Die Amyloidose aus der Sicht des Hämatologen

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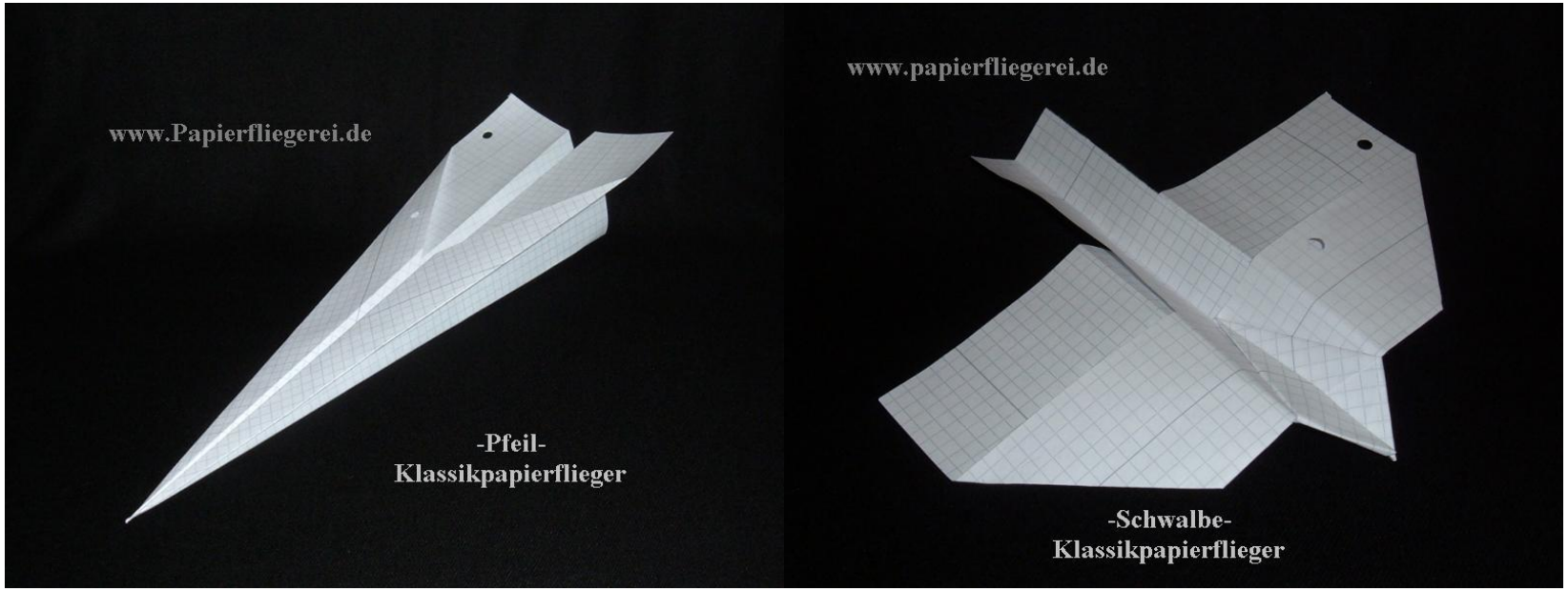
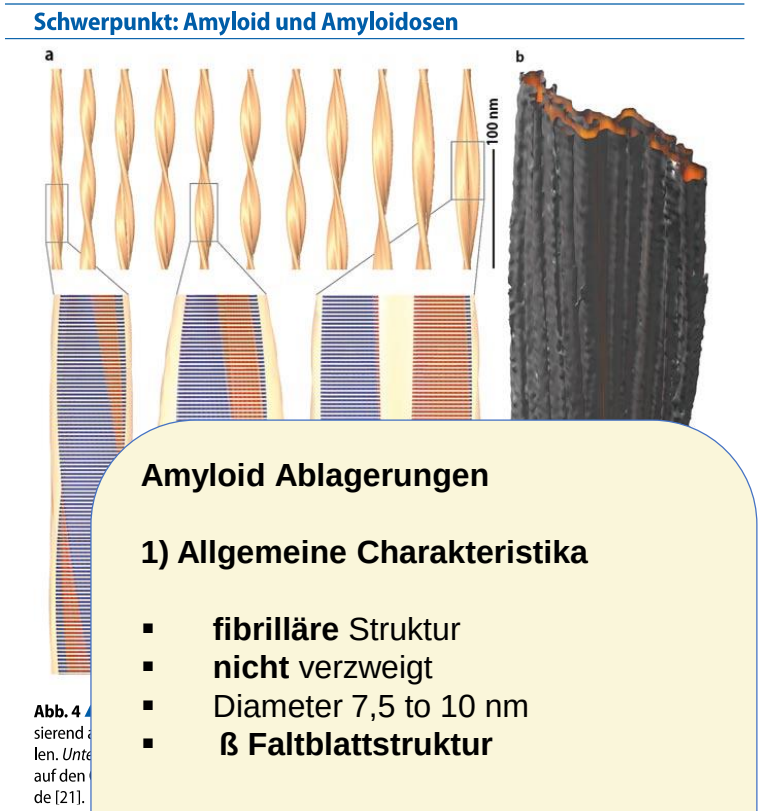
Amyloidosen = Eiweißfehlfaltungserkrankungen

- Proteinfaltungsstörung mit Bildung von **fibrillär** aufgebauten Proteinen
- **Verlust** der **Löslichkeit** & Bildung von extrazellulären **Ablagerungen**





Amyloid Ablagerungen

1) Allgemeine Charakteristika

- **fibrilläre** Struktur
- **nicht** verzweigt
- Diameter 7,5 to 10 nm
- **ß Faltblattstruktur**

