Targeting Macrophages in Amyloidosis

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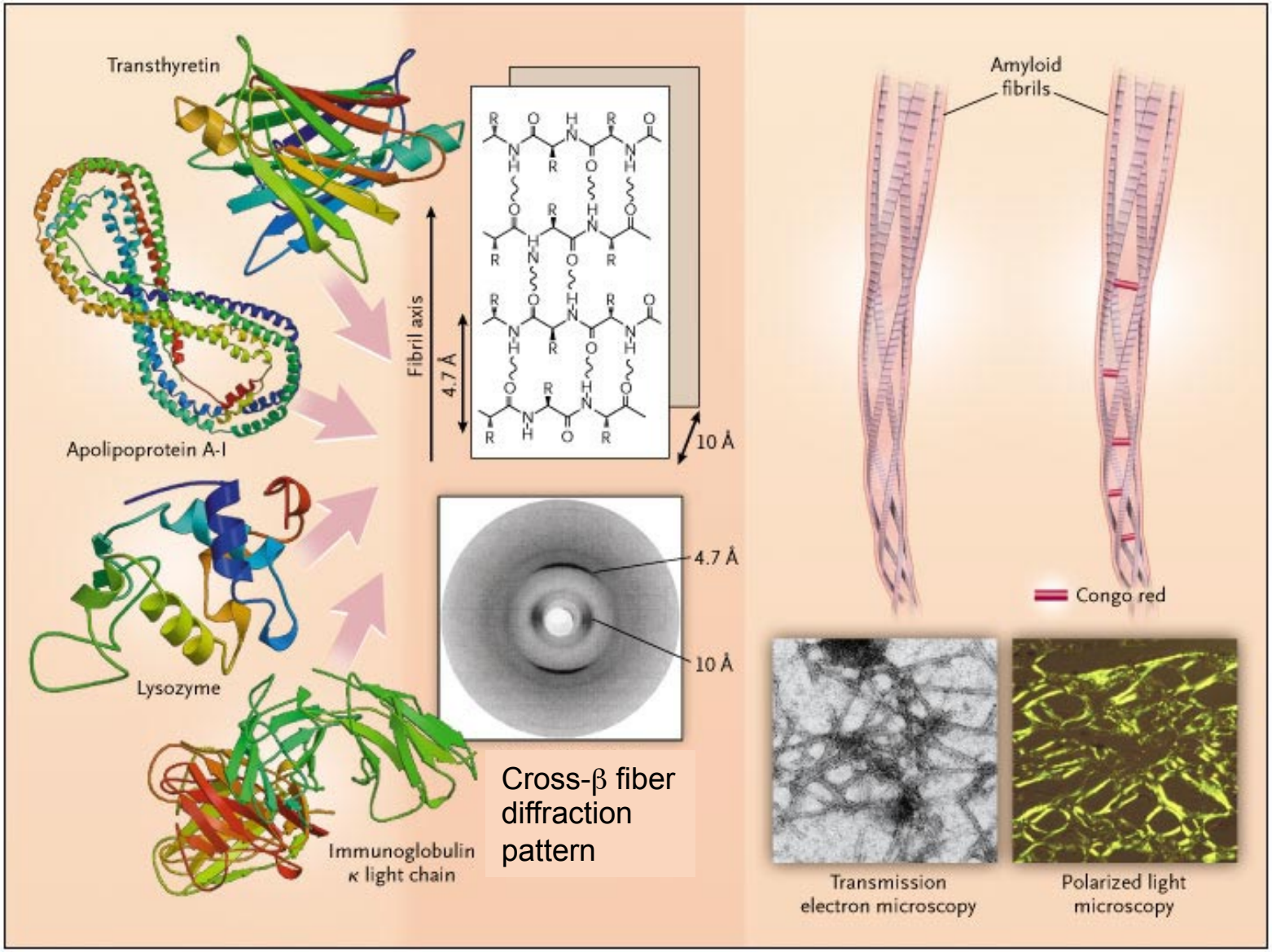
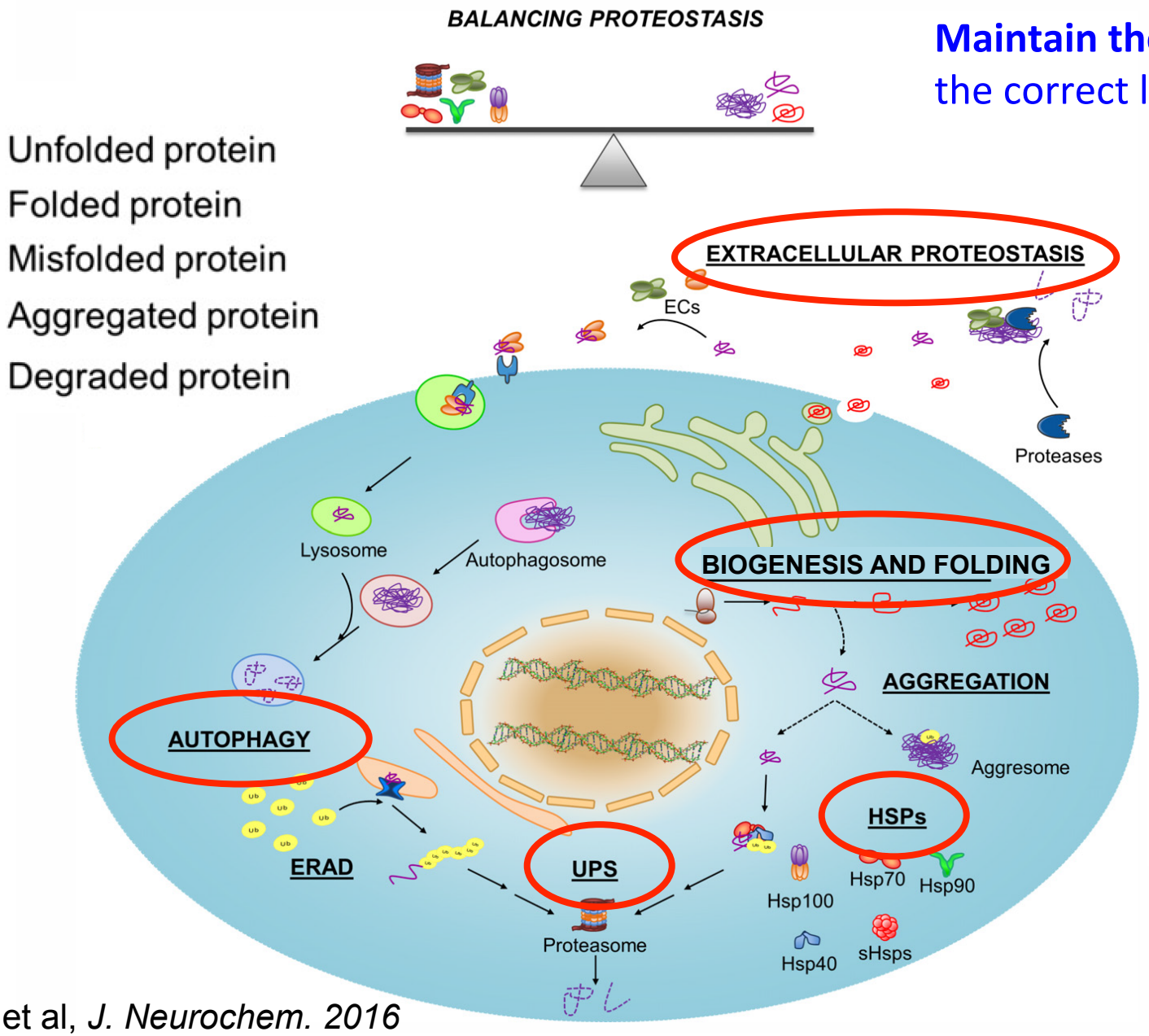
Amyloidoses: Protein Misfolding and Deposition Diseases

