



# AMYLOIDOSIS CENTER

## Basic research session: New treatment targets and biomarkers

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Slides are online at

<https://sites.bu.edu/gareth-morgan/slides/ISA2022>

# Disclosures

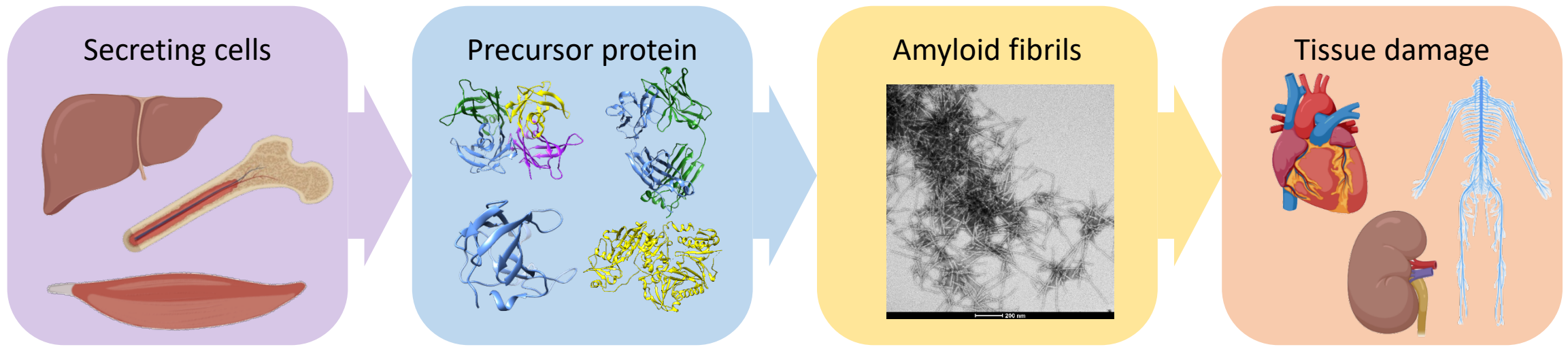
GM is working on stabilization of light chains as a potential therapy for AL amyloidosis

Research support from J&J

Previous work at Scripps Research with Dr. Jeff Kelly was indirectly supported by Pfizer

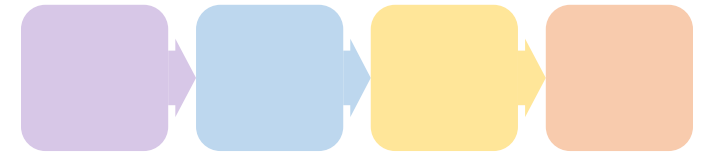
This presentation will discuss investigational therapies

# Systemic amyloidosis overview



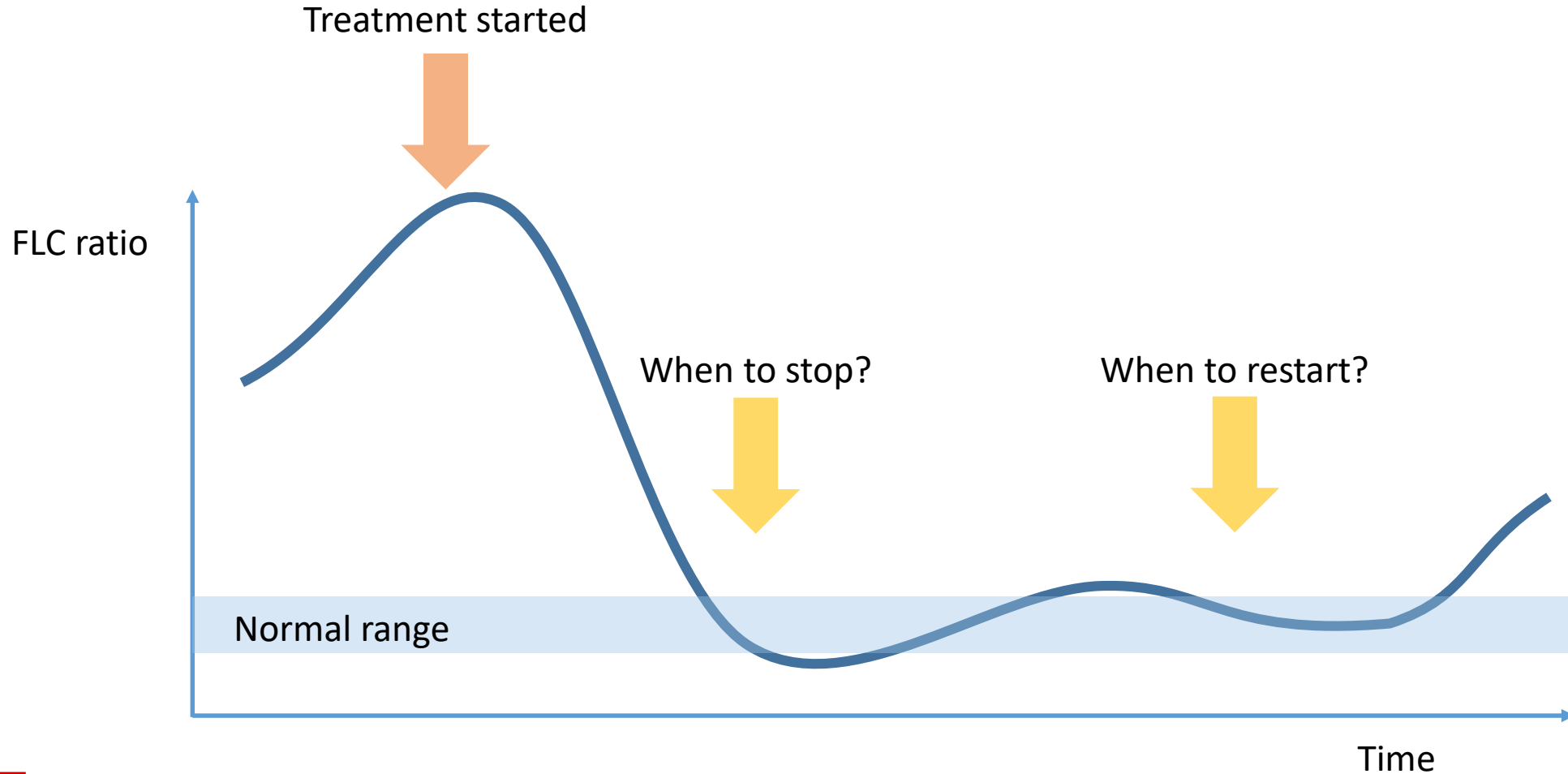
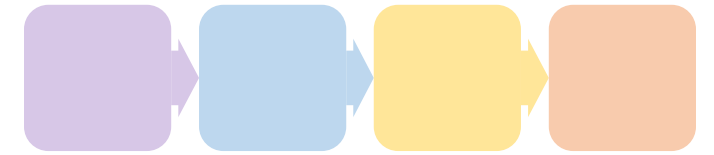
Disease-specific

Shared mechanisms?