2) Spezieller Aufbau

- abhängig vom Ausgangsprotein

Amyloidformen

Amyloid. 2016;23:209-213

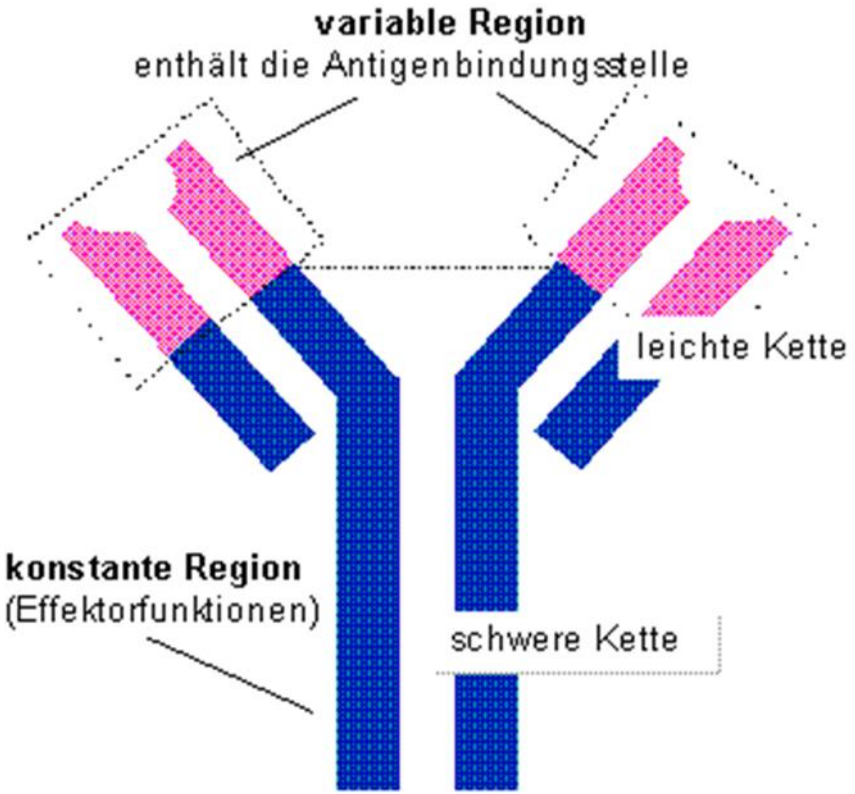
Table 1. Amyloid fibril proteins and their precursors in human[a].

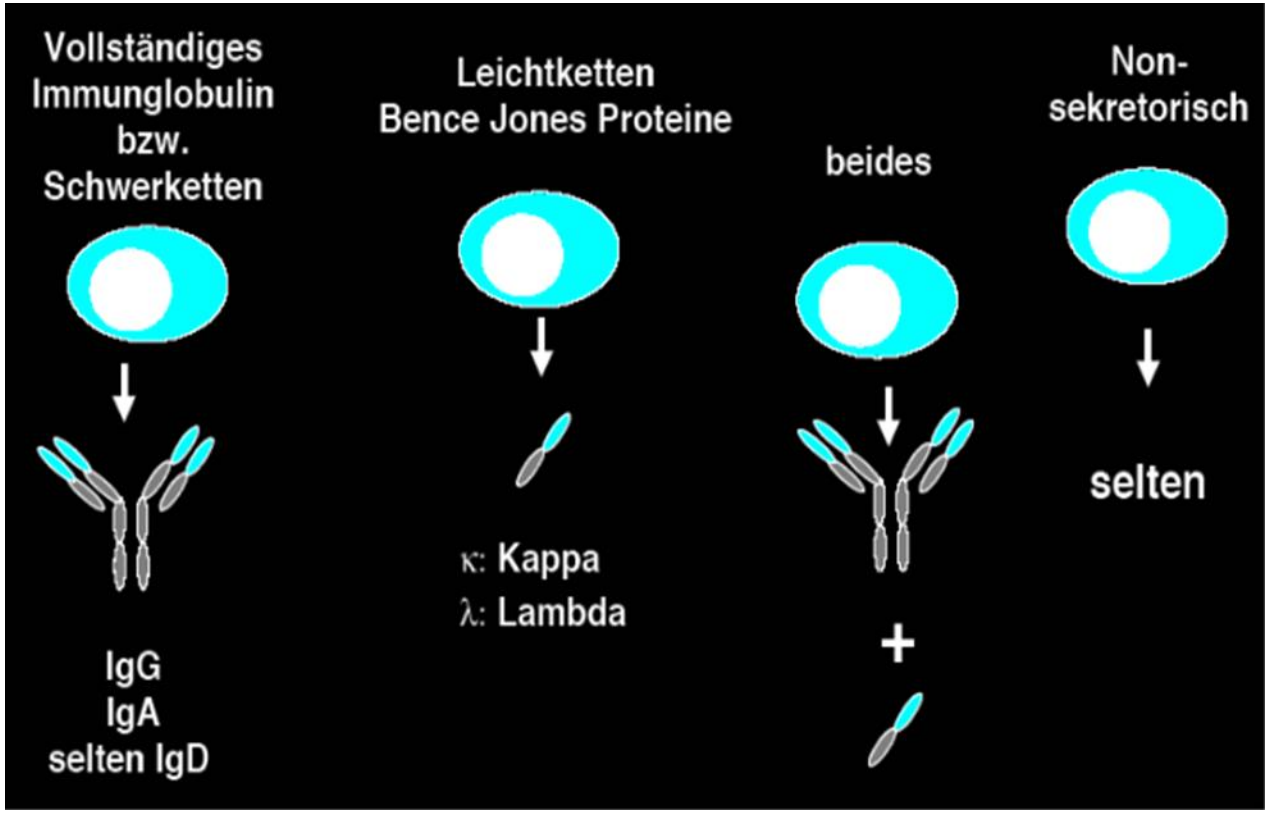
Fibril protein	Precursor protein	Systemic and/or localized	Acquired or hereditary	Target organs
AL	Immunoglobulin Light Chain	S, L	A, H	All organs except CNS
AH	Immunoglobulin Heavy Chain	S, L	A	All organs except CNS
AA	(Apo) Serum Amyloid A	S	A	All organs except CNS
ATTR	Transthyretin, wild type	S	A	Heart mainly in males, Ligaments, Tenosynovium
	Transthyretin, variants	S	H	PNS, ANS, heart, eye, leptomen.
Aβ2M	β2-Microglobulin, wild type	L	A	Musculoskeletal System
	β2-Microglobulin, variant	S	H	ANS
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 and systemic
AGel	Gelsolin, variants	S	H	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
ADan*	ADanPP, variants	L	H	CNS
Aβ	Aβ protein precursor, wild type	L	A	CNS
	Aβ protein precursor, variant	L	H	CNS
APrP	Prion protein, wild type	L	A	CJD, Fatal insomnia
	Prion protein variants	L	H	CJD, GSS syndrome, Fatal insomnia
ACal	(Pro)calcitonin	L	A	C-cell thyroid tumors
AIAPP	Islet Amyloid Polypeptide†	L	A	Islets of Langerhans, Insulinomas
AANF	Atrial Natriuretic Factor	L	A	Cardiac atria
APro	Prolactin	L	A	Pituitary prolactinomas, aging pituitary
AIns	Insulin	L	A	Iatrogenic, local injection
ASPC‡	Lung Surfactant Protein	L	A	Lung
AGal7	Galectin 7	L	A	Skin
ACor	Corneodesmosin	L	A	Cornified epithelia, Hair follicles
AMed	Lactadherin	L	A	Senile aortic, Media
Aker	Kerato-epithelin	L	A	Cornea, hereditary
ALac	Lactoferrin	L	A	Cornea
AOAAP	Odontogenic Ameloblast-Associated Protein	L	A	Odontogenic tumors
ASem1	Semenogelin 1	L	A	Vesicula seminalis
AEnf	Enfurvitide	L	A	Iatrogenic

