Neue Entwicklungen bei der Behandlung des Morbus Sanfilippo (MPS Typ III)

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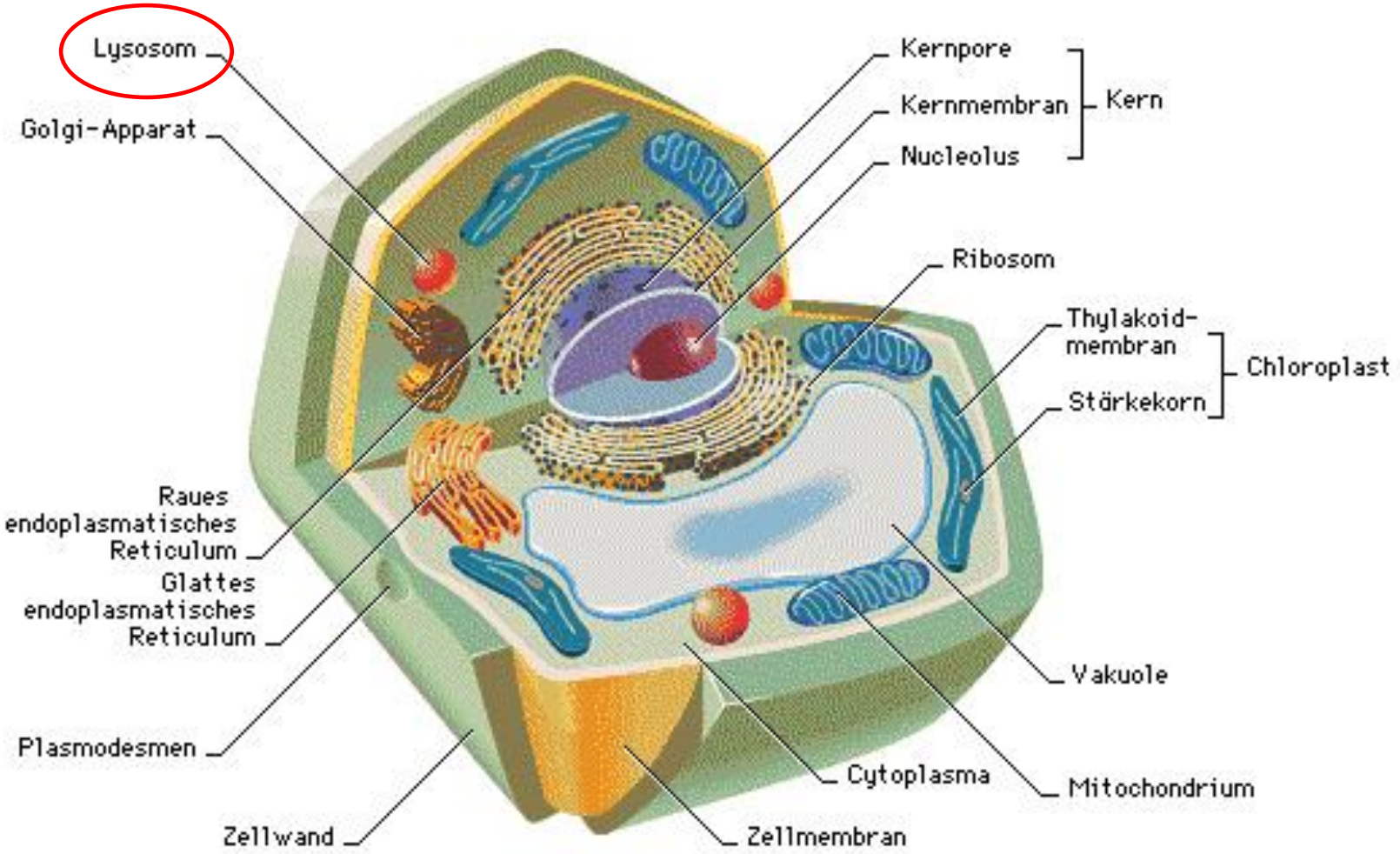
Universitätsmedizin Mainz
Abteilung Lysosomale Speicherkrankheiten
Villa Metabolica