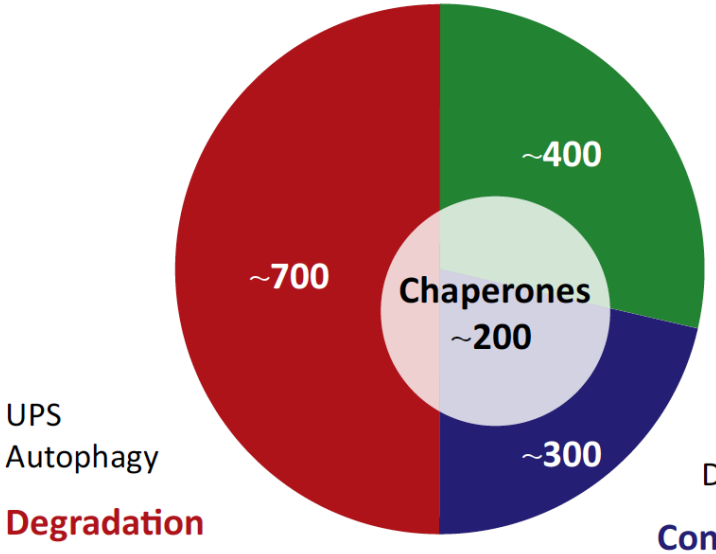


& Bellotti, *N Engl J Med. 2003*

Protein homeostasis (Proteostasis)

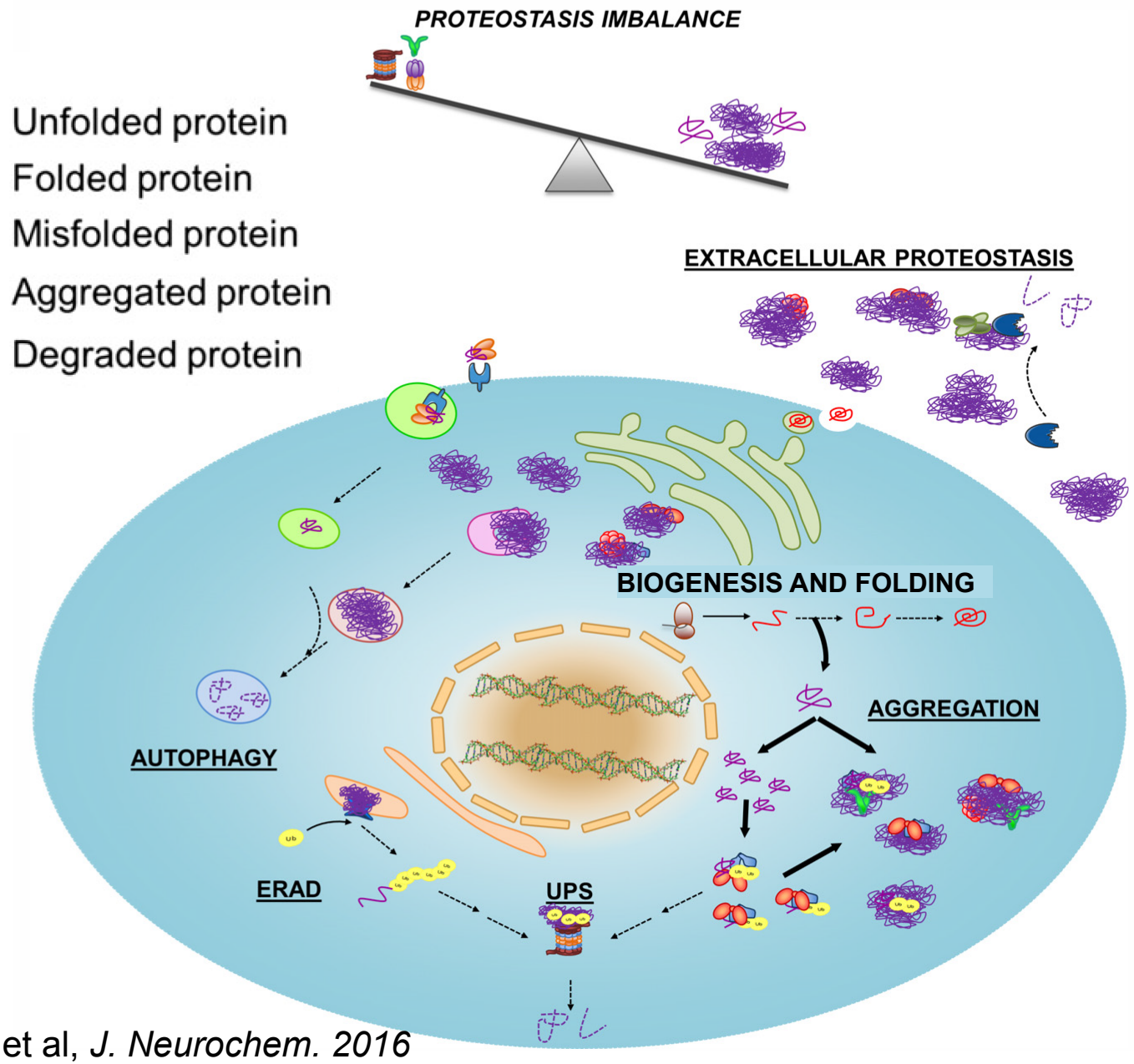


Maintain the proteome in a native conformation, the correct location and concentration



