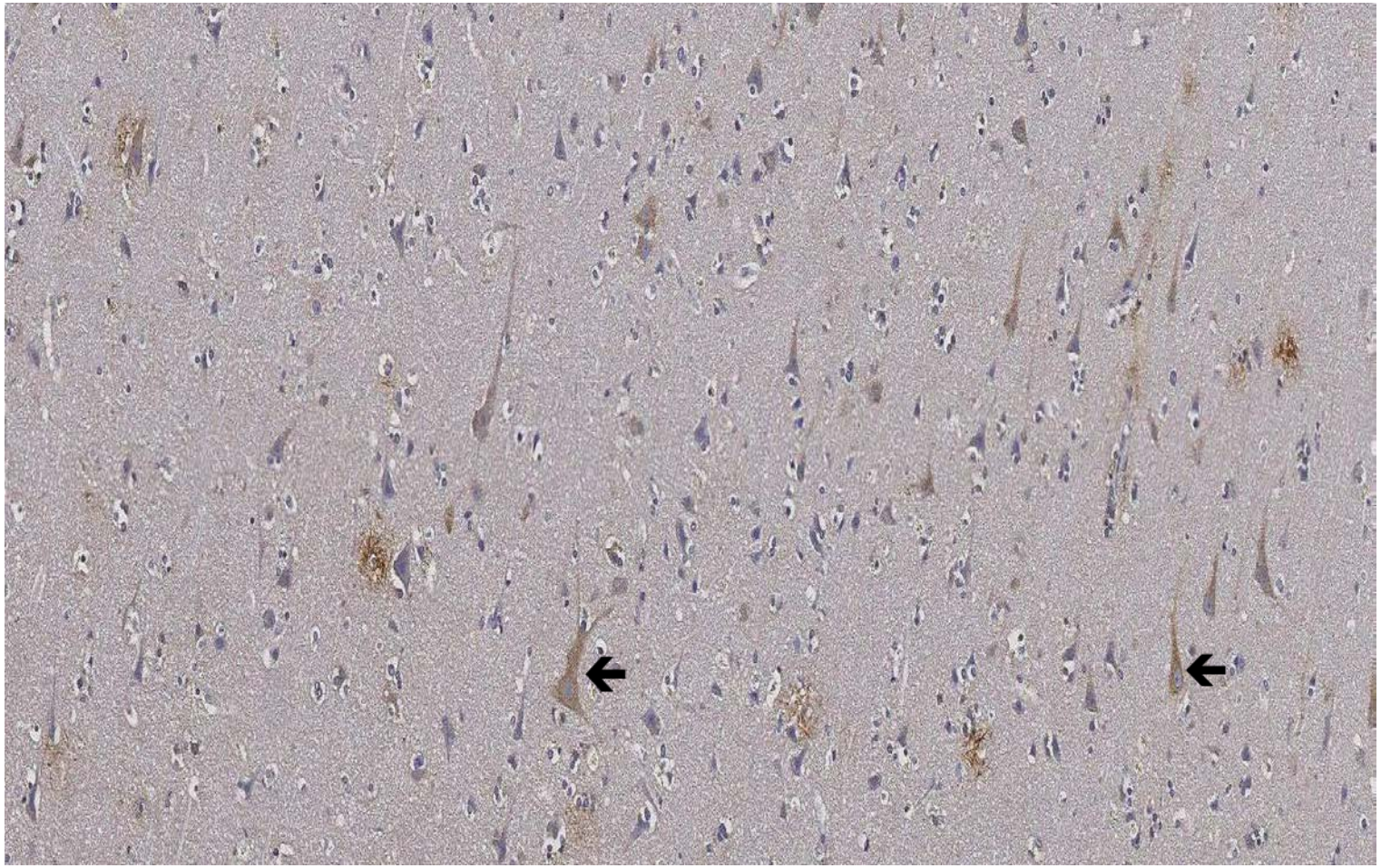
Mechanism of human SAP neurotoxicity?