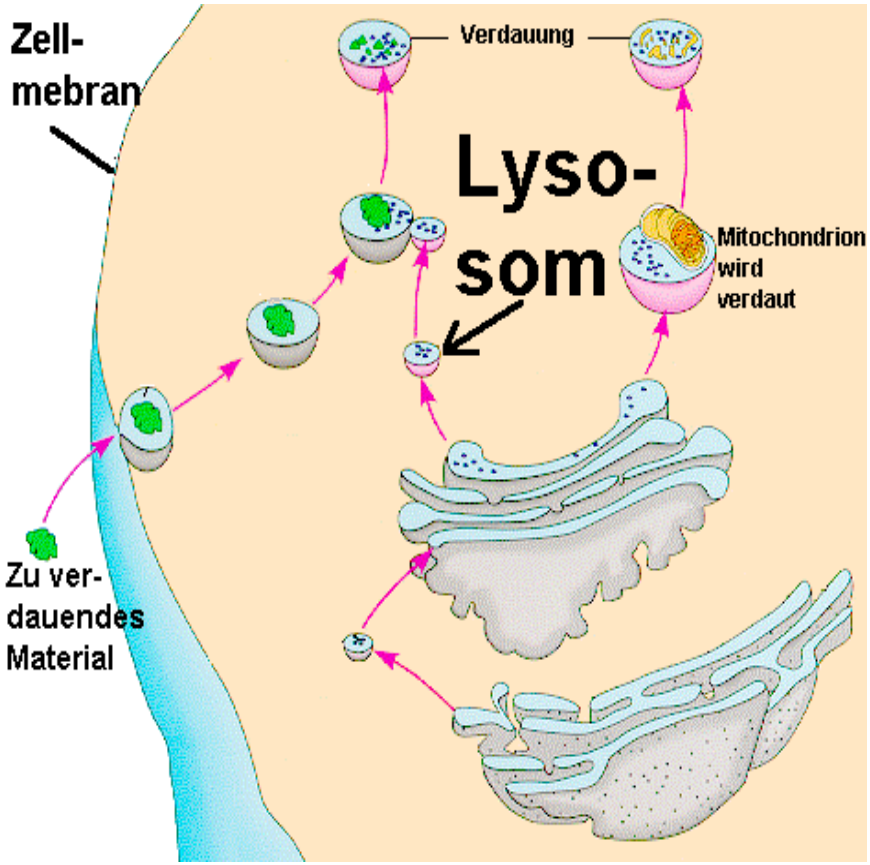
Samstag, den 4.10.2014

1992: First Hungarian MPS Family Meeting

Aufbau der Zelle



Entstehung lysosomaler Speicherkrankheiten



- Defekt eines Enzyms / Membran / Ko-Faktor / Aktivator
- Speichermaterial sammelt sich an
- Funktionsstörung der Zelle
- Funktionsstörung von Organen

