ISA Workshop – Amyloidosis from Bench to Bedside and Back Again
Il Collegio Fondazione Ghislieri
October 13-14, 2025

Selective cellular vulnerability and resilience in amyloidosis

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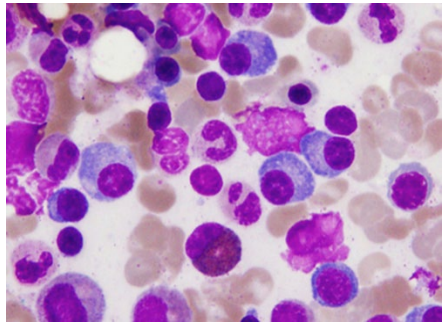
Table 1. Amyloid fibril proteins and their precursors in human[a].

Fibril protein	Precursor protein	Systemic or localised	Acquired or hereditary	Target organs
AL	Immunoglobulin light chain	S, L	A, H	All organs, usually except CNS
AH	Immunoglobulin heavy chain	S, L	A	All organs except CNS
AA	(Apo) Serum amyloid A	S	A, H	All organs except CNS
ATTR	Transthyretin, wild type	S*	A	Heart mainly in males, lung, ligaments, tenosynovium
	Transthyretin, variants	S	H	PNS, ANS, heart, eye, kidneys, leptomeninges
Aβ2M	β2-microglobulin, wild type	S	A	Musculoskeletal system
	β2-microglobulin, variants	S	H	ANS, tongue, heart
AApoAI	Apolipoprotein A I, variants	S	H	Heart, liver, kidney, PNS, testis, larynx (C terminal variants), skin (C terminal variants)
AApoAII	Apolipoprotein A II, variants	S	H	Kidney
AApoAIV	Apolipoprotein A IV, wild type	S	A	Kidney medulla, heart, gastrointestinal
AApoAIV	Apolipoprotein A IV, variant	S	H	Heart, kidney
AApoCII	Apolipoprotein C II, variants	S	H	Kidney
AApoCIII	Apolipoprotein C III, variants	S	H	Kidney
AGel	Gelsolin, variants	S	H	Kidney PNS, cornea
ALys	Lysozyme, variants	S	H	Kidney
ALECT2	Leukocyte chemotactic factor-2	S	A	Kidney, primarily
AFib	Fibrinogen α, variants	S	H	Kidney, primarily
ACys	Cystatin C, variants	S	H	PNS, skin
ABri	ABriPP, variants	S	H	CNS

Buxbaum et al, *Amyloid 2024*

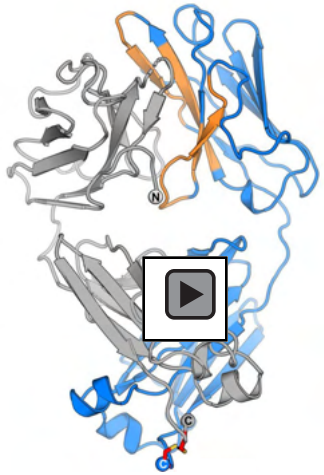
AL amyloidosis



λ LC in ~78%

Dangerous, small clone[1]
Median BMPC infiltrate: 10%

Kinetically/ thermodynamically unstable LC[2-4]



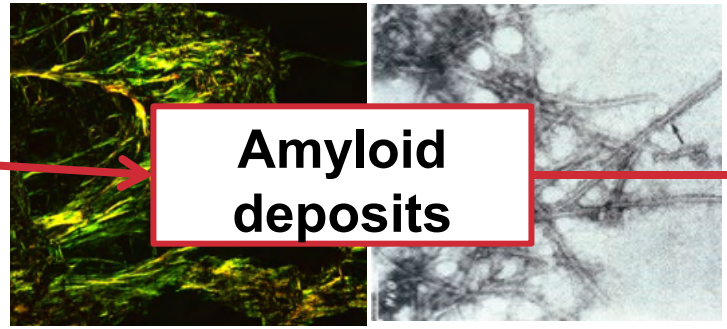
endoproteases, metal ions shear forces, cell interactions

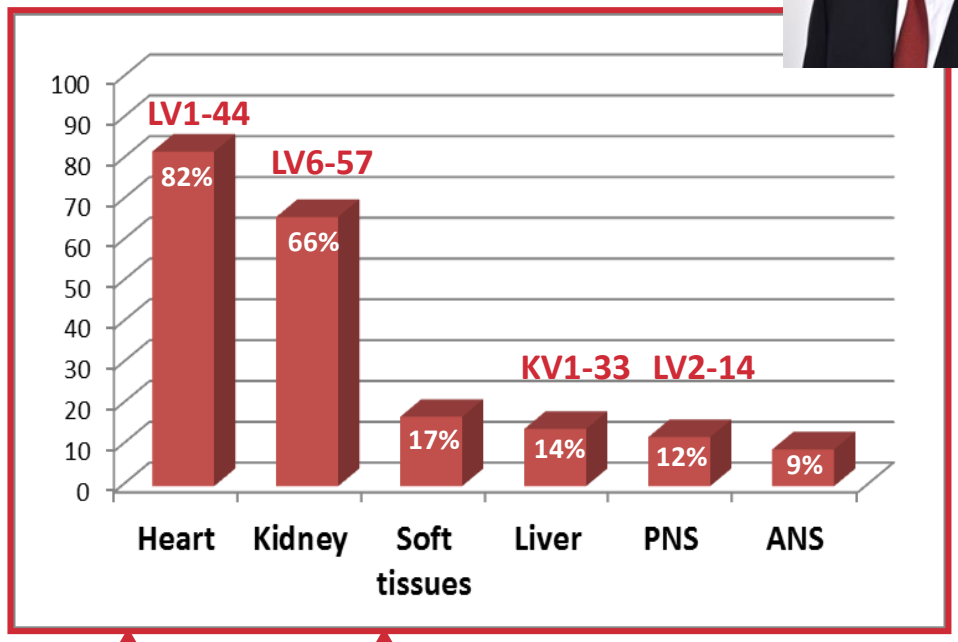
Oligomers

SAP, GAGs

Toxicity

Amyloid deposits

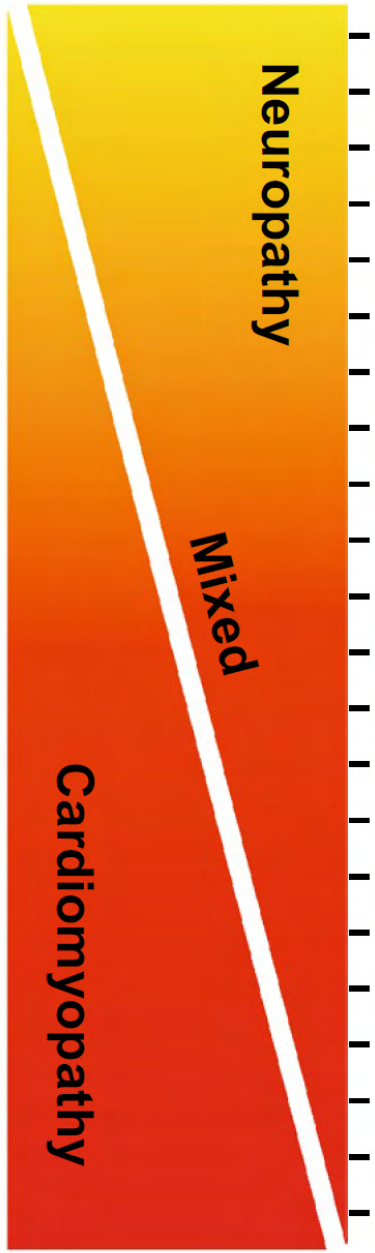




Comenzo et al, *Blood 2001*
Perfetti et al, *Blood 2012*
Kourelis et al, *Blood 2017*

1. Merlini & Stone, *Blood 2006;* 2. Blancas-Mejia et al, *Biophys Chem. 2015;* 3. Oberti et al, *Sci Rep. 2017;* 4. Maritan et al *JMB 2020*

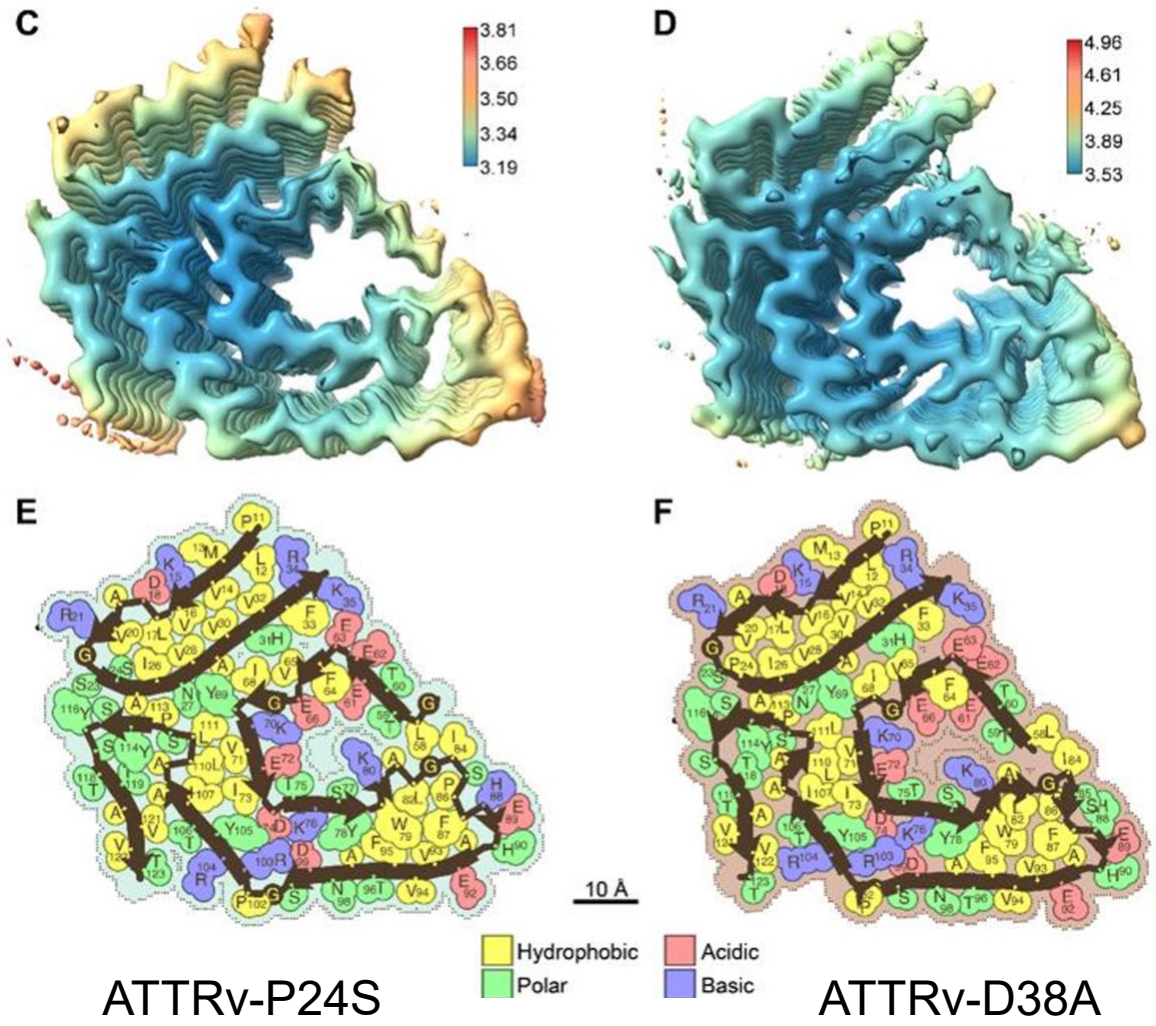
Genotype–phenotype correlations in ATTR amyloidosis



- V30M (early onset)
- V28M
- G54G
- I107P
- S77Y
- E89L
- F64L
- G47A
- V30M (late onset)
- P24S
- E89Q
- I107V
- T49A
- T60A
- L111M
- V20I
- A45T
- G65L
- I84A
- I68L
- V122I
- WT

Castano et al, *Heart Fail Rev 2015*

A Shared Amyloid Architecture in Cardiac Fibrils from Three Neuropathy-Associated ATTR Variants

