Update on Treatments for Systemic Amyloidosis

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Penn Medicine

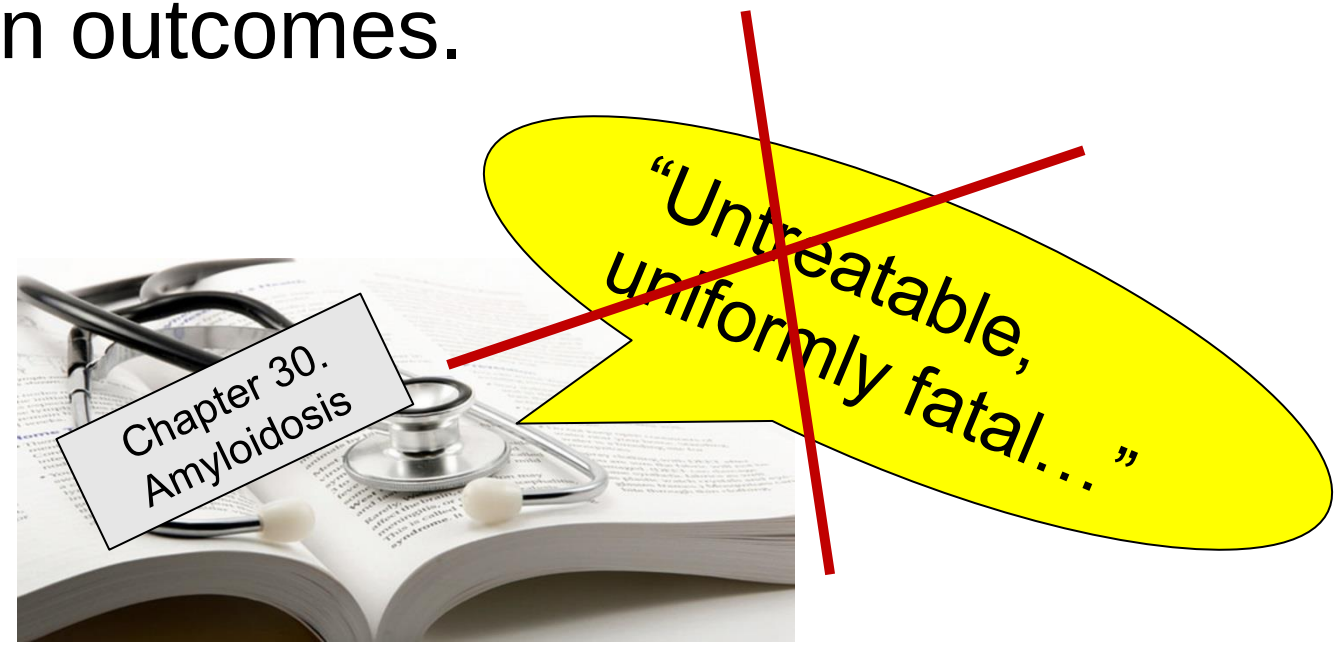
ANZSN

Disclosure

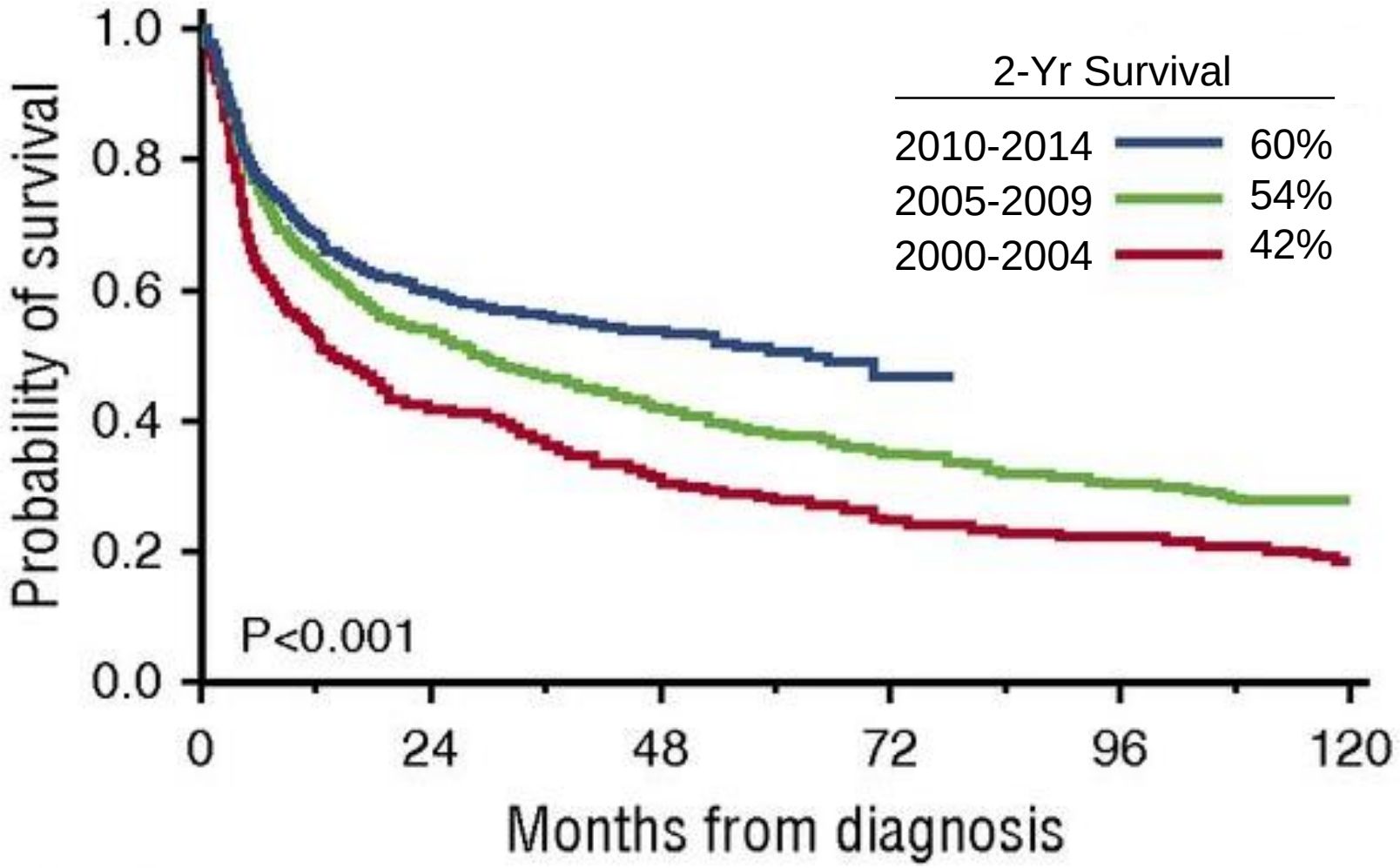
Most of the treatments that will be discussed are not approved for amyloidosis.

Key Message

The development of new treatment approaches during the past 15 – 20 years has resulted in remarkable improvements in outcomes.



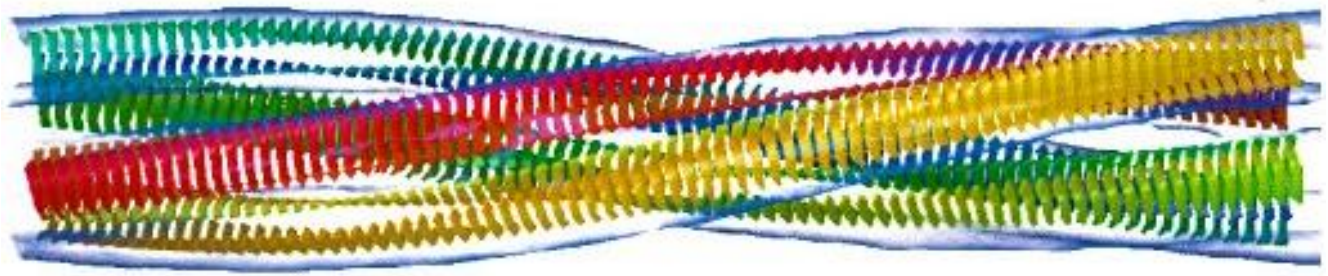
AL Amyloidosis Survival



Muchtar et al; Blood 2017

What is Amyloidosis?

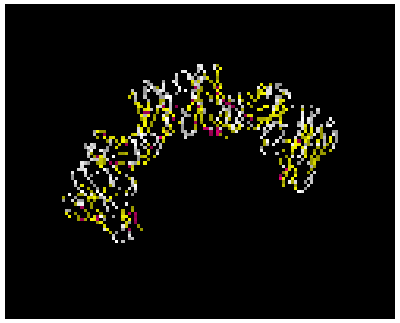
Group of diseases in which a protein that is normally soluble deposits extracellularly in tissues as insoluble fibrils that have a specific biochemical structure



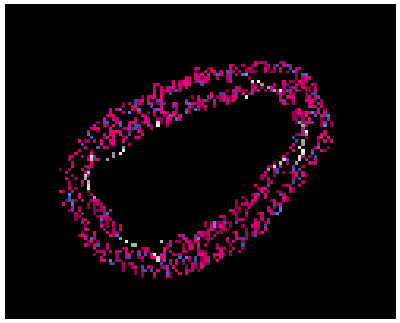
Systemic Amyloidoses

	Precursor Protein
AL (Primary)	Ig Light Chain
AA (Secondary)	Serum AA (SAA)
Hereditary	TTR, lysozyme, fibrinogen, ApoA1, ApoA2, ApoA4 gelsolin
Senile Systemic	TTR
ALect2	Lect2
Dialysis-Related	β2 microglobulin

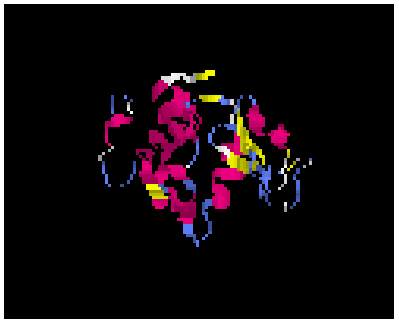
Amyloidogenic Proteins Differ Functionally and Structurally