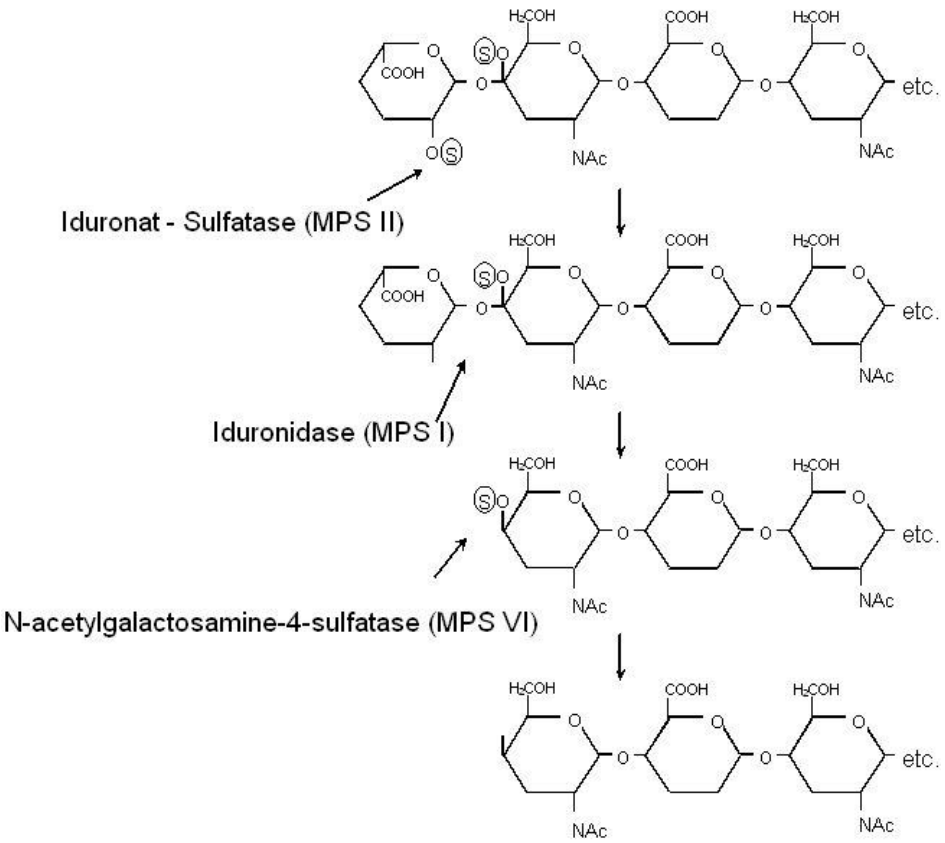
Inzidenz

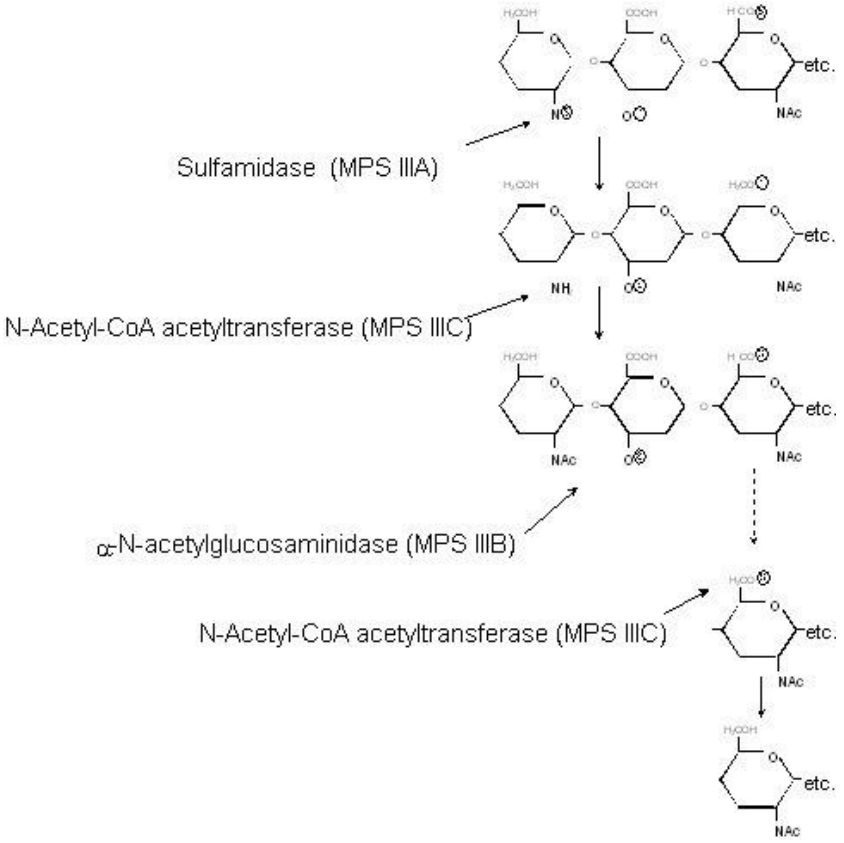
- Ungefähr 60 lysosomale Speicherkrankheiten
- Einzelne Krankheiten sehr selten: 1:40 000 (M. Gaucher) bis 1:200 000 (Morbus Morquio, MPS IV)
- Häufigkeit aller lysosomalen Speicherkrankheiten zusammen ≈ 1 auf 7000
- Hohe Inzidenz in einzelnen Populationen
  M. Gaucher: Jüdische Bevölkerung

MUKOPOLYSACCHARIDOSEN