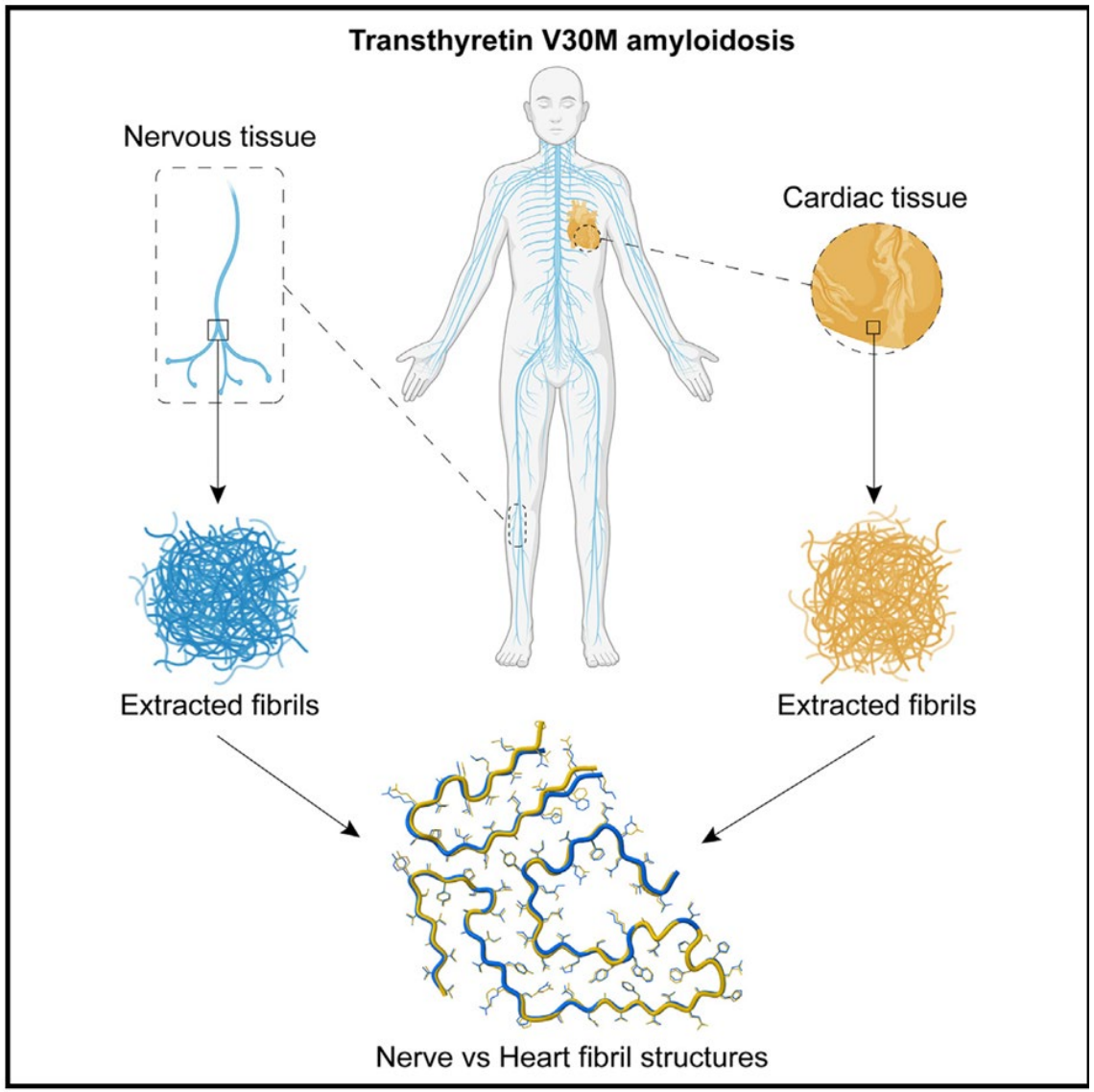


ATTRv-P24S

ATTRv-D38A

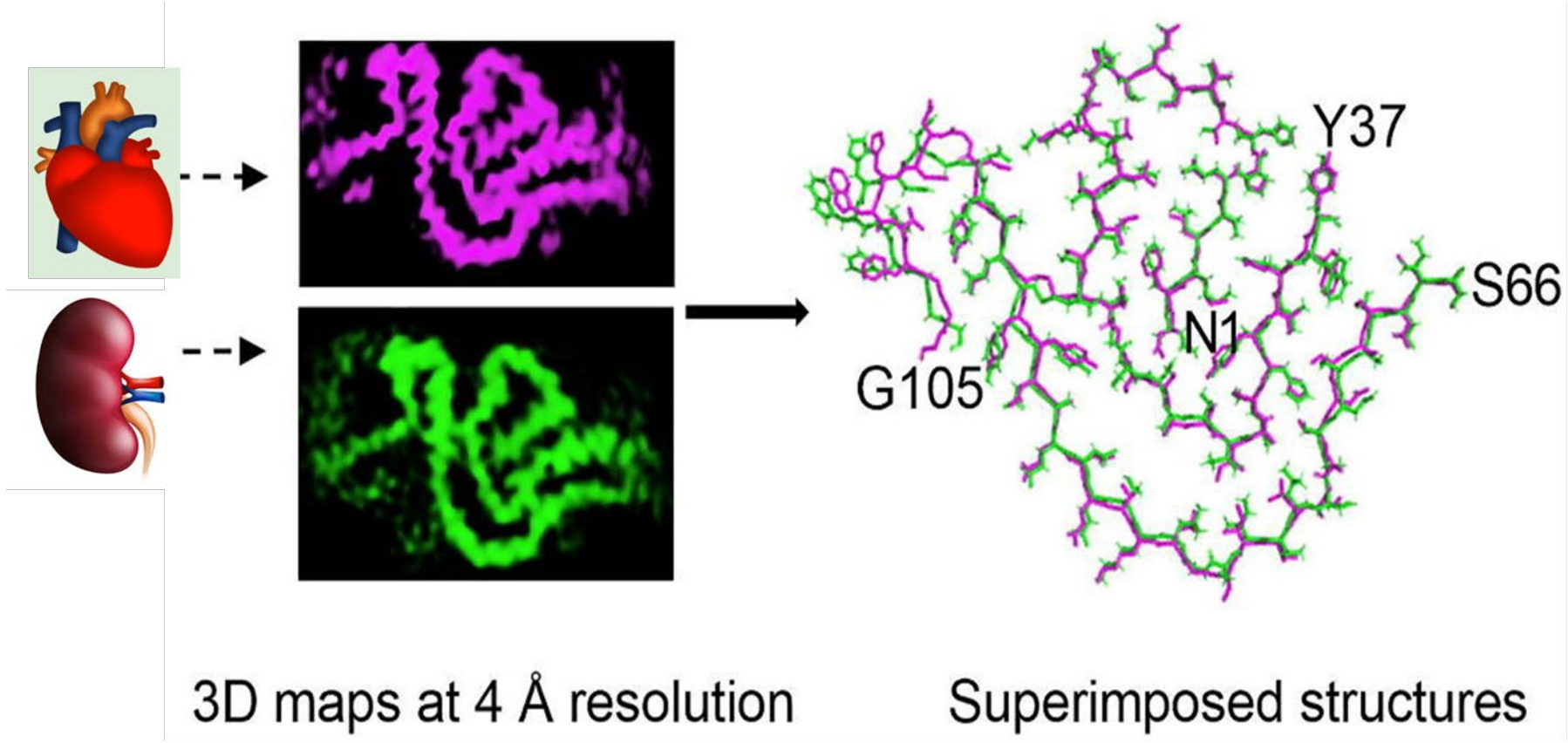
Fernandez-Ramirez et al *bioRxiv 2025*

ATTRv-V30M amyloid fibrils from heart and nerves exhibit structural homogeneity



Nguyen et al, *Structure 2024*

In AL amyloidosis a common fibril structure is present across organs in the same patient



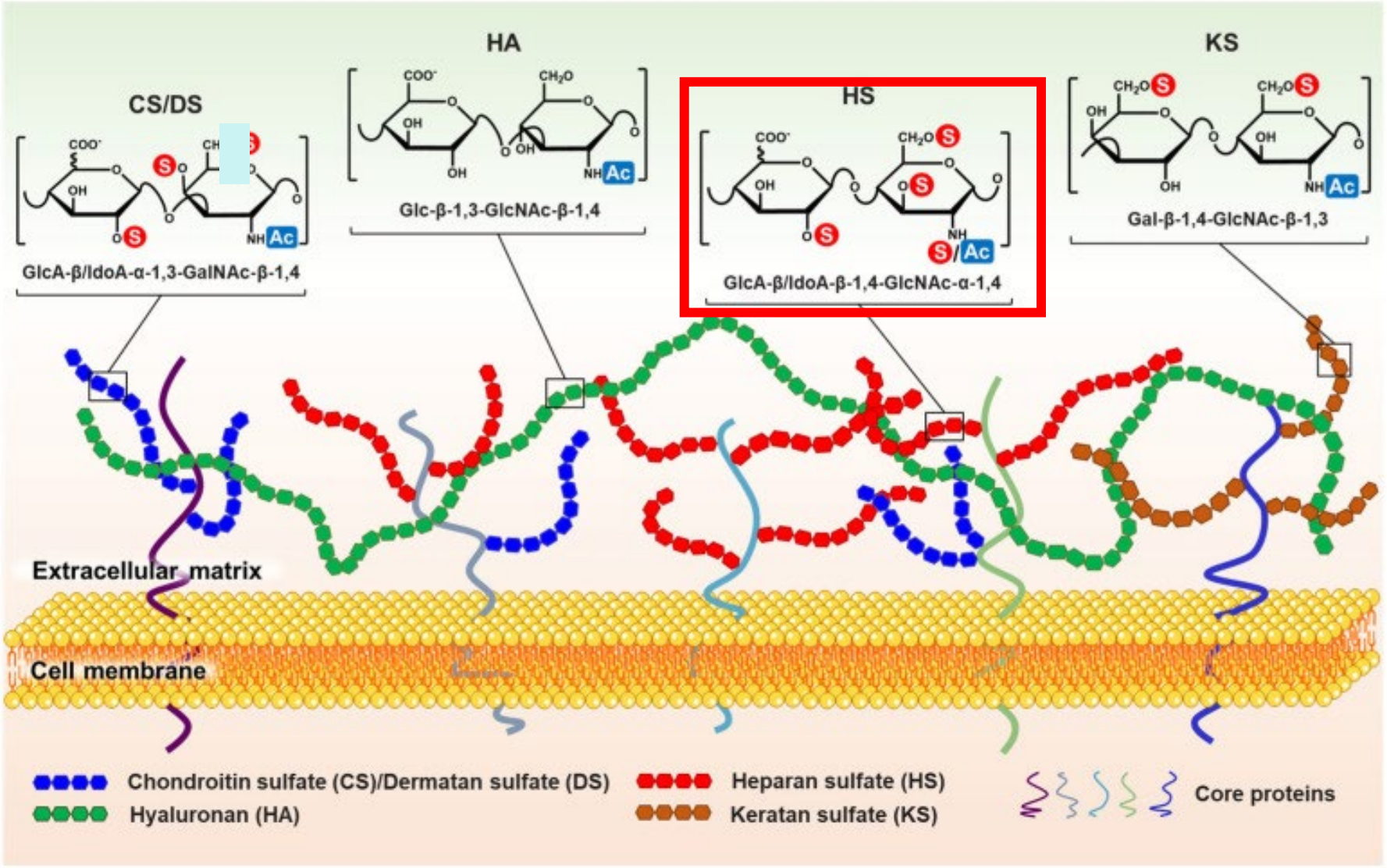
Extracted fibrils from the **kidney** of an AL patient whose **cardiac** fibril structure had been solved previously, and showed the renal fibril is **virtually identical** to the cardiac fibril—supporting a common fold across organs within the same patient.