[a]Proteins are listed, when possible, according to relationship. Thus, apolipoproteins are grouped together, as are polypeptide hormones.
*ADan is the product of the same gene as ABri.
†Also called amylin.
‡Not proven by amino acid sequence analysis.

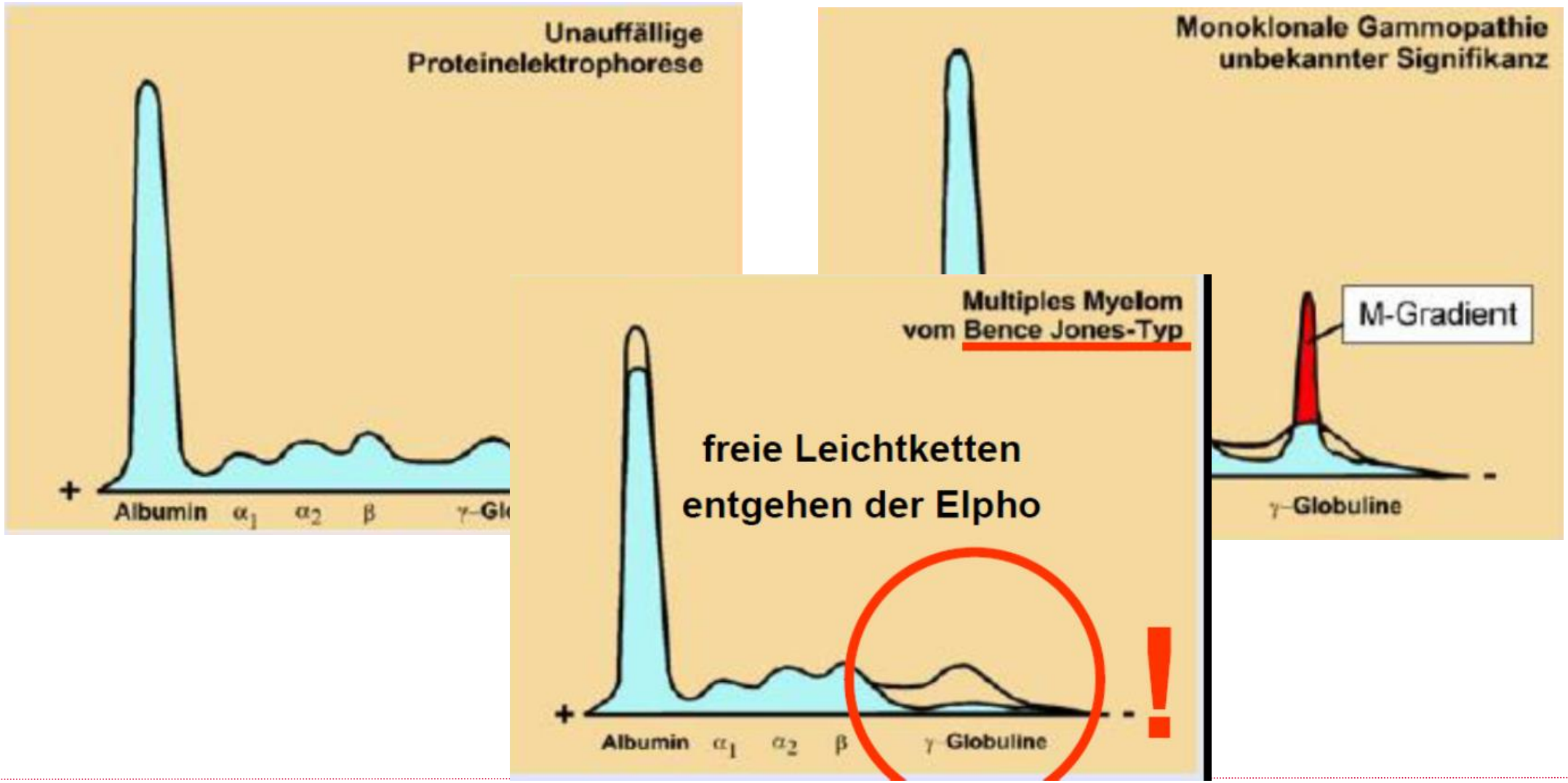
36 definierte Amyloid-formende Proteine bekannt