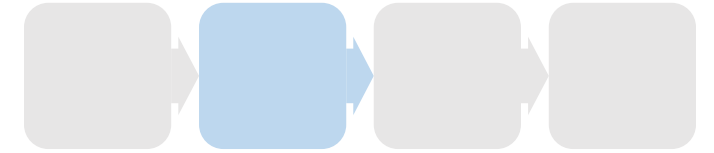


# Biomarkers

# Biomarkers for measuring disease status and effects of therapy



# Biomarkers: Precursor protein



AL: Free light chains

Immunoassay, mass spectrometry

dFLC, iFLC, CR, sCR, MRD?

AA: SAA level

ATTR: Serum prealbumin (TTR) level

Down with silencers, up with stabilizers

Misfolded TTR

Palladini et al. Amyloid 2021

[doi.org/10.1080/13506129.2020.1868810](https://doi.org/10.1080/13506129.2020.1868810)

Jiang et al. PNAS 2021

[doi.org/10.1073/pnas.2016072118](https://doi.org/10.1073/pnas.2016072118)

Dasari et al. Mayo Clinic Proc 2022

[doi.org/10.1016/j.mayocp.2021.07.024](https://doi.org/10.1016/j.mayocp.2021.07.024)

# Biomarkers: Organ damage



Kidney, nerve and heart  
function are all disease-specific

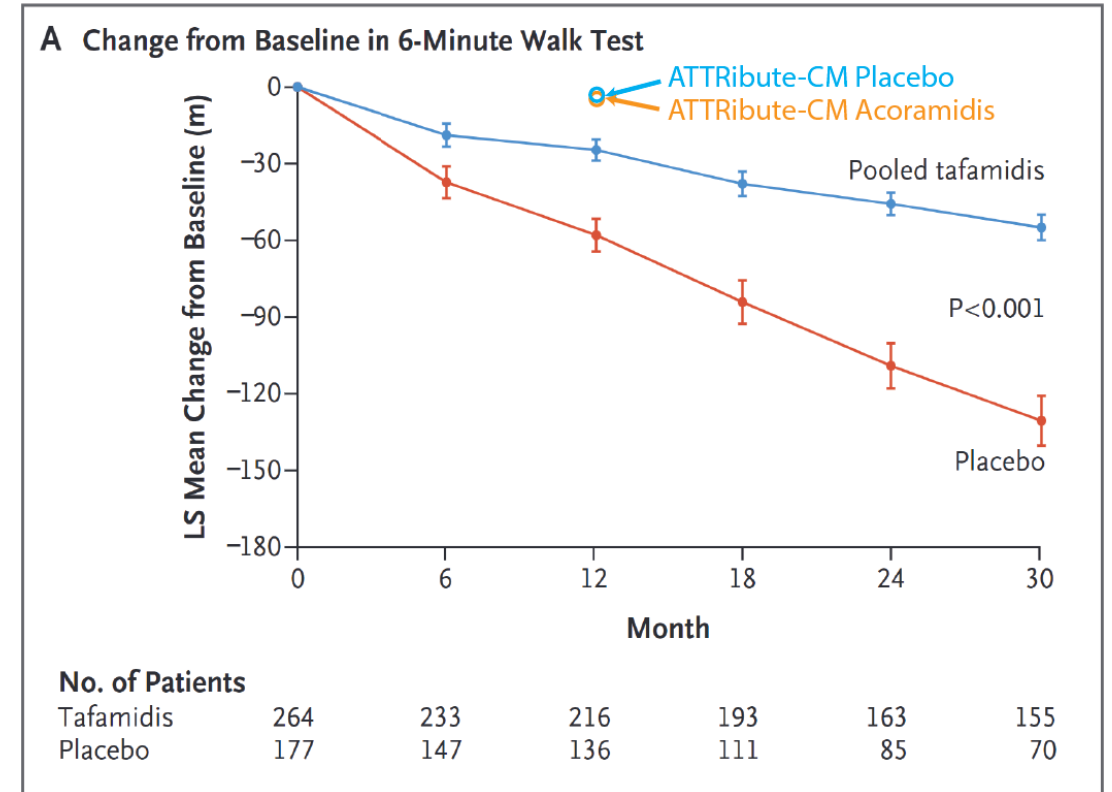
eGFR vs proteinuria

BNP vs NT-proBNP

Mixed results from functional  
biomarkers in trials

Lilliness et al. Blood 2018

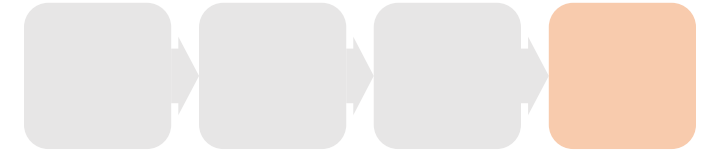
[doi.org/10.1182/blood-2018-06-858951](https://doi.org/10.1182/blood-2018-06-858951)



Modified from Maurer et al. NEJM 2018

[doi.org/10.1056/NEJMoa1805689](https://doi.org/10.1056/NEJMoa1805689)

# Biomarkers: Organ damage



Kidney, nerve and heart  
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eGFR vs proteinuria

BNP vs NT-proBNP

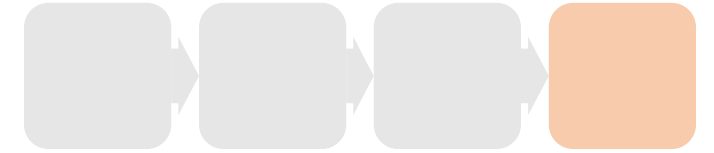
Mixed results from functional  
biomarkers in trials

Selina Hein

Elevated fibrosis associated  
biomarkers in ATTR amyloidosis  
patients are associated with  
impaired cardiovascular outcome.