Glykosaminoglykane = Mukopolysaccharide

- Zuckersäure (Iduron- oder Glukuron-Säure) +
- N-Azetylglukosamin oder N-Azetylgalaktosamin +
- Sulfat



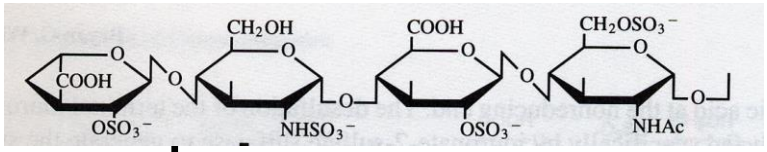


Glykosaminoglykane

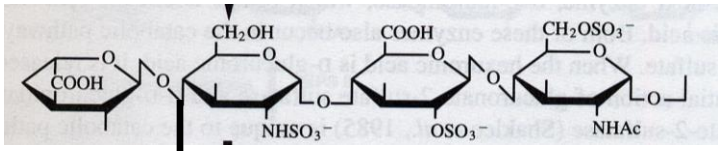
GLYKOSAMINOGLYKAN	VORKOMMEN
Chondroitin-Sulfat	Knorpel, Auge
Dermatan-Sulfat	Haut, Herzklappen
Heparan-Sulfat	Zell-Membranen, Gehirn
Keratan-Sulfat	Knorpel, Auge