Paraproteine

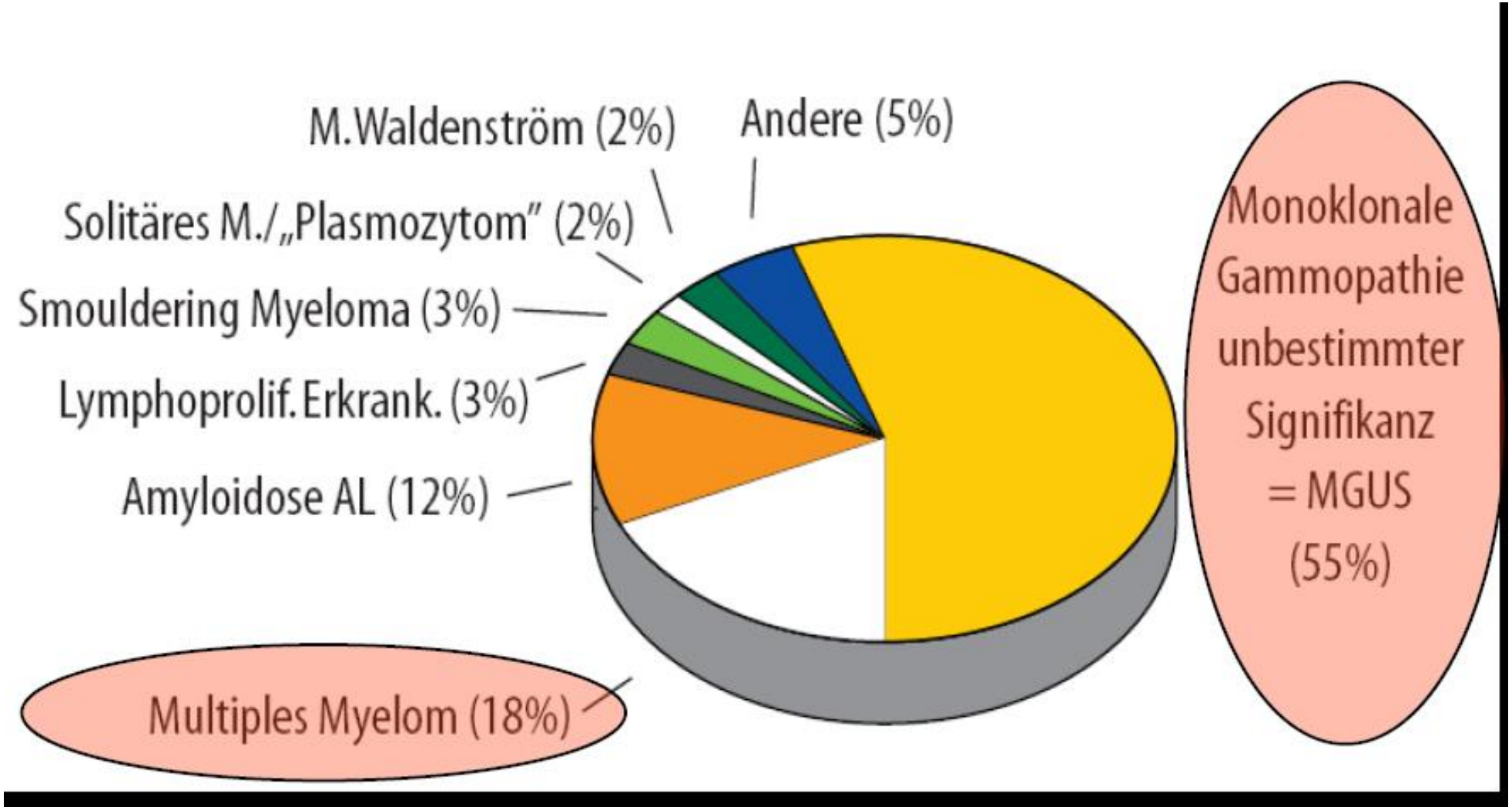




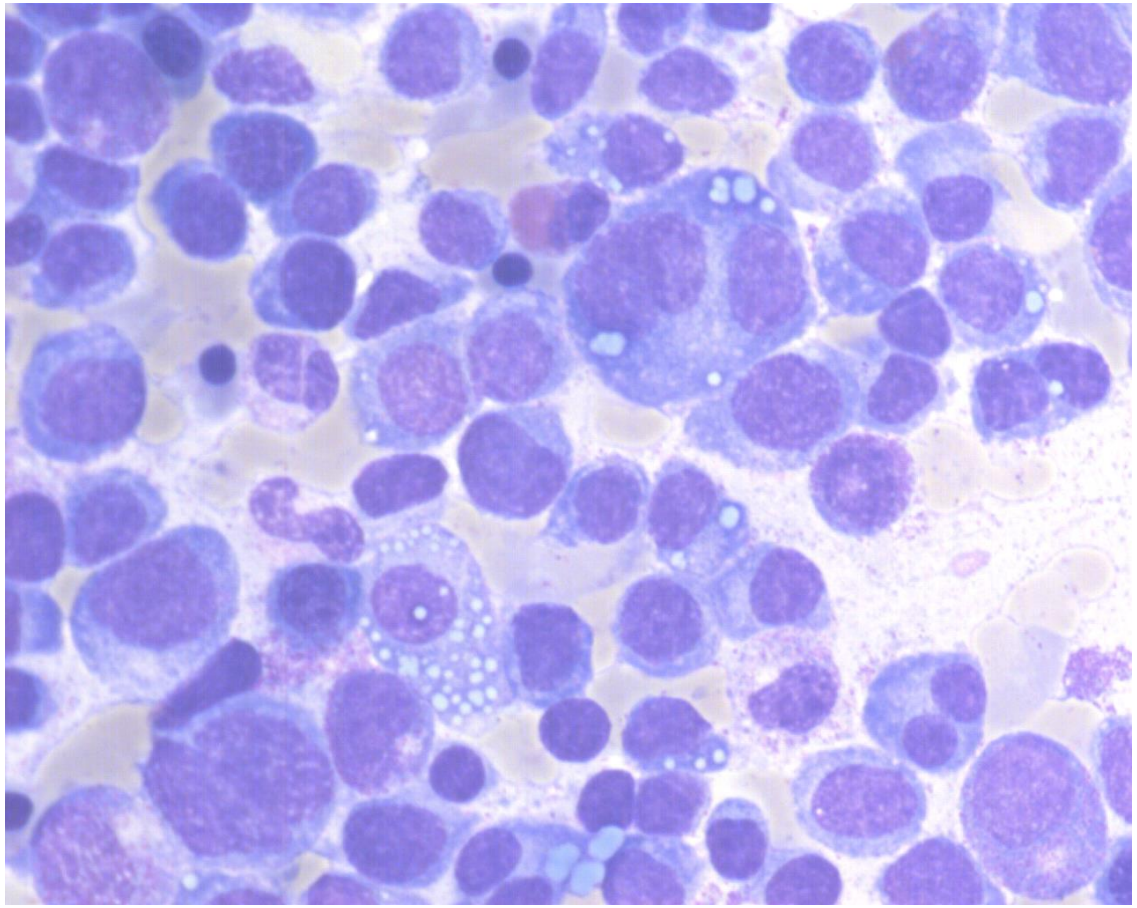
Paraproteine



Paraproteine



AL - Amyloidose



- Proteinfaltungsstörung mit Bildung von **fibrillär** aufgebauten Immun-Eiweißbausteinen
- = freie Leichtketten (kappa oder lambda) = FLC
- Hergestellt in Plasmazellen im Knochenmark
- = ausgereifte Immunzellen (B-Lymphozyten)
- Falsches Protein = Paraprotein