# Biomarkers: Organ damage

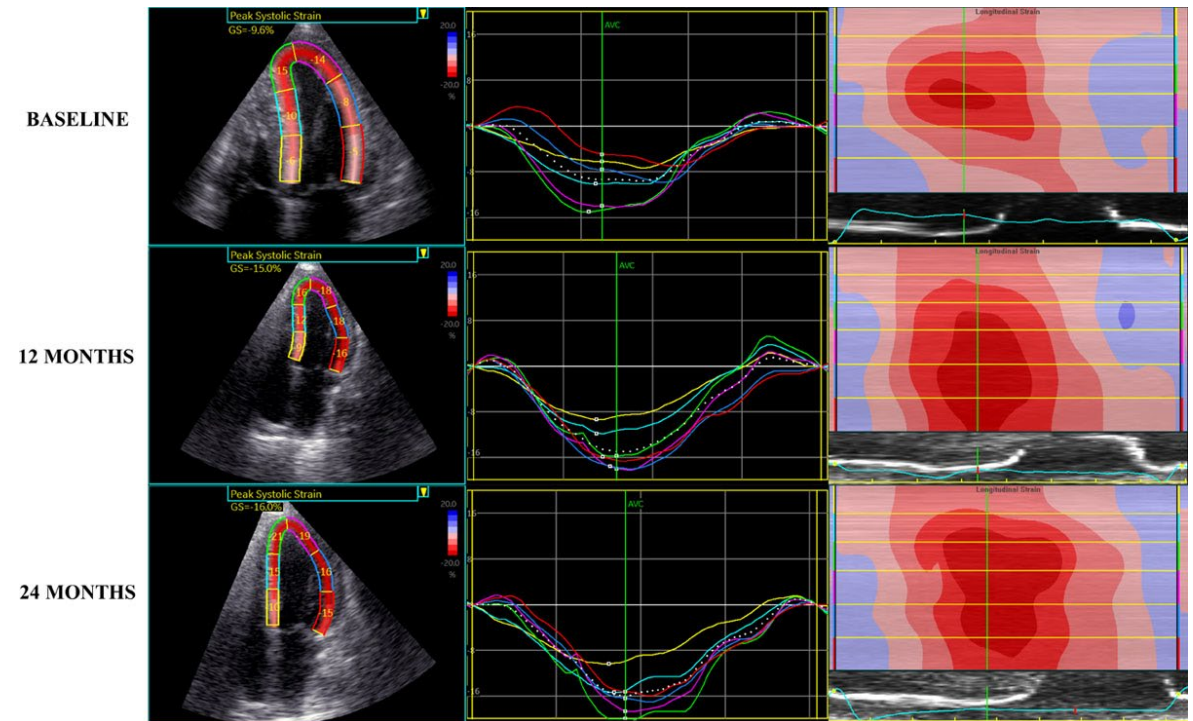


Imaging is playing a larger role

Echo, MRI, scintigraphy

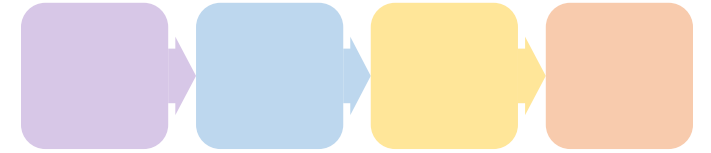
Differential diagnosis of cardiac amyloidosis

Functional recovery after successful treatment



Patel et al. Circulation: Cardiovascular Imaging 2021  
[doi.org/10.1161/CIRCIMAGING.121.009025](https://doi.org/10.1161/CIRCIMAGING.121.009025)

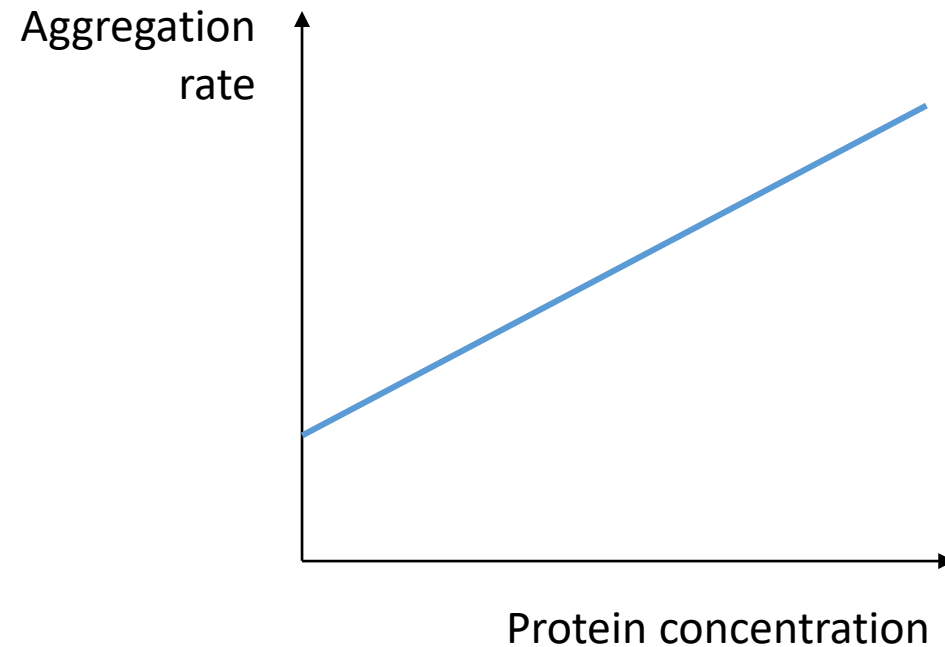
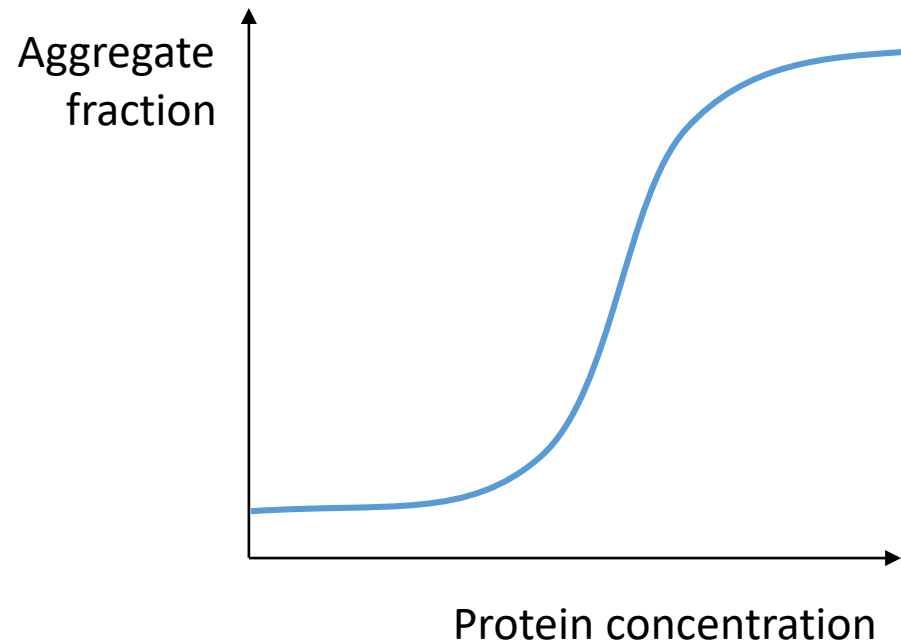
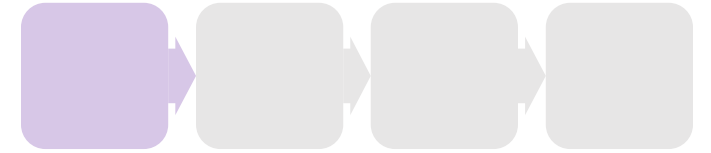
Poster session at 12:05 today covers imaging