Abbau von Heparansulfat

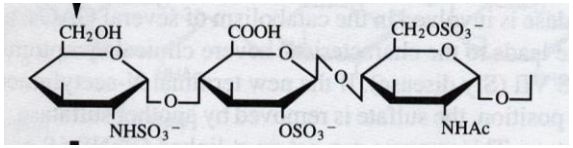
(Defekt bei M. Sanfilippo, MPS III)



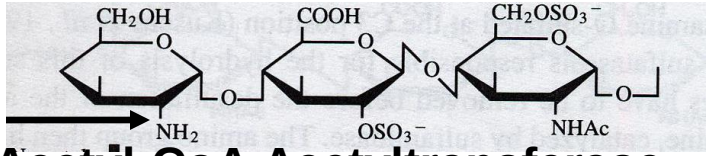
Iduronatsulfatase: MPS-II



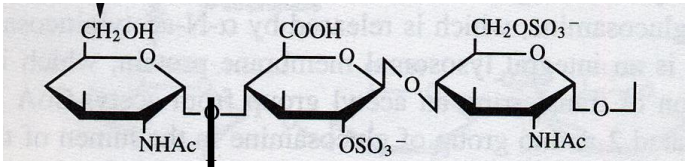
α-L-Iduronidase: MPS-I



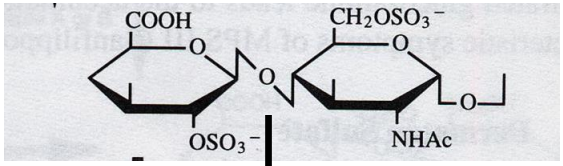
Heparan N-Sulfatase: MPS III-A



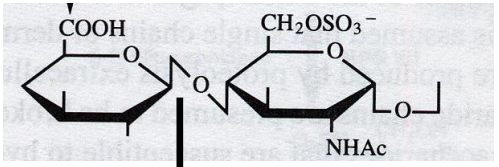
Acetyl-CoA Acetyltransferase: MPS III-C



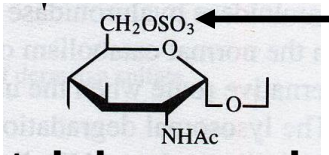
α-N-Acetylglucosaminidase: MPS III-B



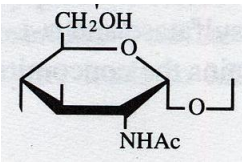
Glucuronat-Sulfatase



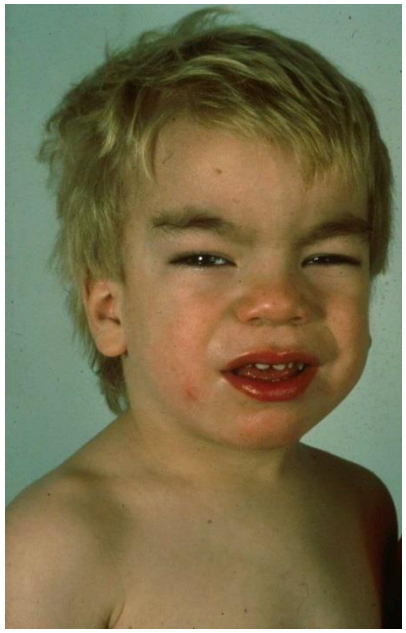
β-Glucuronidase: MPS VII

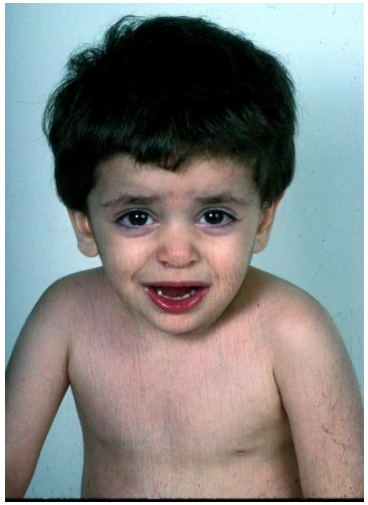


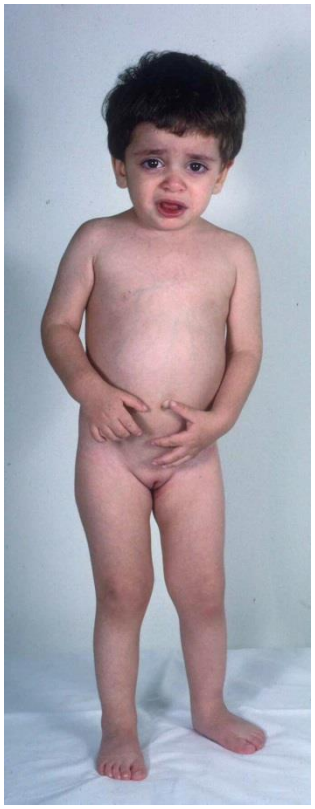
N-acetylglucosamin 6-Sulfatase: MPS III D

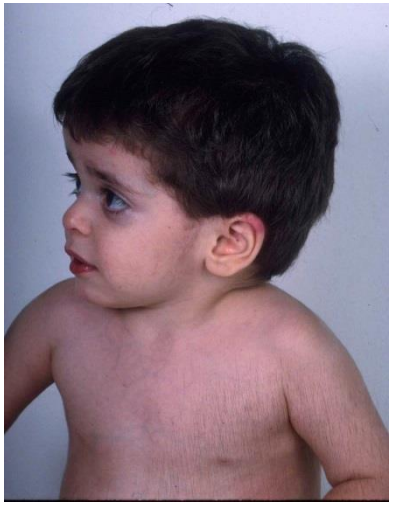


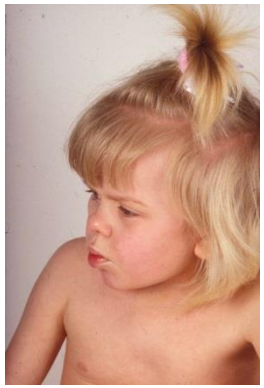
Mukopolysaccharidose Typ III (M. Sanfilippo)