AL - Amyloidose

- Es muß ein **Paraprotein/M-Protein/Freie Leichtketten** vorliegen **(oft „kleiner Gradient“)**
- Es muß eine klonale Paraprotein-produzierende Plasma- oder B-Zell Erkrankung vorliegen

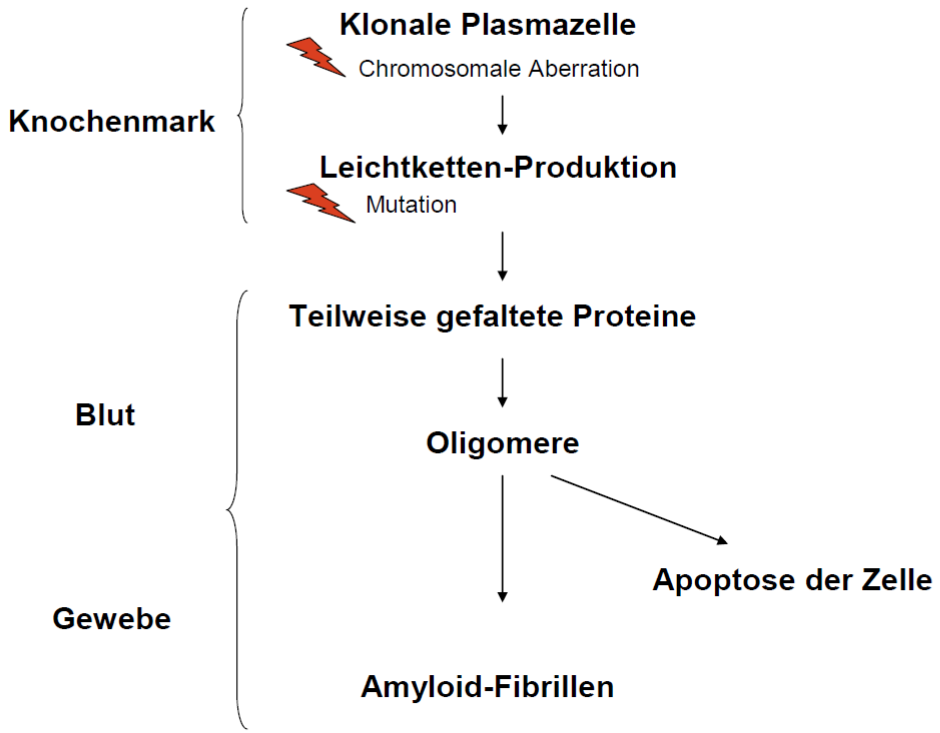
CAVE: **Jedes Paraprotein** kann eine **AL-Amyloidose** hervorrufen

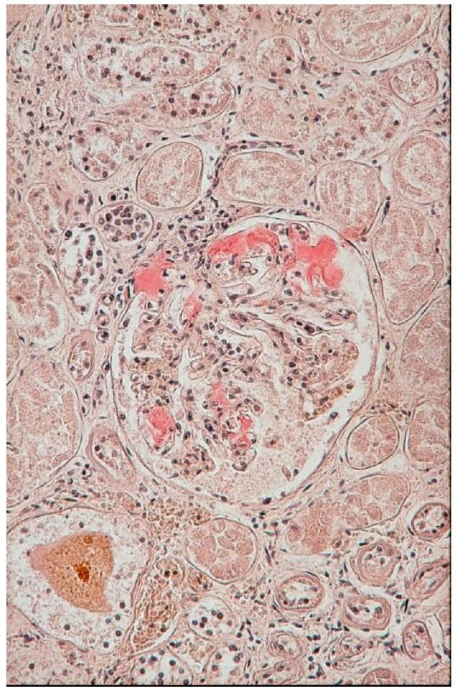
CAVE: **MGUS**, SMM, Paraprotein-bildende niedrig maligne NHL (CLL,…..)

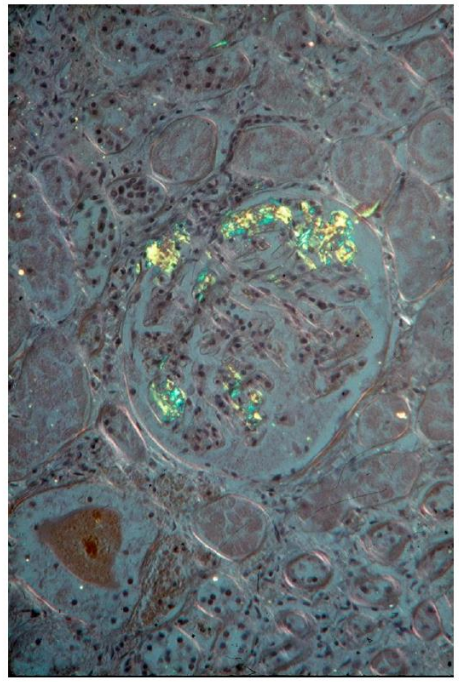
- Bisher häufigste Amyloidose weltweit
- 8-15 neue/Jahr/1.000.000 Einwohner (120 = Austria)