Human SAP:

- binds avidly to DNA and chromatin
- contains nuclear localisation sequence PLVKKGLRQ
- from cytoplasm rapidly enters nucleus & binds to chromatin



Human SAP in ‘normal’ aged brain



Molecular dissection of Alzheimer's disease neuropathology by depletion of serum amyloid P component

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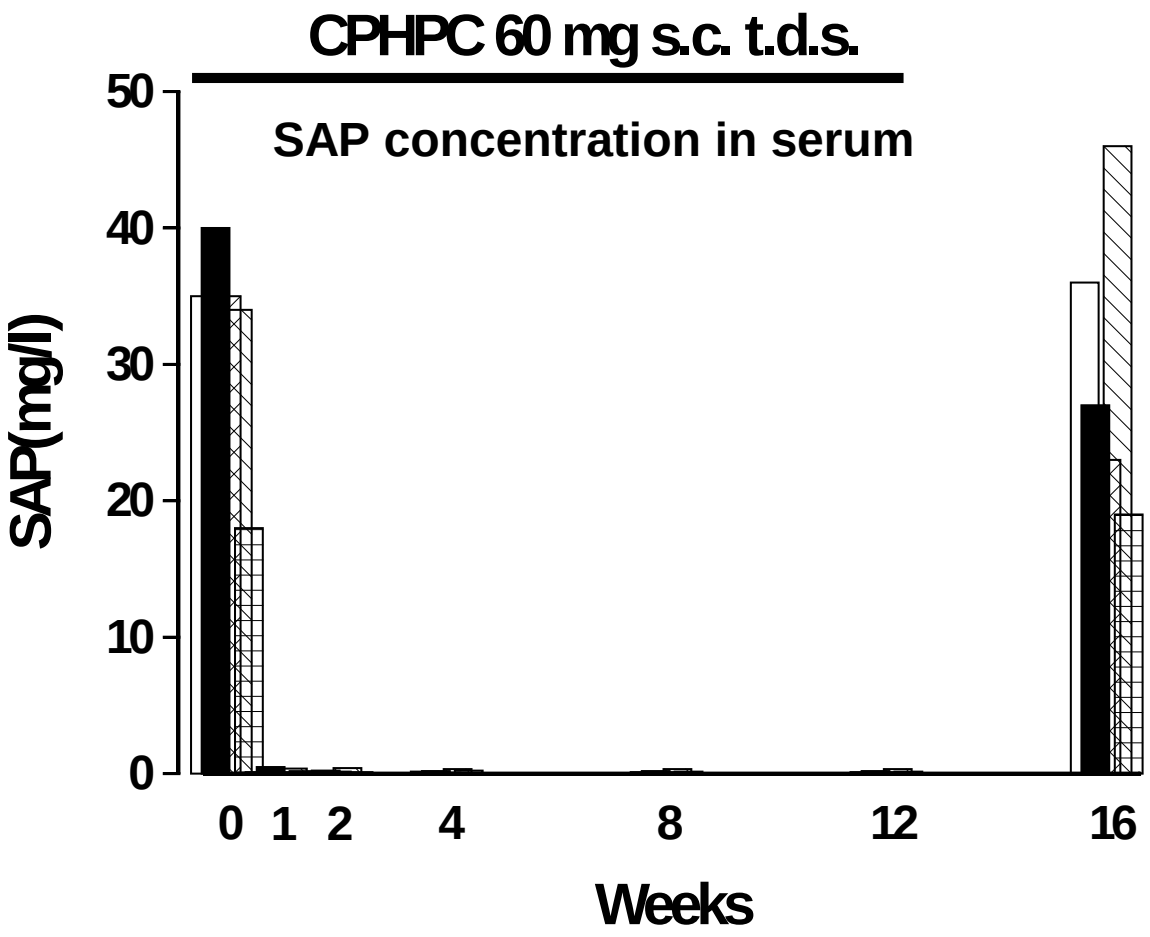