Puri et al, *J Mol Biol 2023*

Interactions of the amyloid protein with the extracellular matrix

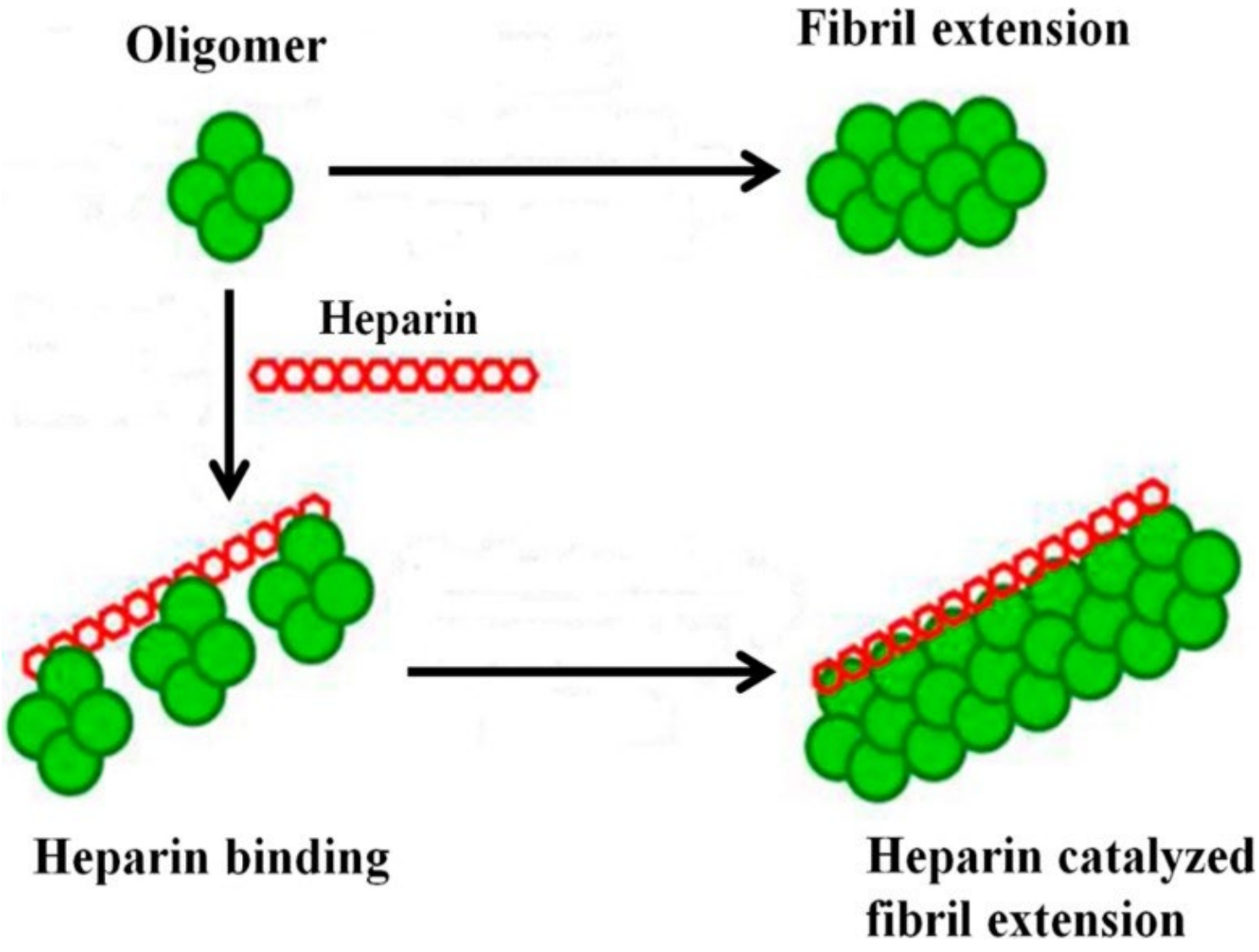
- Glycosoaminoglycans
- Collagens
- Endoproteases (shear forces)

Distribution and structures (repeating disaccharide units) of GAGs in the extracellular matrix



Wang & Chi, *Polymers 2022*

Polyanionic heparin works as scaffold in enhancing aggregation by aligning the peptide molecules in the correct orientation and with the appropriate periodicity



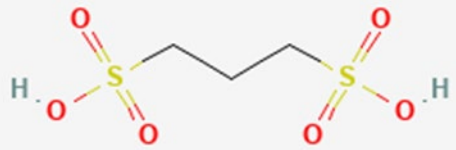
Iannuzzi et al, *Molecules 2015*

Amyloid seeding is strongly influenced by **which HSPGs are present**, **how their HS chains are sulfated**, and **whether local disease signals remodel them**. This creates **organ- and microdomain-specific "permissive matrices"** that capture seeds, enable cell entry, and stabilize nascent fibrils

Holmes et al, *PNAS 2013*
Oskarsson et al, *JBC 2015*
Rauch et al, *Sci Rep 2018*

GAGs modulate amyloid formation across proteins

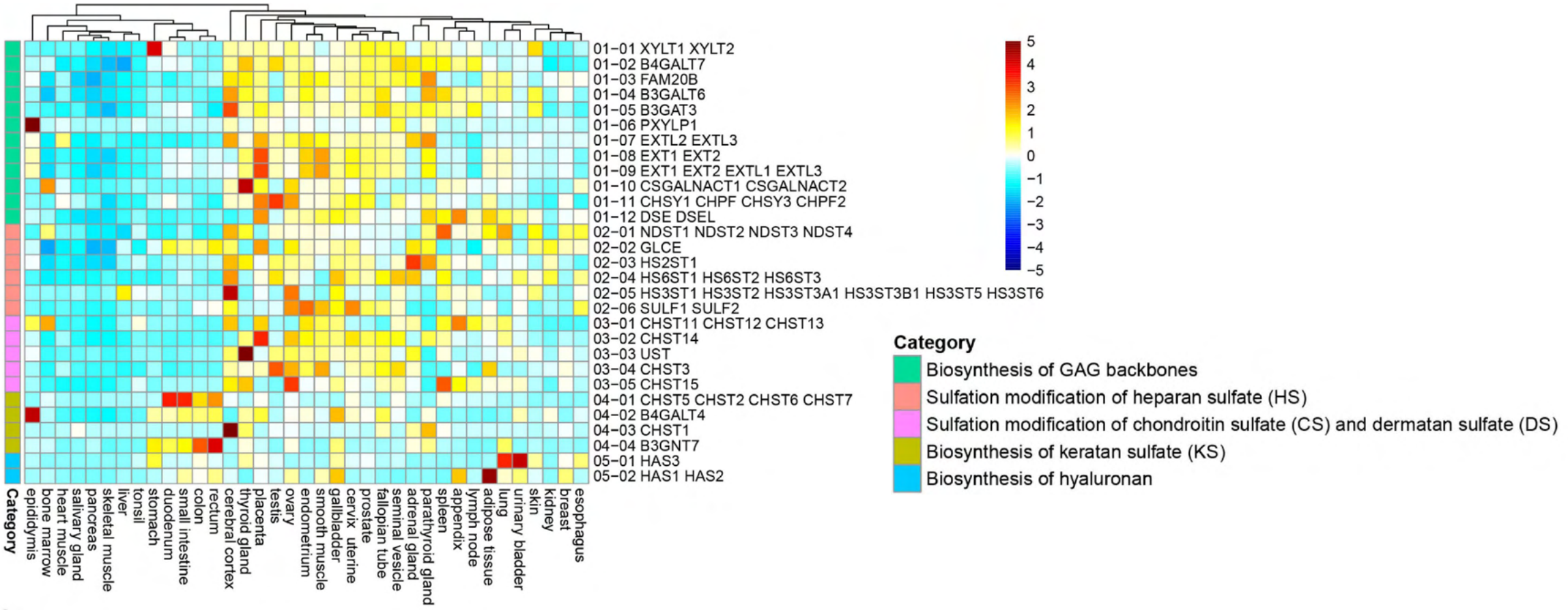
- **Aβ (Alzheimer's amyloid-β)** McLaurin et al., *FASEB J 1999*
- **Tau** Zhu et al, *J Biol Chem 2009*
- **α-Synuclein** Tao et al, *Nat Commun 2022*
- **Prions** Warner et al, *J Biol Chem 2002*
- **Serum Amyloid A** Kisilevsky, *J Clin Invest 1988*
- **Transthyretin** Noborn et al, *PNAS 2011*
- **β2-Microglobulin** So et al, *Protein Sci 2017*
- **Immunoglobulin light chains** Blancas-Mejía et al., *J Biol Chem 2014*



Eprodisate

Glycosaminoglycans display notable heterogeneity in their distribution, composition (e.g., chain length, disaccharide units), sulfation patterns and attachment to proteoglycans across human organs.

Expression profiles of GAG-related genes in human tissues.



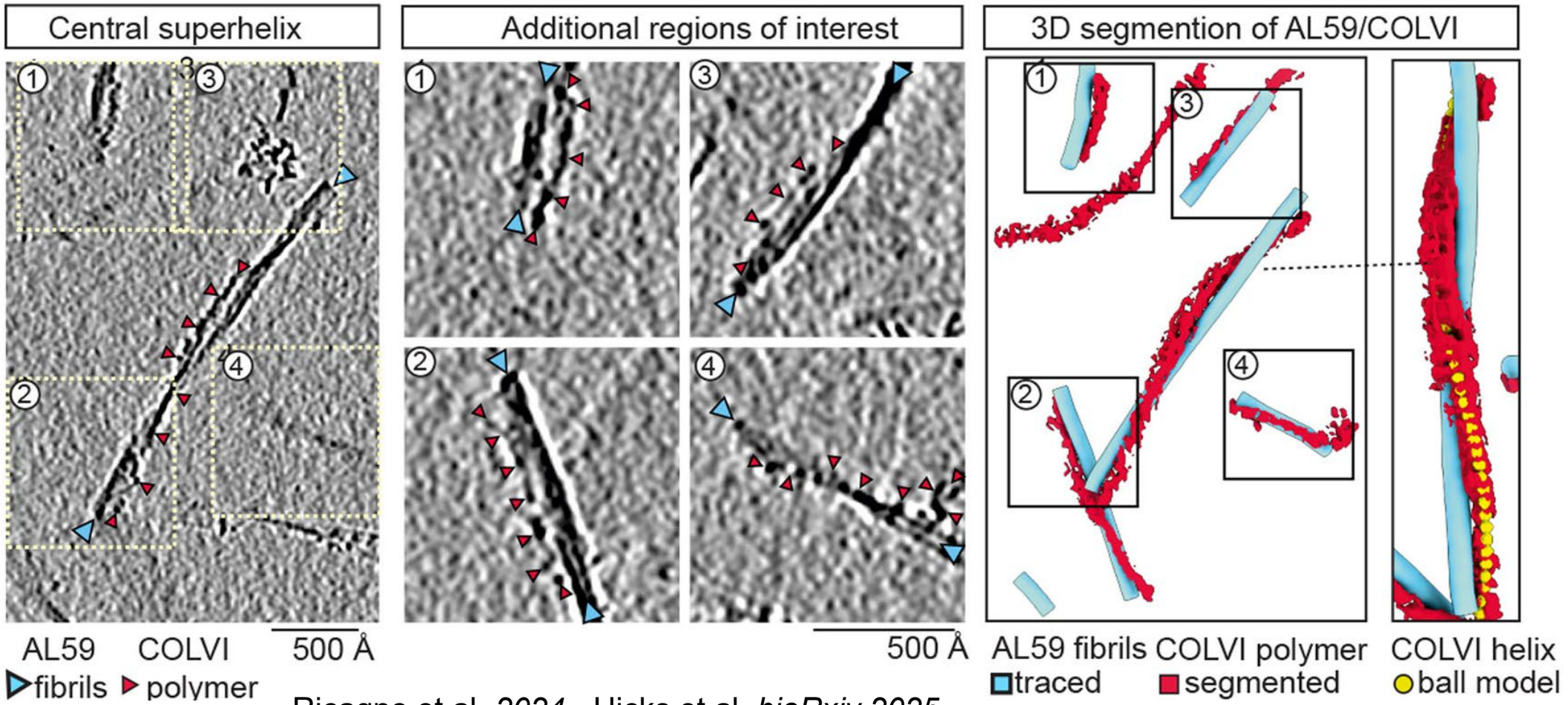
Huang et al, *Front. Cell Dev. Biol. 2021*

nature communications

Article

https://doi.org/10.1038/s41467-024-50686-2

Helical superstructures between amyloid and collagen in cardiac fibrils from a patient with AL amyloidosis