Entstehung der AL - Amyloidose

Entstehung der AL Amyloidose



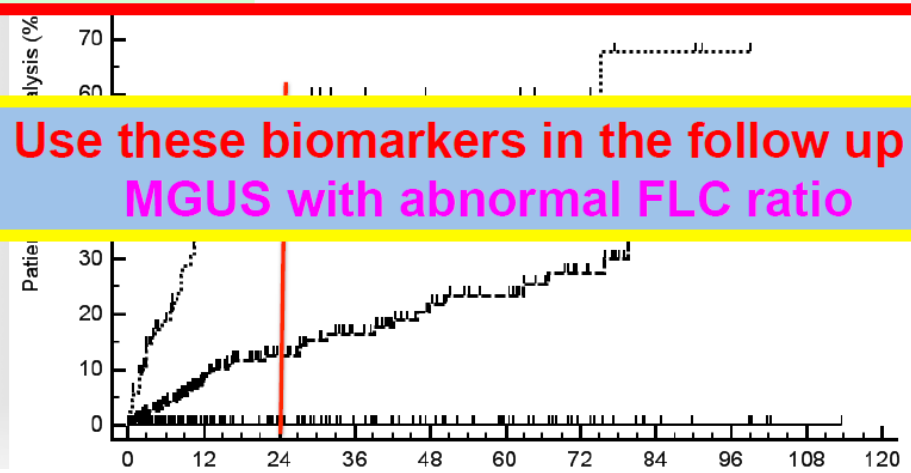




Frühsymptome, Laborveränderungen

Progression to dialysis in patients with renal AL amyloidosis undergoing treatment

Organ or syndrome	Present in	Early "red flags"
Heart	74%	NT-proBNP >332 ng/L (100% sensitivity)
Kidney	65%	Urinary albumin > 0.5 g/day



Use these biomarkers in the follow up of MGUS with abnormal FLC ratio

Screening Biomarker für Früherkennung

AL Amyloidose

- Pat. mit Paraproteinämie
- MGUS, SMM
- B-cell Neoplasias with paraproteinemia

AL Amyloidose

Be aware!

LABOR

Serum

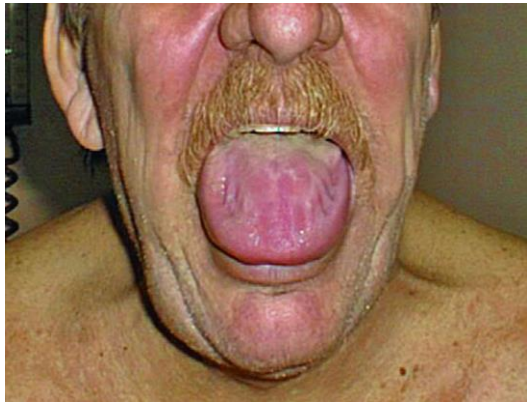
- **NT Pro-BNP**
- **TnT**
- alkalische Phosphatase
- Total Protein
- Albumin
- Kreatinin

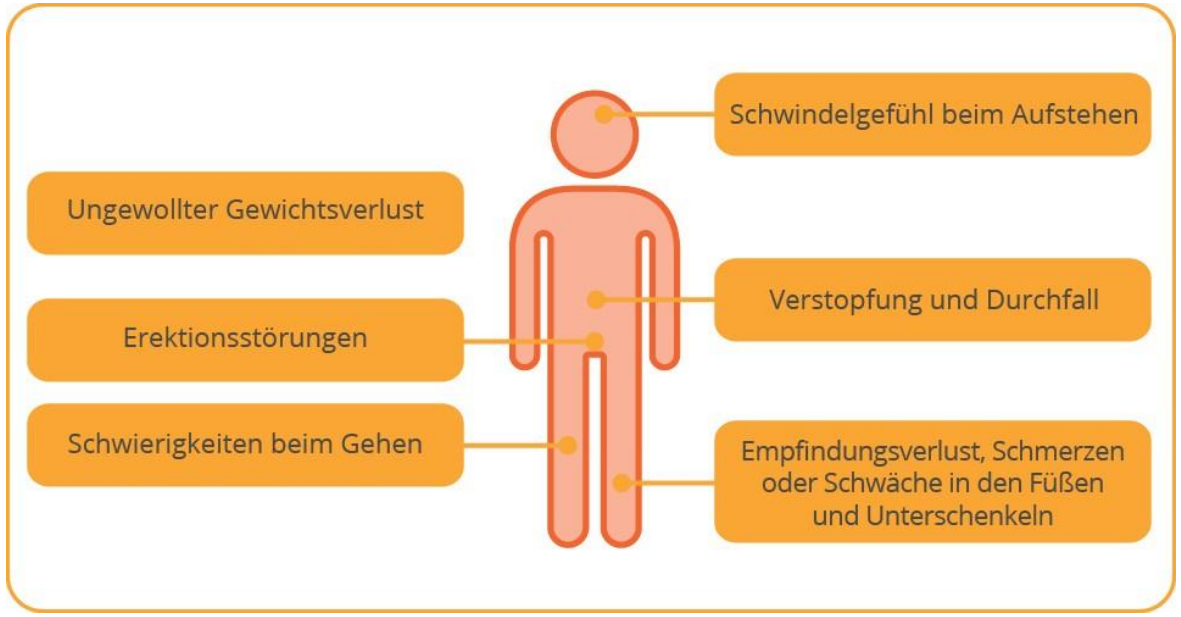
Urine

- **Protein-/Kreatinin-Quotient**
- **Albumin-/Kreatinin-Quotient**
- Protein & Albumin in 24h-urine
- Elektropheresis(UPEP) & Immunofixation in urine

Symptome

- Leistungsschwäche
- Schwindel, „Umfallen“
- Ödemneigung (dicke Beine, nächtlice Harnflut)
- Durchfälle
- Druckschmerz im OB
- Blutungsneigung (blaue Flecken)
- Polyneuropathien
- Beidseitiges Karpaltunelsyndrom
- Chon. Heiserkeit





Alleinige Amyloidose oder Amyloidose + Plasmazellerkrankung/B-Zellerkrankung ?

