Amyloidosis Research Consortium

Amyloidosis 101 webinar

Presented by: Sarah Cuddy, MD

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Boston, USA

Wednesday, February 19, 2025 | Noon – 1 p.m.

Disclosures

- Grant support from NIH 1K23HL166686-01 and AHA 23CDA857664;
- Site PI for Helios-B (Alnylam), Cardio-TTRansform (Ionis, Astra Zeneca), DepleTTR (Alexion), Magnitude (Intellia). Sub-PI for ACT-Early (Bridgebio), Phase II Acoramidis Trial (Bridgebio, formerly Eidos).
- Personal fees from Pfizer, Bridgebio, Intellia, Ionis, AstraZeneca, Alexion and Novo-Nordisk, Life Molecular Imaging.

Objectives

Overview of Amyloidosis

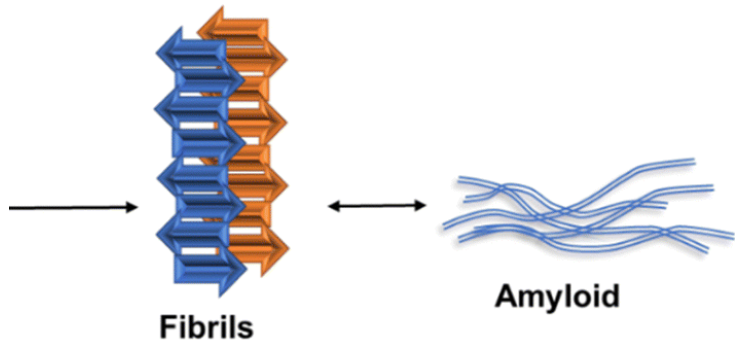
- Types of Amyloid
- Organ involvement

Diagnosis

Treatments

Amyloid and Amyloidosis

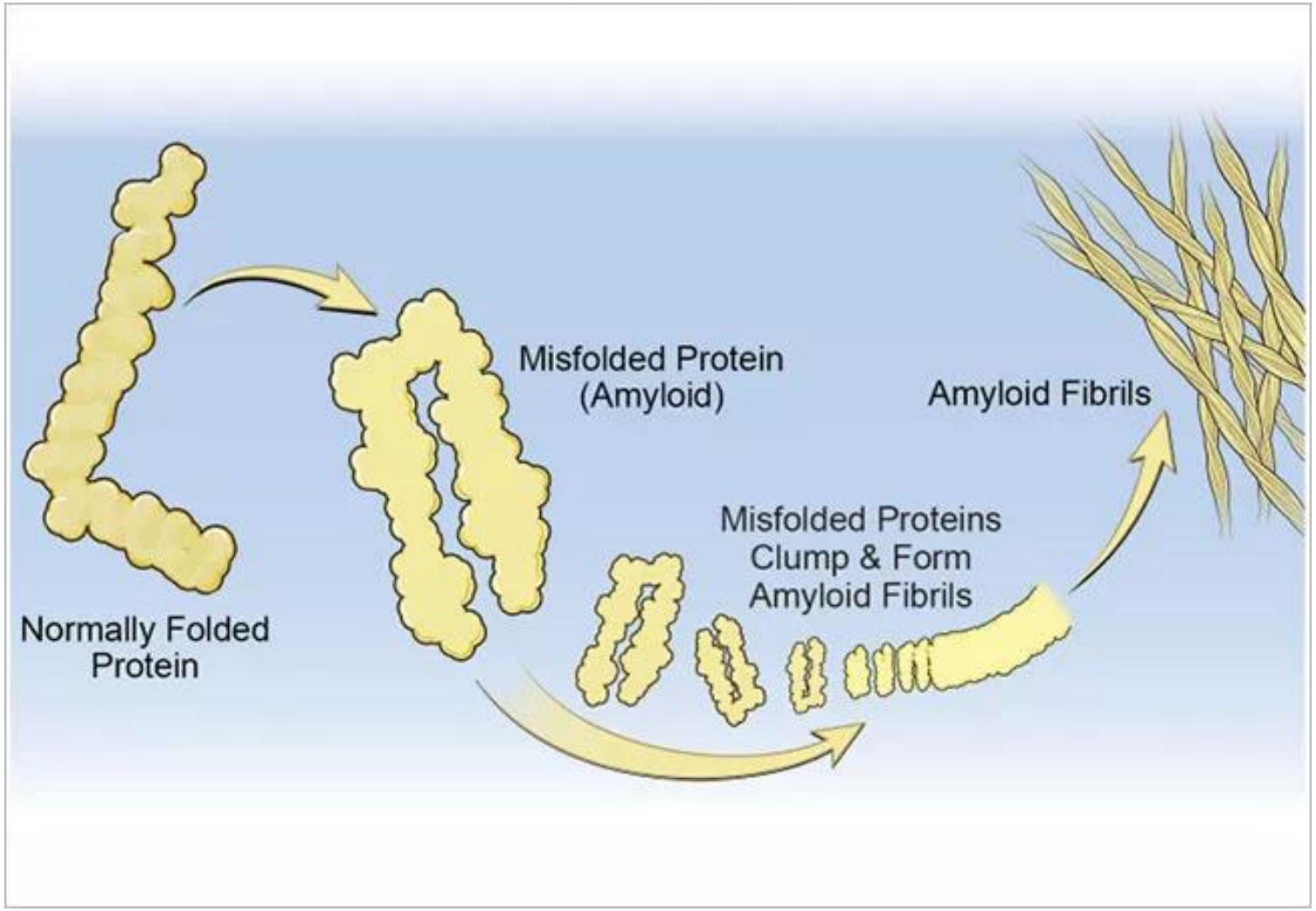
- Group of complex diseases caused by **protein misfolding** and aggregation into highly ordered **amyloid fibrils**
- Deposit in tissues, resulting in **progressive organ damage**
- **Localized** deposition
- **Systemic** amyloidosis- at least 17 proteins identified
  - Transthyretin (ATTR)
  - Light Chain (AL)
  - Reactive systemic amyloidosis – serum amyloid A protein (AA)