# Therapeutic targets

Poster session tomorrow includes innovative targets

# Targets: Prevent protein production





# AA: Control of underlying inflammation

Chronically high SAA levels due to inflammatory disease can lead to AA deposition

Suppression of inflammation reduces SAA production and deposition

Specific therapies for different etiologies

Colchicine

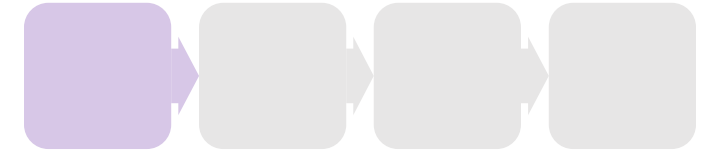
Anti-TNF $\alpha$

Anti-IL6

Westermarck et al. Ann Rev Pathology 2015  
[doi.org/10.1146/annurev-pathol-020712-163913](https://doi.org/10.1146/annurev-pathol-020712-163913)

AA session at 13:15 today

# ATTR: Gene therapy



Surgical gene therapy – liver transplant for ATTRv

mRNA-directed gene silencing

small interfering **RNA** (patisiran and vutrisiran)

**Antisense oligonucleotide** (inotersen and eplontersen)

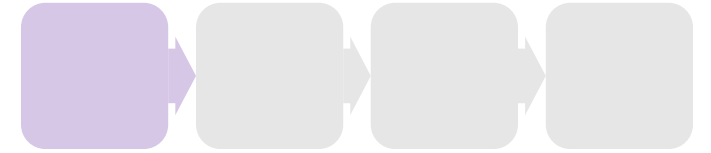
DNA-directed gene editing

CRISPR-Cas9 mediated knockout (NTLA-2001)

Target sequences are the untranslated region of the *TTR* gene and therefore therapies suppress production of both alleles

Currently only affects liver production

# AL: Cytotoxic therapies to eradicate clonal plasma cells



Therapies are adapted from myeloma

Melphalan, proteasome inhibitors, anti-CD38, BCMA CAR-T

Long-term remission is achievable

Important role for stem cell transplant

Eradication may not be necessary if amyloid formation is inhibited and tissues can recover

Only a fraction of individuals with a hematological response have an organ response 6 months later

# AL: Cytotoxic therapies to eradicate clonal plasma cells



Enrico Milan

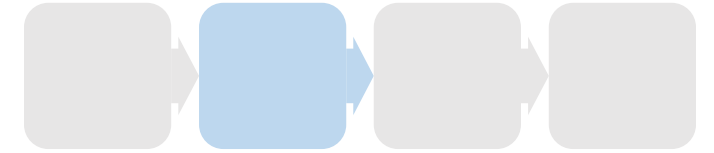
Dissecting FAM46C-dependent tuning of antibody secretion in systemic AL amyloidosis.

Hila Fishov

Regulation of BCL2 family members by microRNA-9 and microRNA-181a in AL amyloidosis

Maria Moscvin

Targeting protein secretion as a therapeutic strategy in AL amyloidosis



# Targets: Prevent protein aggregation

Direct binding by small molecules or antibodies

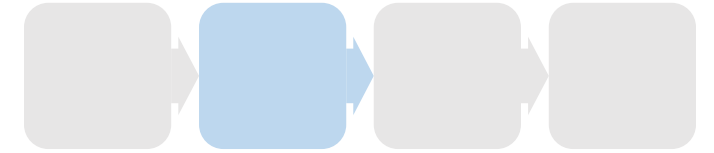
Indirect modulation of extracellular proteostasis

Nakajima Kichitaro

In-vitro ultrasonic assay indicates importance of extracellular chaperon-like effect of serum albumin to protect dialysis patients from dialysis-related amyloidosis