- Plasmazellinfiltration des Knochenmarks
- Konzentration des monoklonalen Immunglobulins
- Isotyp des monoklonalen Immunglobulins

- **Endorganschäden „CRAB“ - Kriterien**

C	**Hypercalcämie**	**Ca > 0.25 mmol/l ULN, oder > 2.75 mmol/l**
R	**Nierenversagen**	**Clearance < 40 ml/min oder Creatinin > 2.0 mg/d**
A	**Anämie**	**Hb < 2g/dl LLN oder < 10 g/dl**
B	**Osteolysen**	**in Röntgen, low-dose CT, PET-CT**

Therapieprinzipien

Derzeit **KEINE zugelassene** Therapie gegen **AL Amyloidose**

1) Reduktion des Paraproteins

- Anti-Plasmazell Therapie
- Anti-B-Zell Therapie

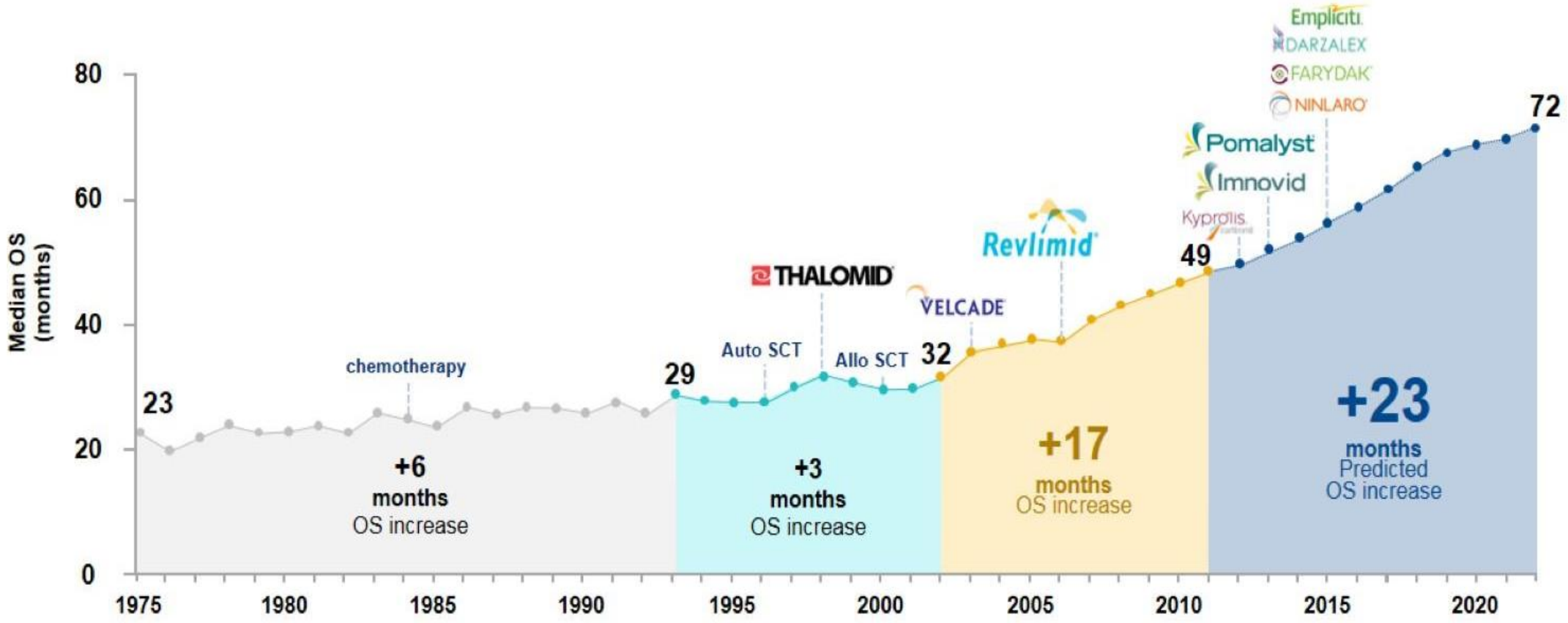
2) Aktive Auflösung der vorhanden Ablagerungen

- Antifibrilläre Therapie
- Anti-SAP Therapie

3.) Optimierung der symptomatischen Therapie

Sekundäre AL-Amyloidose bei Myelom, CLL, Waldenströmscher Erkrankung

Der Preis des Erfolgs….



1. Drawid A et al. Impact of Novel Therapies on Multiple Myeloma—Current and future outcomes. Poster presented at the 20th Congress of the European Haematology Association; Vienna, Austria, June 11-14, 2015
Note: Historical median OS for MM patients based on analysis of the National Cancer Institute Surveillance, Epidemiology, and end results Program. Predictive analysis of OS modelled using data from clinical trials, cancer registries and insight from key opinion leaders

Therapie?

Anti-plasmazelluläre Medikamente

Derzeit KEINE zugelassene Therapie gegen AL Amyloidose

aber Myelom – Medikamente möglichst ohne Herz-, Nieren, Neurotoxizität sind wirksam (i.d.R. in Kombinationen)