et al, *J. Neurochem.* 2016

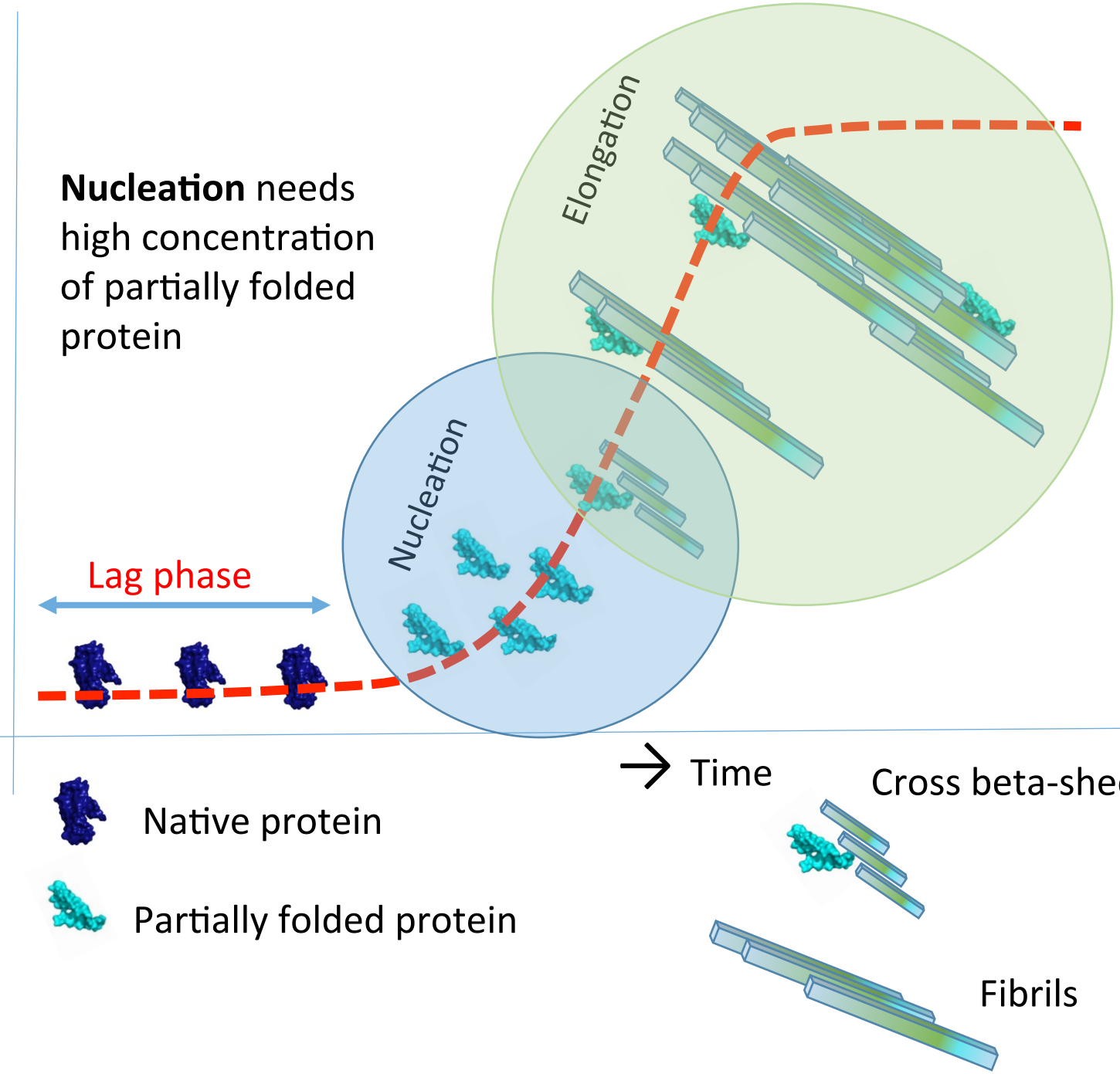
Proteostasis imbalance during aging



Proteostasis collapse and cell death

Olzscha et al, *Cell 2011*
Woerner et al, *Science 2016*

y et al, *J. Neurochem. 2016*



Nucleation needs high concentration of partially folded protein

Elongation can proceed even at low concentration of the precursor protein

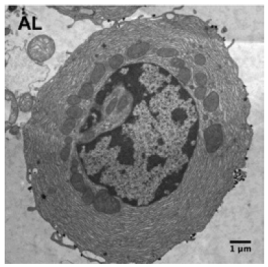
Early diagnosis

Rapid and profo
decrease of the
amyloid precurs

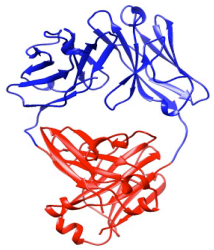
Reduction of th
load of amyloid
fibrils

Molecular events leading to AL amyloidosis

nce 10.5 per million person-years[1] - 10-15% of multiple myeloma patients develop AL amyloidosis[2]



Small dangerous
B cell clone[3]
λ LC in ~78%



Kinetically/
thermodynamically
unstable LC[4,5]

et al, *Blood 1994* - 2. Madan et al, *Mayo Clin Proc. 2010* – 3. Merlini & Stone, *Blood 2006* – 4. Blancas-Mejia et al, *Biophys Chem. 2015*
ti et al, *Sci Rep. 2017*

Macrophages and amyloid clearance

ient Amyloid A Clearance in the Absence of unoglobulins and Complement Factors

narova,* Mario Nuvolone,*†‡§ Charlotte Whicher,* Nathalie Frei,* Veronika Kana,* Petra Schwarz,* Westermark,¶ and Adriano Aguzzi*

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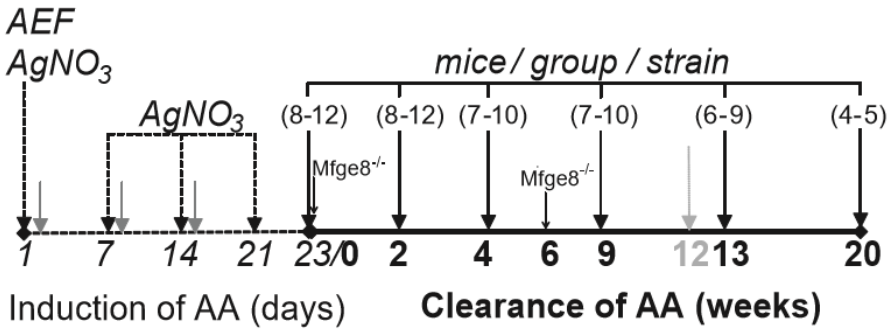
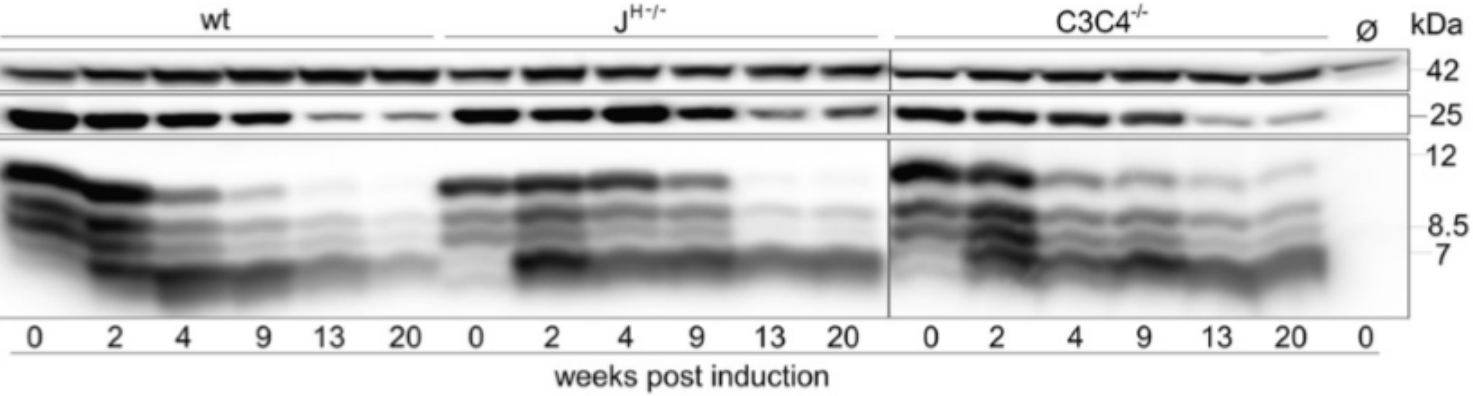
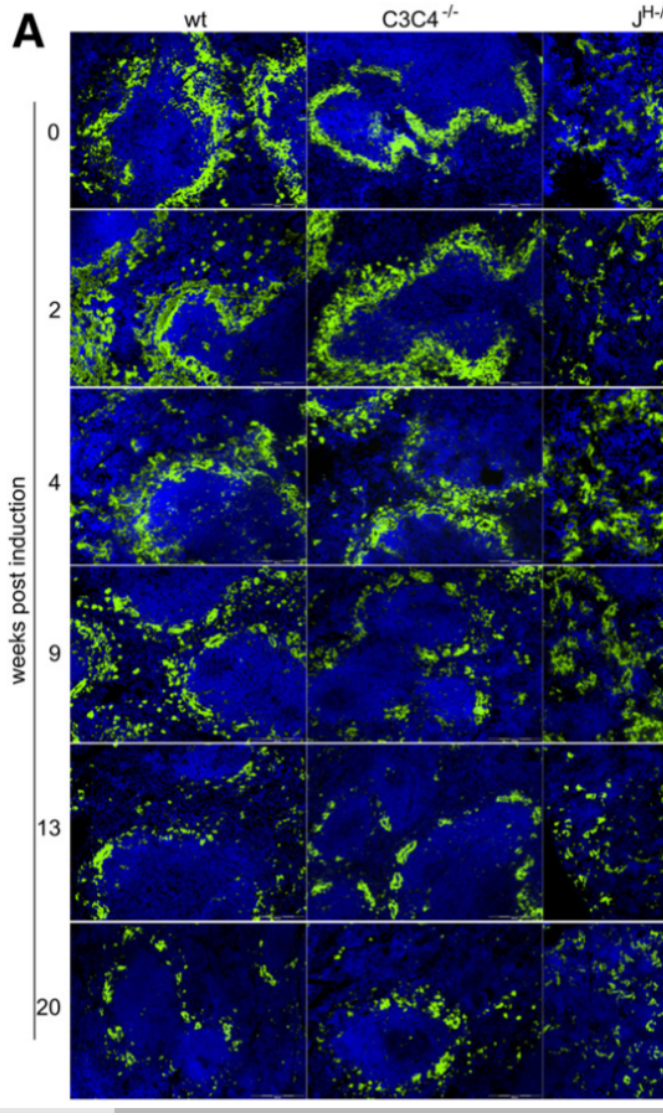
ajp.amjpathol.org