Mater. Adv., 2024, 5, 4078-4090

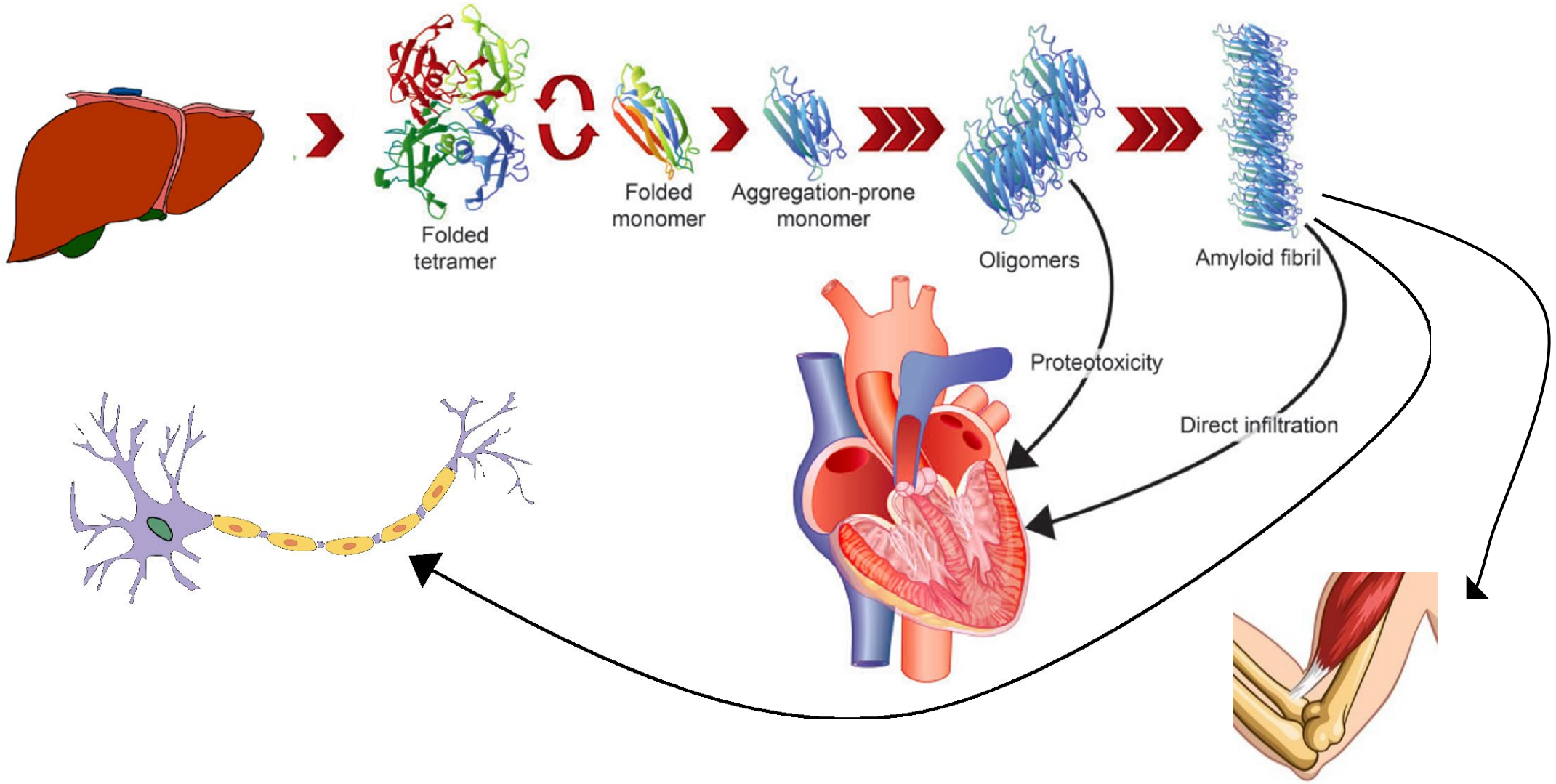
Falk et al. N Engl J Med 1998; 338:264-265

Precursor Protein forms Amyloid Fibrils



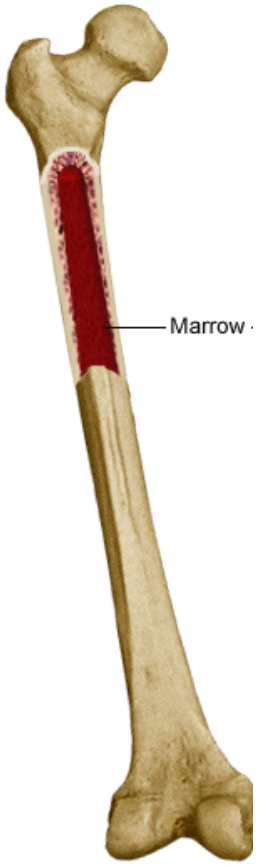
https://consultqd.clevelandclinic.org/antibody-treatment-holds-promise-in-treating-patients-with-relapsed-or-refractory-light-chain-amyloidosis