# ATTR: stabilization



TTR binds many small, drug-like molecules in the T4 site

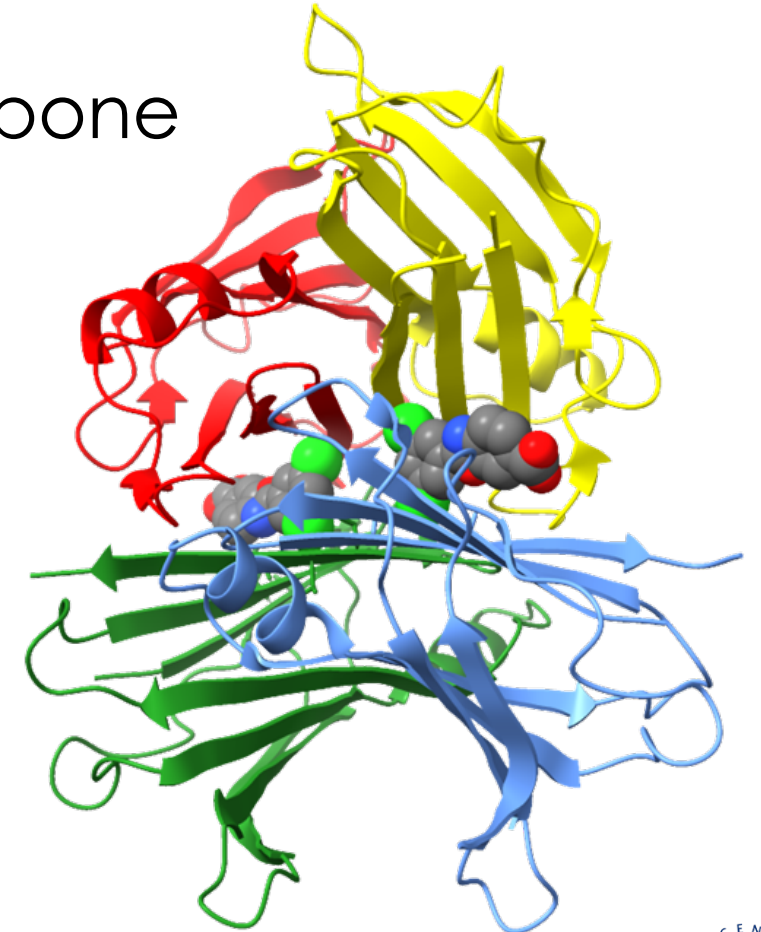
Tafamidis, diflunisal, acoramidis and tolcapone have identical mechanisms of action but different pharmacologic properties

Will we need brain-penetrating stabilizers?

Is there a limit to achievable stabilization?

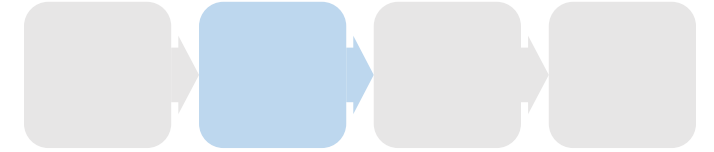
What counts as sufficient stabilization?

Can stabilization and silencing be synergistic?



Sant'Anna et al. Nature Comms 2016  
[doi.org/10.1038/ncomms10787](https://doi.org/10.1038/ncomms10787)

# AL: stabilization?

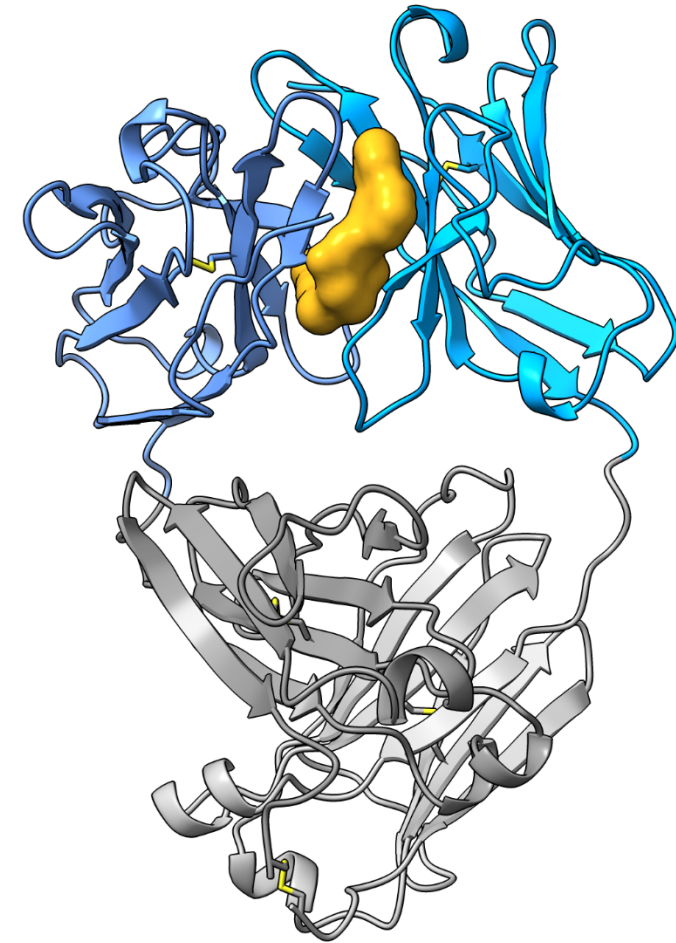


Can we stabilize light chains?

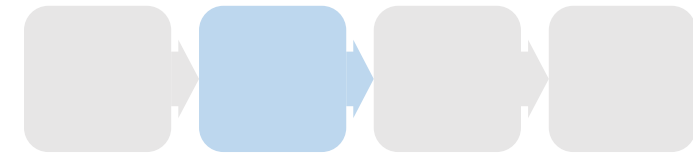
High affinity stabilizer molecules  
can inhibit aggregation

Learn about our progress at  
posters 292 and 294 tomorrow!