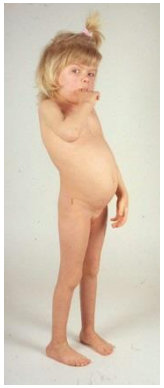


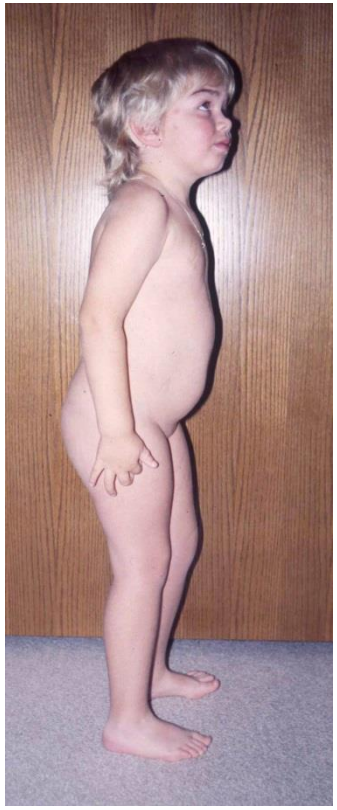


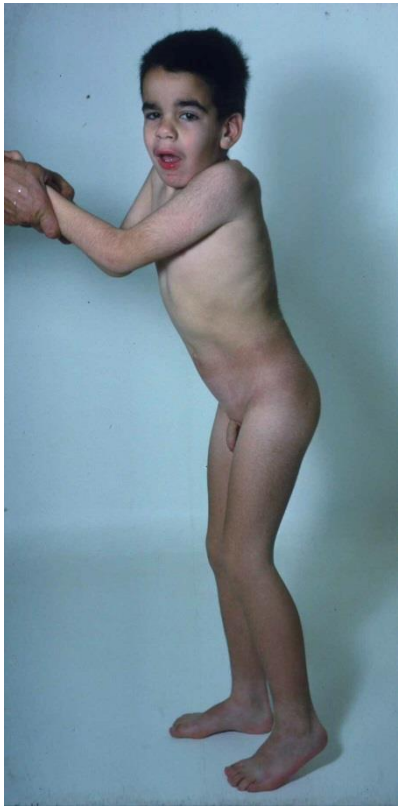


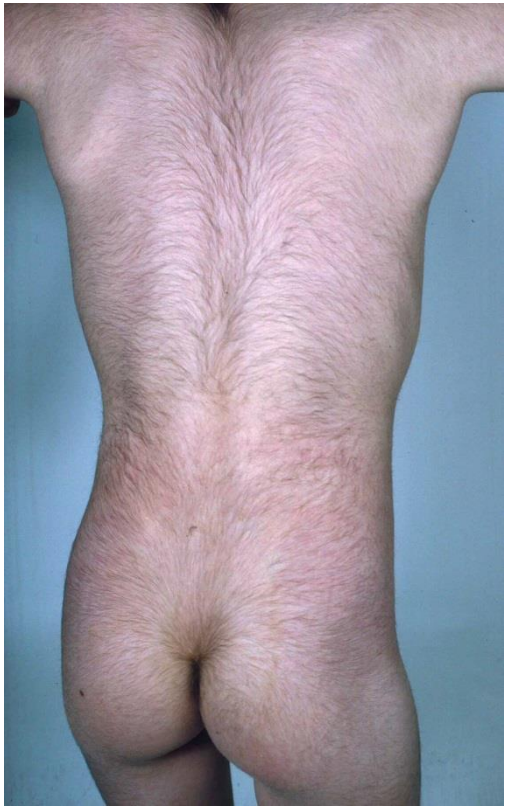


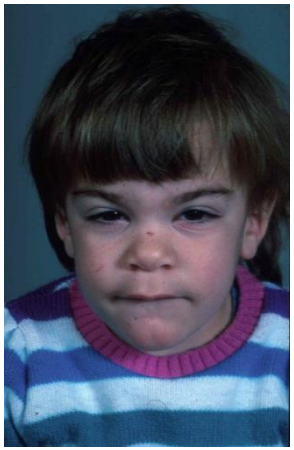












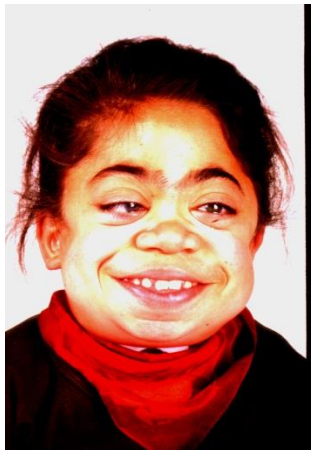
THERAPEUTISCHE MÖGLICHKEITEN

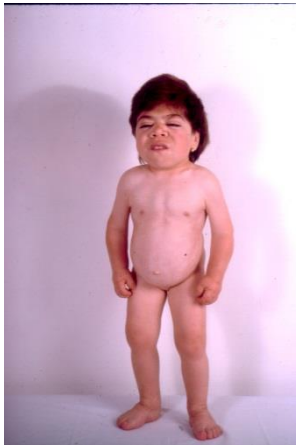
A) ENZYMERSATZ-THERAPIE

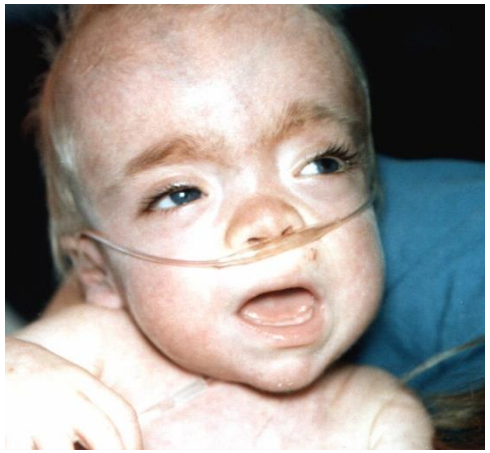
Enzymersatz-Therapie

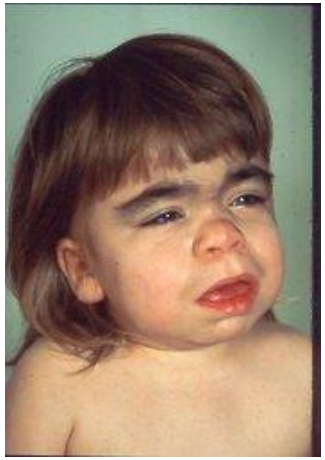
Was können wir erwarten ?