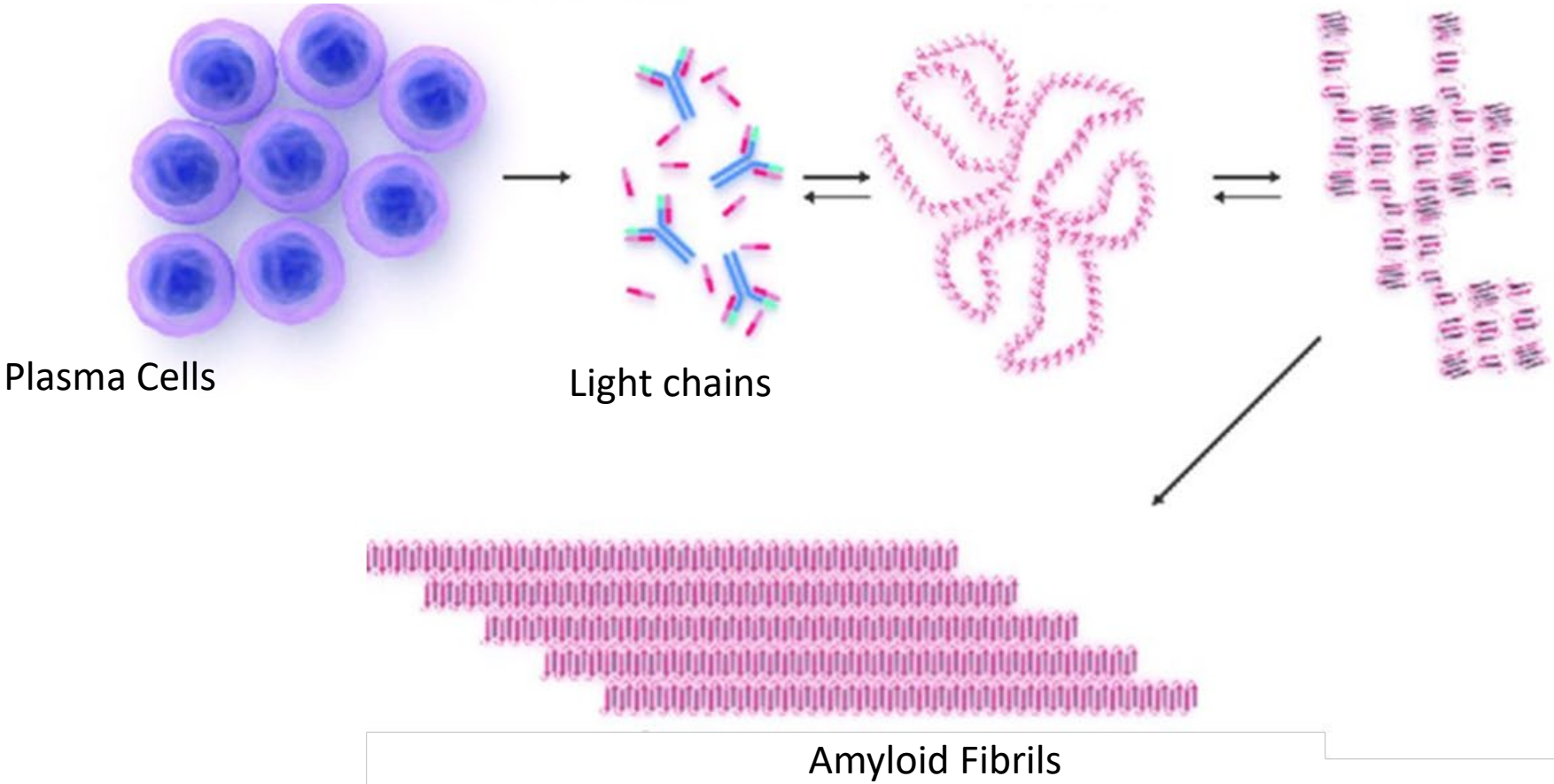
ATTR Amyloidosis: Transthyretin Protein



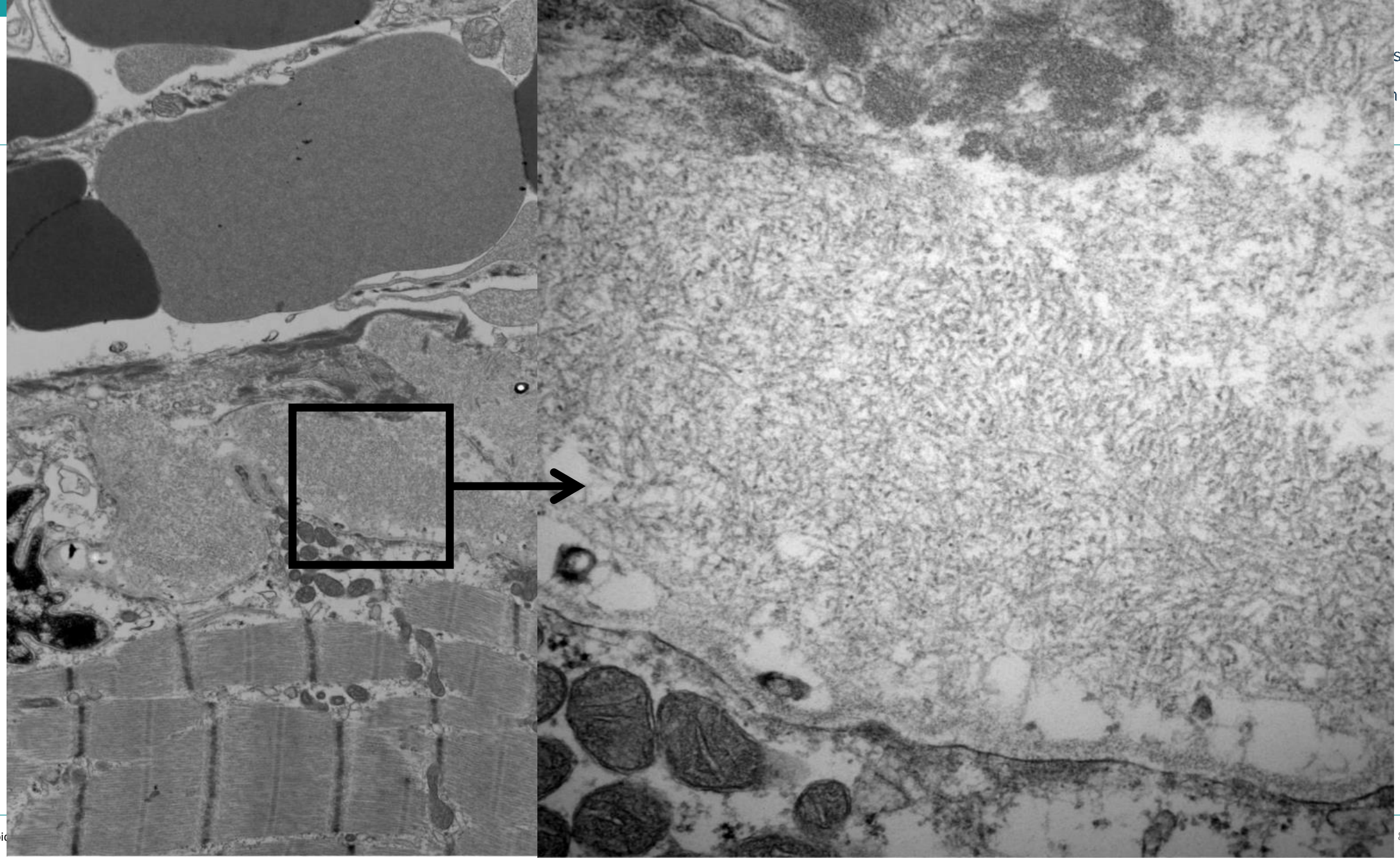
Falk RH, EHJ 2019;40(12): 1009-1012.