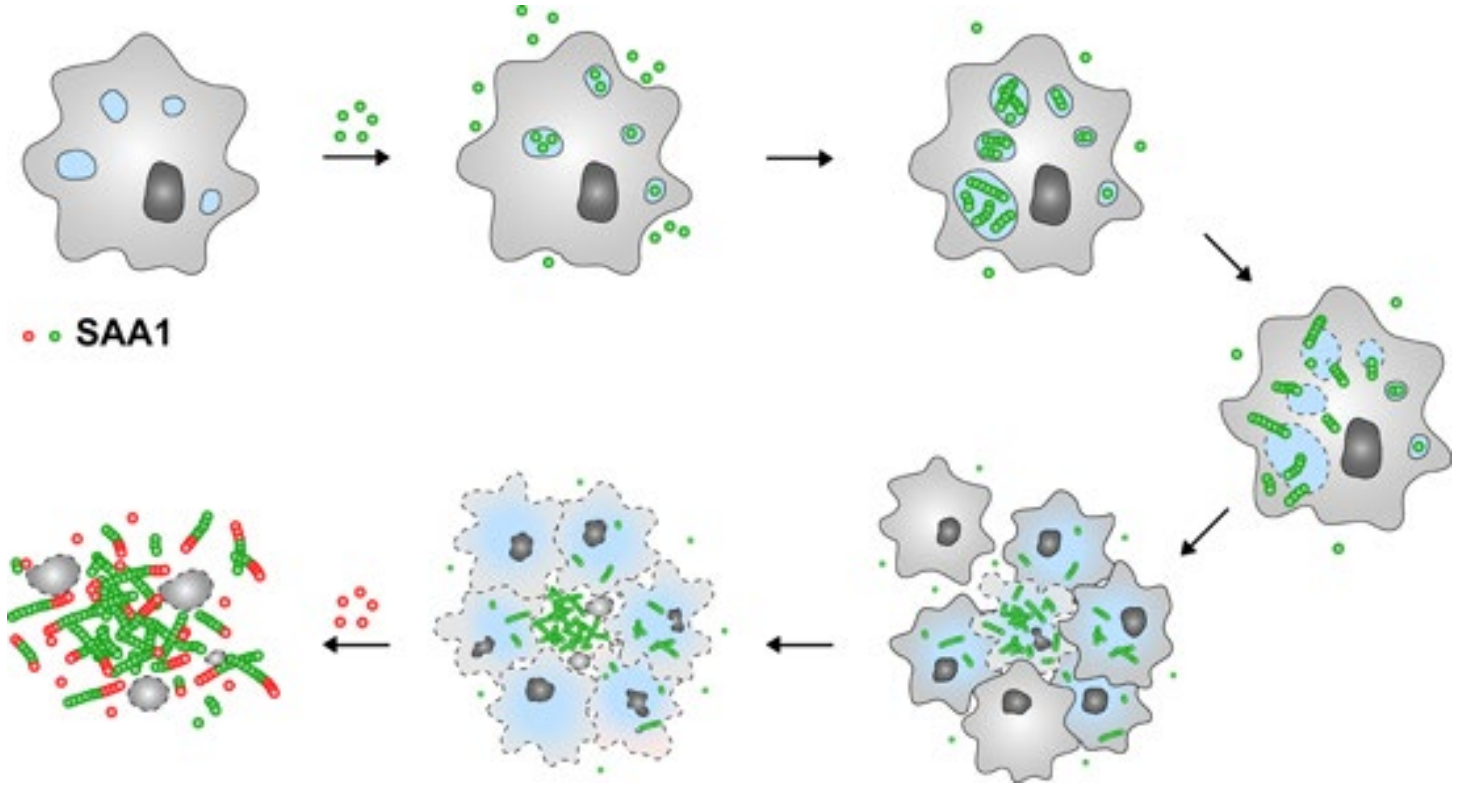


Ricagno et al, *2024* - Hicks et al, *bioRxiv 2025*

The role of amyloid protein-cell interaction in tissue vulnerability

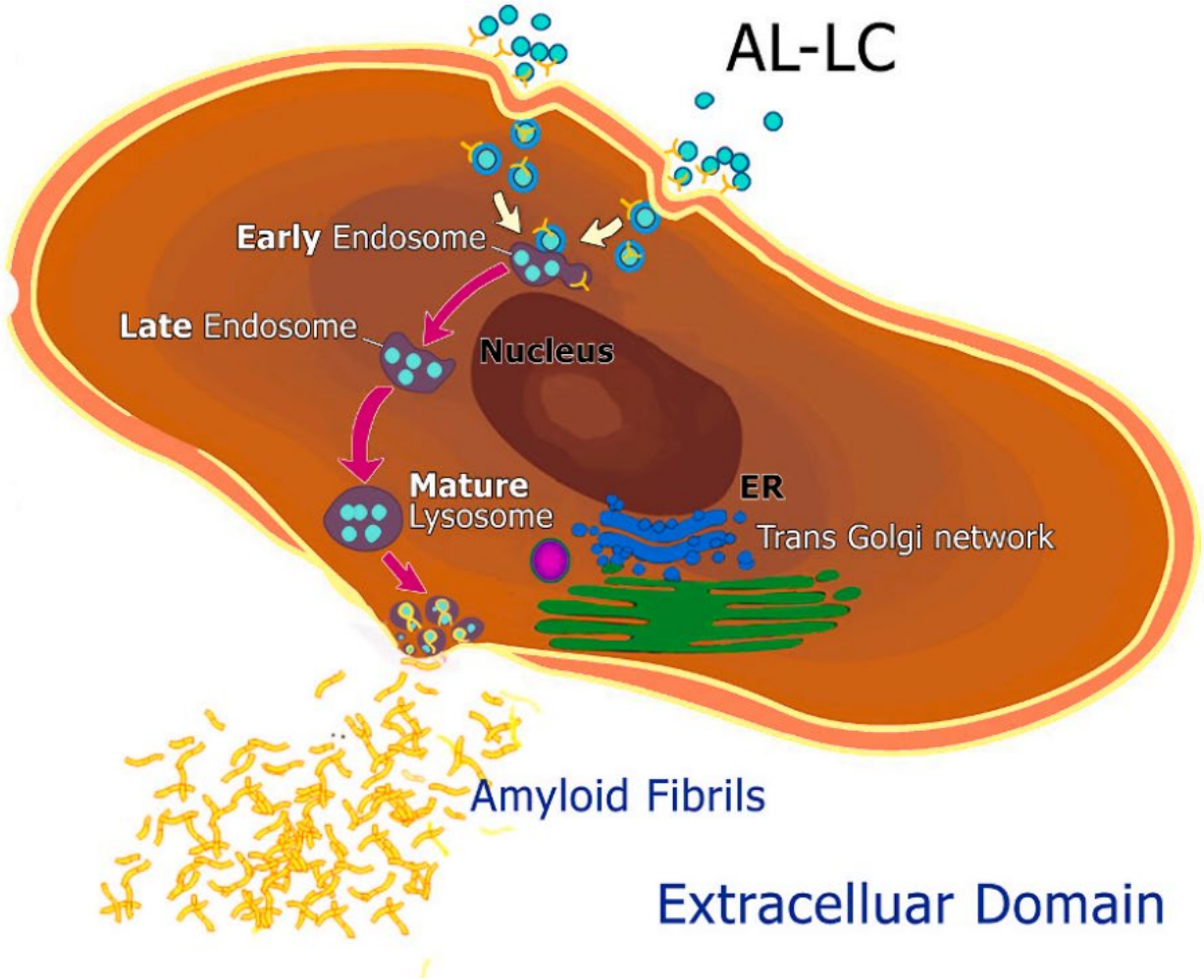
Cellular mechanism of fibril formation from serum amyloid A1 protein

- SAA1 is taken up by cells via clathrin-dependent endocytosis.
- Internalized SAA1 can be directed to the lysosomes.
- FRET demonstrates the formation of intracellular SAA1 aggregates.
- SAA1 aggregation induces lysosomal leakage and cellular death.



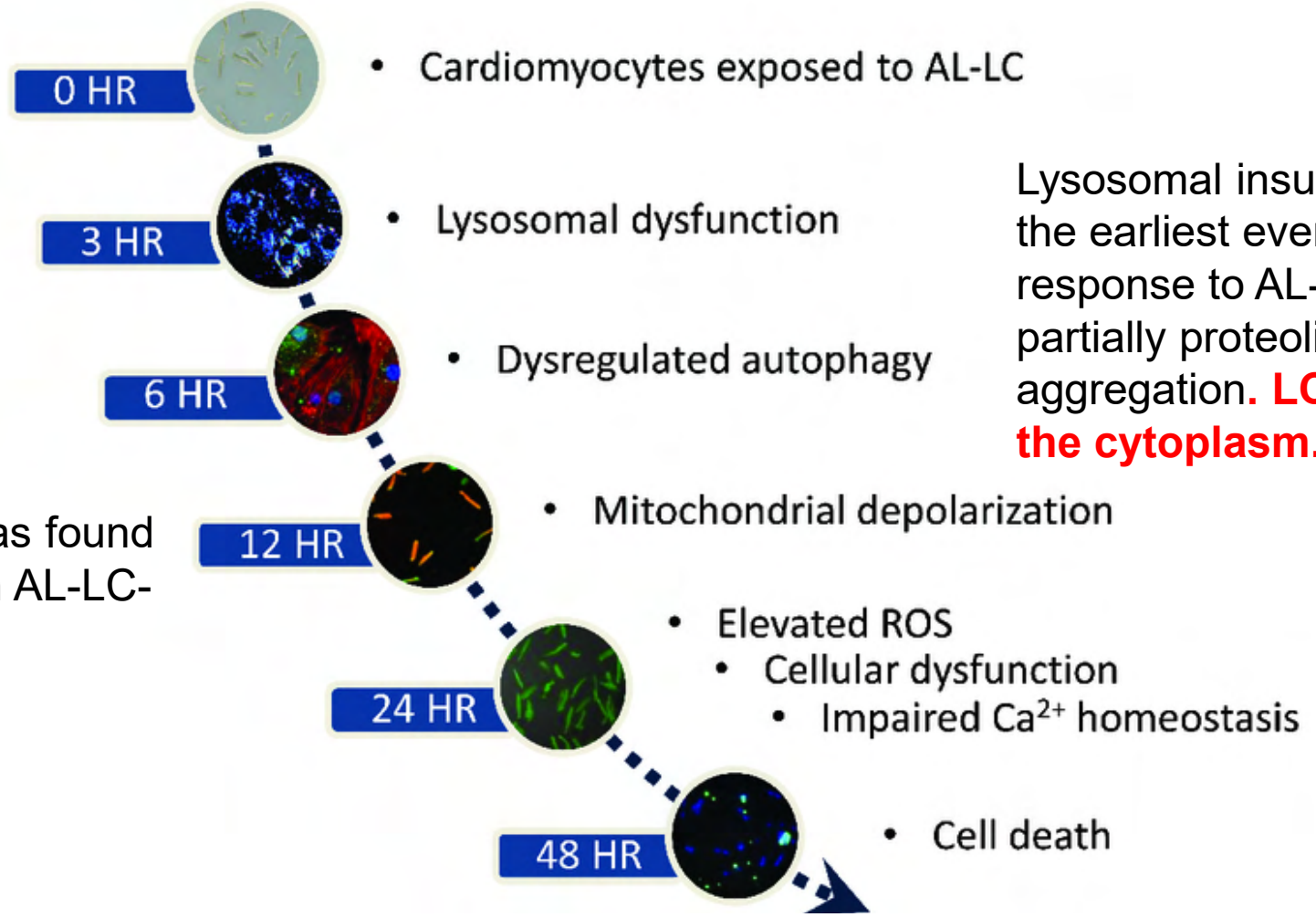
Claus et al, *EMBO Rep 2017*

Light chain-amyloidogenesis by mesangial cells involves active participation of lysosomes



Herrera et al, *Kidney Int Rep 2021 - Heliyon 2023*

Lysosomal dysfunction and impaired autophagy underlie the pathogenesis of amyloidogenic light chain-mediated cardiotoxicity