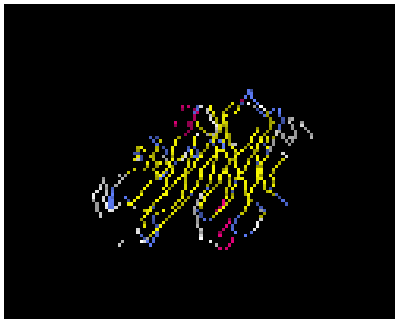
IgG Kappa



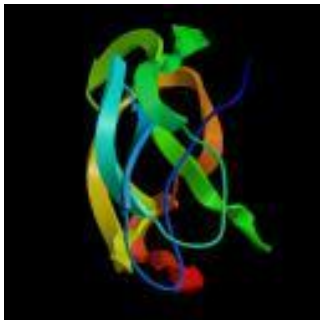
Apolipoprotein A-I



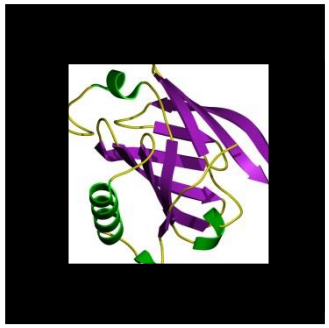
Lysozyme



Transthyretin

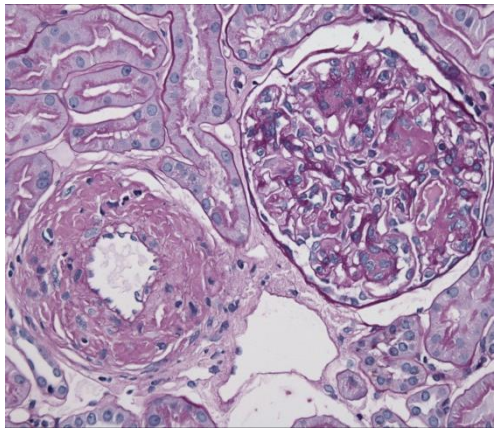


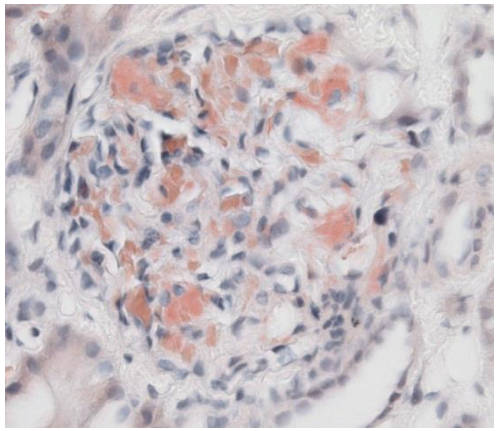
A-beta

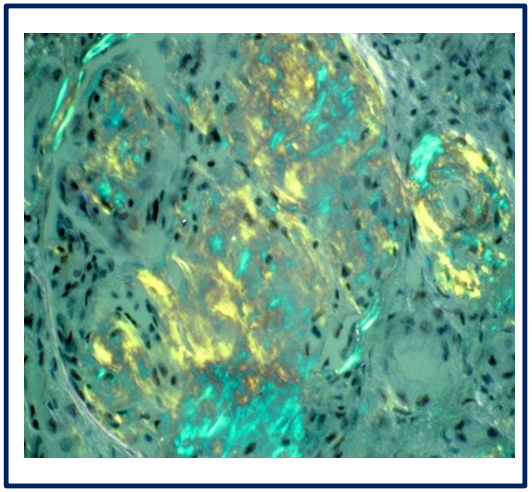


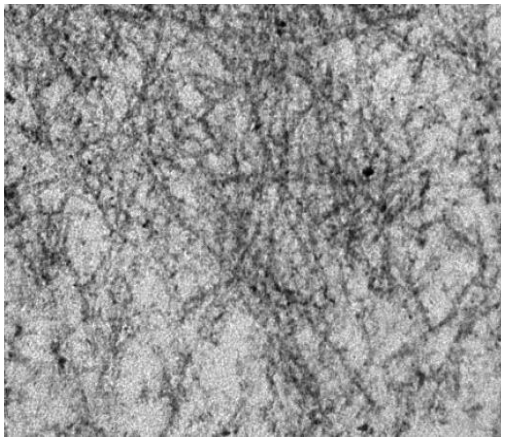
Beta 2M

But Resulting Amyloid is Morphologically Indistinguishable

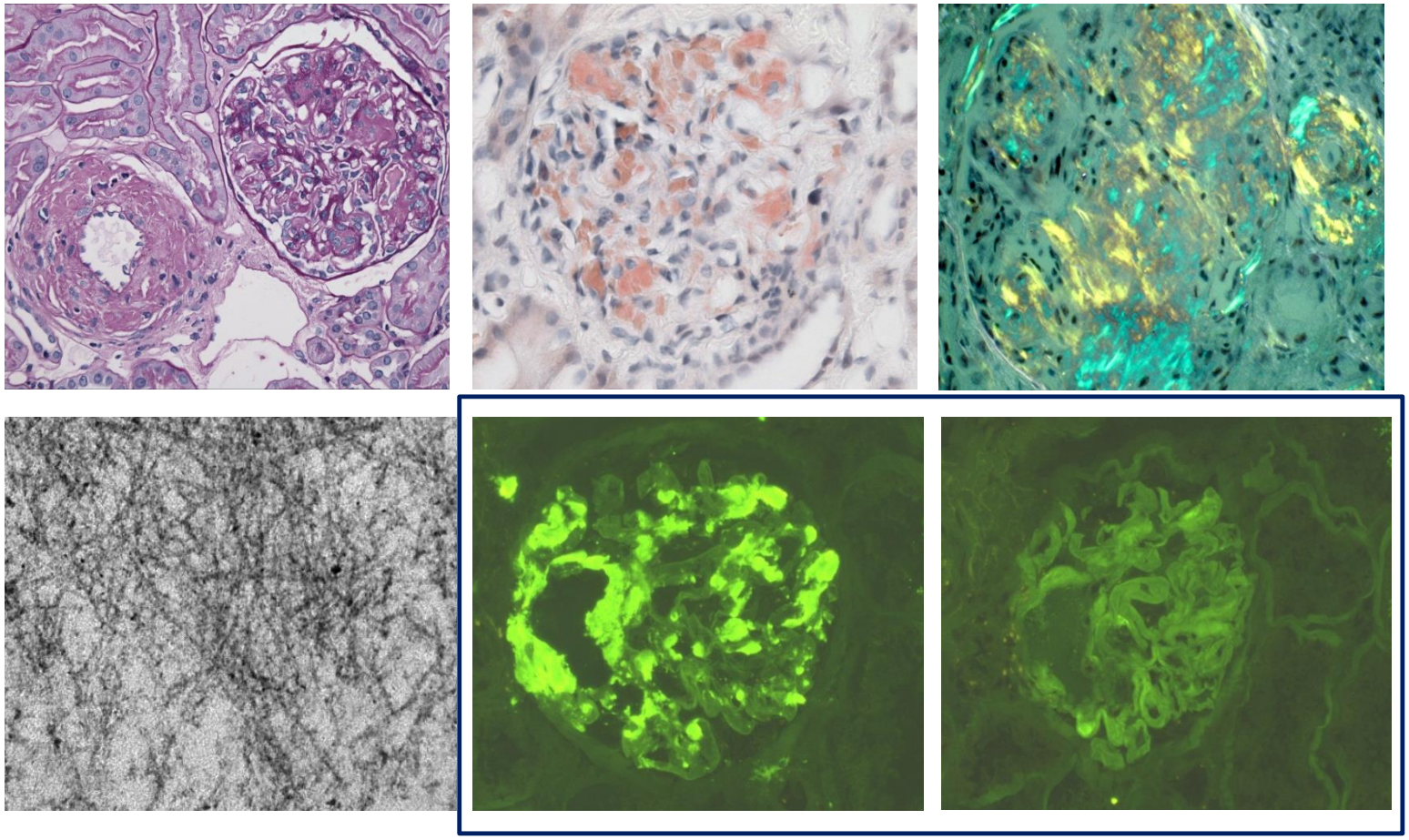








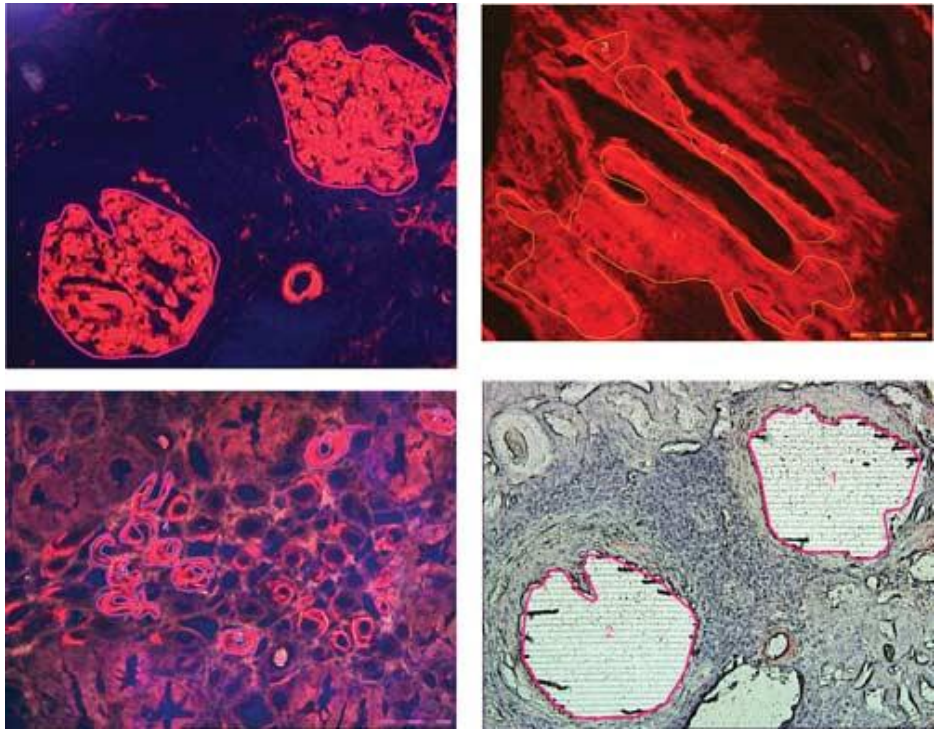
But Resulting Amyloid is Morphologically Indistinguishable



Lambda LC

Kappa LC

Laser Capture Microdissection / Mass Spectrometry for Typing Amyloid



#	Starred?	Probability Legend: over 95% / 80% to 94% / 50% to 79% / 20% to 49% / 0% to 19% — Bio View: Identified Proteins (595)	Accession Number	Molecular Weight	Sample 1	Sample 2	Sample 3
1	☆	Serum amyloid P-component	SAMP_HUMAN	25 kDa	18	18	20
2	☆	Apolipoprotein E	APOE_HUMAN	36 kDa	14	25	17
3	☆	Ig kappa chain V-I region	KV117_HUMAN	12 kDa	13	12	14
4	☆	Ig kappa chain C region	IGKC_HUMAN	12 kDa	6	9	8
5	☆	Keratin, type I cytoskeletal 9	K1C9_HUMAN	62 kDa	38	8	63
6	☆	Vimentin	VIME_HUMAN	54 kDa	27	32	34
7	☆	Actin, cytoplasmic 1	ACTB_HUMAN	42 kDa	22	32	28
8	☆	Vitronectin	VTNC_HUMAN	54 kDa	23	25	30
9	☆	Lactotransferrin	TRFL_HUMAN	78 kDa			56
10	☆	Apolipoprotein D	APOD_HUMAN	21 kDa			41
11	☆	Apolipoprotein A-IV	APOA4_HUMAN	45 kDa	15	11	14
12	☆	Zinc-alpha-2-glycoprotein	ZA2G_HUMAN	34 kDa			26
13	☆	Keratin, type II cytoskeletal 2	K22E_HUMAN	65 kDa	9		27
14	☆	Collagen alpha-1(I) chain	CO1A1_HUMAN	139 kDa	6	7	6
15	☆	Actin, alpha cardiac muscle 1	ACTC_HUMAN	42 kDa	19	26	30

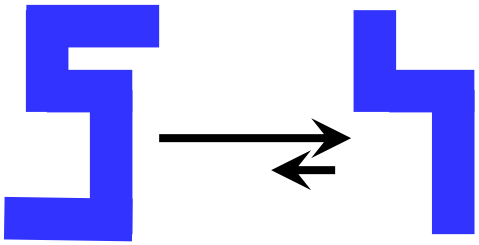
Sethi S et al Kidney Int 2012; Leung N et al Blood 2012

Partial List of Manifestations

- Kidney: nephrotic syndrome, progressive renal failure
- Heart: restrictive cardiomyopathy
- Liver: hepatomegaly
- GI tract: bleeding, malabsorption
- Nervous system: autonomic or peripheral neuropathy
- Endocrinopathies: thyroid, adrenal
- Soft tissue disease: dermopathy, carpal tunnel syndrome, muscle involvement