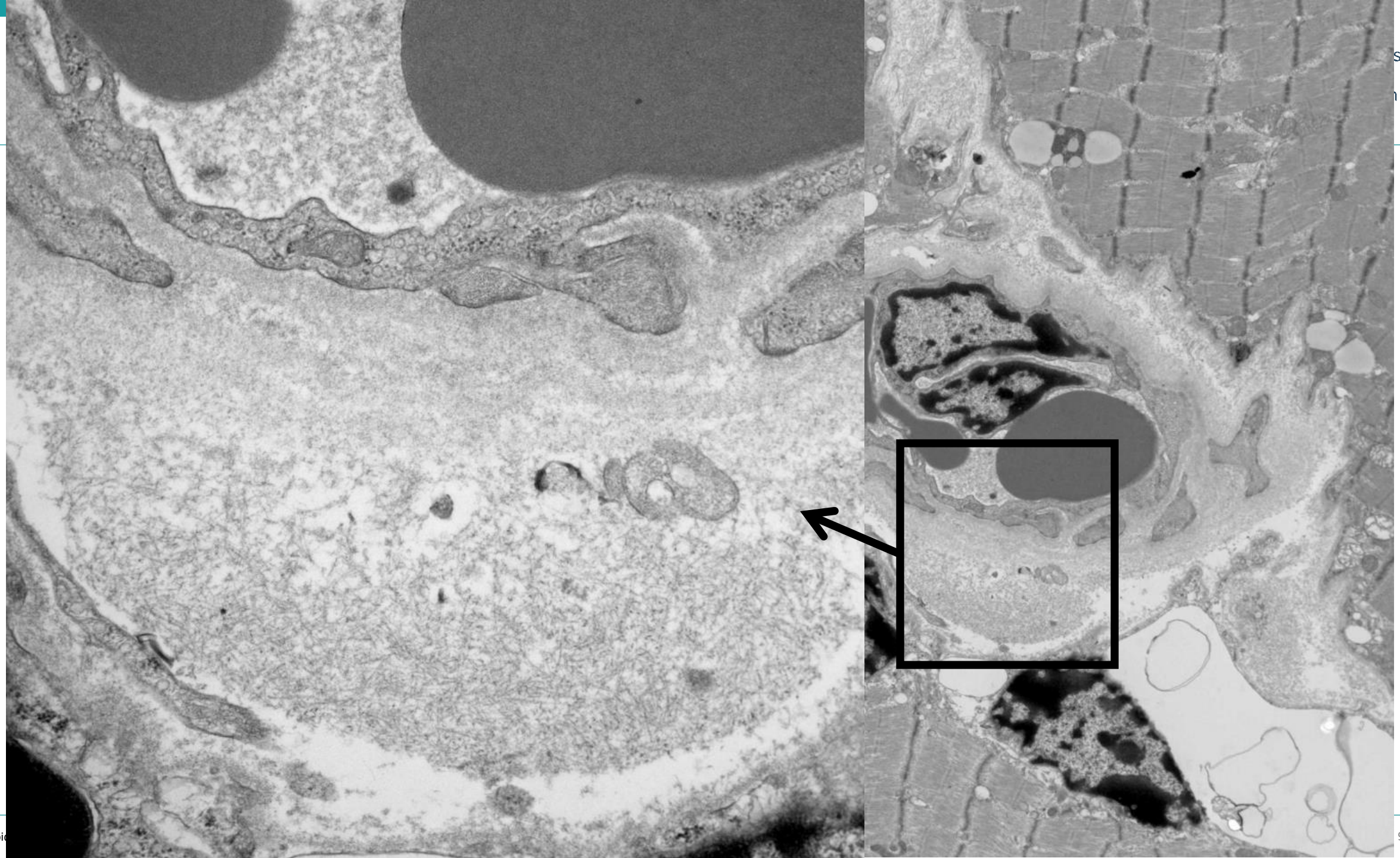
Light Chain (AL) Amyloidosis: Plasma Cells in Bone Marrow Overproducing Light Chains





Falk et al. *J Am Coll Cardiol*. 2016

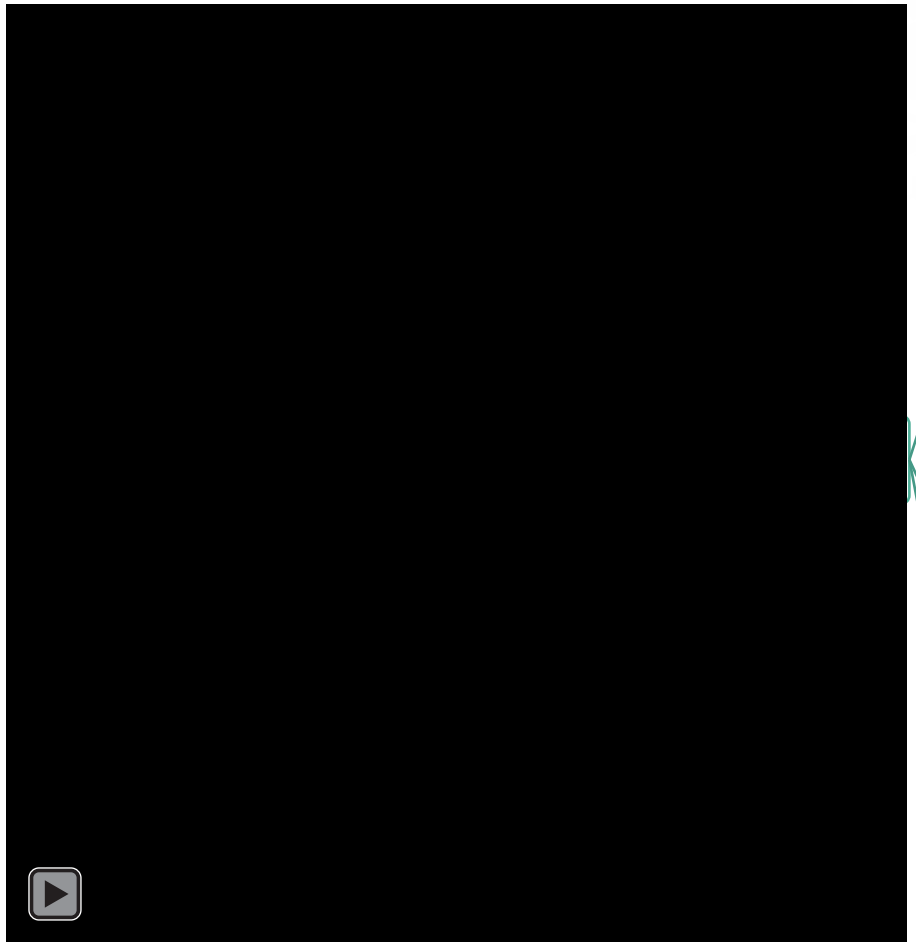




Some of the proteins that cause systemic amyloidosis

Precursor Protein	Amyloid Type	Clinical Presentation/ Involvement
Monoclonal immunoglobulin light chain	AL	Localized or systemic (heart, kidney, GI tract, liver, peripheral nerves, soft tissue)
Monoclonal immunoglobulin heavy chain	AH	Localized or systemic (heart, kidney, GI tract, liver, peripheral nerves, soft tissue)
Serum amyloid A (SAA)	AA	Renal (most common), liver, GI tract, autonomic nervous system
TTR wild-type (senile systemic)	Wild-type ATTR	Heart, soft tissue
TTR mutant*	Mutant ATTR	Hereditary peripheral or autonomic neuropathy, cardiomyopathy, vitreous opacities
LECT2	ALect2	Hepatic and renal; in Hispanic populations and those with preexisting liver disease (eg, hepatitis C)
β_2-microglobulin	Aβ_2M	Triad of carpal tunnel syndrome, shoulder pain, and flexor tenosynovitis of hands in long-term dialysis patients
Fibrinogen Aα-chain*	AFib	Visceral (mainly renal, also liver, spleen)
Gelsolin*	AGel	Cranial nerves and cornea
Lysozyme*	ALys	Visceral (mainly renal, also liver, spleen, lung, GI)

Cardiac Amyloidosis



- Transthyretin ATTR
  - Wild-type
  - Variant (Mutant/hereditary)
- Light Chain AL
- AA, Apolipoprotein AI-4, B2Microglobulin