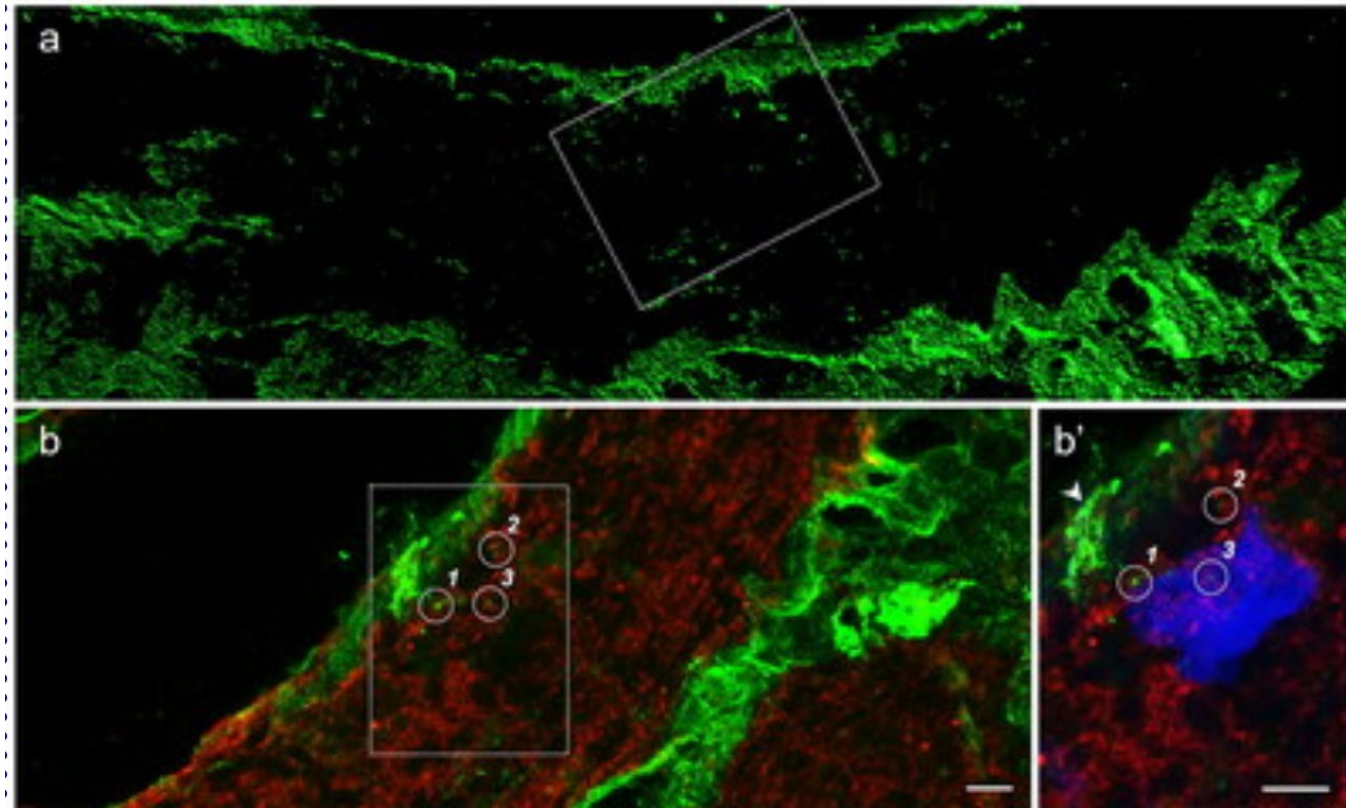
Lysosomal insufficiency is among the earliest events that occur in response to AL-LC. They are partially proteolized favoring their aggregation**. LC are released into the cytoplasm.**

Mitochondrial dysfunction was found to be closely associated with AL-LC-induced pathology.

Guan et al, *EMBO Mol Med 2014*

Internalisation of immunoglobulin light chains by cardiomyocytes in AL amyloidosis

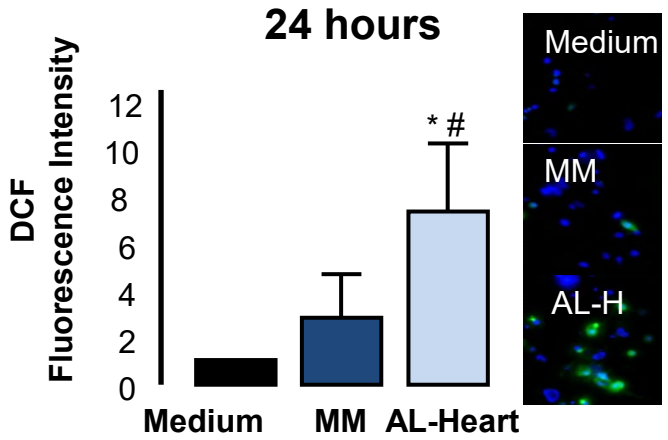
We show, for the first time **directly in patient tissue,** the presence of LCs inside cardiomyocytes, and report their proximity to nuclei and to caveolin-3-rich areas. Our observations point to **macropinocytosis as a probable mechanism of LC uptake.**



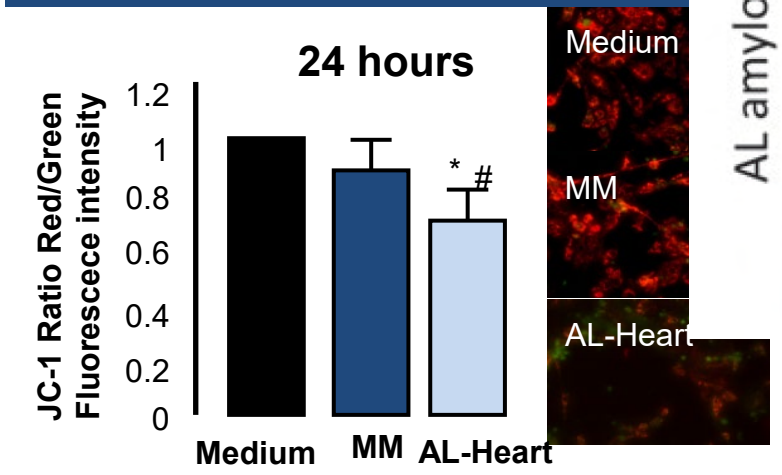
Bezard et al, *Amyloid 2024*
In cardiac cell cultures: Monis et al, *Am J Pathol 2006;* Sikkink et al, *Cell Death Dis 2010*