Disorder of Protein Misfolding

Mutation
Proteolytic event
Local environmental factors

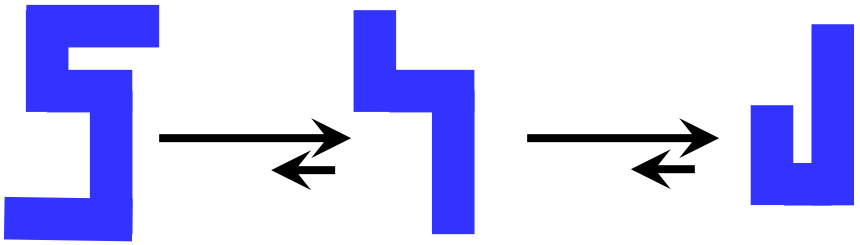


Soluble Precursor

Unstable Variant

Disorder of Protein Misfolding

Mutation
Proteolytic event
Local environmental factors



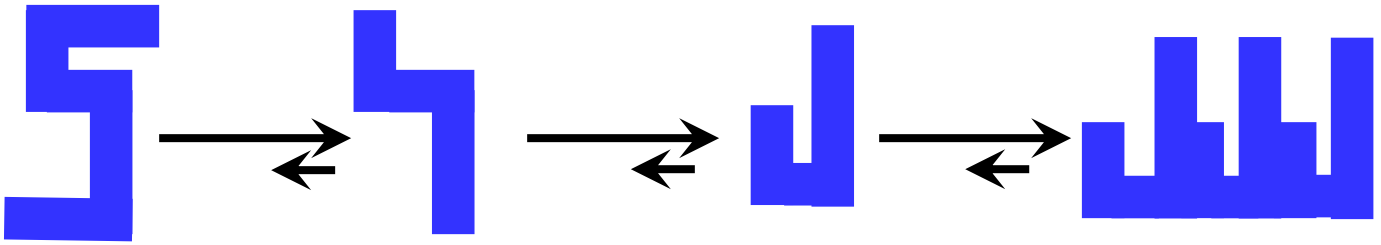
Soluble Precursor

Unstable Variant

Folding Intermediate

Disorder of Protein Misfolding

Mutation
Proteolytic event
Local environmental factors



Soluble Precursor

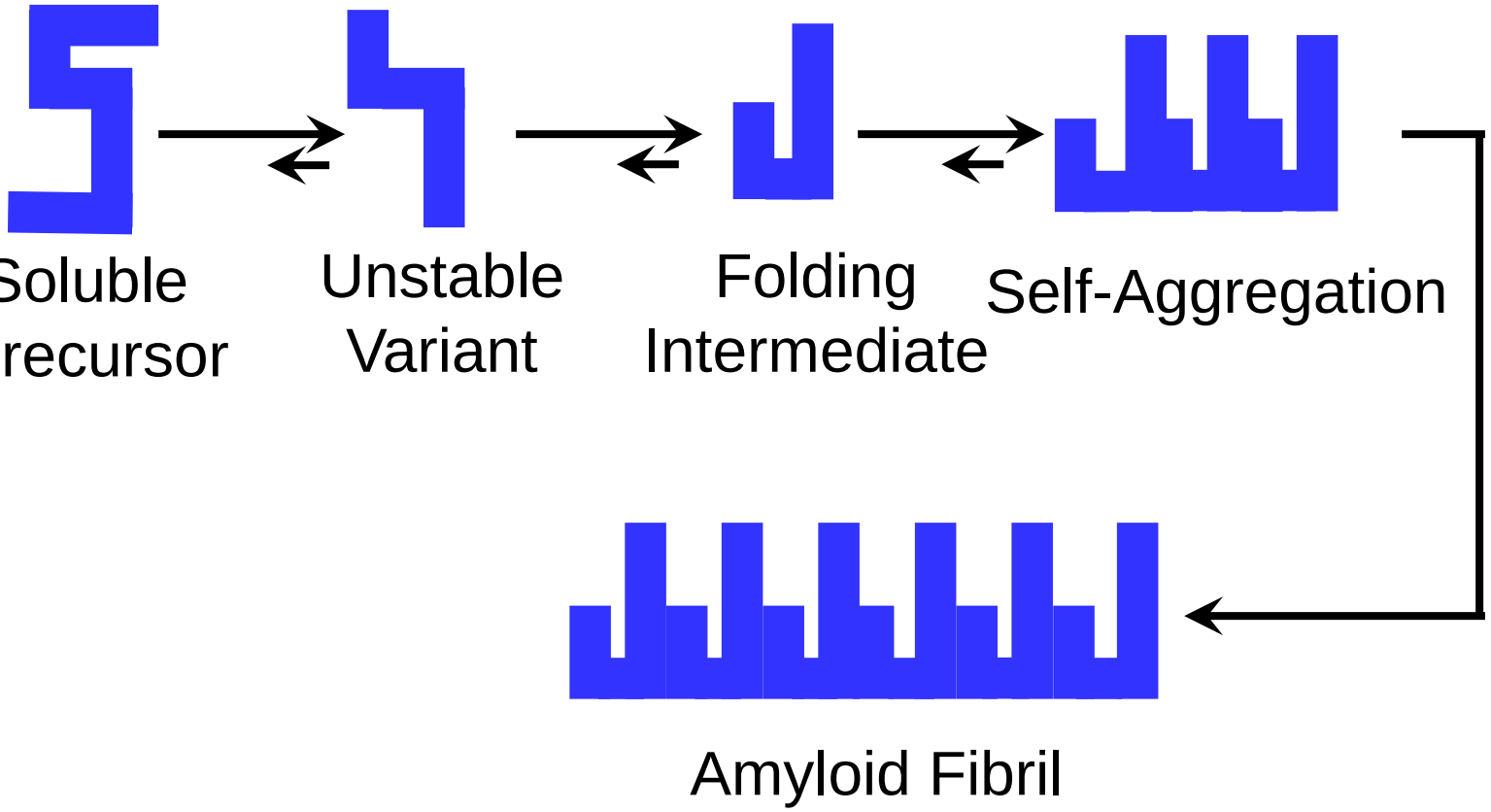
Unstable Variant

Folding Intermediate

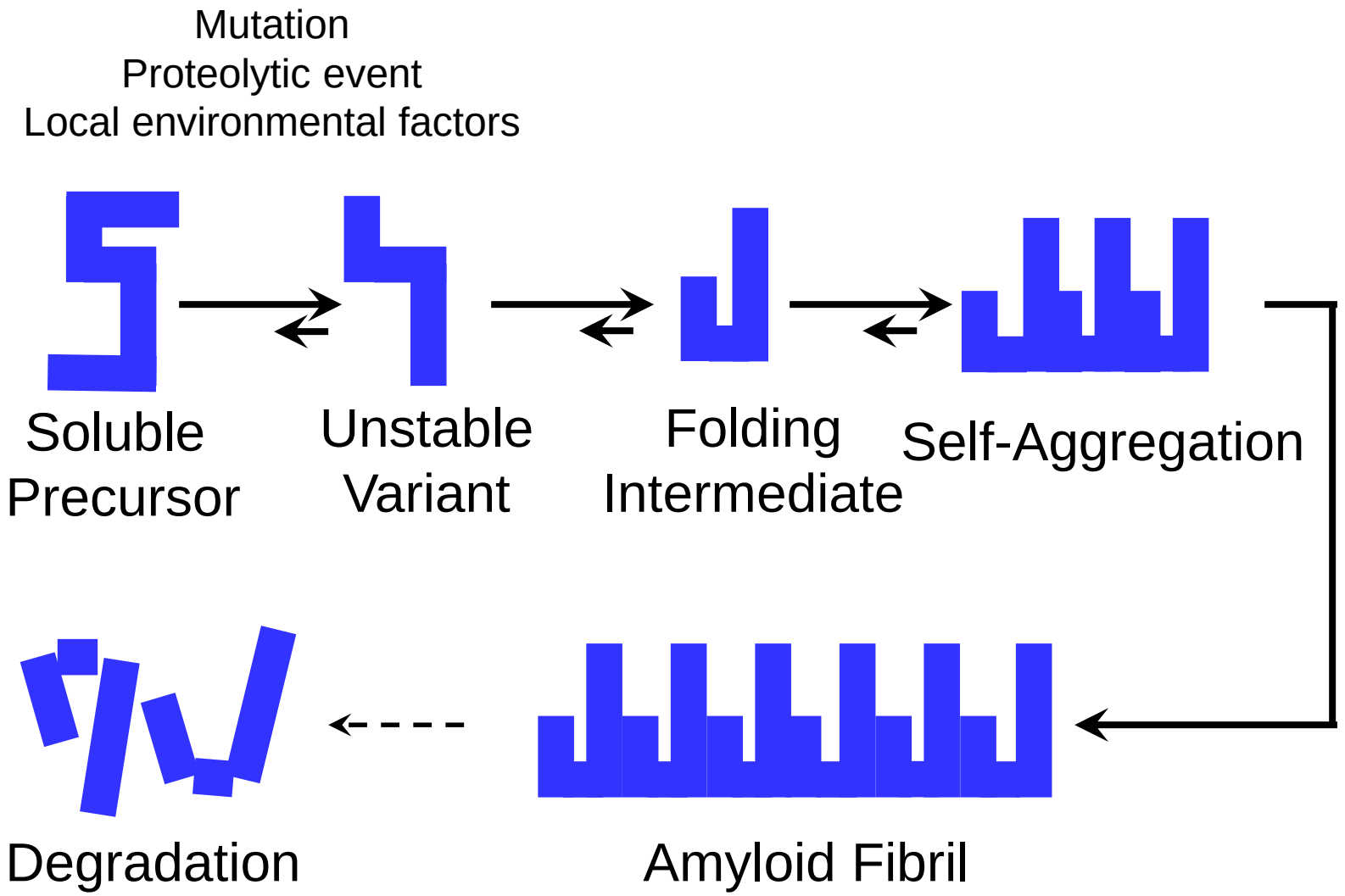
Self-Aggregation

Disorder of Protein Misfolding

Mutation
Proteolytic event
Local environmental factors



Disorder of Protein Misfolding

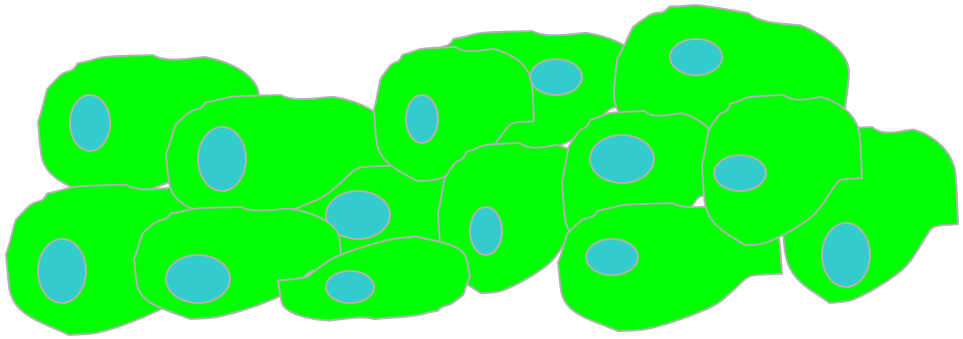


How Does Amyloid Cause Disease Manifestations?

Unstable Fragment or Variant

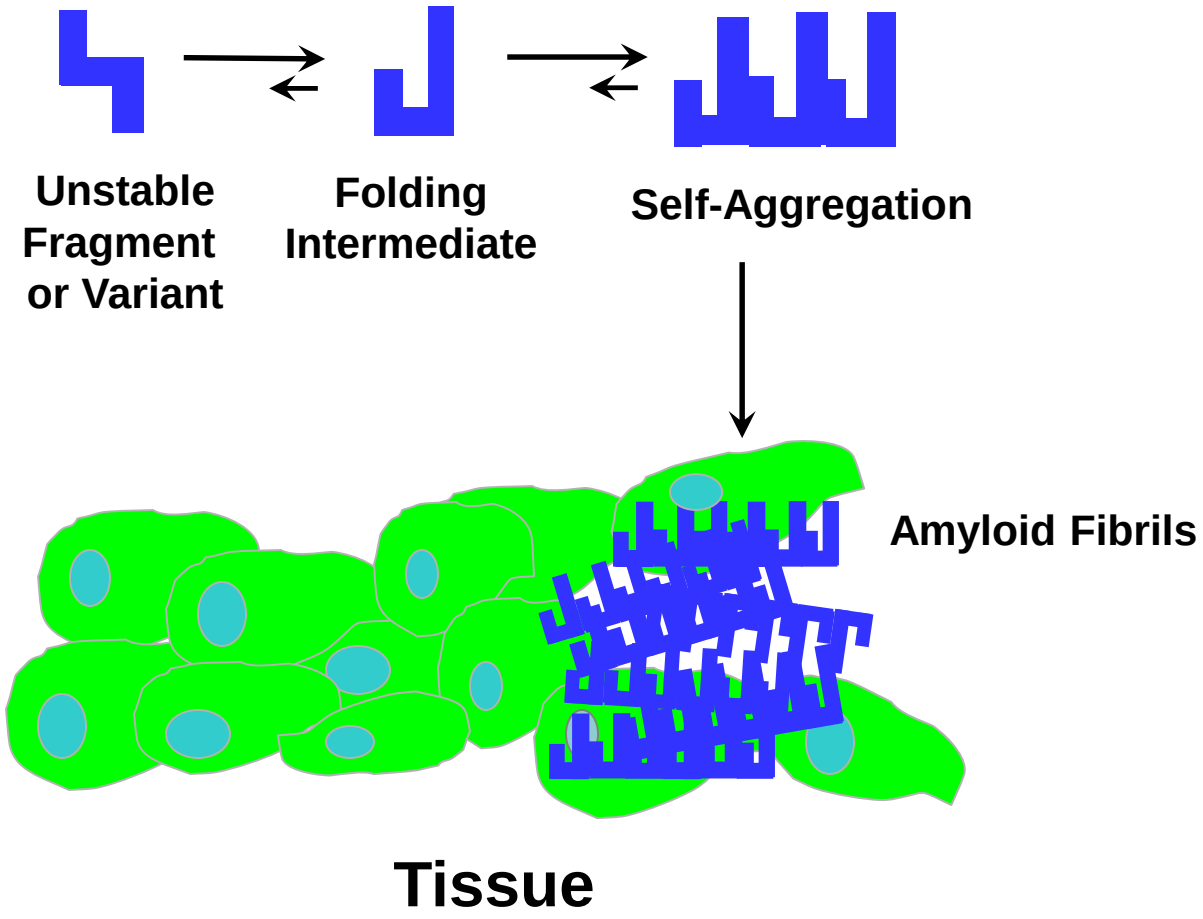
Folding Intermediate

Self-Aggregation

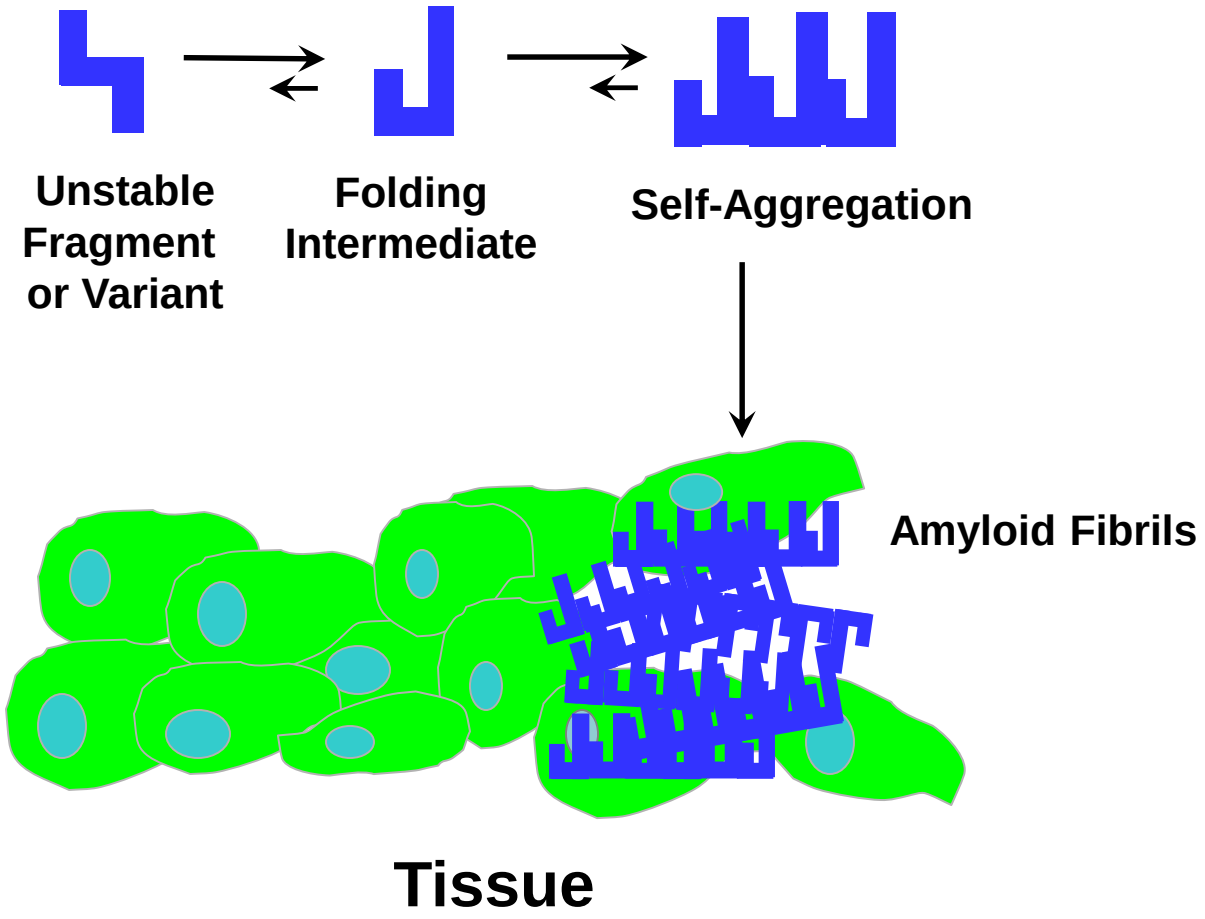


Tissue

“The Amyloid Hypothesis”