Falk et al. N Engl J Med 1998; 338:264-265

Clinical presentation: Cardiac Manifestations

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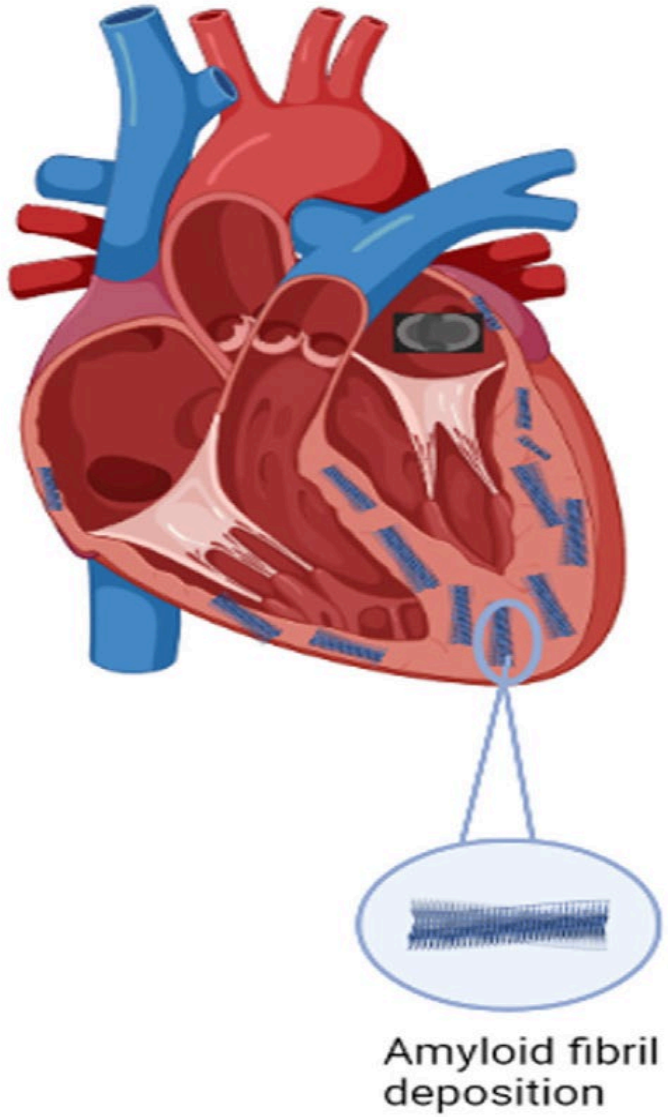
Heart Failure

Atrial Fibrillation

Thromboembolic Events = Stroke



Conduction System Disease = disrupt the electrics

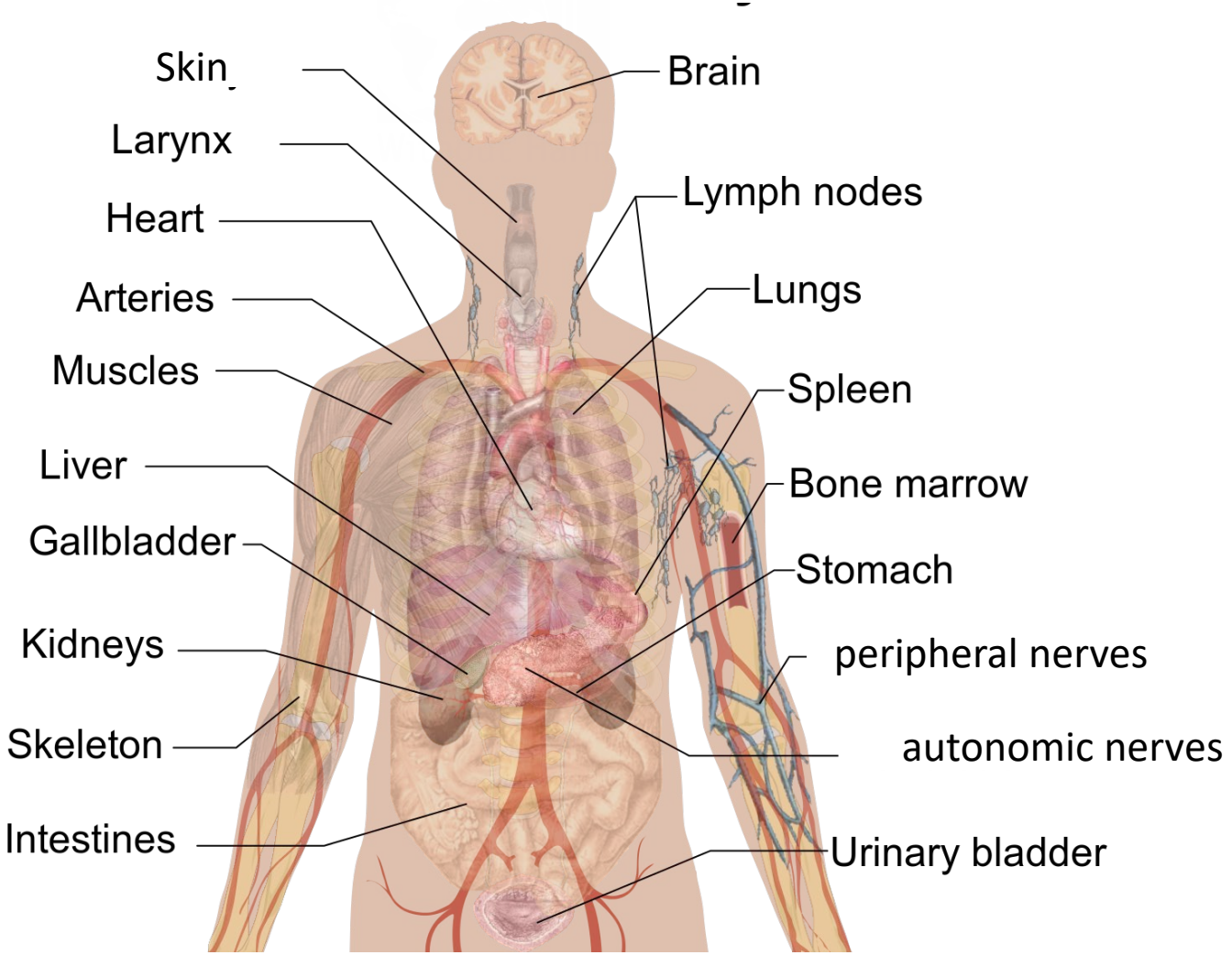
Chronotropic Incompetence = Heart rate is blunted