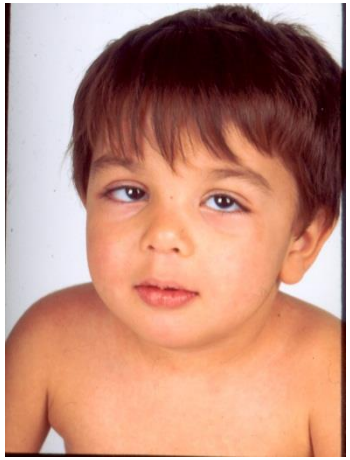
I. Reduktion des Speichermaterials: Zum Beispiel Mukopolysaccharidosen





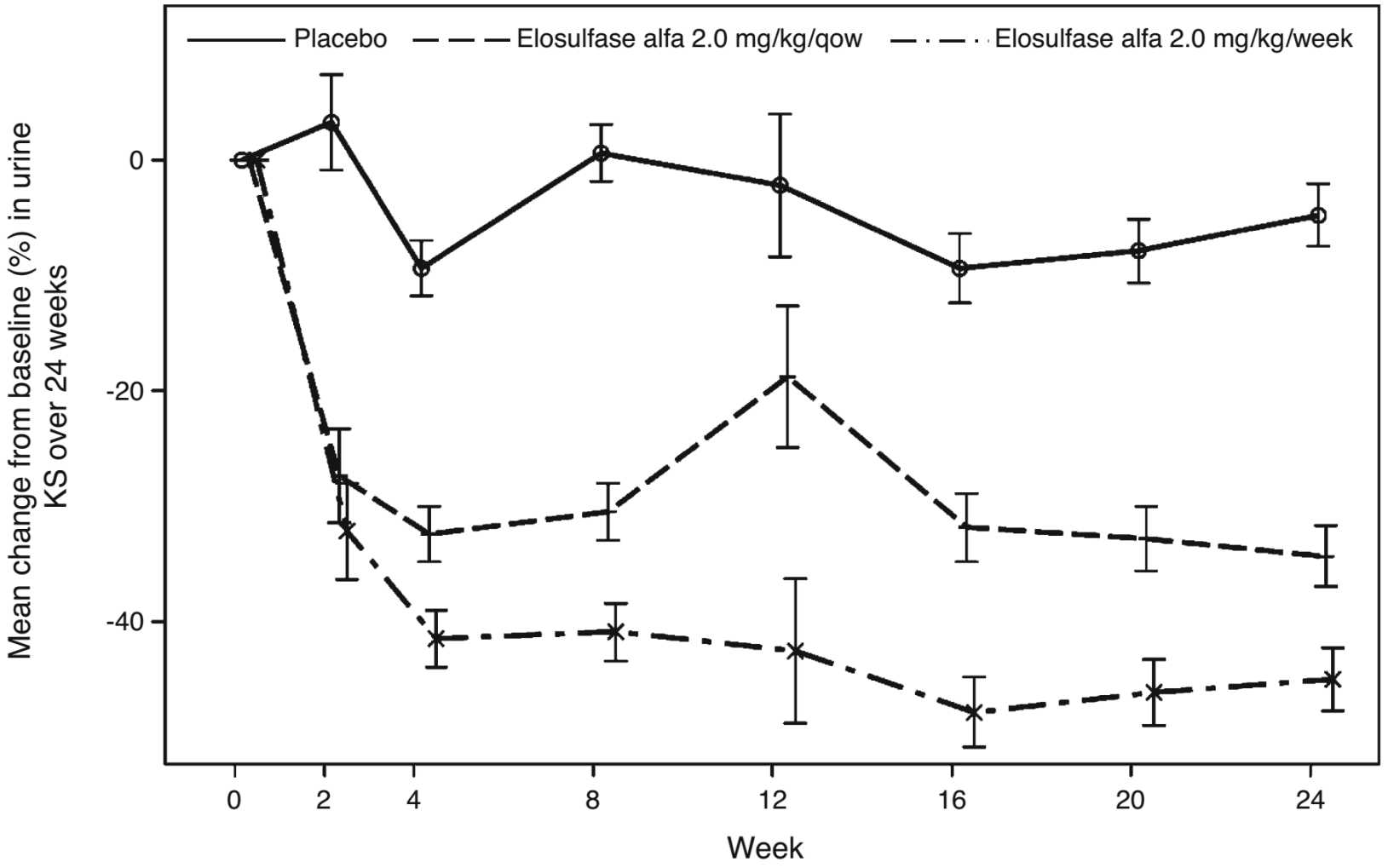






MPS – Ausscheidung

M. Morquio A (MPS IVA)



Hendriksz, CJ et al. J Inherit Metab Dis (2014)