Morgan et al. PNAS 2019  
[doi.org/10.1073/pnas.1817567116](https://doi.org/10.1073/pnas.1817567116)



# Inhibition of fibril nucleation and extension



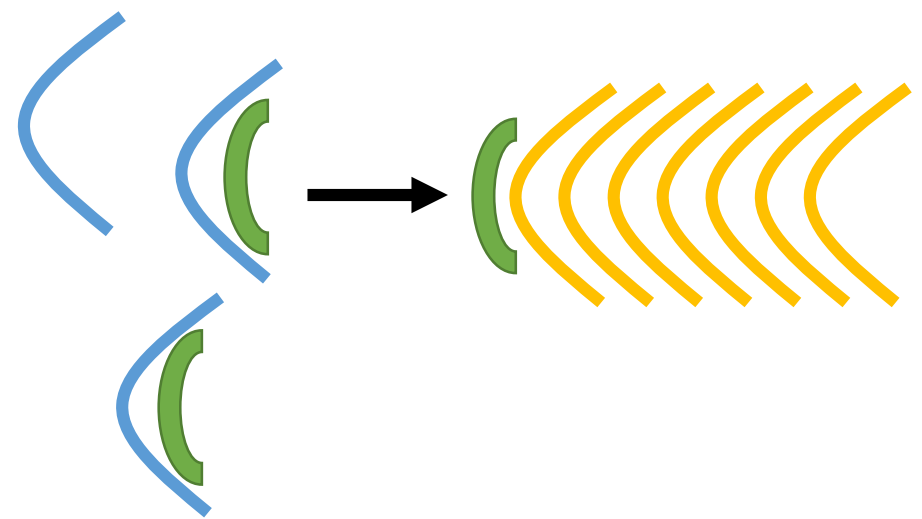
Target self-assembly, rather than native protein

Less misfolded protein to hit

- Less drug needed

- Harder to make effective inhibitors

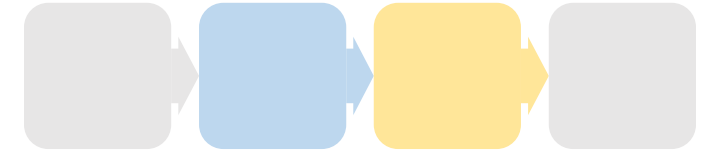
Focus on peptides and proteins



Murray et al. PNAS 2022  
[doi.org/10.1073/pnas.2206240119](https://doi.org/10.1073/pnas.2206240119)

Saelices et al. JBC 2019  
[doi.org/10.1074/jbc.RA118.005257](https://doi.org/10.1074/jbc.RA118.005257)

# Eprodinate



Glycosaminoglycan mimic intended to disrupt interactions between amyloid and extracellular matrix

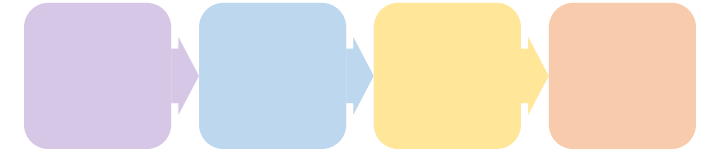
Some clinical efficacy in AA amyloidosis in phase 2 trial  
NCT00035334

Results from a phase 3 trial NCT01215747 have not been published

Dember et al. NEJM 2007

[doi.org/10.1056/NEJMoa065644](https://doi.org/10.1056/NEJMoa065644)

# Doxycycline



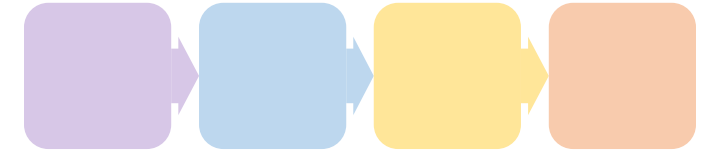
Doxycycline inhibits  $\beta_2$ -microglobulin aggregation *in vitro* and may be beneficial in dialysis-related ( $A\beta_2M$ ) amyloidosis

Some clinical studies show potential benefit in AL amyloidosis but a recent randomized trial showed no effect

Complex pharmacology with multiple potential mechanisms

Montagne et al. Amyloid 2007  
[doi.org/10.3109/13506129.2013.803463](https://doi.org/10.3109/13506129.2013.803463)

Shen et al. Circulation 2022  
[doi.org/10.1161/CIRCULATIONAHA.121.055953](https://doi.org/10.1161/CIRCULATIONAHA.121.055953)



**Epigallocatechin gallate** is a natural product found in green tea

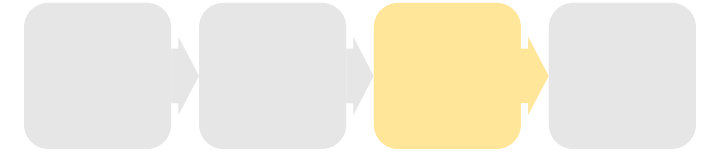
Phase 2 studies from Heidelberg NCT02015312 and Tokyo NCT02015312 showed no benefit in AL

Complex pharmacology with multiple potential mechanisms

Challenging to work with *in vitro*

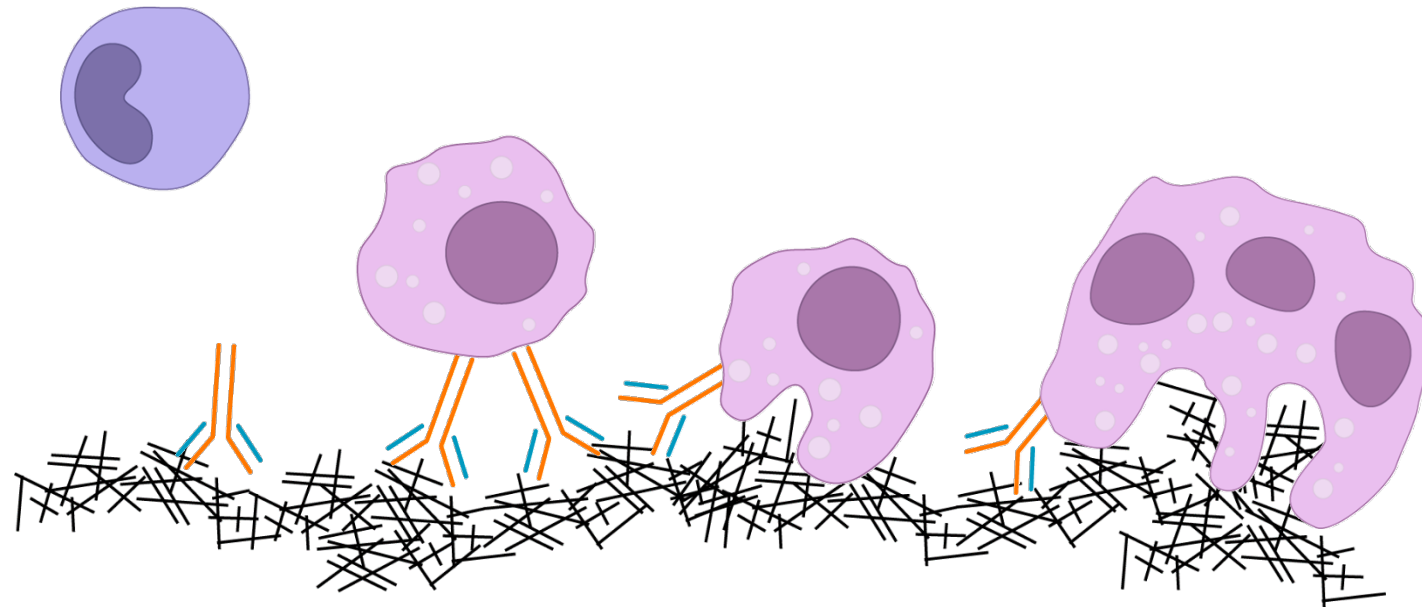
Meshitsuka et al. IJ Hematology 2017  
[doi.org/10.1007/s12185-016-2112-1](https://doi.org/10.1007/s12185-016-2112-1)