Syncope = Faint

Sudden Cardiac Death

Angina

Organ Involvement – lots of variability

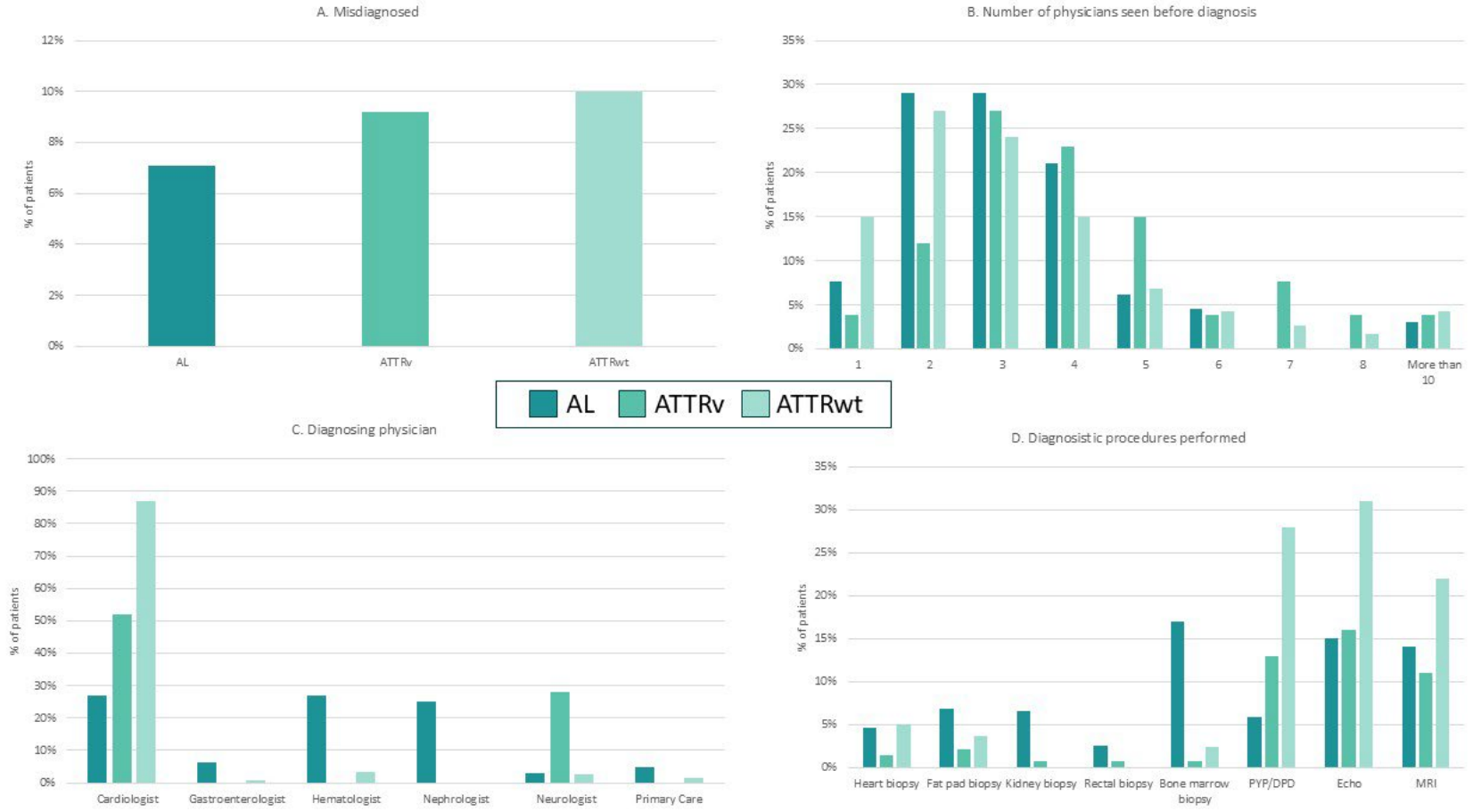


https://bio.libretexts.org/@api/deki/files/16182/Internal_organs.png?revision=1&size=bestfit&width=580&height=515

Diagnostic Work-up Depends on Presentation

- Relates to organ involvement
- This is where delays are very frequent

ARC Data

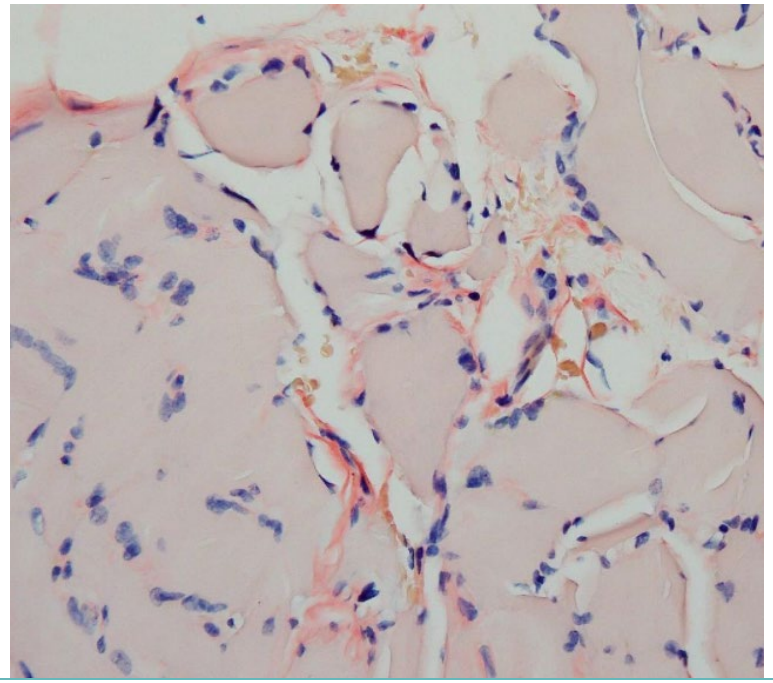


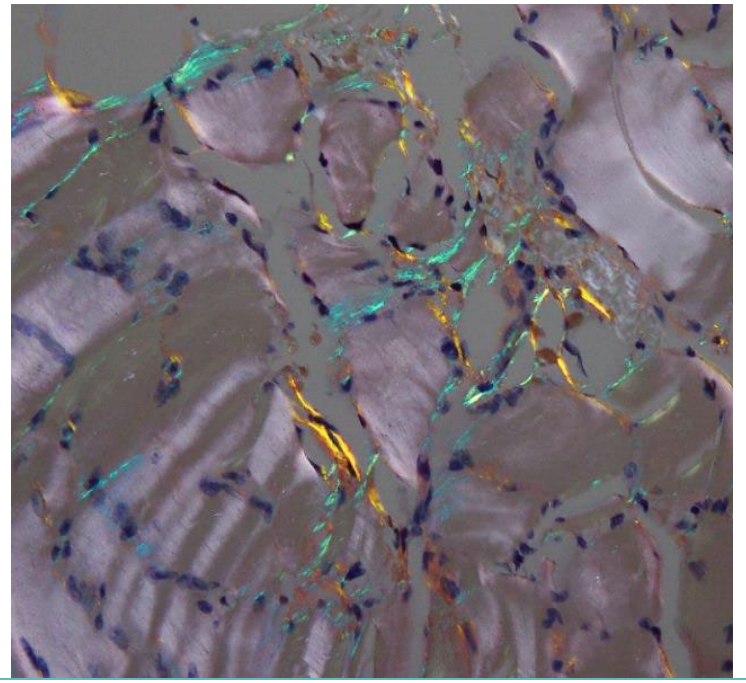
Cardiac Work up

- Echo is often the first imaging tool we use.