Revised “Amyloid Hypothesis”



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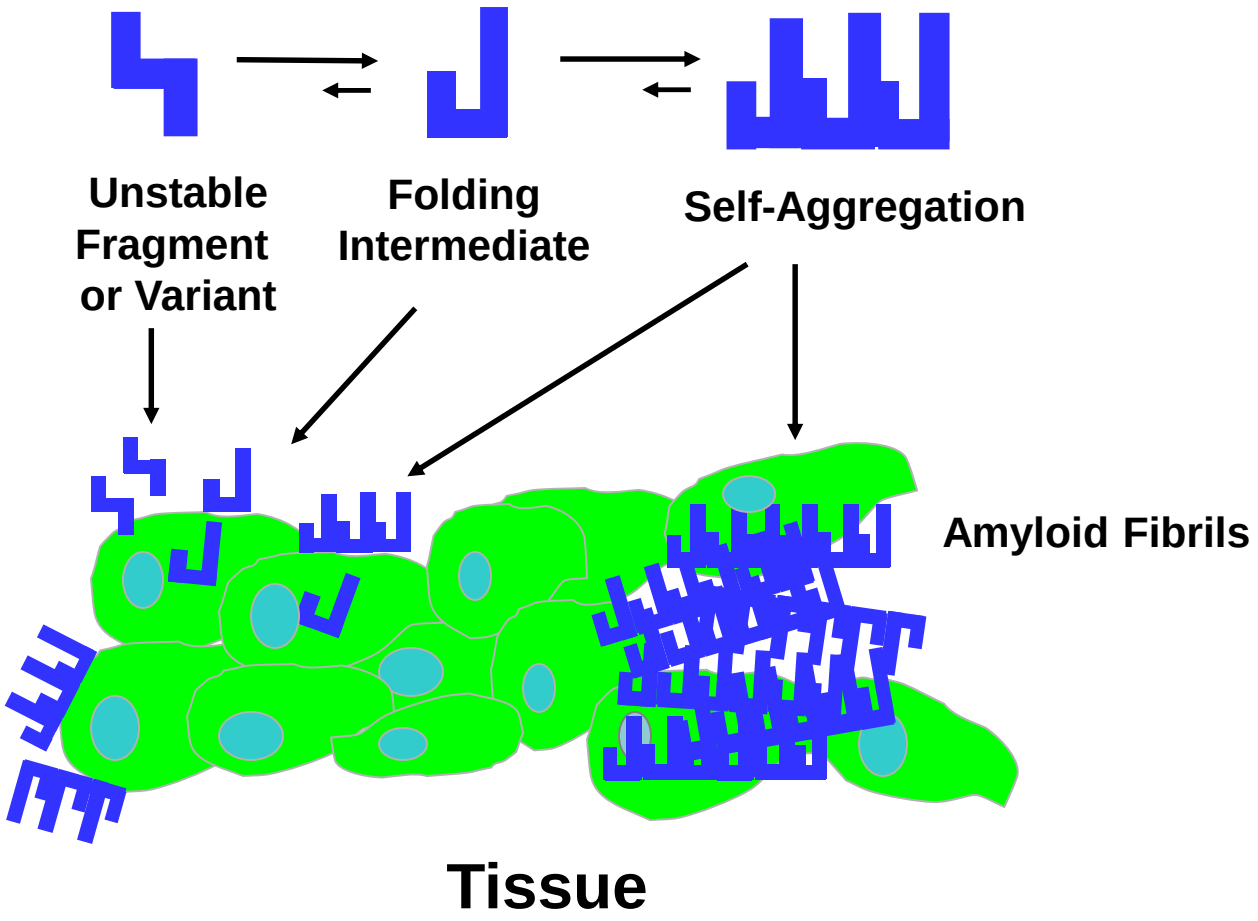

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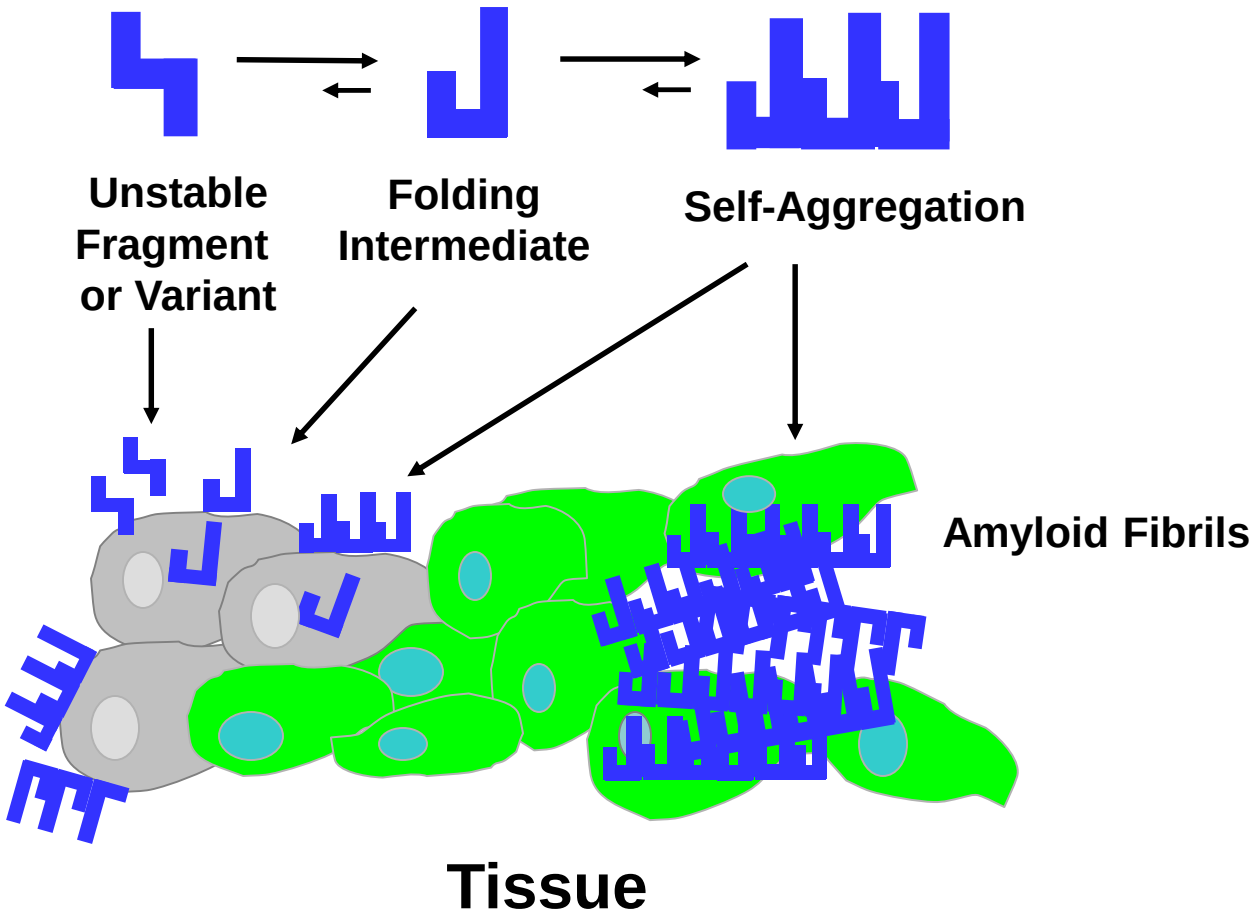
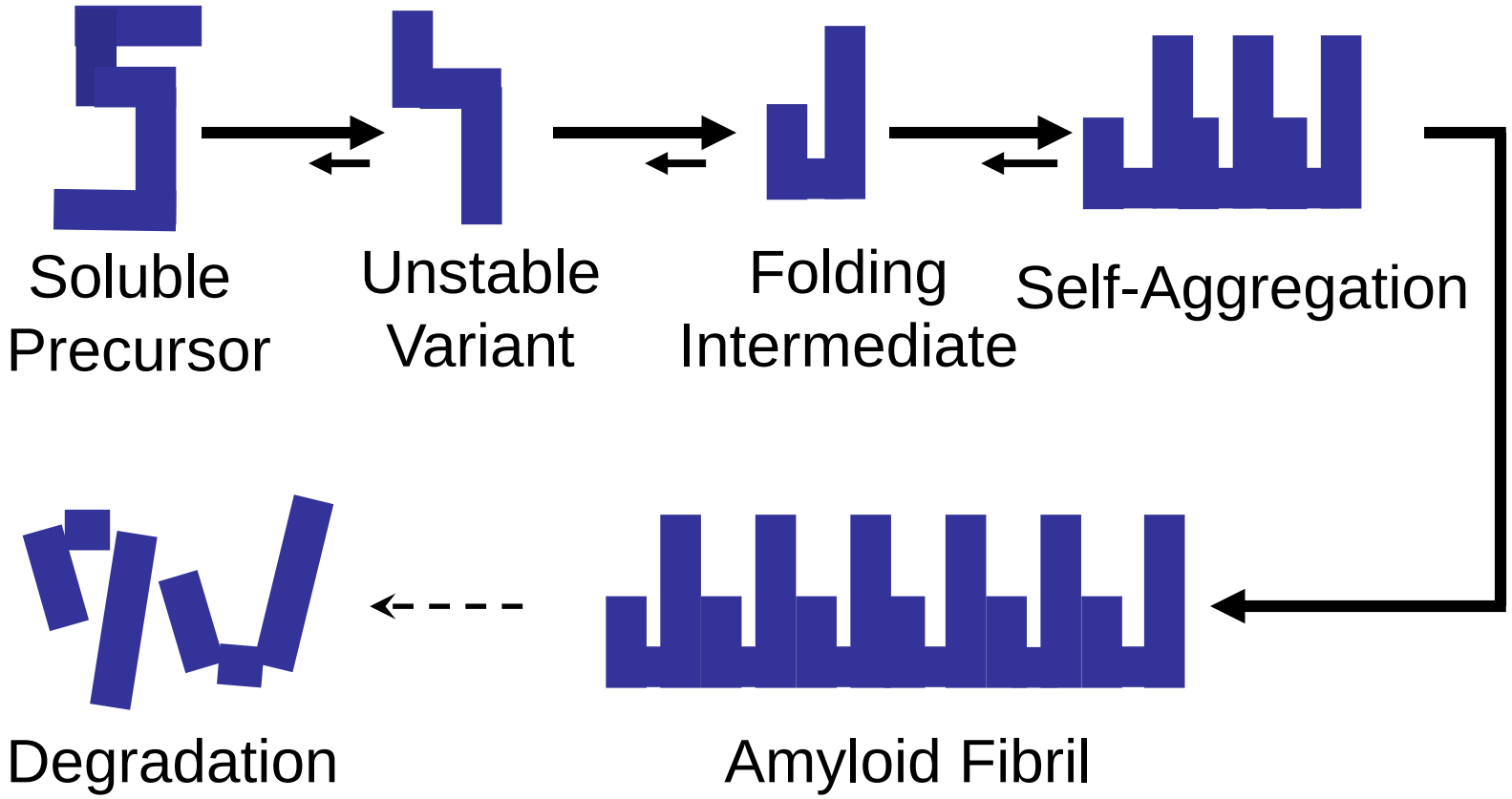


Multiple Potential Treatment Targets



Treatment Targets

- Precursor Protein Production
- Unstable Variant Formation
- Fibril Formation
- Tissue Deposition
- Protease Resistance

Treatment Target 1

- Precursor Protein Production
- Unstable Variant Formation
- Fibril Formation
- Tissue Deposition
- Protease Resistance