# Targets: Clear amyloid deposits

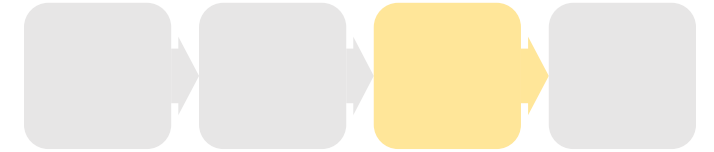


Amyloid can continue to inhibit organ function after deposition is stopped

Removal of amyloid by phagocytic cells could allow regeneration



# Antibodies in trials

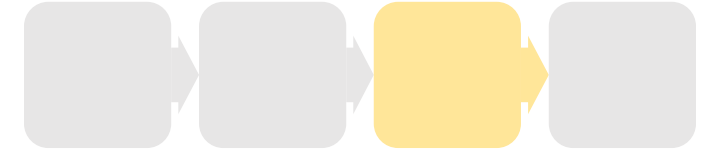


Molecule	Phase 1	Phase 2	Phase 3	Approved
Dezamizumab/miridesap (SAP)	Completed	Terminated (NCT01777243)		
CAEL-101 (AL)	Completed	Completed	Ongoing (NCT04512235)	
Birtamimab NEOD001 (AL)	Completed	Completed	Terminated (NCT02312206)	
			Ongoing (NCT04973137)	
PRX004 (ATTR)	Completed (NCT03336580)			
AT-01 (Pan-amyloid imaging)	Completed	Completed (NCT05235269)		





# Targets: Clear amyloid deposits



Joseph W. Jackson

Collagen associated with AL amyloid inhibits fibril phagocytosis - Collagen degradation renders amyloid sensitive to uptake by the innate immune system

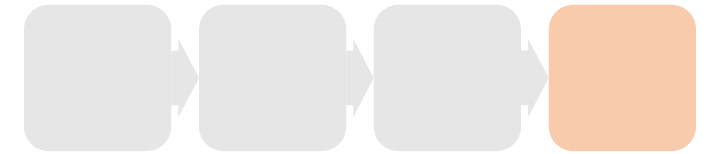
Manasi Balachandran

Development of novel human chimeric antigen receptor-macrophages (CAR-M) as a potential therapeutic for amyloid clearance