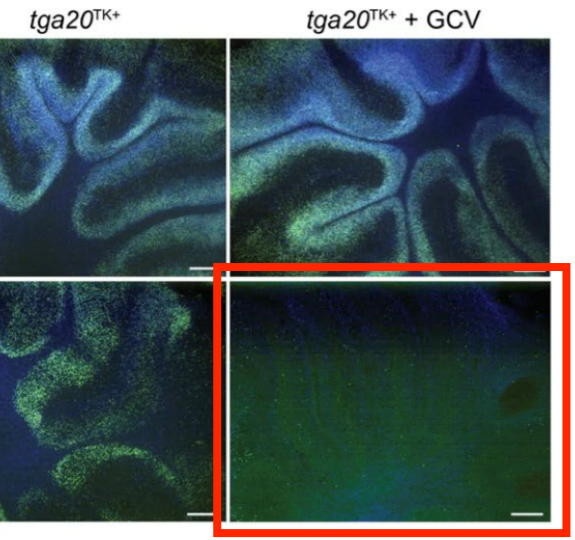
tic ablation of either Ig ($J^{H-/-}$) or complement components $^{-/-}$) does not impinge spontaneous amyloid resorption

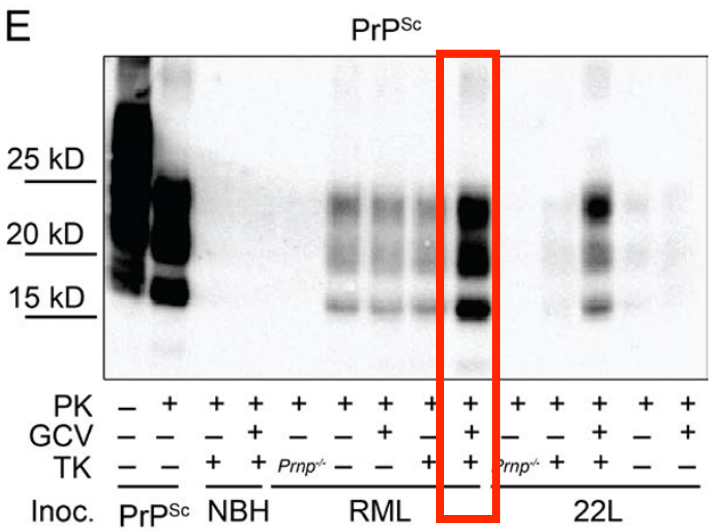
dundancy of mechanisms of natural amyloid clearance

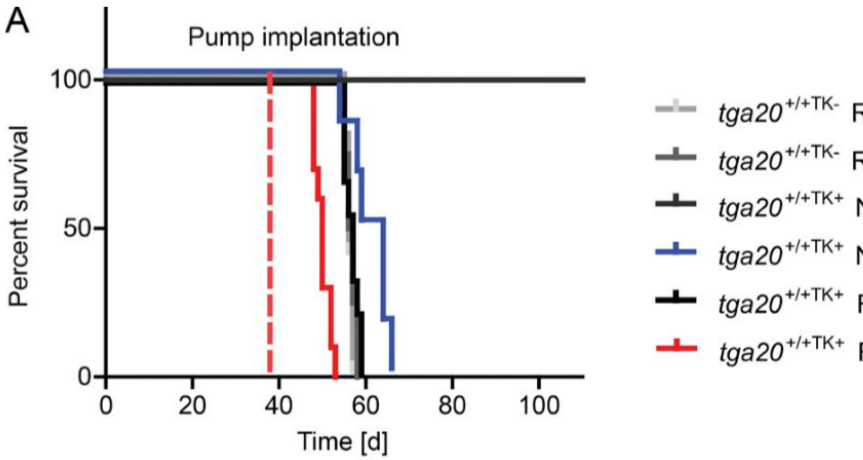
europrotective role for microglia in prion diseases

ng Zhu,* Uli S. Herrmann,* Jeppe Falsig, Irina Abakumova, Mario Nuvolone, Petra Schwarz,
Frauenknecht, Elisabeth J. Rushing, and Adriano Aguzzi

f Neuropathology, University Hospital Zurich, 8091 Zurich, Switzerland







oglia removal in cerebellar orgnotypic slices from mice expressing a suicide transgene
en neuronal loss and accumulation of misfolded, disease-associated prion protein