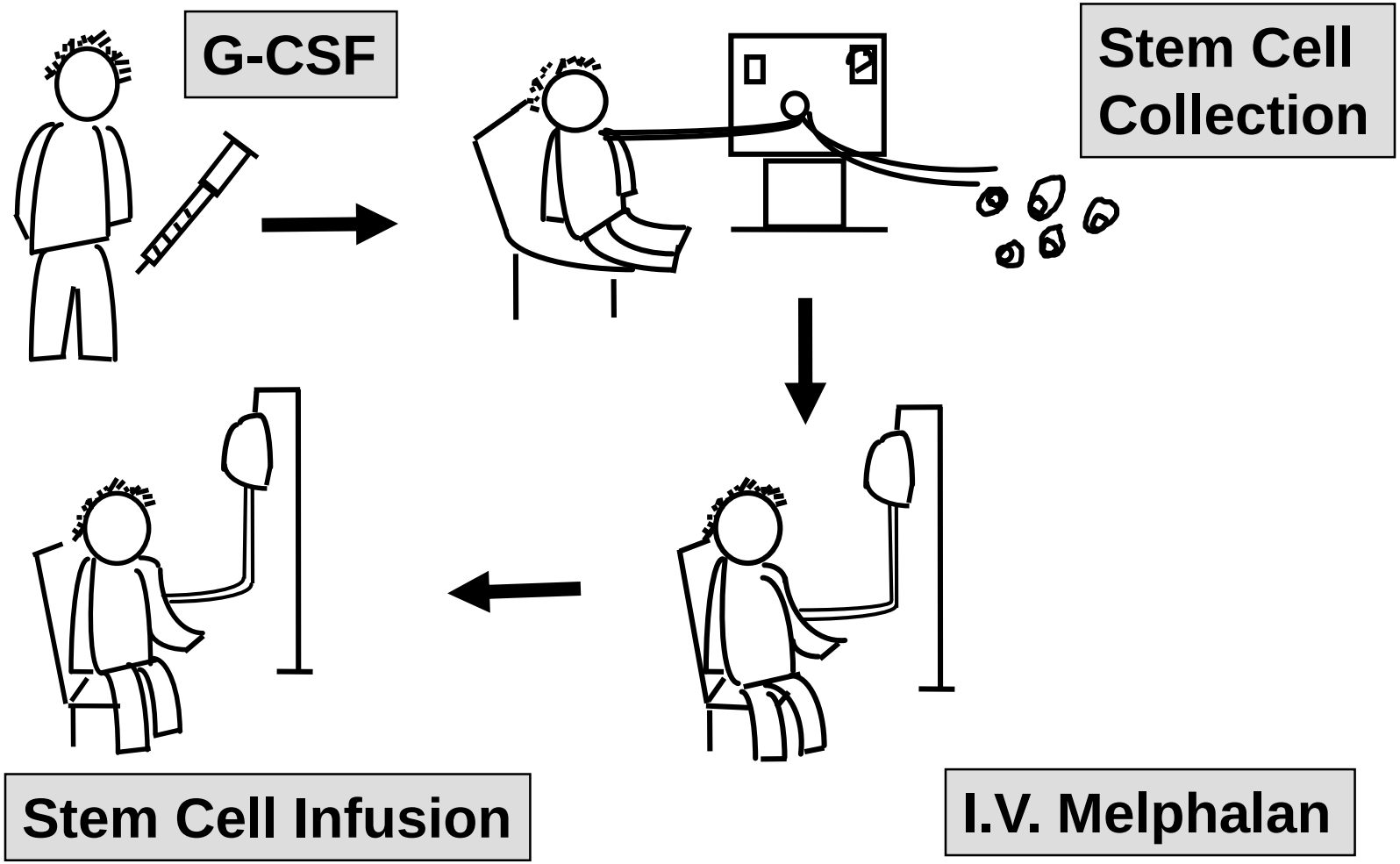
Anti-Plasma Cell Therapy for AL Amyloidosis

Melphalan and Prednisone

1. Skinner et al, Am J Med 1996	Median Survival
--Melphalan/Prednisone/Colchicine	12 months
--Colchicine	7 months

2. Kyle et al, NEJM 1999	Median Survival
--Melphalan/Prednisone	18 months
--Melphalan/Prednisone/Colchicine	17 months
--Colchicine	8 months

High-Dose Melphalan with Autologous Stem Cell Transplantation



Treatment Toxicities

- Heart Failure
- Anasarca, capillary leak syndrome
- Splenic Rupture
- Arrhythmias
- Sepsis, infection
- Gastrointestinal bleeding
- Mucositis
- Acute Kidney Injury

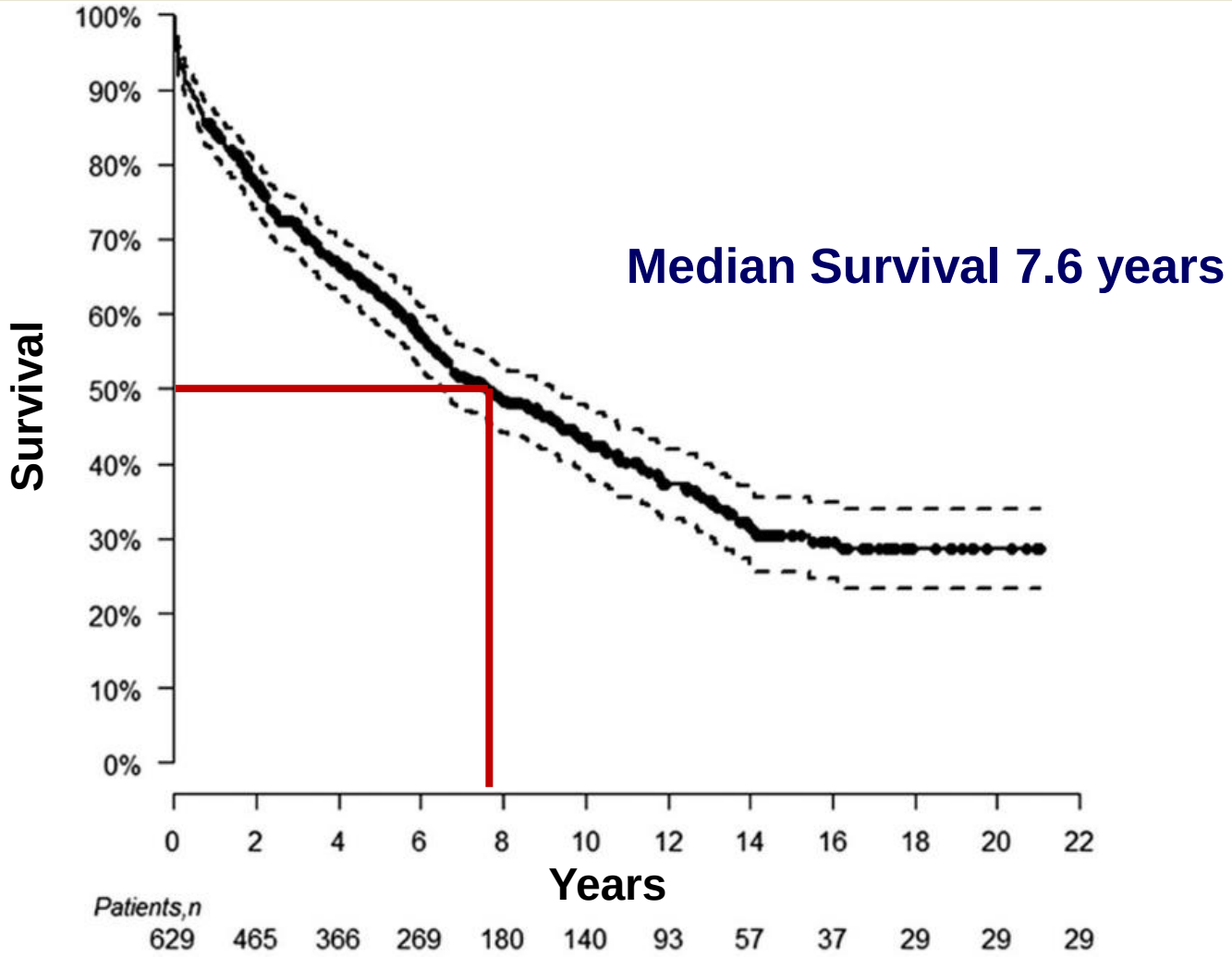
Treatment-Related Mortality

- 1994-2000 14%
- 2000-2005 9%
- 2005-2014 <3.4%

Tolerability Improves with Experience

Sanchorawala et al ASH 2014, Blood 2015

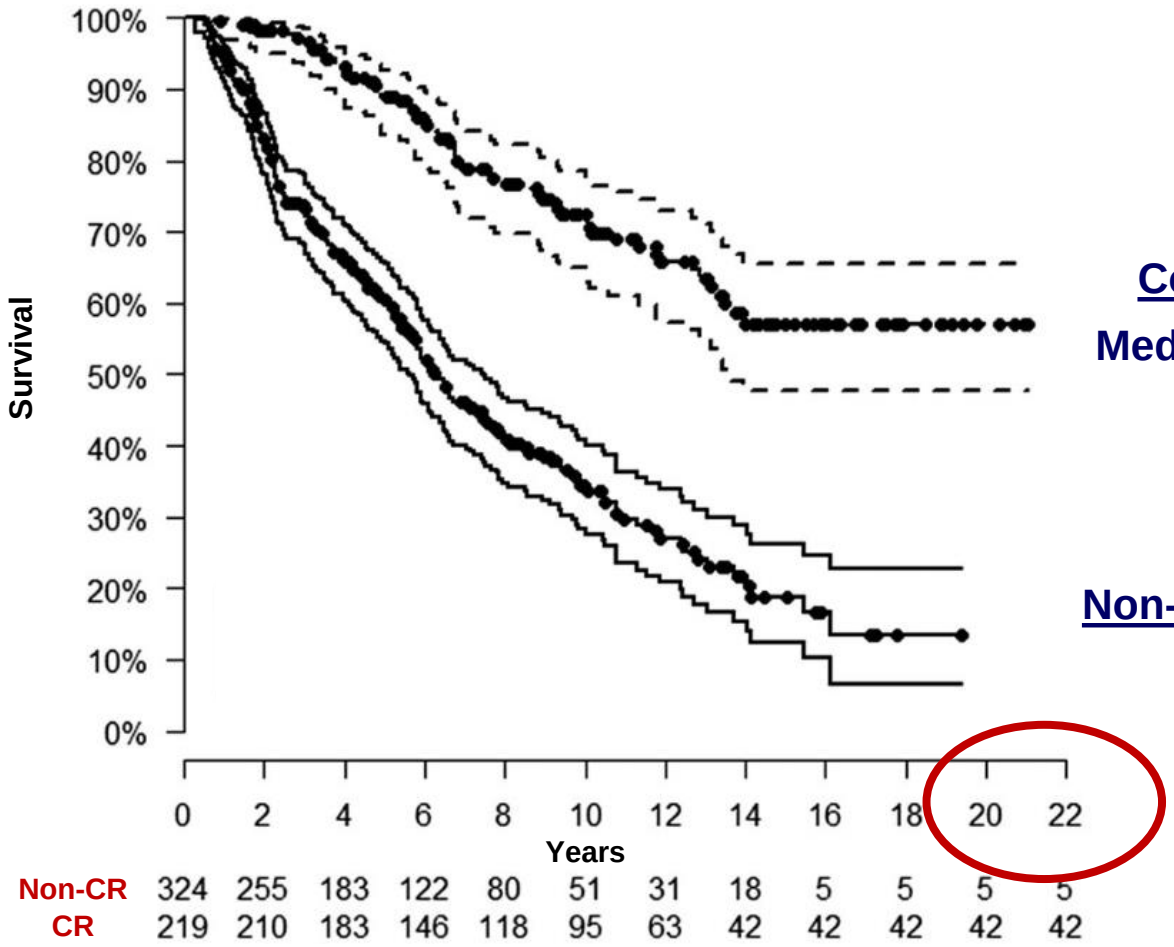
Boston University Experience with HDM/SCT 1994-2014