AL LCs impair mitochondrial function and survival in human cardiac cells

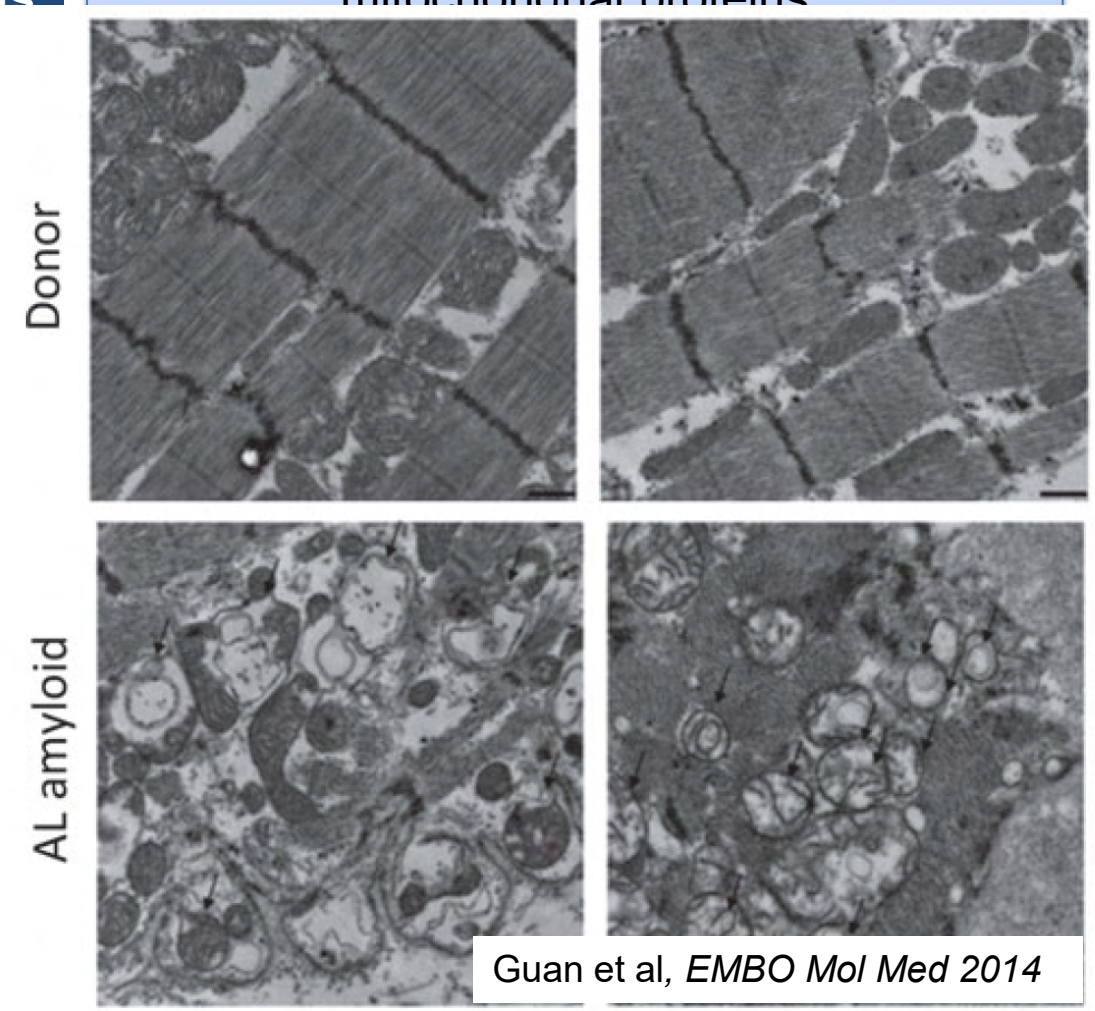
ROS increase driven by metals



Loss of transmembrane poten

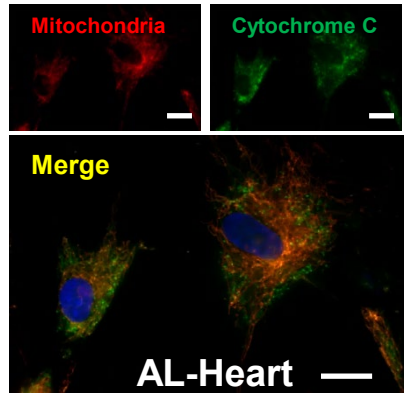


Cardiotropic LCs interact with mitochondrial proteins



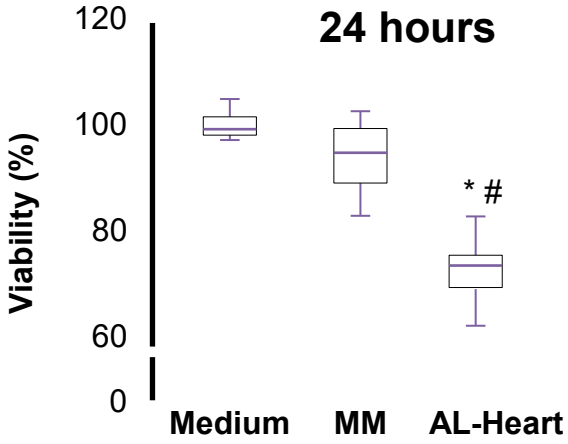
Guan et al, *EMBO Mol Med 2014*

Apoptotic signals



Cytochrome C release

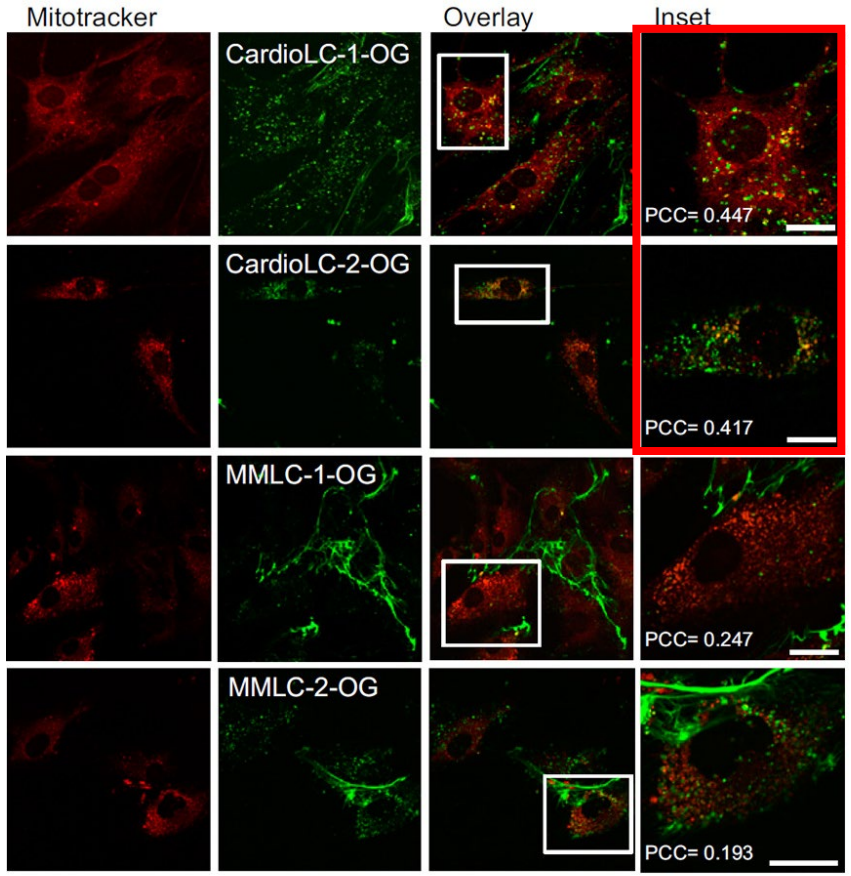
Cell loss



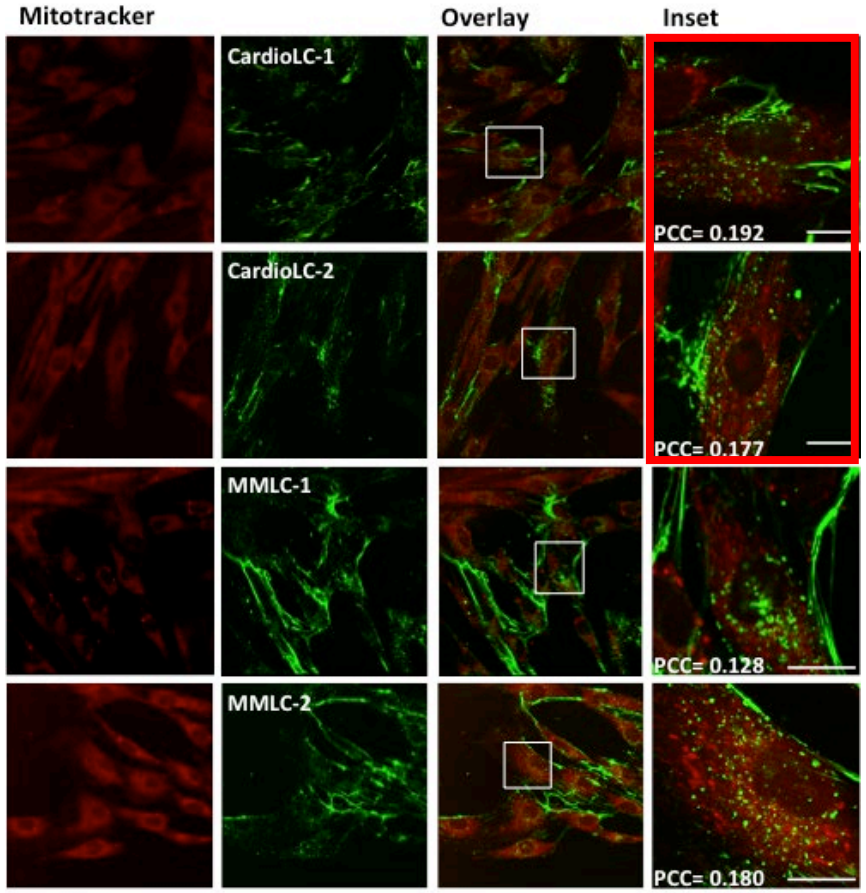
Lavatelli et al, *FASEB J, 2015* – Diomede et al, *Antioxid Redox Signal. 2017* – Imperlini et al, *Sci Rep 2017*

Cardiotoxic LC colocalize with mitochondria in human cardiac fibroblasts but not in dermal fibroblasts

Cardiac fibroblasts



Dermal fibroblasts

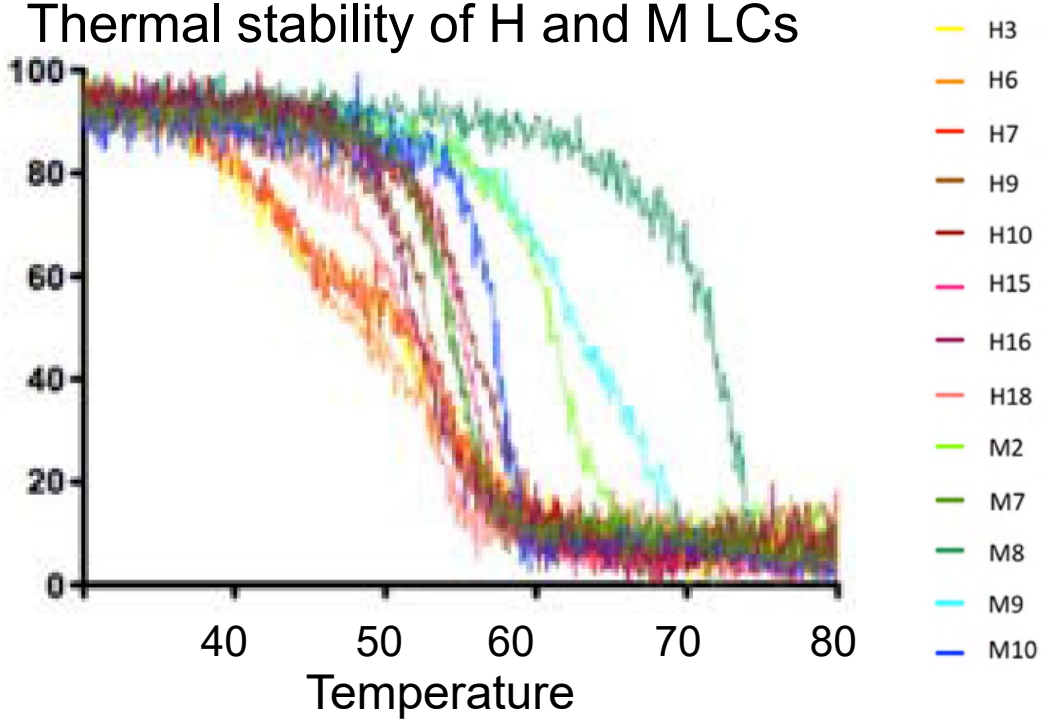


No colocalizations between mitochondria, OPA1 or ACOX1 and all tested LCs in dermal fibroblasts

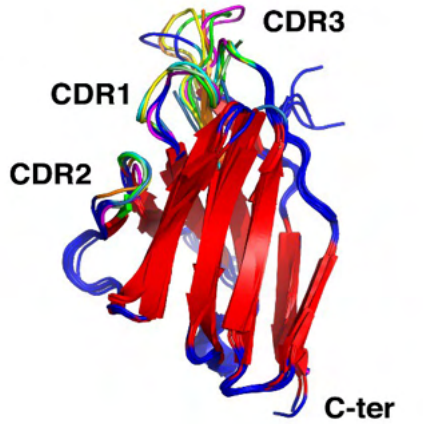
Lavatelli et al *FASEB J 2015*

Low fold stability and high protein dynamics correlate with amyloidogenic LCs

Thermal stability of H and M LCs



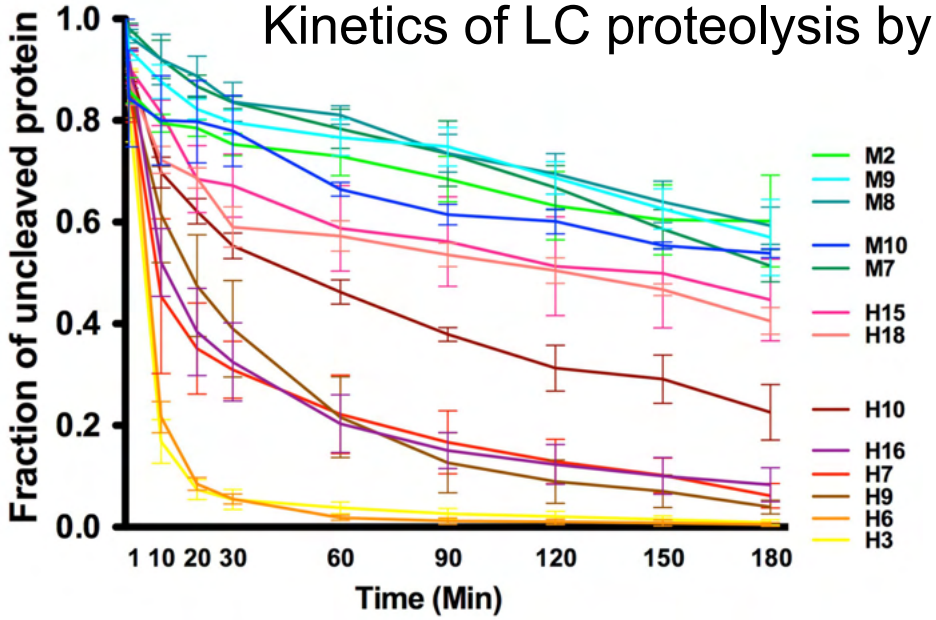
Crystal structure of 8 amyloidogenic cardiotoxic LCs (H), and 5 non amyloid LCs (M)



- **low fold stability**
- **high protein dynamics**

correlate with amyloidogenic LCs,
while hydrophobicity and structural rearrangements are not relevant

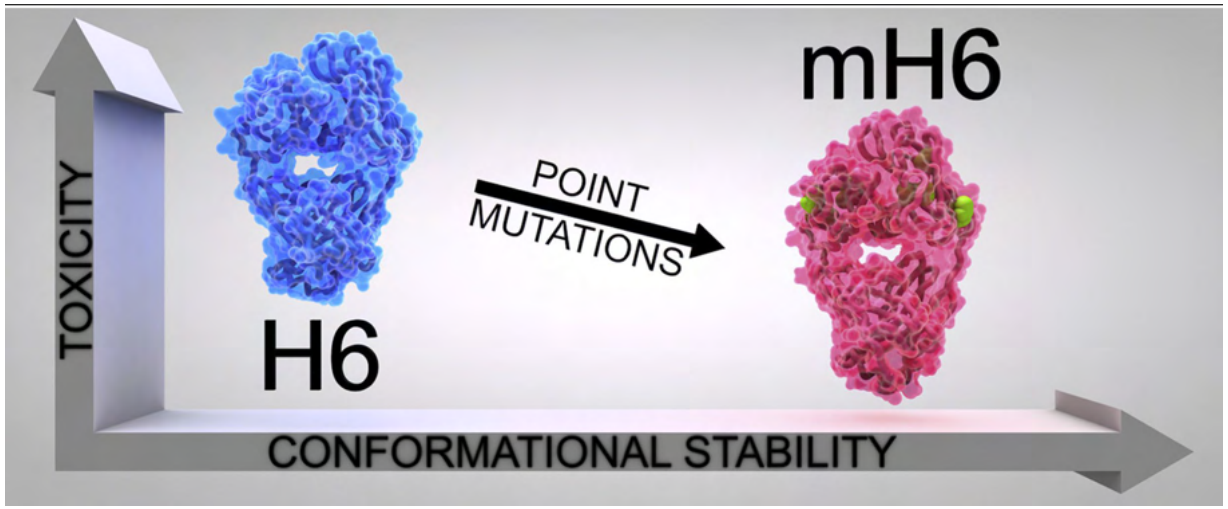
Kinetics of LC proteolysis by trypsin

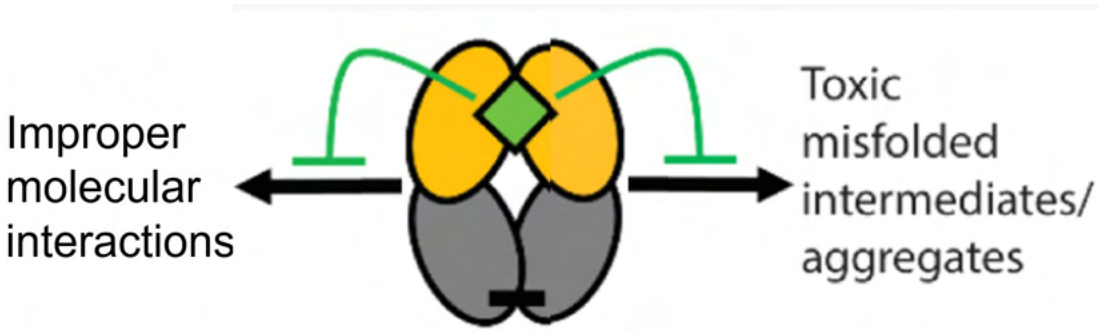


Oberti et al, *Sci Rep 2017*

Light chain instability is linked to cardiotoxicity

We rationally engineered the amino acid sequence of the highly cardiotoxic LC H6 by introducing three residue mutations (V47L, T70N, and G75T), designed to reduce the dynamics of its native state.