oglia removal *in vivo* through osmotic minipumps leads to accelerated disease

europrotective role for microglia in prion diseases

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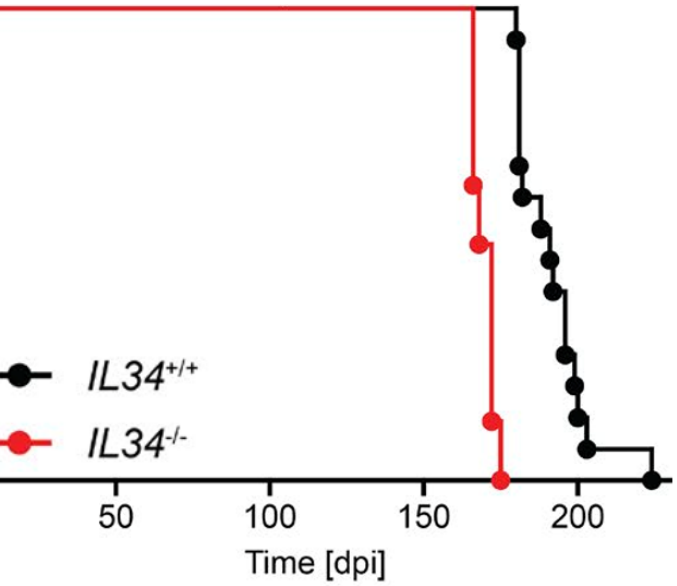
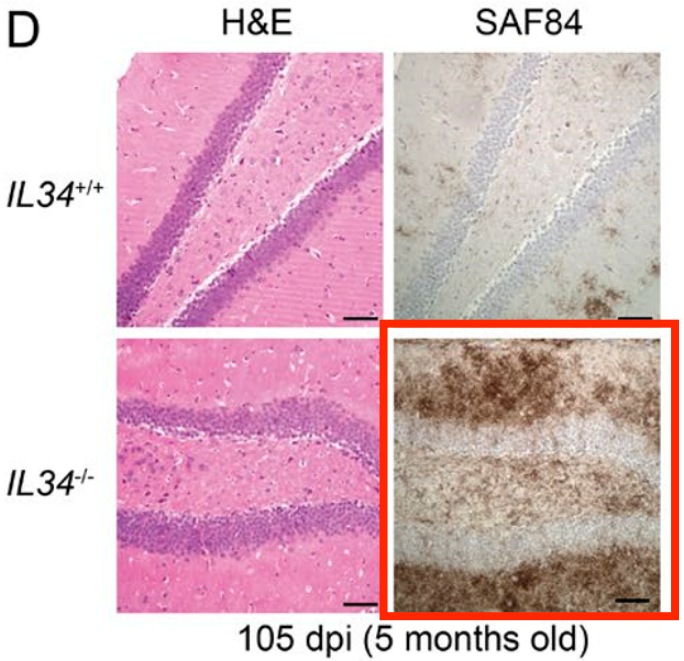
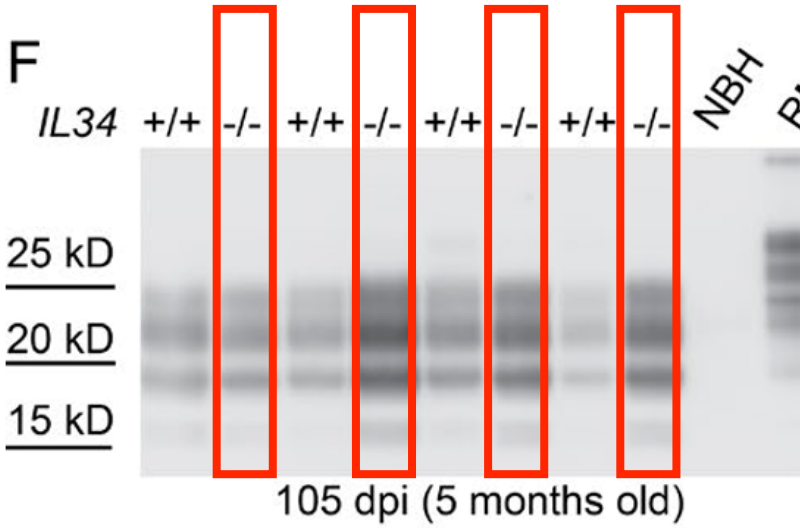




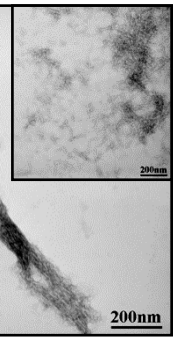


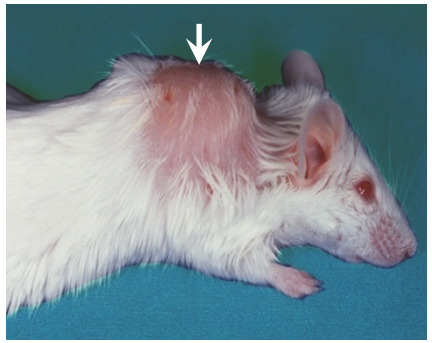
inoculation of mice with reduced numbers of microglia (IL34$^{-/-}$) leads to accelerated se and increased accumulation of misfolded, disease-associated prion protein

icroglia exert a neuroprotective role in prion disease

Arming Macrophages to promote amyloid clearance
A novel therapeutic paradigm in amyloidoses

assive immunotherapy to promote amyloid clearance: 11-1F4 A

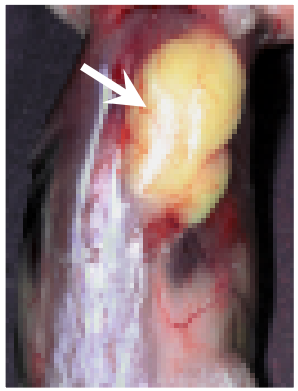




m11-1F4 Ab: mouse IgG1 monoclonal Ab recognizing a conformation epitope present in AL (κ and λ) and other type of amyloids

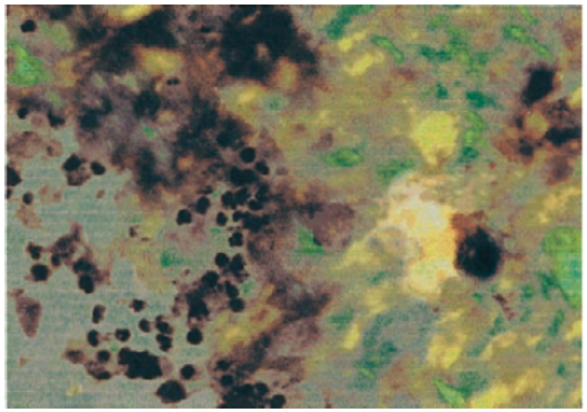
Repeated administrations of m11-1F4 to mice bearing a subcutanou amyloidoma resulted in accelerates amyloid resorption

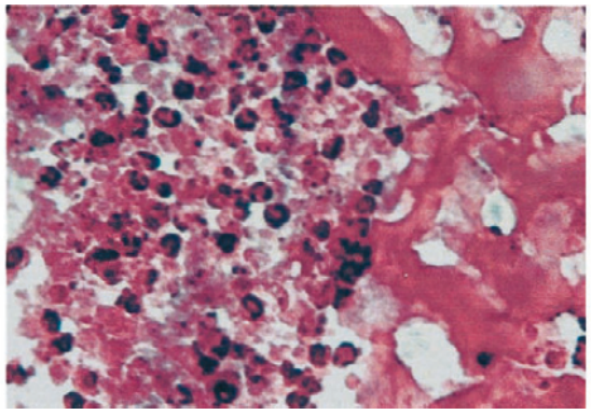
Amyloidolysis was accompanied by neutrophil infiltration



Untreated

Treated





Wall JS et al. Blood 2010;116:2241-2244.

himeric m11-1F4 is currently under clinical evaluation

Hrncic et al. Am J Patho
Walls et al. Bloo

Clinical evaluation of chimeric m11-1F4 Ab

-label, dose-escalation phase 1a/b of fibril-reactive antibody 11-1F4 (CAEL-101)

sed / refractory patients

Ab 11-1F4 as a single intravenous infusion (phase 1a)
eries of weekly infusions for 4 weeks (phase 1b)

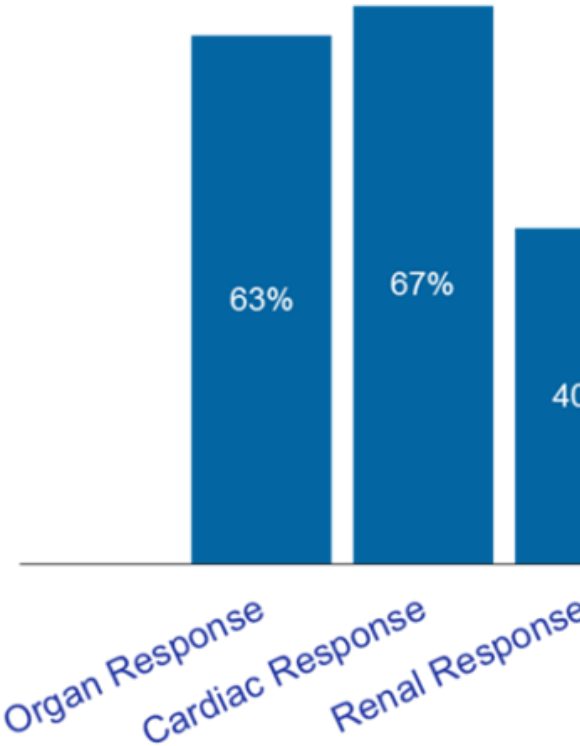
-escalation "up and down" design

ients completed phase 1a and 19 patients completed phase 1b

5 grade AEs

patients with skin rash (neutrophil infiltration surrounding amyloid at biopsy)