Median Survival 7.6 years

Sanchorawala et al Blood 2015

Impact of Hematologic Response on Survival



Complete Response

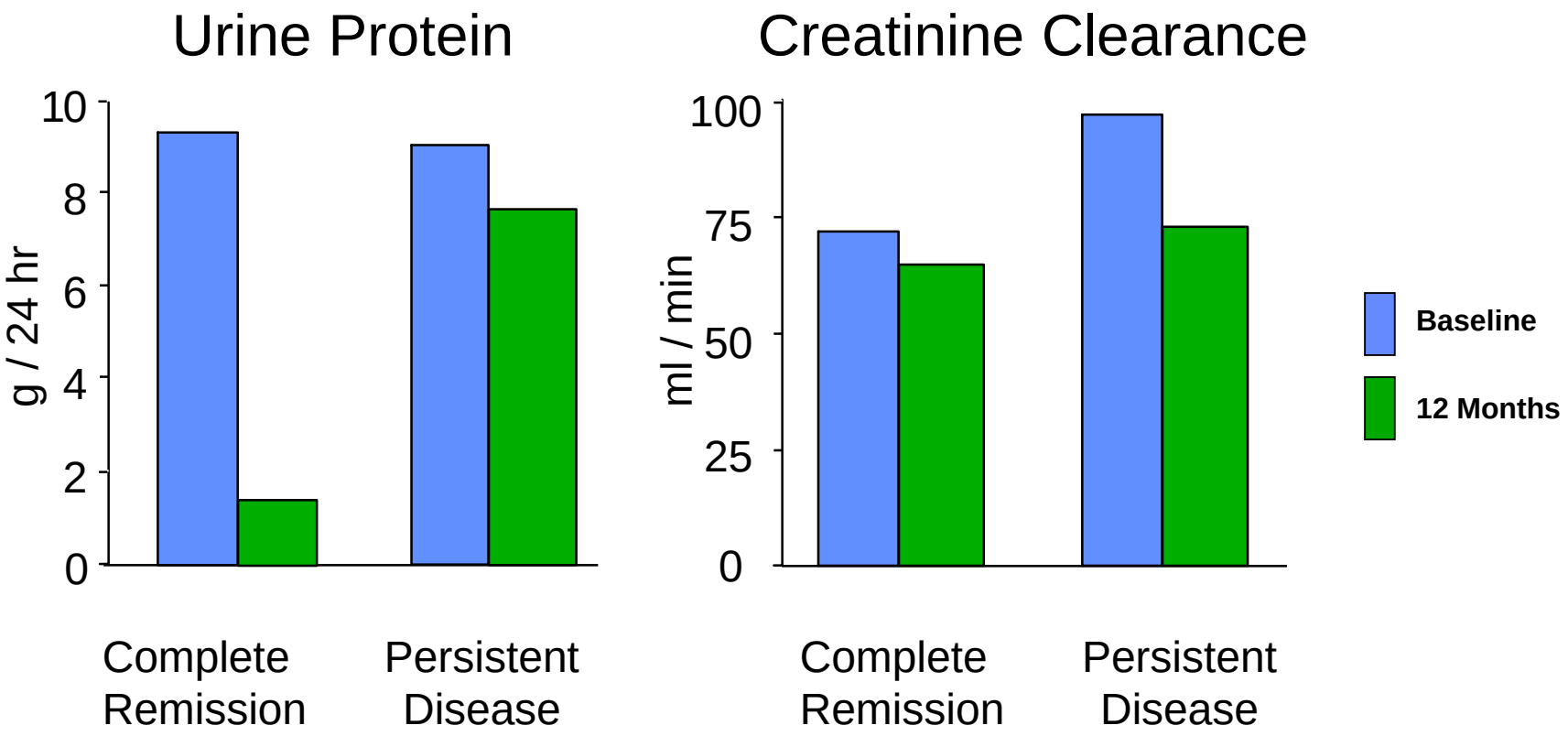
Median Not Yet Reached

Non-Complete Response

Median 6.3 yrs

Sanchorawala et al Blood 2015

Proteinuria Improves with Hematologic Remission



Dember et al, Ann Intern Med 134:746-53, 2001

Summary: High-Dose Melphalan with ASCT for AL Amyloidosis

- Can produce a complete hematologic remission in a substantial proportion of patients
- Complete hematologic remission is associated with prolonged survival and with improvement in organ function
- Complete hematologic remission is more likely with higher dose of melphalan
- The hematologic response appears to be durable
- Treatment toxicity is prohibitive for many patients

Additional Anti-Plasma Cell Agents

- Bortezomib
- Carfilzomib
- Ixazomib

} Proteasome inhibitors

- Lenalidomide
- Pomalidomide

} IMiDs

- Daratumumab

} Anti-CD38

All target the source of the amyloidogenic protein

Treatment Decisions are Challenging

Alternatives to autologous stem cell transplantation are less intensive but…..

- Treatment is prolonged
- Unclear when to expect response
- Unclear how long to treat
- Durability of response not as well established

Treatment Targets

- Precursor Protein Production ✓
- Unstable Variant Formation
- Fibril Formation
- Tissue Deposition
- Protease Resistance

Treatment Targets

- Precursor Protein Production ✓
- Unstable Variant Formation **- TTR**
- Fibril Formation
- Tissue Deposition
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Treatment Targets

- Precursor Protein Production ✓
- Unstable Variant Formation **- TTR**
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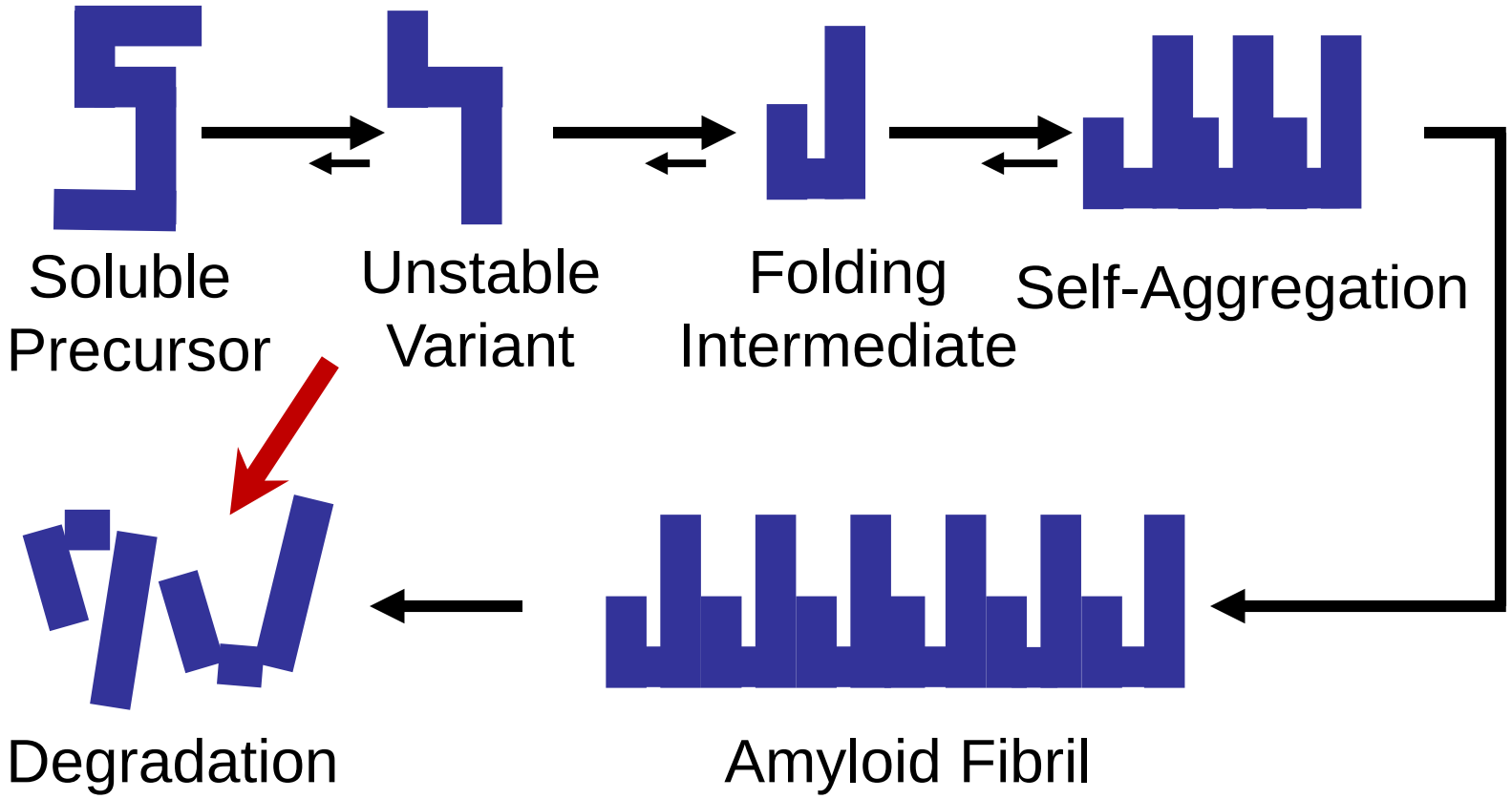
AA

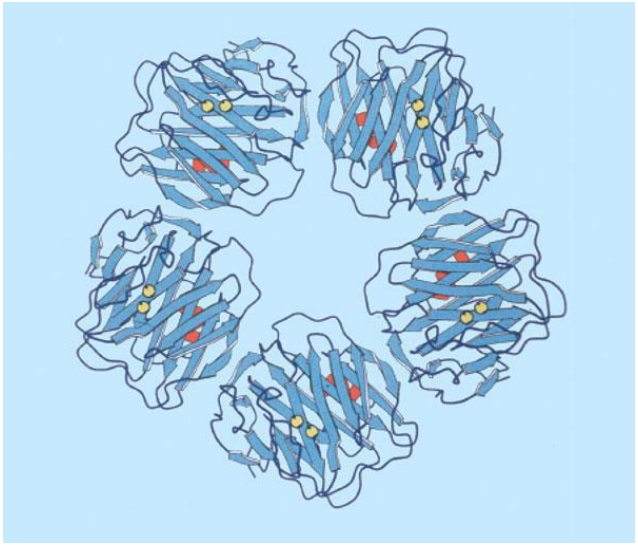
- Protease Resistance

Multiple Potential Treatment Targets



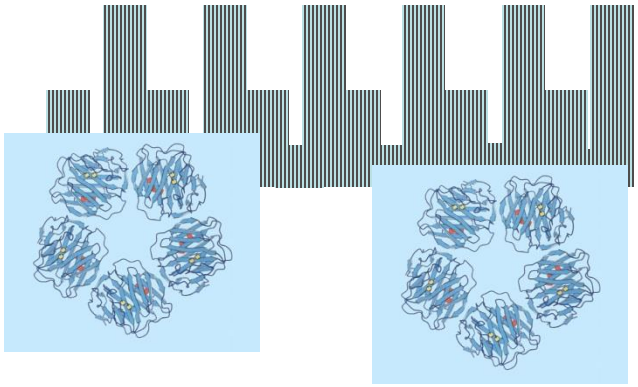
Serum Amyloid P (SAP)

- SAP is a plasma glycoprotein, member of the pentraxin family
- Present in all amyloid deposits
- Exists in dynamic equilibrium between plasma and tissue