These findings support the ongoing development of a new class of drugs: LC stabilizers

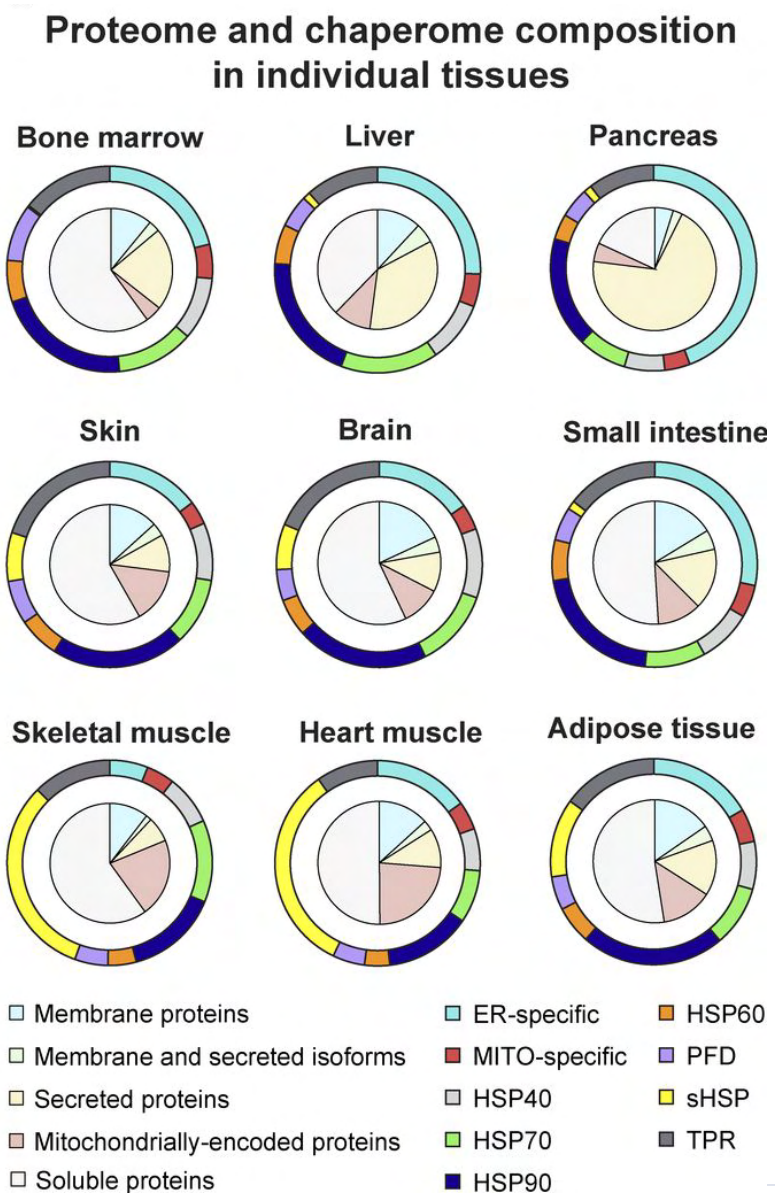
The stabilized LC, restored the cardiac cells viability, ATP production, pumping rate of C. elegans, and reduced oxidative stress

Maritan et al, *JMB 2020*

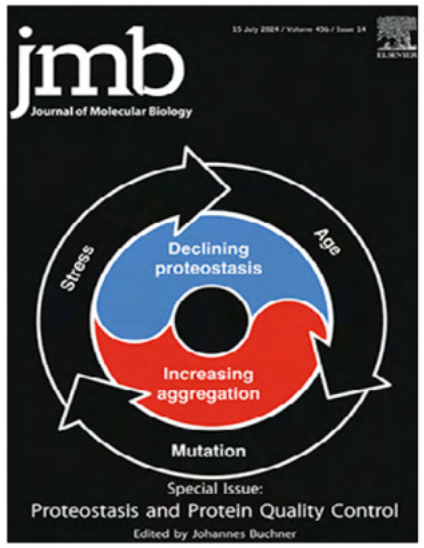
Yan et al, *J Med Chem 2021*

The proteostatic capacity, the cell’s ability to preserve protein homeostasis by balancing protein synthesis, folding, and clearance, varies in different tissues/organs and may underlie tissue vulnerability and resilience in amyloidosis

Shaping proteostasis at the cellular, tissue, and organismal level



Morimoto et al, *J Cell Biol 2017*

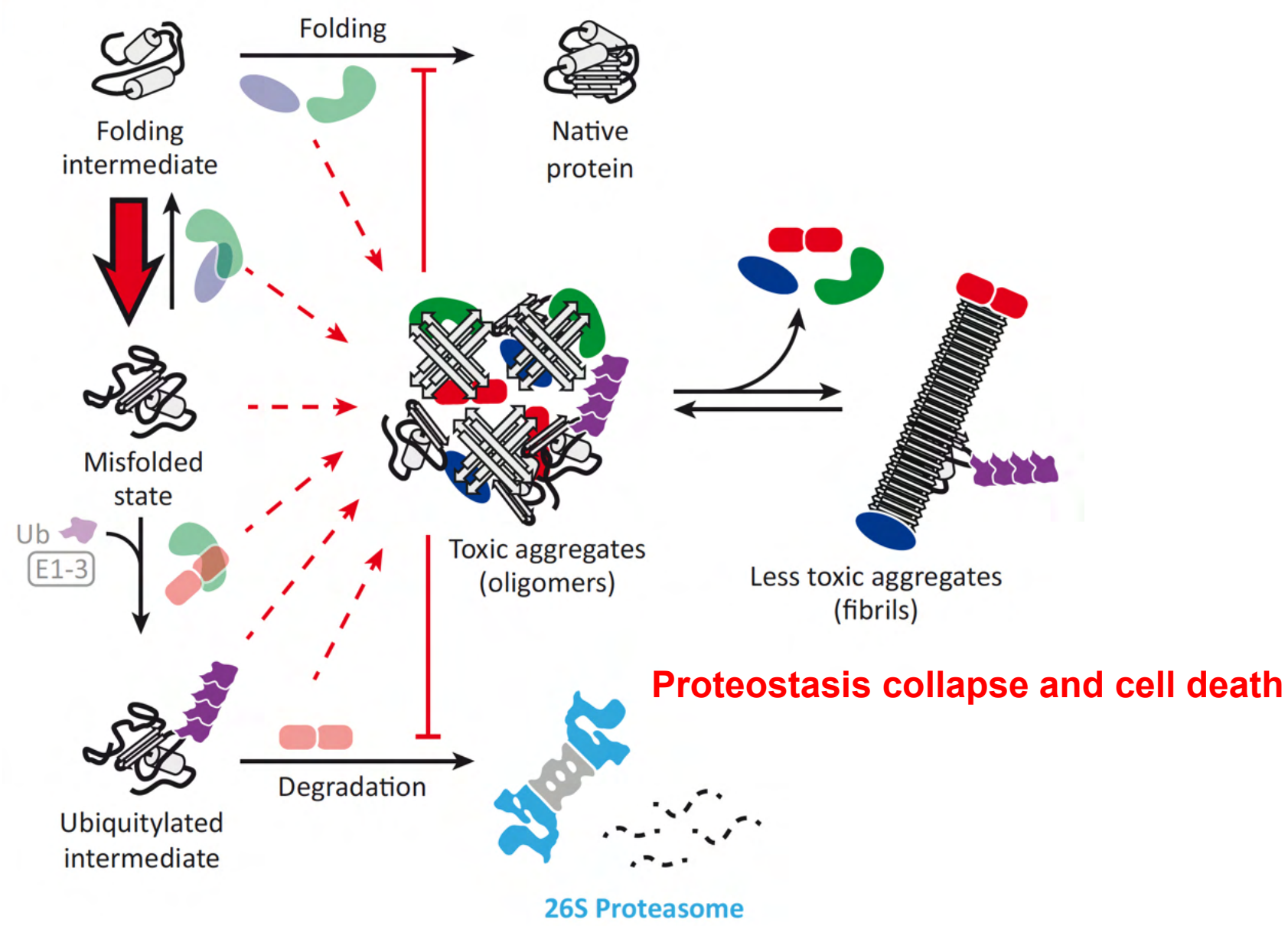


Interplay of Proteostasis Capacity and Protein Aggregation: Implications for Cellular Function and Disease

Mark S. Hipp [1,2,3,*] **and F. Ulrich Hartl** [4,5,6,*] **2024**

When the intracellular protein aggregates overwhelm the proteostasis capacity, cytotoxic protein aggregates accumulate and place an excessive burden on the proteostasis network's ability to maintain proteome integrity. This initiates a feed-forward loop, wherein the generation of misfolded and aggregated proteins ultimately leads to proteostasis collapse and cellular demise.