an time to response: 2 weeks



ch, et al. abstract 509, ASH 2017

Passive immunotherapy to promote amyloid clearance: anti-SAP therapy

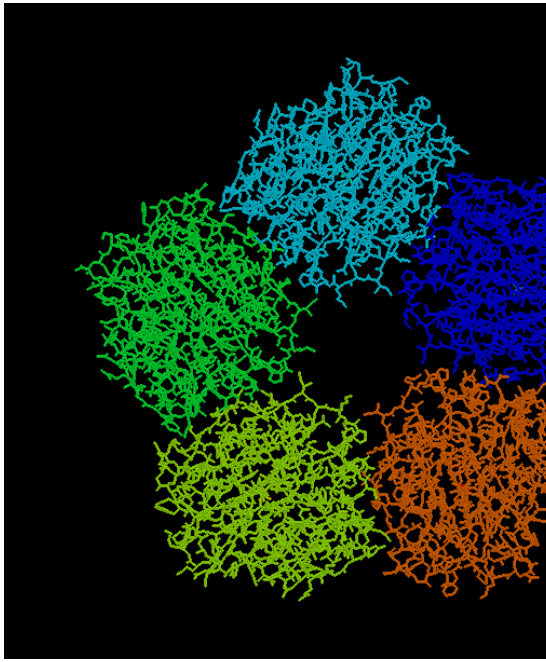
um amyloid P component (SAP):

ormal plasma glycoprotein

ommon, minor constituent of all human amyloid

s presence stabilizes amyloid deposits

myloid deposition is delayed in *Sap*$^{-/-}$ mice



tibodies to human serum amyloid P componen
minate visceral amyloid deposits

din[1]*, Stephan Ellmerich[1]*, Melvyn C. Kahan[1], Glenys A. Tennent[1], Andrzej Loesch[1], Janet A. Gilbertson[1], Winston L. Hutch
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. Brad
Petrie[7], Julian D. Gillmore[1], Vittorio Bellotti[1,2], Marina Botto[8], Philip N. Hawkins[1] & Mark B. Pepys[1]

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igate therapeutic partnership of CPHPC and anti-SAP mAb

PC: crosslinking and elimination of circulating SAP

i-SAP mAb: binding to residual SAP within amyloid deposits

tibodies to human serum amyloid P componen
minate visceral amyloid deposits

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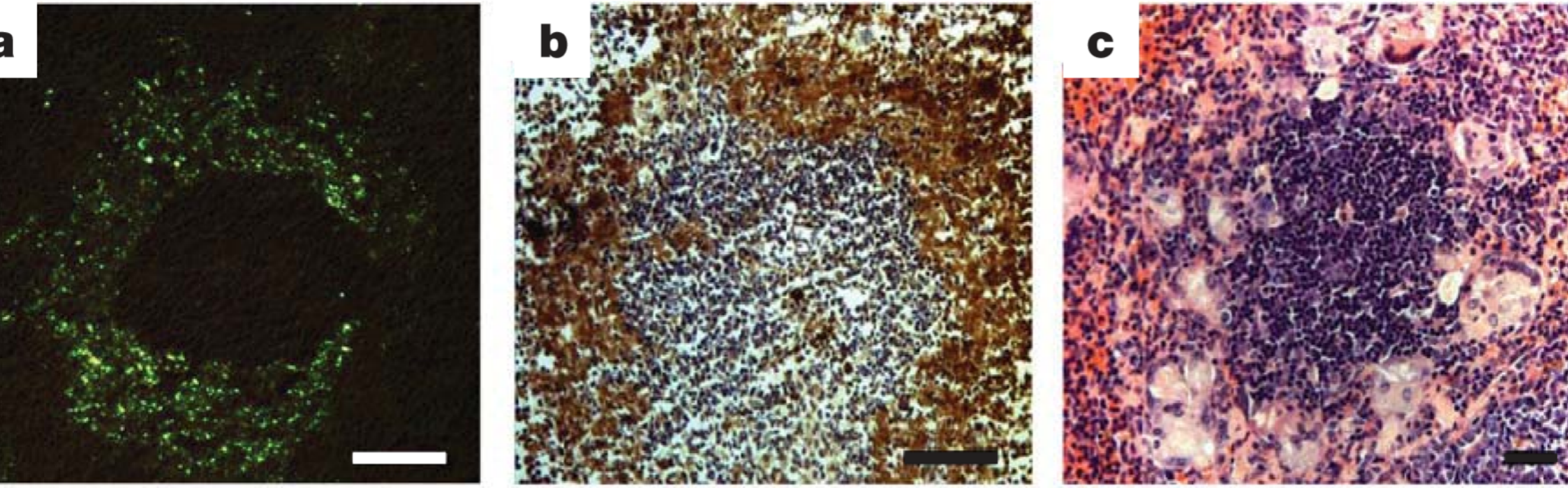
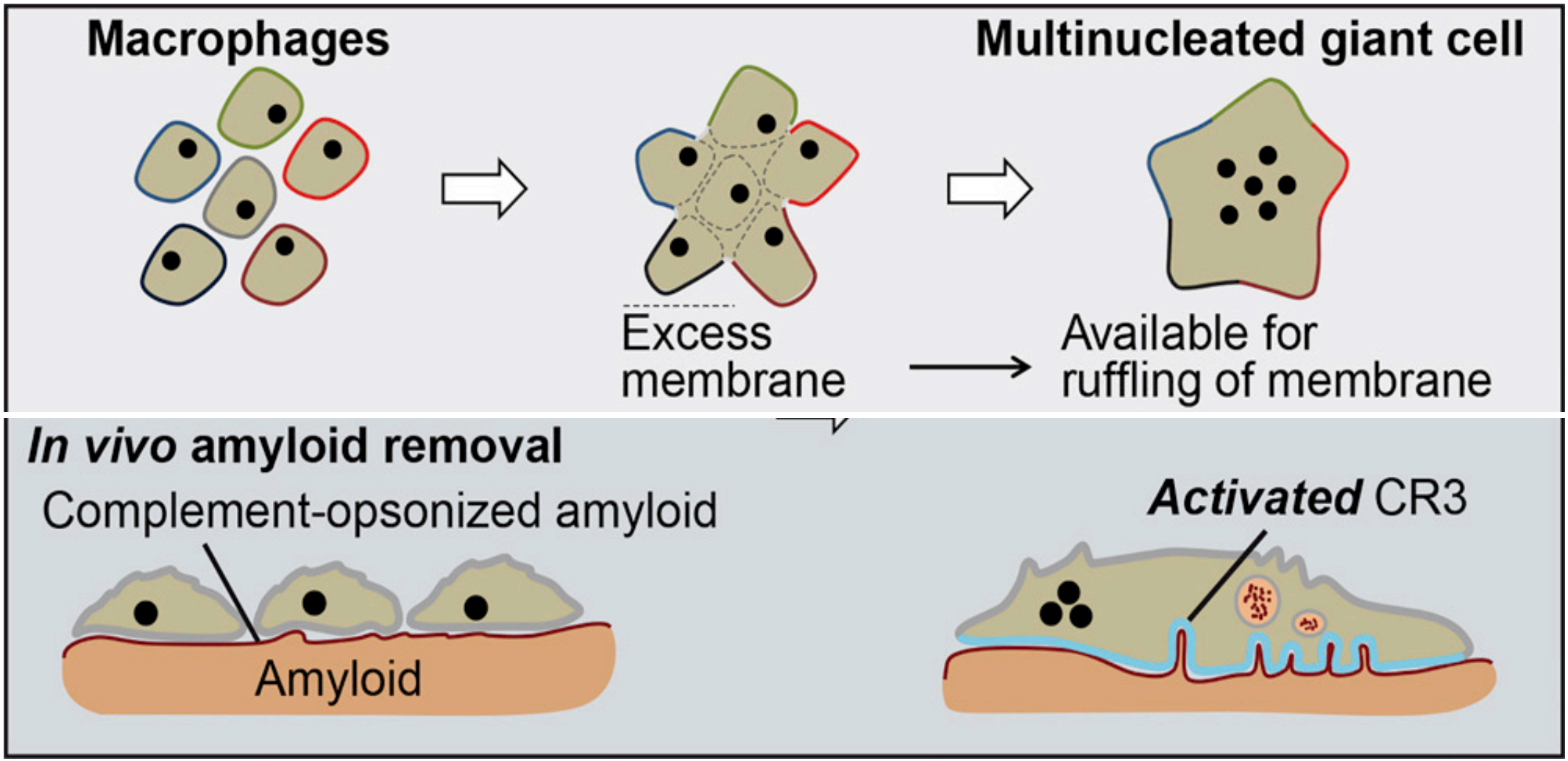