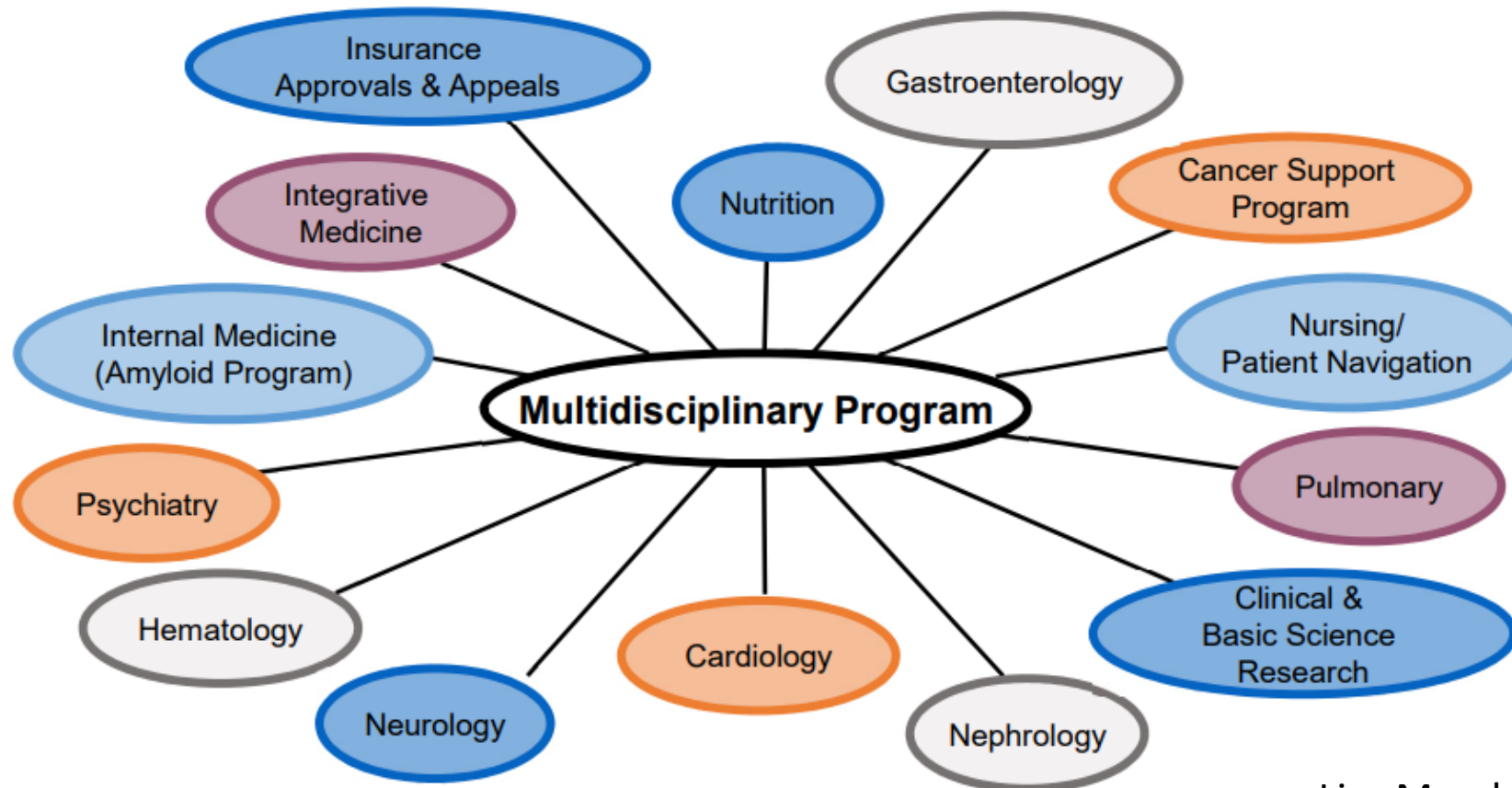
Jonathan Wall

Preclinical characterization of AT-02, a pan-amyloid-binding immunoglobulin-peptide fusion protein capable of inducing enhanced phagocytosis of amyloid

# End organ-directed therapies

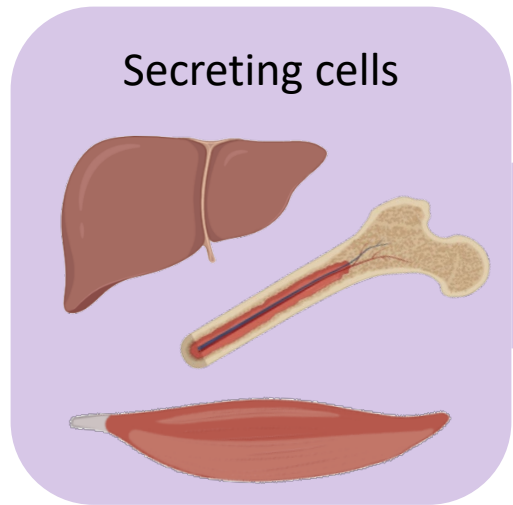


Integrated care at specialist centers helps patients and physicians navigate the challenges of these rare diseases.

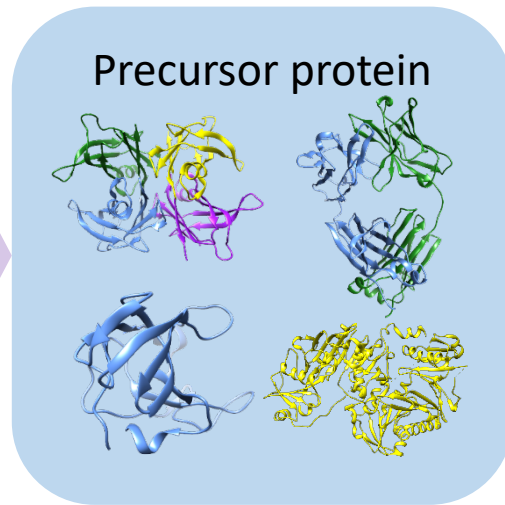


# Combining therapies to treat complex diseases

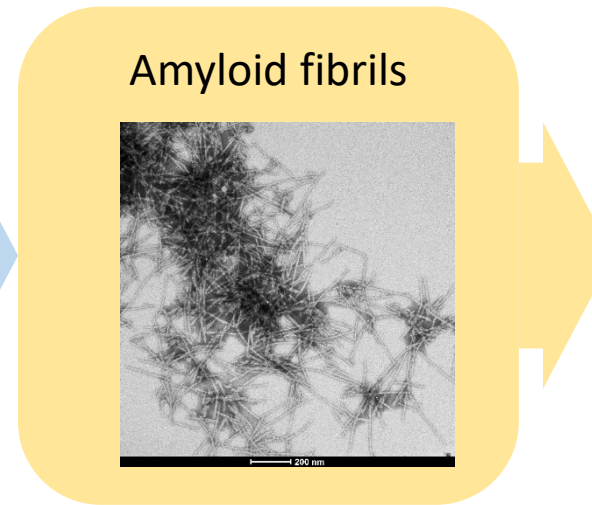
Suppression



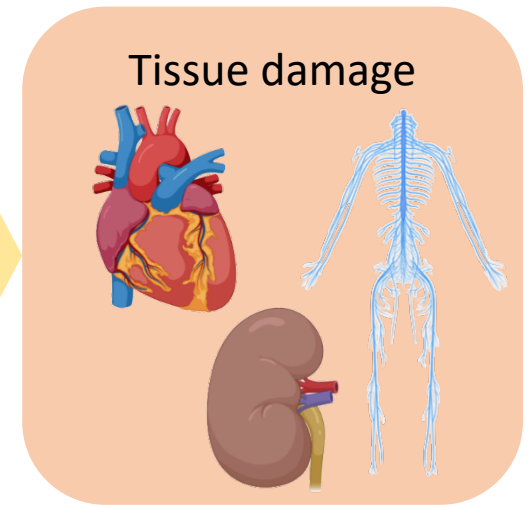
Stabilization



Clearance



Regeneration

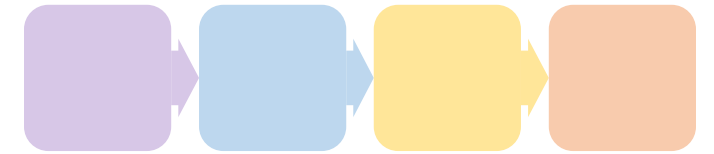


Disease-specific

Shared mechanisms?

Organ images created with BioRender.com

# Open questions and challenges



Continued need for better models and molecules with the potential for clinical efficacy

How can we apply the lessons learned for ATTR and AL to rarer forms of amyloidosis?

How can we optimally combine different therapies?

Who will fund and run trials of combinations?

Which therapies are cost effective?

How can we ensure equitable access to therapy?