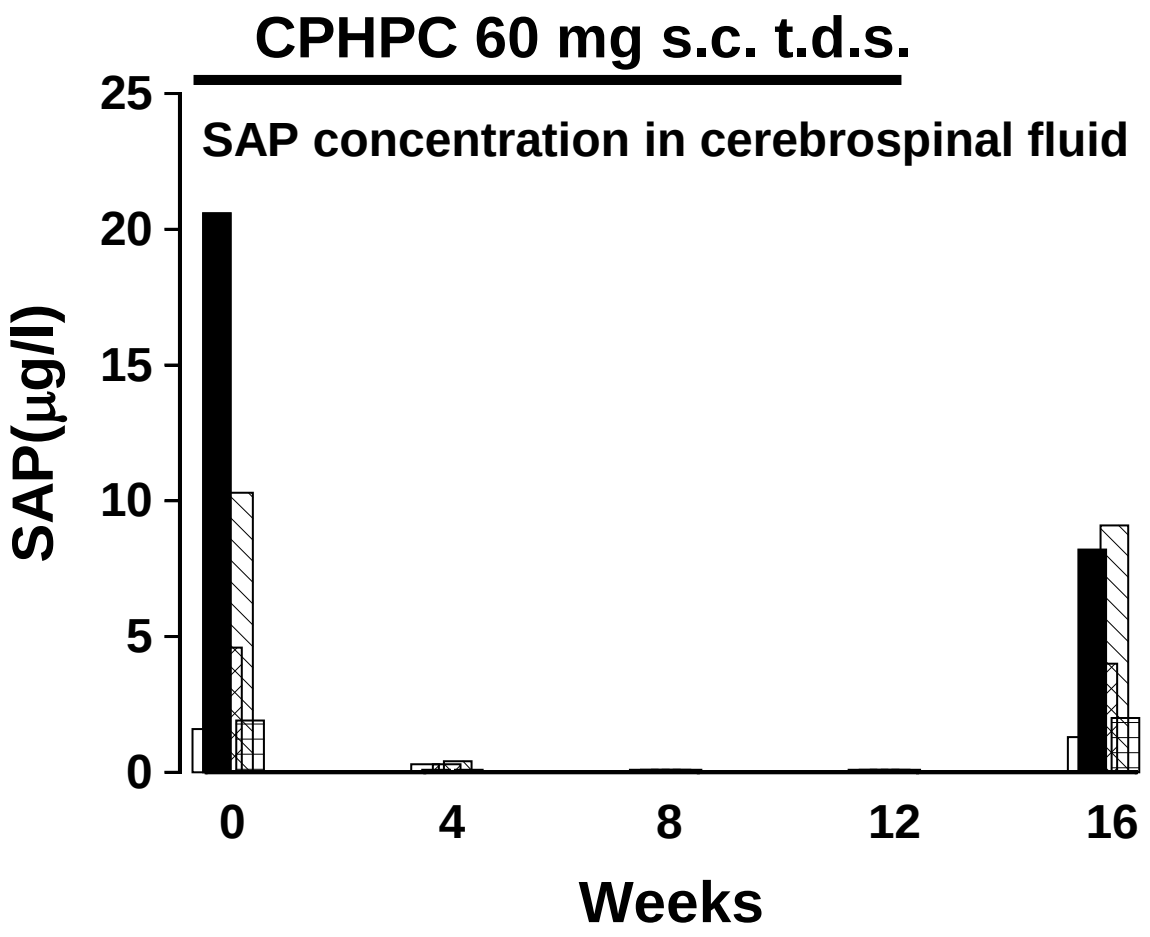
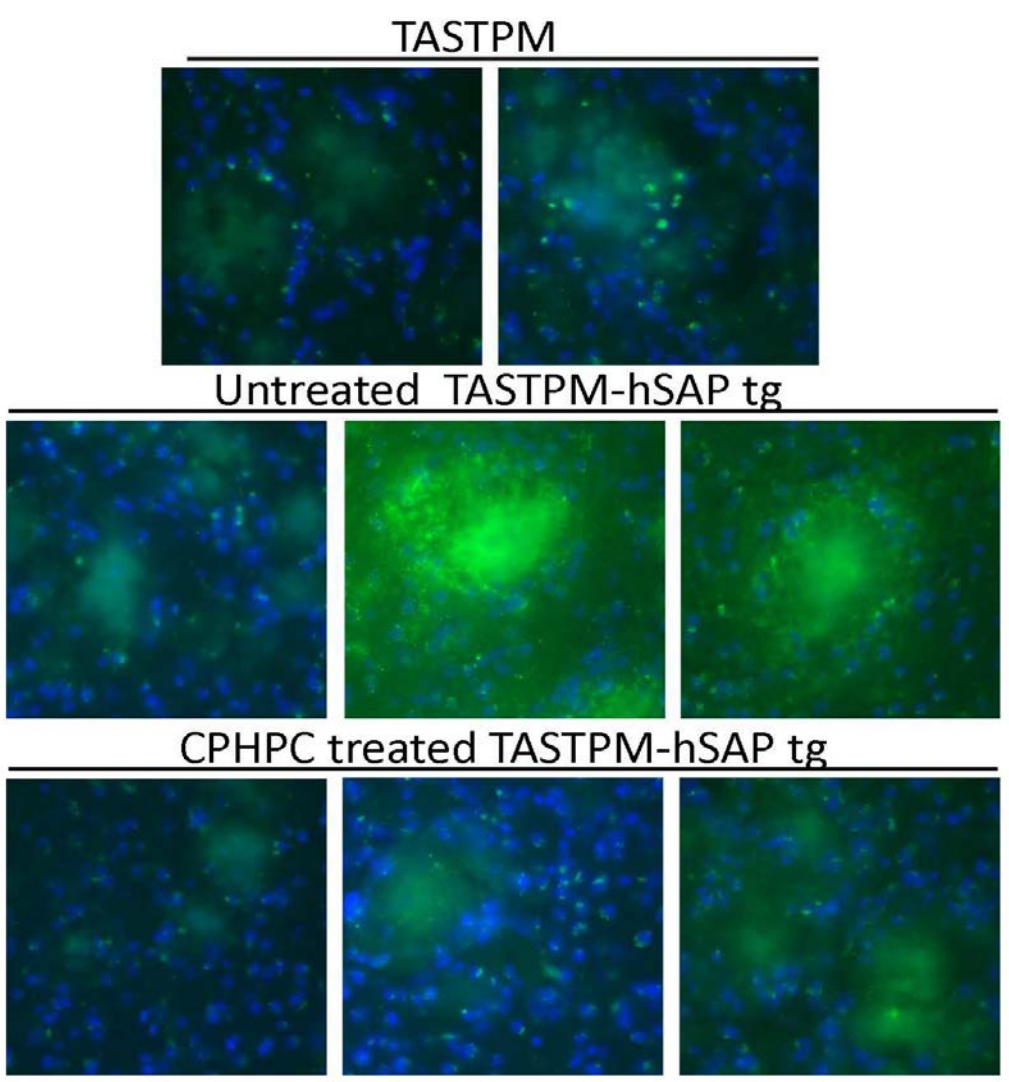
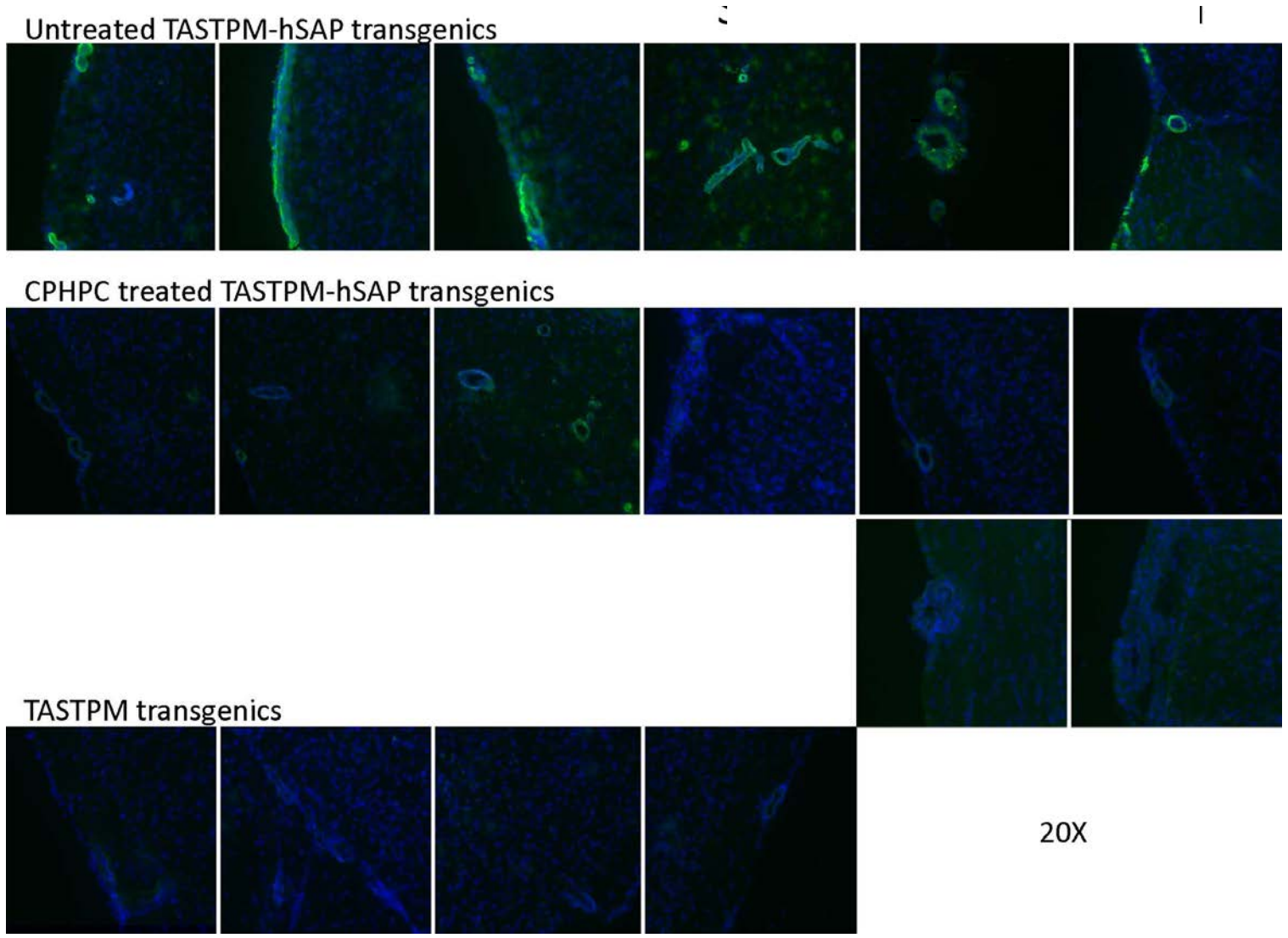
Miridesap (CPHPC) in Alzheimer's disease