HPC + anti-SAP mAb lead to accelerated amyloid removal in a murine model of AA amyloidosis
oid removal occurrd through a complement-dependent, macrophage-derived giant cell reaction

Multinucleated Giant Cells Are Specialized for mplement-Mediated Phagocytosis and Large Target Destruct



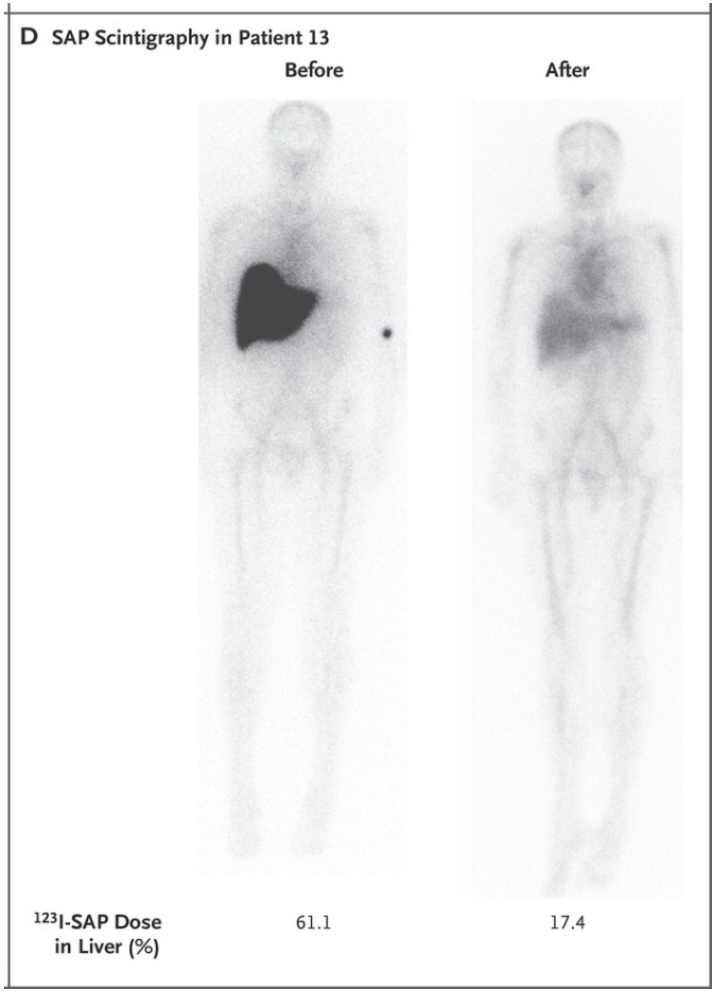
t al, Cell Rep 2015

The NEW ENGLAND JOURNAL of MEDICINE

Therapeutic Clearance of Amyloid by bodies 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.,
na Fontana, M.D., James C. Moon, M.D., Massimo Pinzani, M.D., Ph.D.,
lian D. Gillmore, M.D., Ph.D., Philip N. Hawkins, Ph.D., F.Med.Sci.,
and Mark B. Pepys, Ph.D., F.R.S.

BER 17, 2015



Deplete plasma of SAP using CPHPC

↓

e SAP still remains on amyloid deposits

↓

anti-SAP antibody to target amyloid deposits

- 15 pts with different forms of systemic amyloidosis
- Intravenous infusion of CPHPC (**Miridesap**)
- Single intravenous administration of a fully humani monoclonal IgG1 anti-SAP antibody (**Dezamizumab**

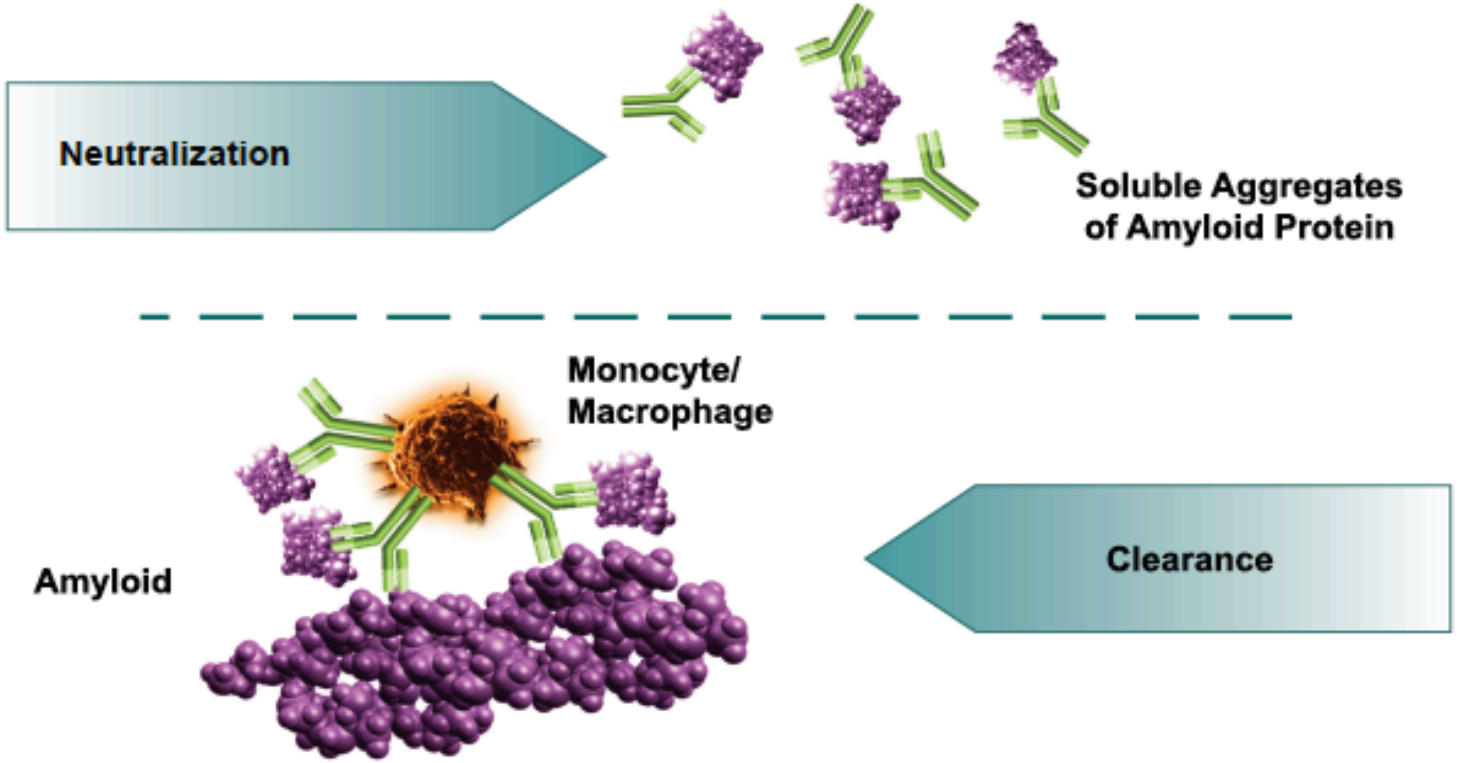
→ Reduced hepatic amyloid load and liver stiffness