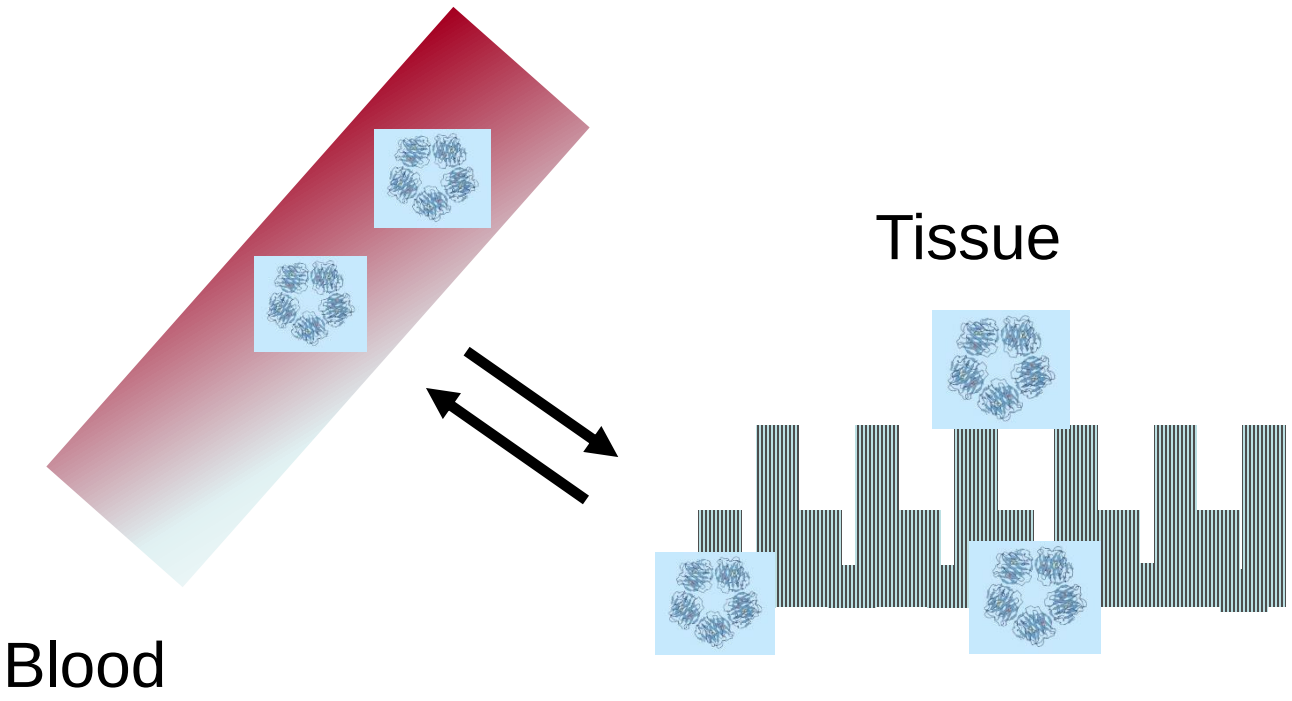


SAP and Amyloid

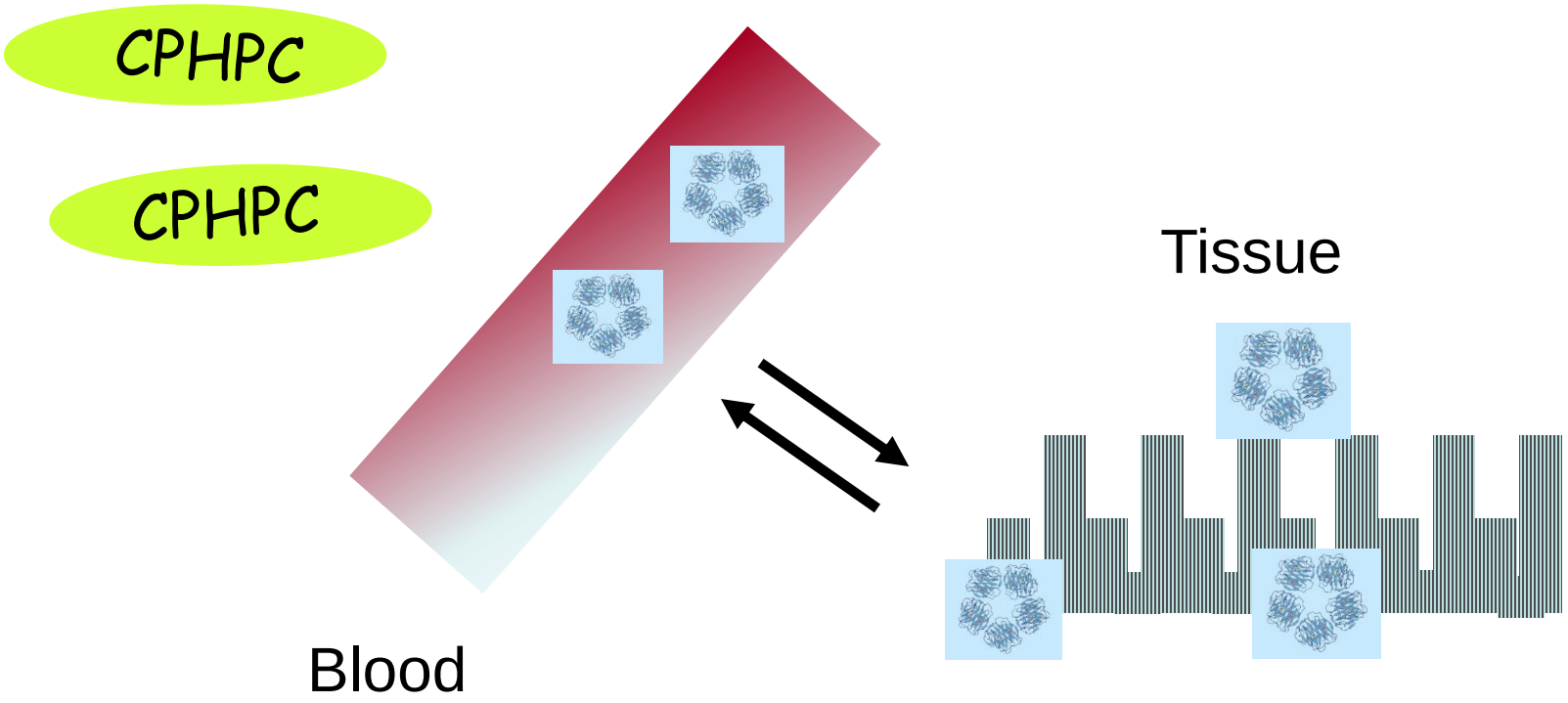
- SAP is highly resistant to proteolysis and protects amyloid fibrils from degradation *in vitro*
- Thought to contribute to failure to clear amyloid deposits *in vivo*



SAP is in Equilibrium between Plasma and Tissue (amyloid-bound)

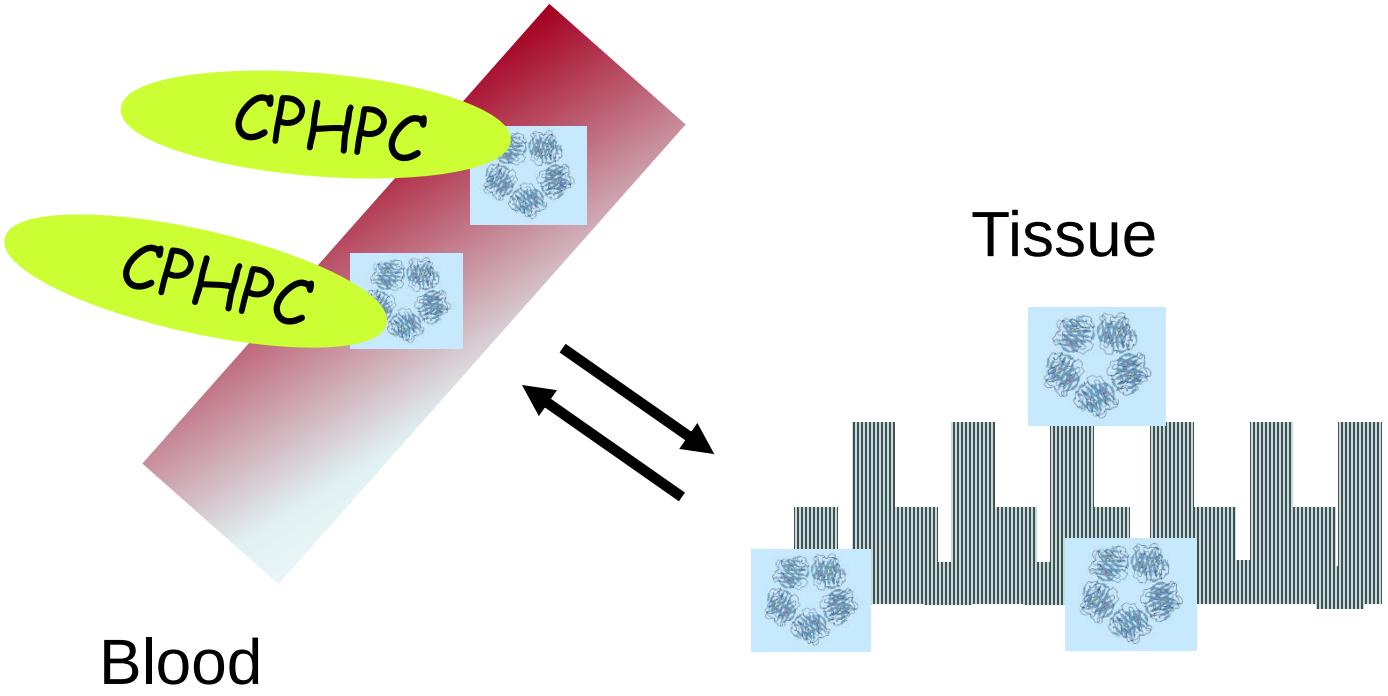


CPHPC Binds to Circulating SAP



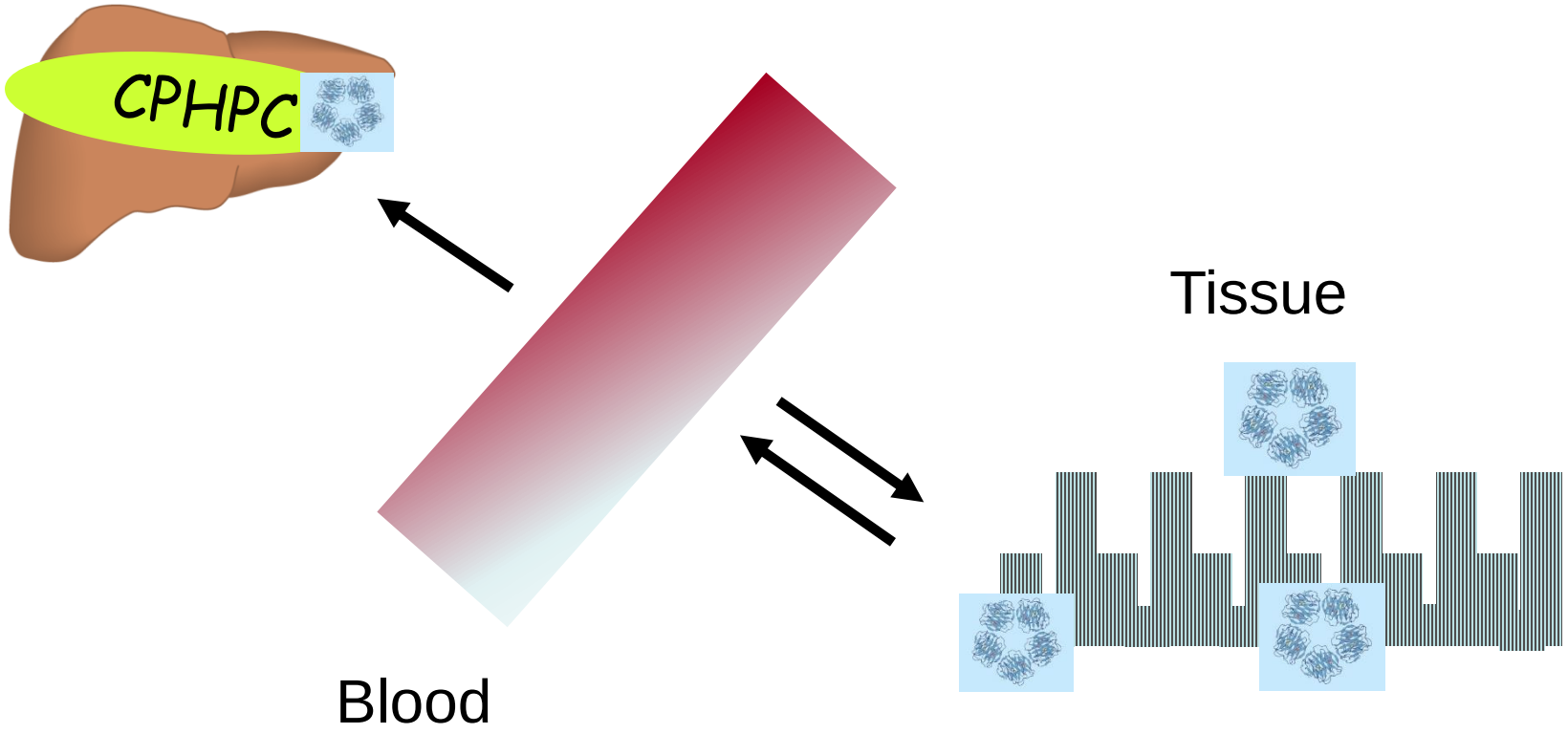
Pepys et al, Nature 2002

CPHPC Binds to Circulating SAP



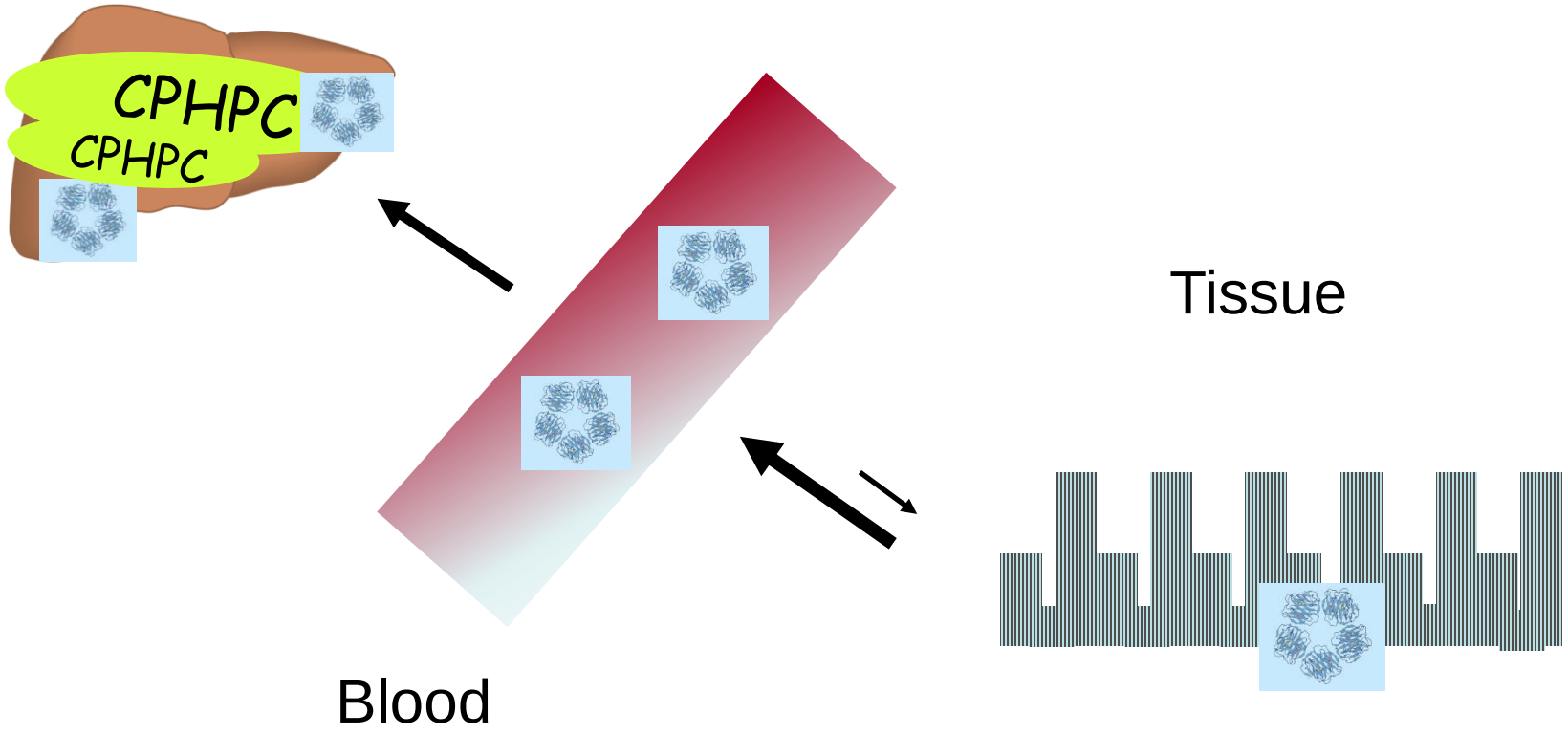
Pepys et al, Nature 2002

CPHPC Depletes SAP from Plasma (and Secondarily from Tissue)