Miridesap (CPHPC) eliminates SAP from cerebral & cerebrovascular amyloid





SAP, brain and miridesap

- SAP only produced by liver; not in brain exome
- Plasma SAP depletion by miridesap: removes all CSF SAP & thus SAP from cerebral parenchymal & vascular amyloid & NFT, in contrast to systemic amyloid deposits
- Miridesap will abrogate direct SAP neurotoxicity, may reduce Aβ amyloid fibrillogenesis & may promote regression of plaque & vascular amyloid & NFTs

The DESPIAD trial: **DE**pletion of **S**erum amyloid **P** component **I**n **A**lzheimer's **D**isease

- 1 year phase 2b double blind 1:1 placebo controlled study of miridesap in 100 AD patients
- Confirm safety and tolerability
- Seek improvement in clinical and other disease measures
- Global and regional cerebral atrophy (MRI), cerebral amyloid (PET), cognition, CSF concentrations of SAP, Aβ and τ.
- Funded by NIHR, ARUK, Dana Foundation of NY

New treatments?

- Systemic amyloidosis is rare, Alzheimer’s disease is common; both remain major unmet medical needs
- Deeper and broader understanding of the underlying pathobiology is enabling rational design of new therapies
- Development, testing and introduction of new medicines is increasingly challenging: glacially slow, extraordinarily expensive and hideously complex
- There is no alternative but to keep trying!

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