Biopsy

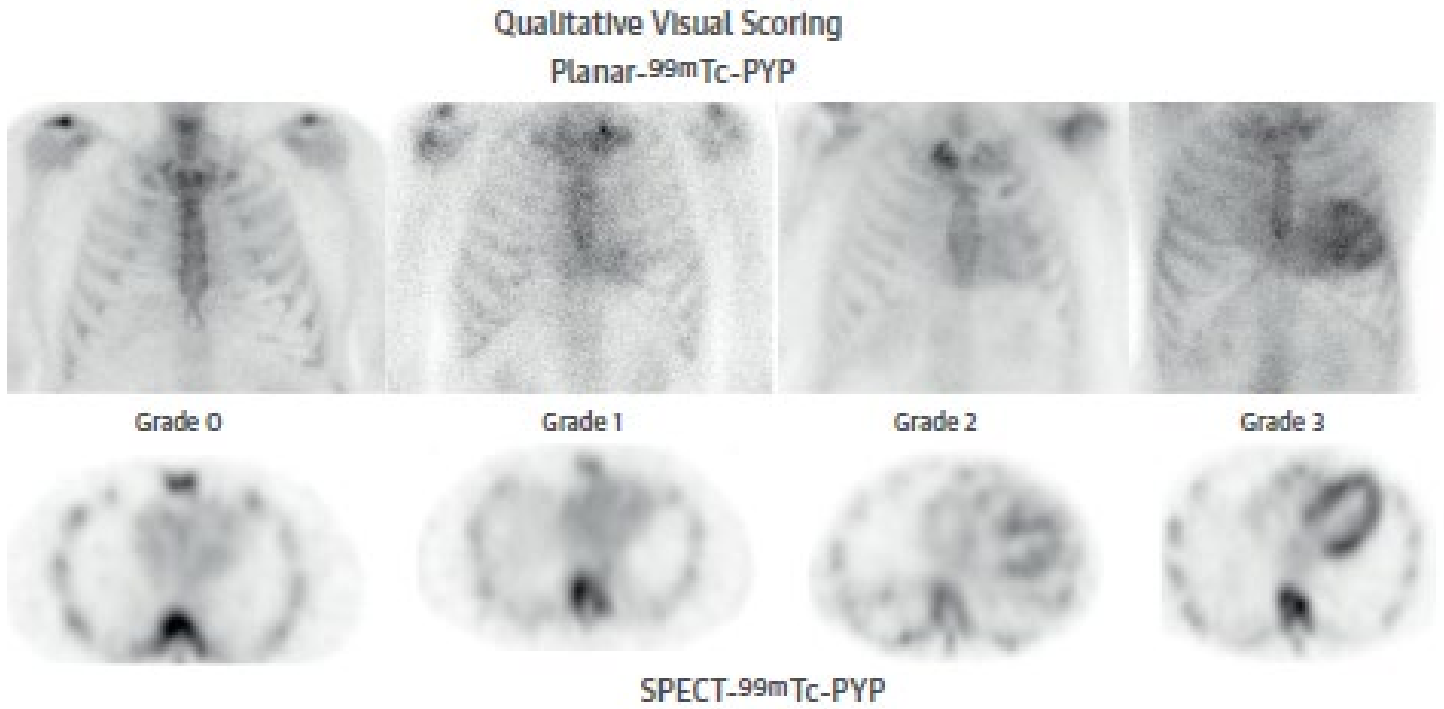
- "Gold Standard"
  - 1. Identify amyloid deposition
  - 2. identify what type – the precursor protein





Non-biopsy Diagnosis of ATTR Amyloidosis

- ATTR- cardiomyopathy
  - Nuclear Imaging
  - "Amyloid Scan"
  - "Bone Scan" – bone avid radiotracer
  - "Cardiac Scintigraphy"
- Have to rule out Light Chain Abnormality
- Genetic Test



Treatments - principles

- Addressing precursor protein

- Supportive Management

Light Chain (AL) Amyloidosis: Dara + CyBorD

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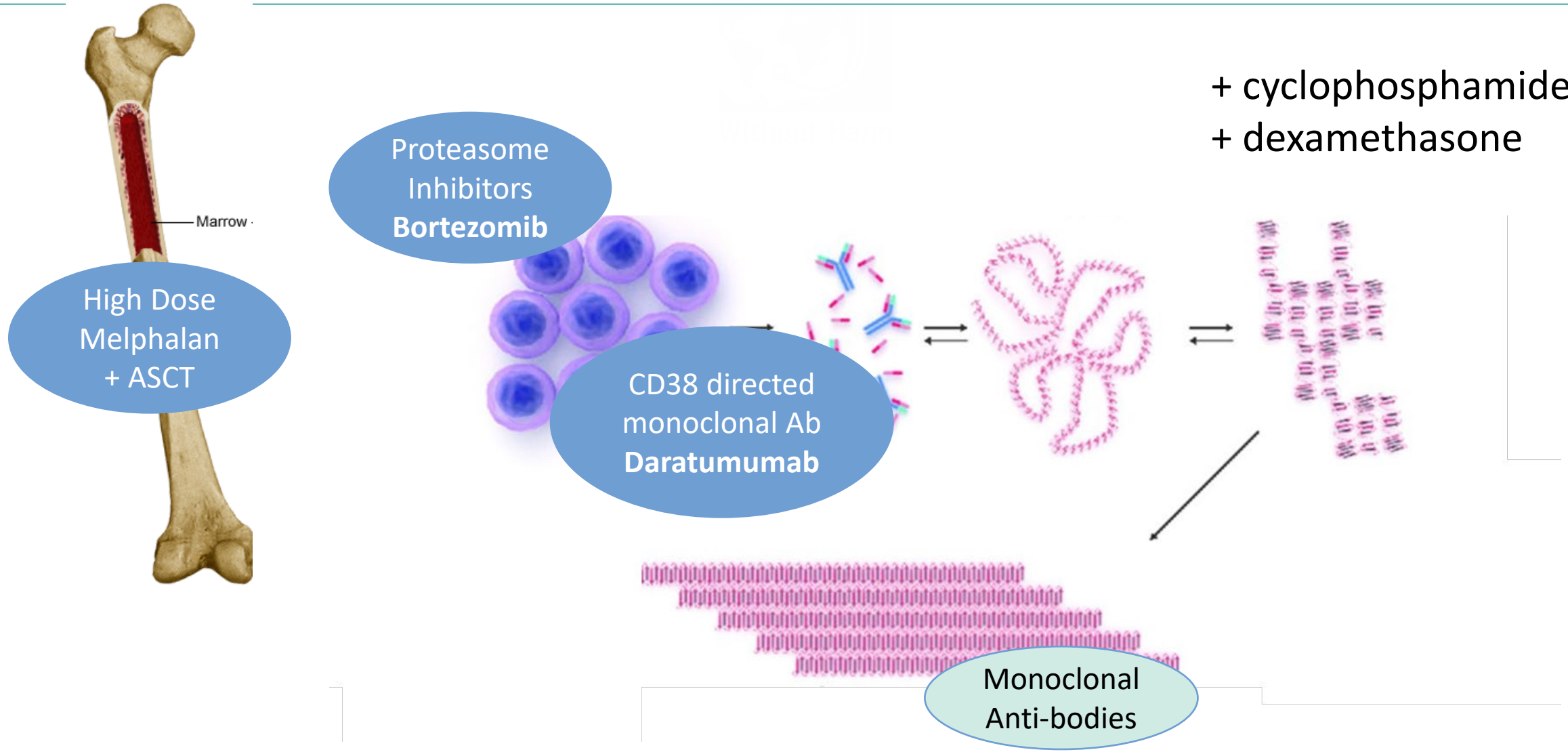