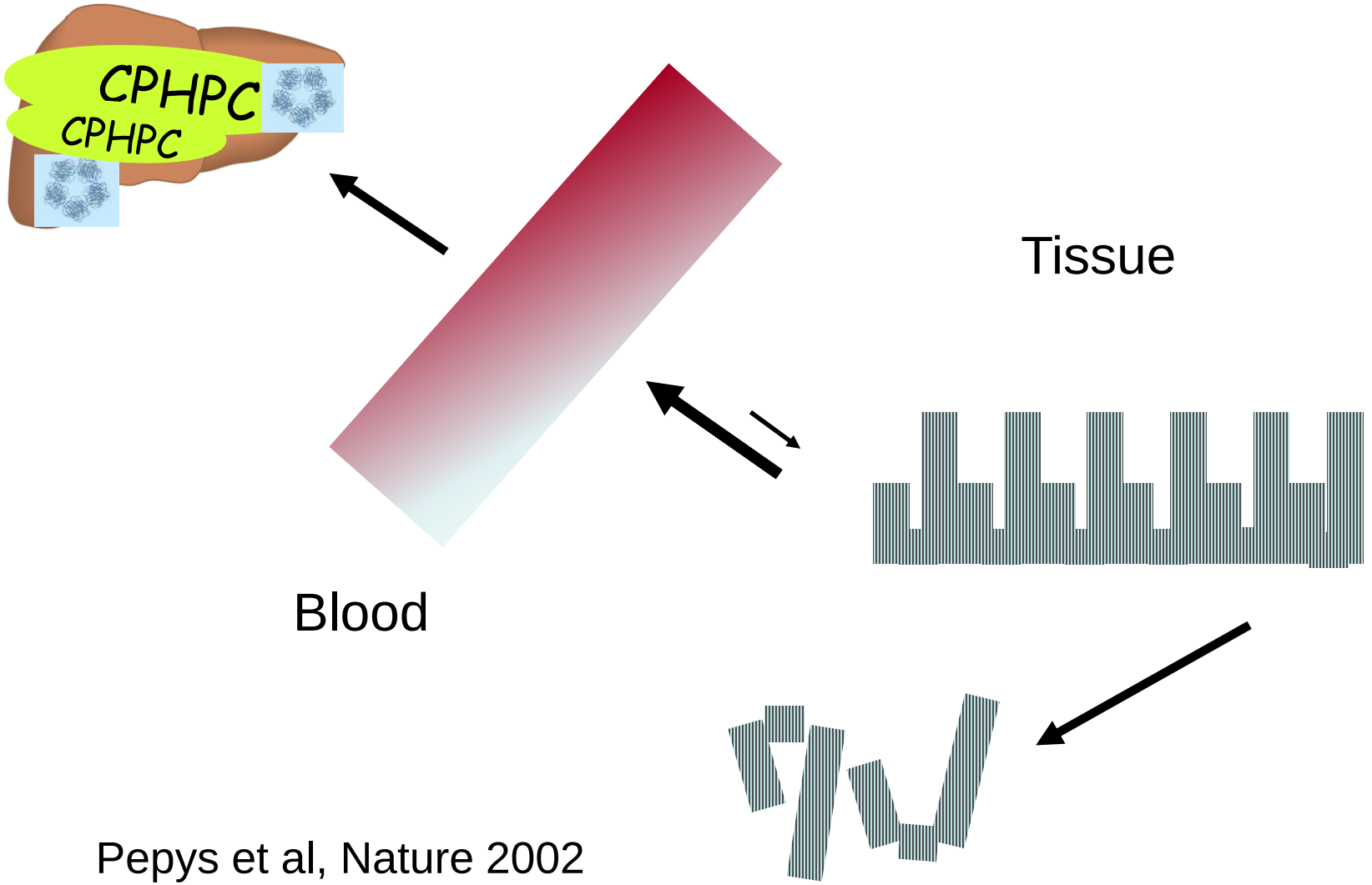
Pepys et al, Nature 2002

CPHPC Depletes SAP from Plasma (and Secondarily from Tissue)



Pepys et al, Nature 2002

Without SAP, Amyloid is Degraded by Endogenous Proteases



Pepys et al, Nature 2002

Results with CPHPC

- CPHPC infusion depleted SAP from tissue amyloid deposits in murine AA amyloidosis and in hSAP transgenics.
- In humans, CPHPC infusion was accompanied by nearly complete clearance of SAP from plasma
- What happens to amyloid deposits????

Pepys et al, Nature 2002

2010: CPHPC Coupled with Anti-SAP Ab

- Some SAP remains in amyloid deposits after CPHPC treatment
- New approach: deplete SAP from circulation using CPHPC and then administer anti-SAP Ab
  - Goal is to trigger endogenous mechanisms for clearing anti-SAP-amyloid complexes
  - Dense macrophage infiltration observed at site of amyloid deposits
  - Clearance of amyloid in mouse models

Bodin K et al. Nature 2010; 468:93-7

2010: CPHPC Coupled with Anti-SAP Ab

- Some SAP remains in amyloid deposits after CPHPC treatment
- New approach: administer anti-SAP Ab after CPHPC-induced depletion of SAP from circulation
  - Goal is to trigger endogenous mechanisms for clearing anti-SAP-amyloid complexes
  - Dense macrophage infiltration observed at site of amyloid deposits
  - Clearance of amyloid in mouse models
  - **What happens in humans??**

Bodin K et al. Nature 2010; 468:93-7

CPHPC Coupled with Anti-SAP Ab: Phase 1 Human Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

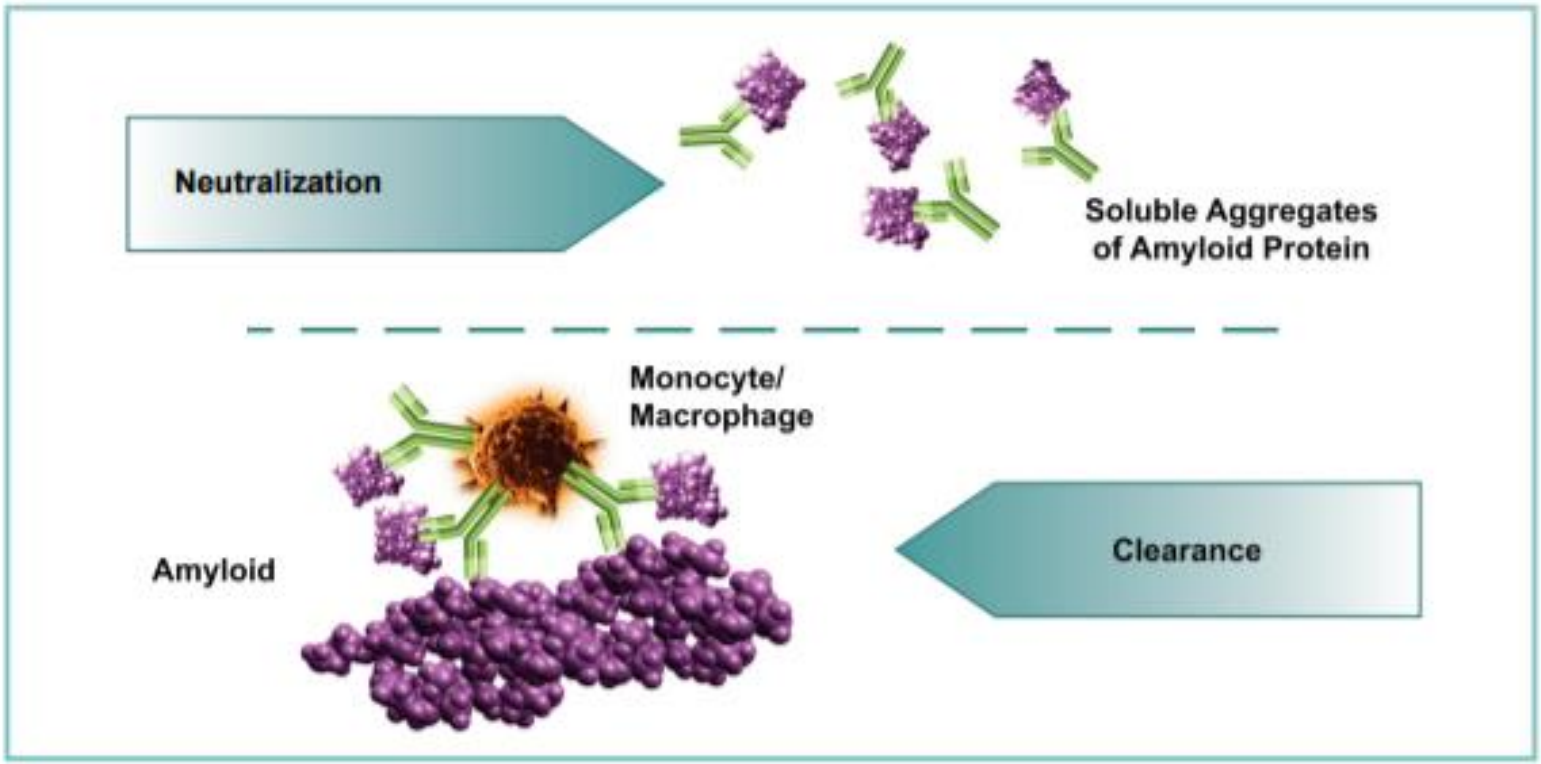
Therapeutic Clearance of Amyloid by Antibodies to Serum Amyloid P Component

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; 373:1106-1114

- Open-label, phase 1 study, 15 patients with AL, AA, Afib, or AApoA1 amyloidosis
- CPHPC followed by humanized monoclonal anti-SAP antibody
- Well-tolerated
- SAP cleared from circulation
- Decreased SAP in liver and kidney tissue
- Reduction in liver stiffness, liver volume

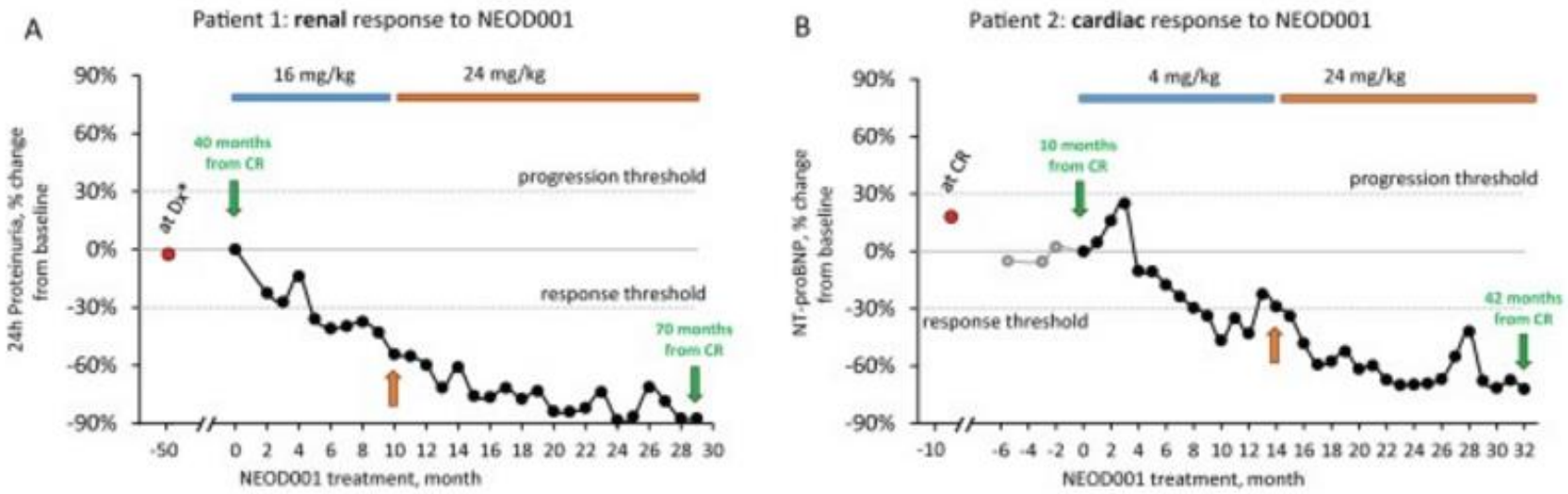
Anti-LC Amyloid Antibody: "NEOD001"



Targets epitope of misfolded LCs and triggers Ab-mediated phagocytosis

Gertz et al JCO 2015

NEOD001 Early Experience



Gertz et al. Am J Hematol 2015

NEOD001 Trials

- PRONTO
  - Cardiac involvement, prior anti-plasma cell therapy, no current therapy
  - Placebo-controlled, 100 participants
  - Primary outcome: change in NT-proBNP
  - Completion expected Jan 2018
- VITAL
  - Cardiac, treatment-naïve, concurrent anti-plasma cell therapy
  - Placebo-controlled, 236 participants
  - Primary outcome: cardiac mortality or cardiac hospitalization
- RAIN
  - Renal involvement, prior anti-plasma cell therapy, no current therapy
  - Placebo-controlled, 100 participants
  - Primary outcome: renal response
  - Not yet started

Why So Much Progress in Amyloidosis?

- Fascination by biochemists, biophysicists, structural biologists with these protein folding disorders
- Vibrant collaboration between basic scientists and clinicians
- Tremendous efforts by patient support groups and rare disease organizations as well as interest by industry

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