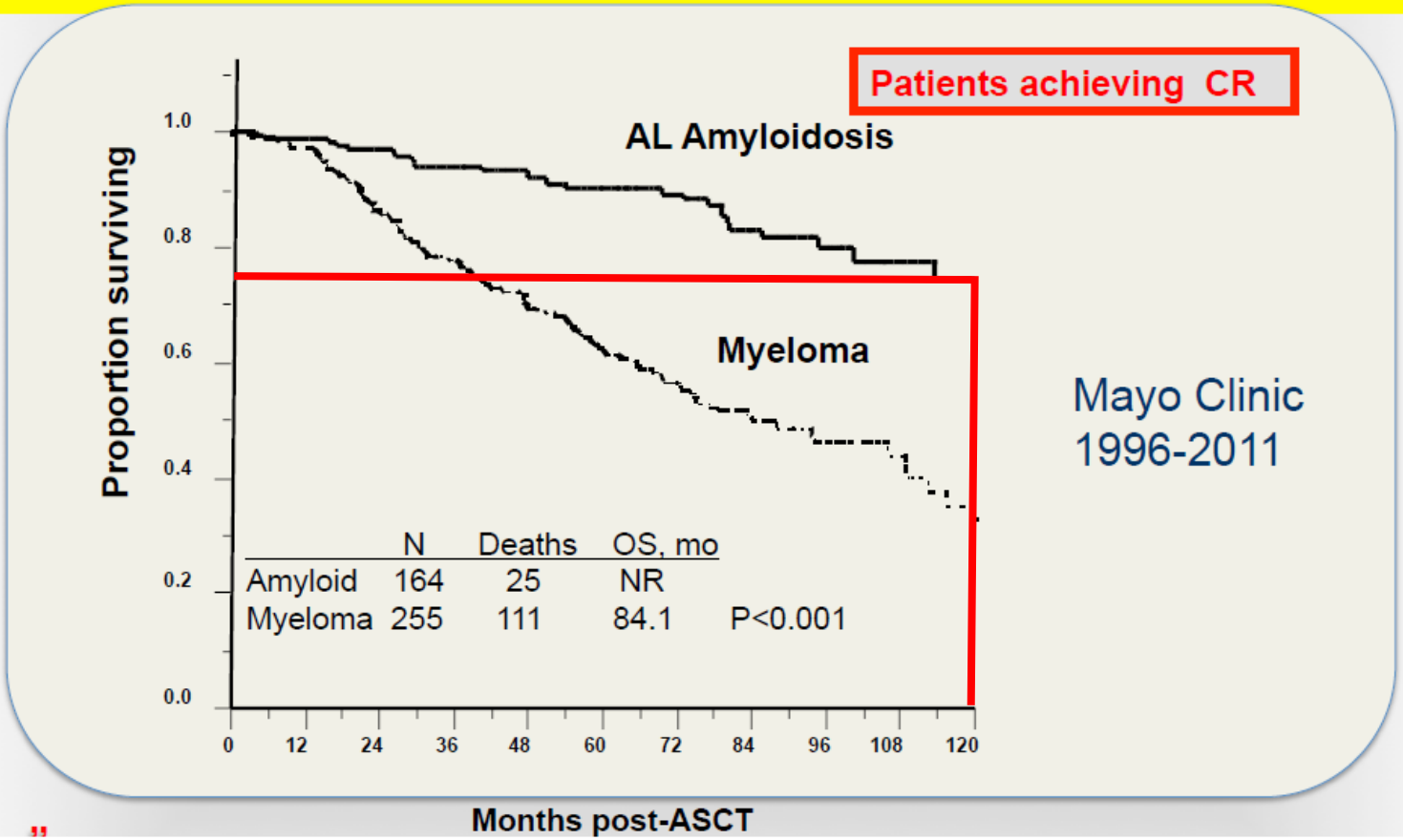
Immunmodulatoren	Proteasom-Inhibitoren	Steroide(Kortison)	Anti-körper	Zellgifte
Thalidomid	Bortezomib	Prednison	Daratumumab	Melphalan
Lenalidomid	Ixazomib	Dexamethason	Isatuximab	Cyclophosphamid
Pomalidomid	Carfilzomib			

Therapie?

Stammzelltherapie

Patients with AL amyloidosis undergoing ASCT have superior outcomes as compared to patients with MM

Seenithamby et al, *Bone Marrow Transplant. 2013;48:1302-7*



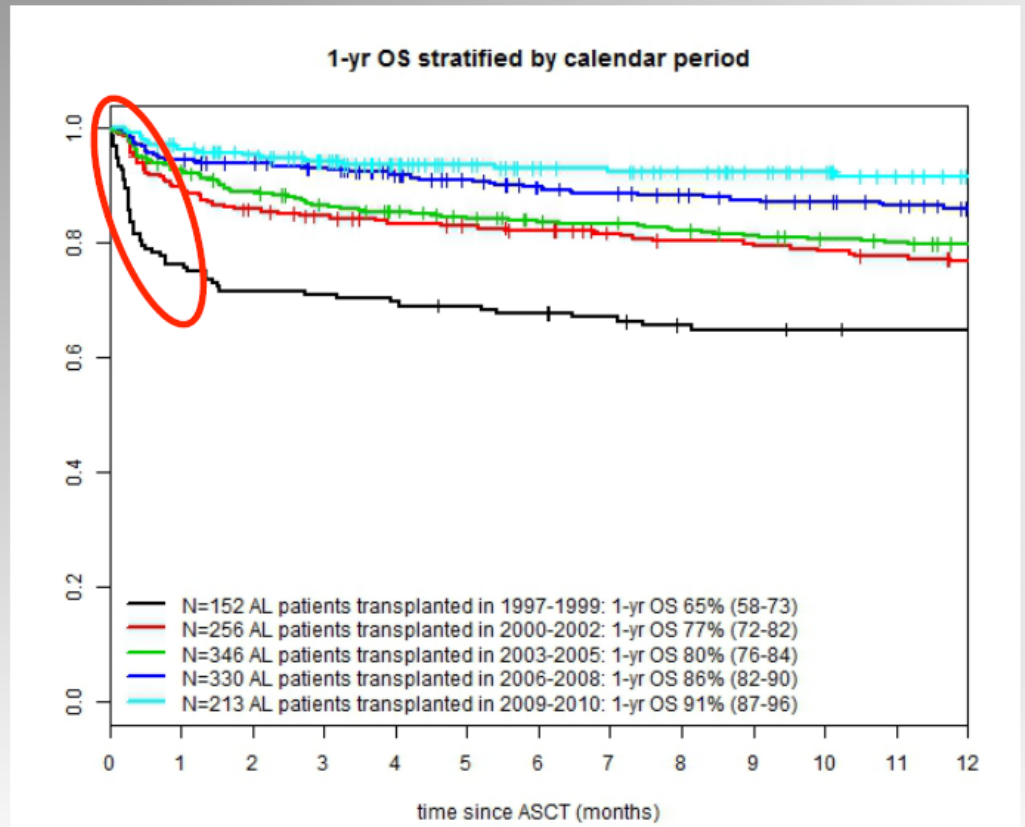
Therapie?

Stammzelltherapie

Autologous Stem Cell Transplantation in Amyloidosis

between 1997 and 2010 Schönland et al, EBMT 2014

N=1315 patients from 259 centers and 29 countries



Wichtige Anmerkungen!

- Röntgenkontrastmittel nur mit strengster Indikation und begleitenden Maßnahmen (Wässerung, Acetylcystein), Absprache

- CAVE: NSAR!

- CAVE: Amyloidose Red Flags! (NT-Pro-BNP > 332 ng/l, U-Albumin > 500 mg/24h)

- Bei Nachweis einer Osteoporose – Basistherapie:
  2 x jährlich Zoledronsäure oder Denosumab, Calcium, Vitamin D3

Danke für Ihre Aufmerksamkeit!

Danke für Ihre Aufmerksamkeit!