Passive immunotherapy to promote amyloid clearance: NEOD001

manized monoclonal antibody (IgG1)

ds to an epitope that is unique to the misfolded LC protein

e proposed mechanism of action involves:



st-in-Human Phase I/II Study of NEOD001 in Patients th Light Chain Amyloidosis and Persistent gan Dysfunction

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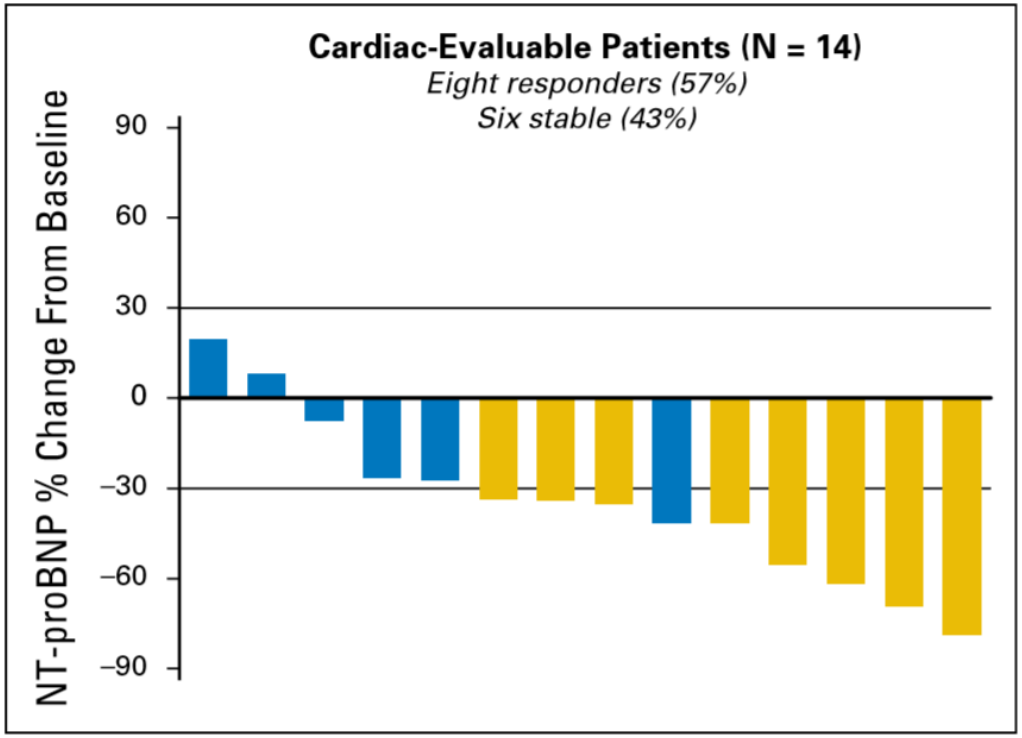
e A. Gertz, Heather Landau, Raymond L. Comenzo, David Seldin,† Brendan Weiss, Jeffrey Zonder, npaolo Merlini, Stefan Schönland, Jackie Walling, Gene G. Kinney, Martin Koller, Dale B. Schenk, cer D. Guthrie, and Michaela Liedtke



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Conclusions

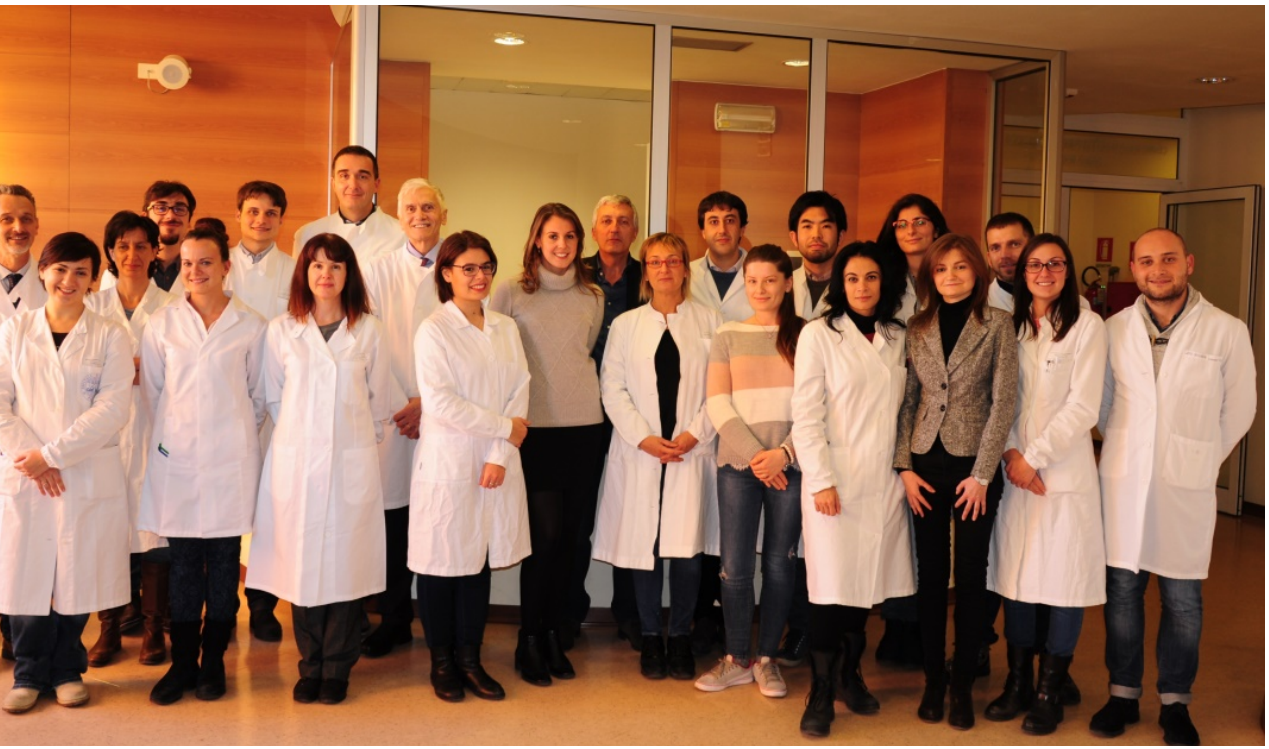
olishing or reducing the production of the amyloidogenic precursor, when
ssible, remains the mainstay of therapy against amyloid diseases

ssive therapy to promote macrophage-mediated amyloid clearance is a
tential novel therapeutic approach deserving further investigations

ti-SAP therapy is particularly attractive for those forms of amyloid disease
here reduction of the amyloidogenic precursor is currently not feasible

Acknowledgements

Amyloidosis Research and Treatment Center



Giampaolo Merlini
Laura Obici
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Roberta Mussinelli
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