+ cyclophosphamide
+ dexamethasone

Falk et al. *J Am Coll Cardiol*. 2016

Therapeutic Targets in ATTR

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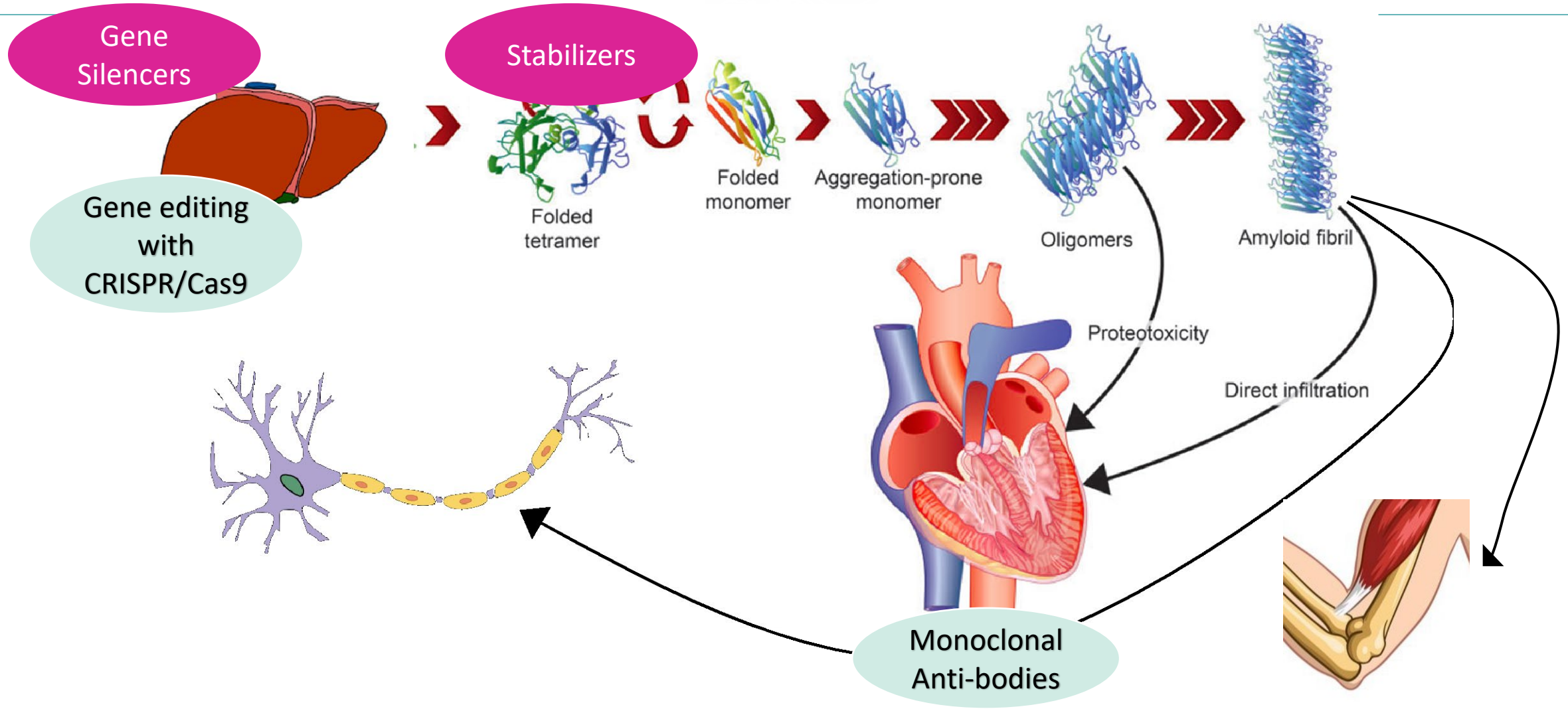

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Supportive Therapy Targets

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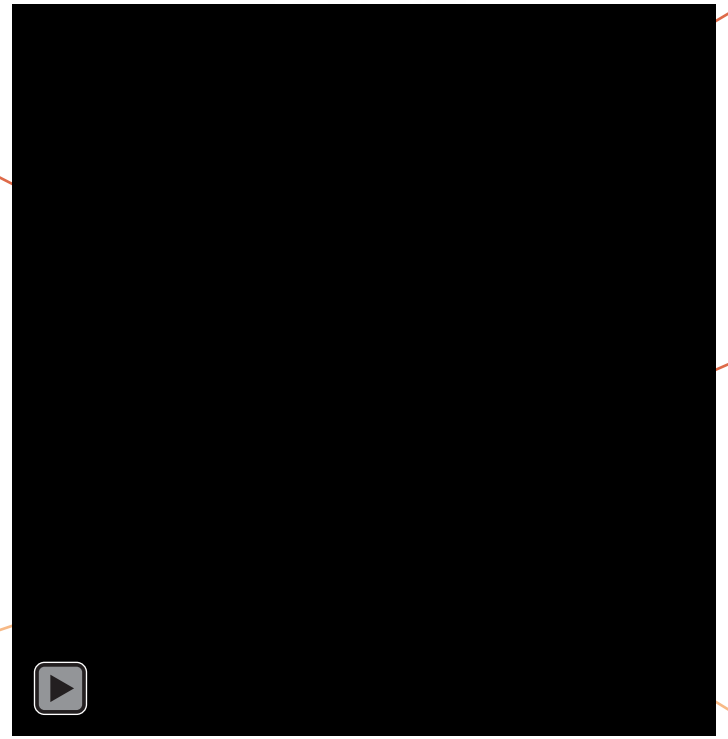
Heart Failure

Transplant

Loop Diuretics
MRAs
SGLT2i



Conduction system disease

Pacemaker

Chronotropic incompetence

Atrial Fibrillation/ poor atrial function

Anticoagulation

Amiodarone

Beta Blockers
~~CCBs~~
ACEi/ARBs
Digoxin

Hypotension

Other organs

- Kidneys

- Nerves: peripheral and autonomic
- Carpal Tunnel and spinal stenosis

- Lungs/pleural effusions

- GI system
- Liver

Thank you