Proteostasis network impairment by aggregate formation



Proteostasis collapse and cell death

1. Olzscha et al, *Cell 2011*; 2. Woerner et al, *Science 2016*; 3. Hipp et al, *Trends Cell Biol 2014*

MOLECULAR AGEING

The proteostasis network and its decline in ageing

*Mark S. Hipp, Prasad Kasturi and F. Ulrich Hartl**

Nat Rev Mol Cell Biol 2019

Aged / Declining capacity

Basal ER stress; PERK→eIF2α/ATF4/CHOP bias; IRE1α/XBP1s & ATF6 programs wane

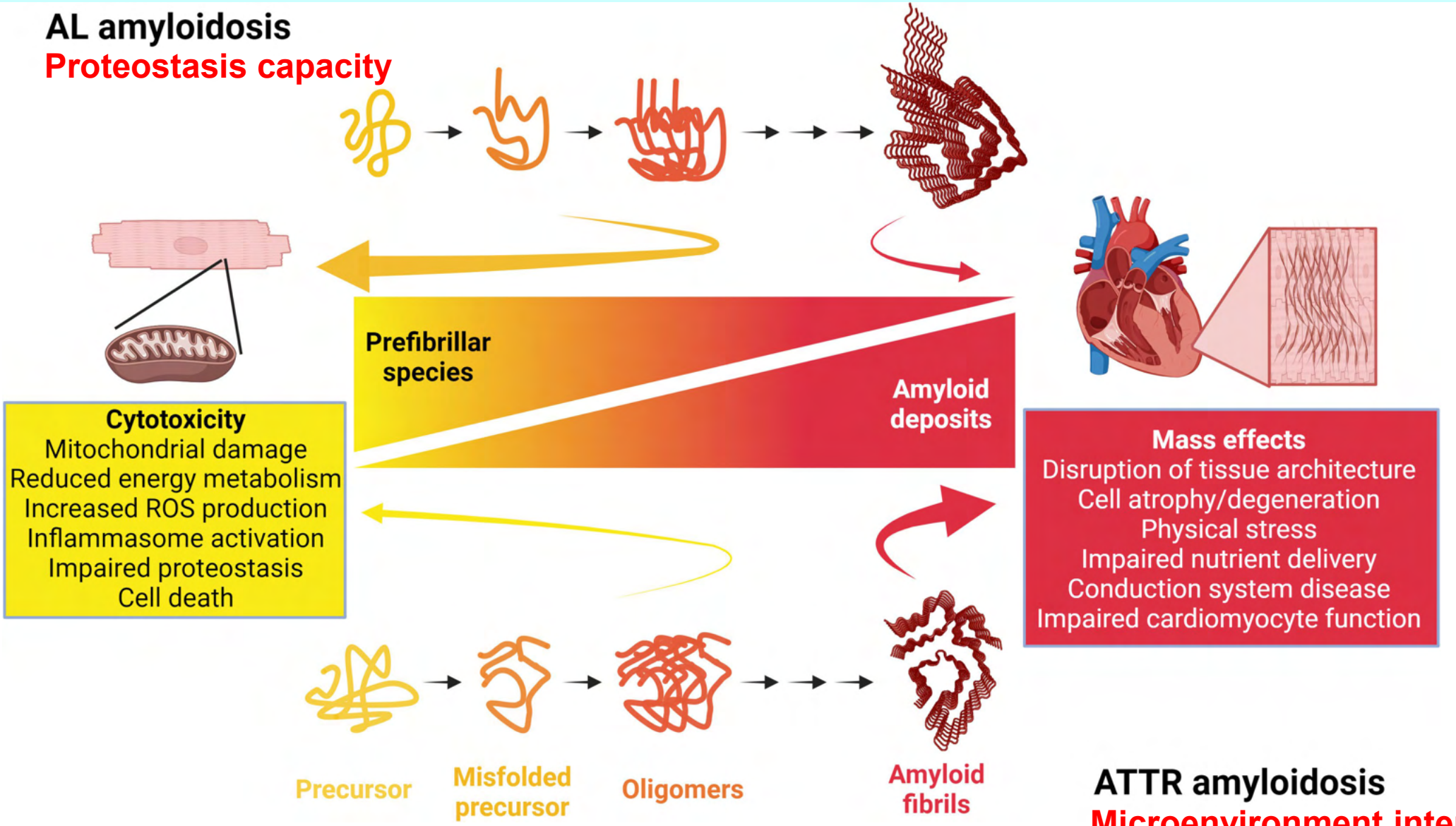
Chaperone/co-chaperone insufficiency; ERAD, proteasome & autophagy flux fall

Secretory QC slippage → amyloidogenic intermediates escape ER

Extracellular chaperone capacity declines

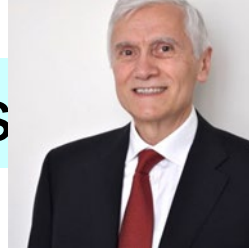
Net result: increased misfolded/aggregated species, organ vulnerability

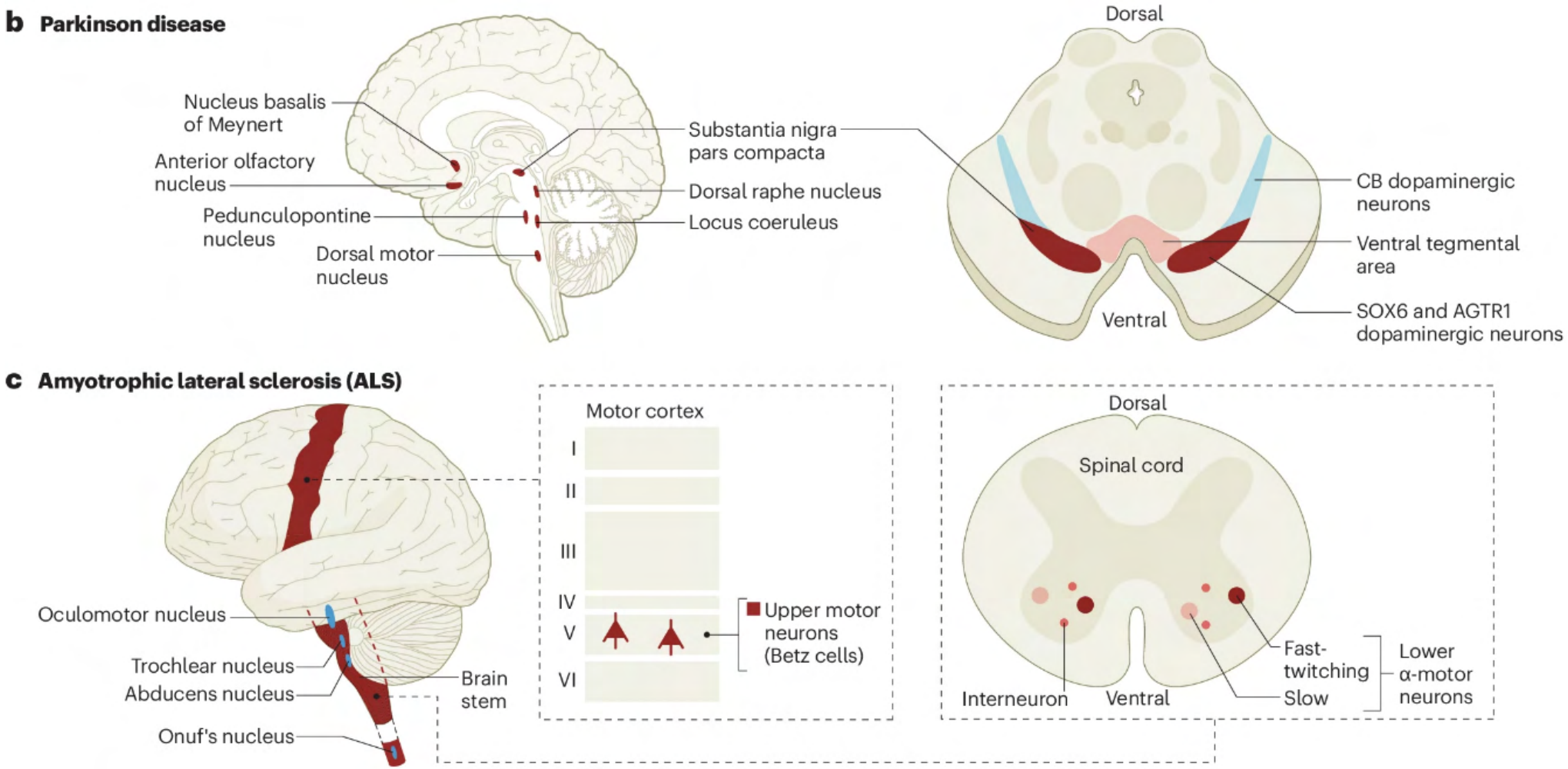
Proteostasis capacity and microenvironment interactions play a different role in various amyloidosis types



Schilling, Nuvolone, Merlini *JACC HF 2024 commentary to Voss et al, JACC HF 2024*

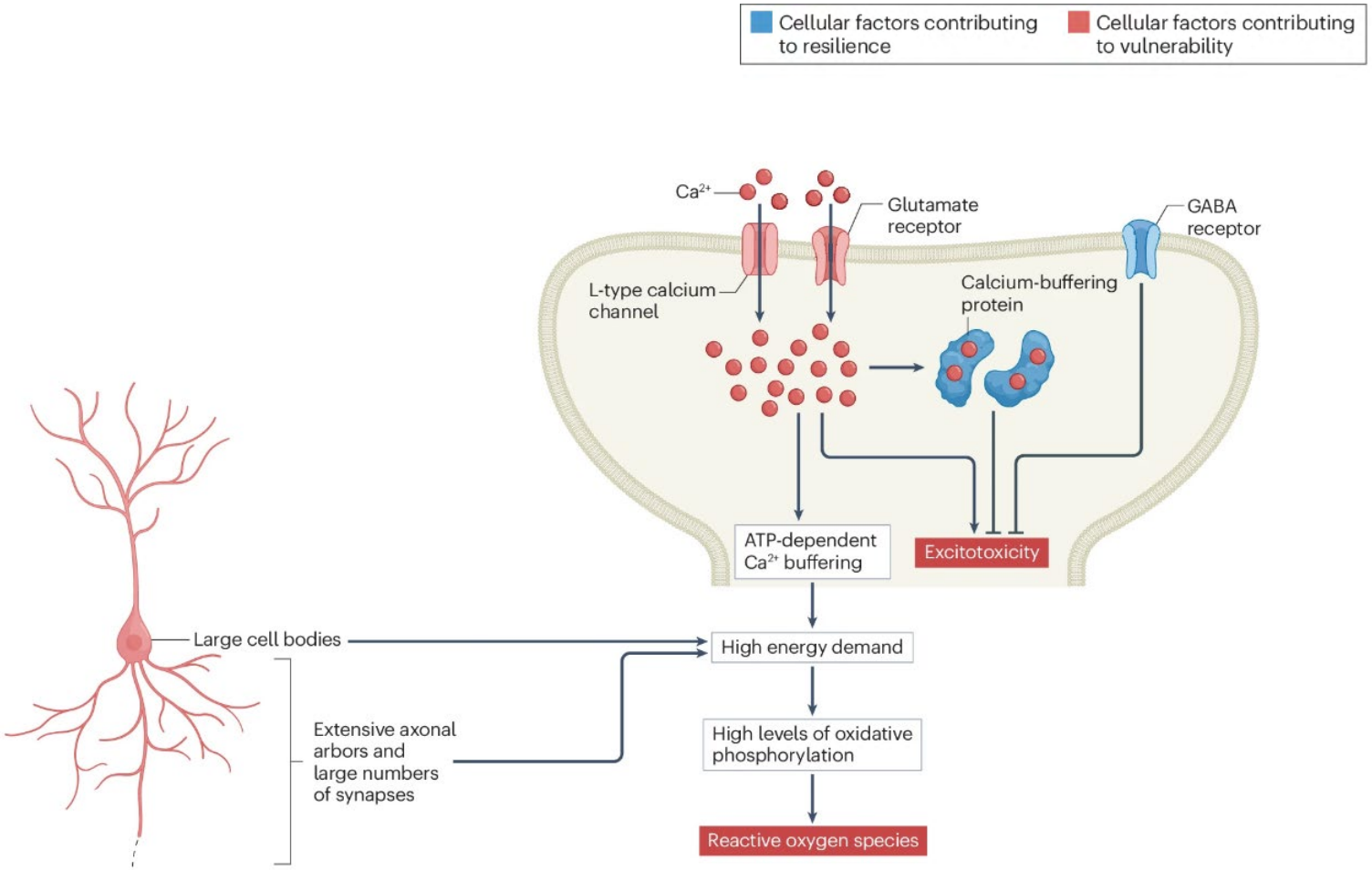
Selective vulnerability is a hallmark of neurodegenerative diseases

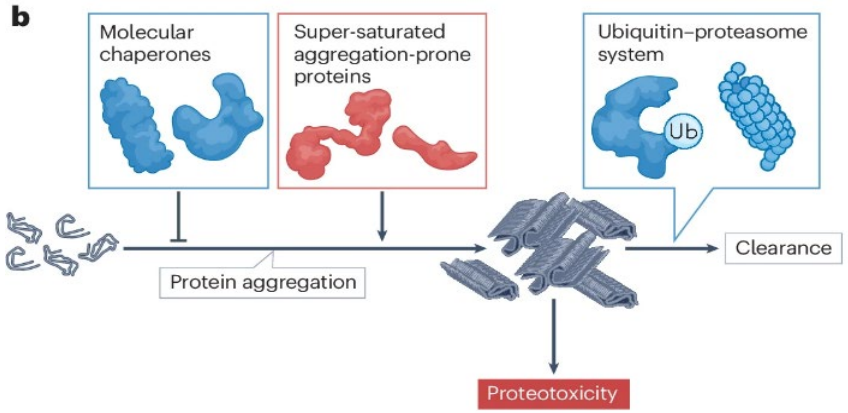




Kampmann, *Nat Rev Neurosci, 2024*

Cell-autonomous mechanisms of selective vulnerability





Kampmann, *Nat Rev Neurosci, 2024*

Microenvironment + proteostasis capacity gate organ vulnerability and resilience

Further research is required to elucidate the underlying molecular mechanisms

These factors represent actionable targets for improving the management of both systemic and localized amyloidosis

THANK YOU!