II: Reduktion der Organvergrößerung

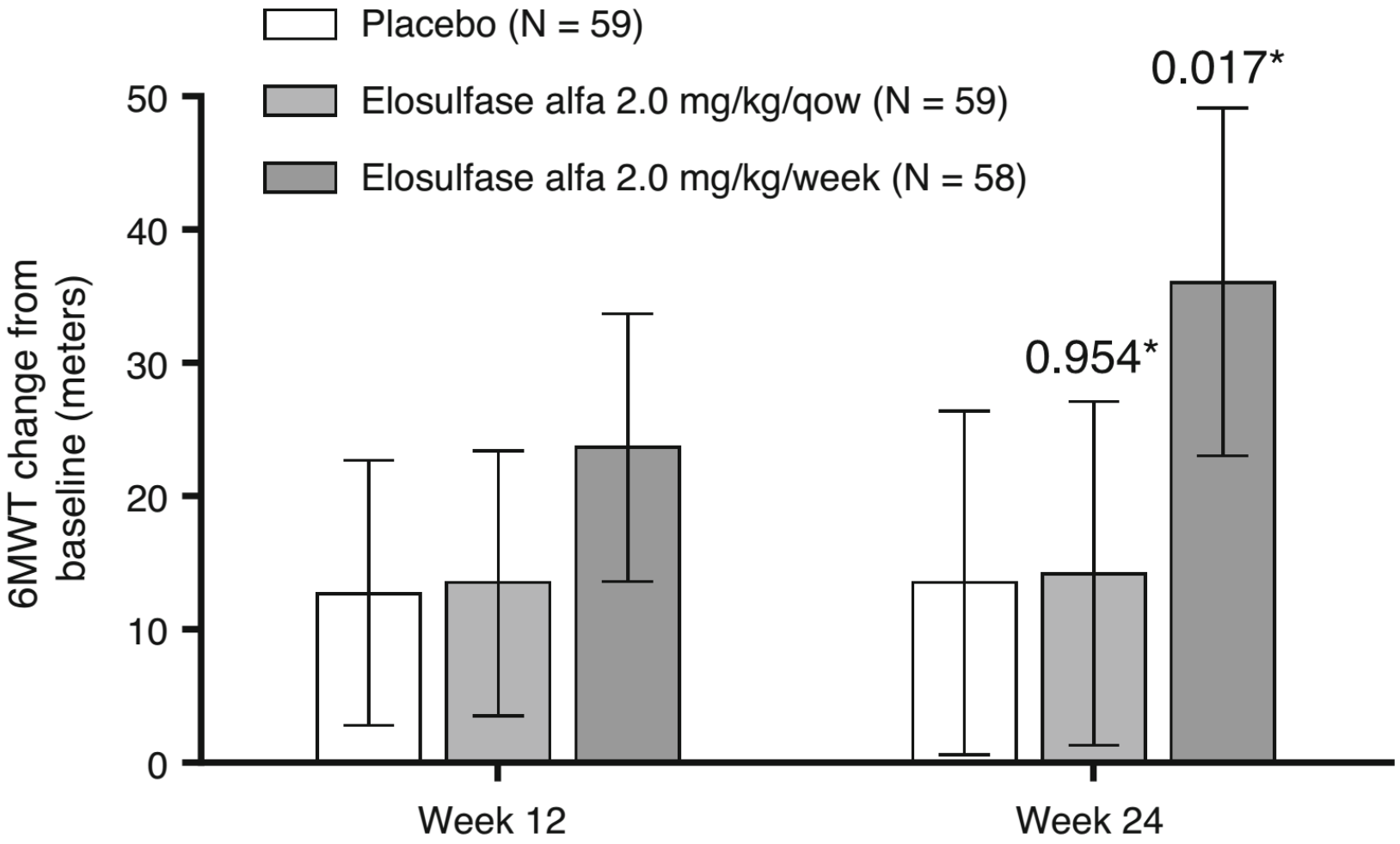
MPS I: Lebergröße

	Baseline (ml)	Woche 26 (ml)	Δ	Differenz Plazebo	P
Aldurazyme (n=22)	1212.2 ± 283.36	979.8 ± 321.45	-18.9 ± 19.44		
				- 20.0	0.001
Plazebo (n-23)	1368.1 ± 314.88	1366.5 ± 316.94	1.3 ± 19.22		

Wraith JE et al. (2004) J Pediatr;144:581

III: Verbesserung der Funktion

MPS IVA: 6-Minuten Gehtest

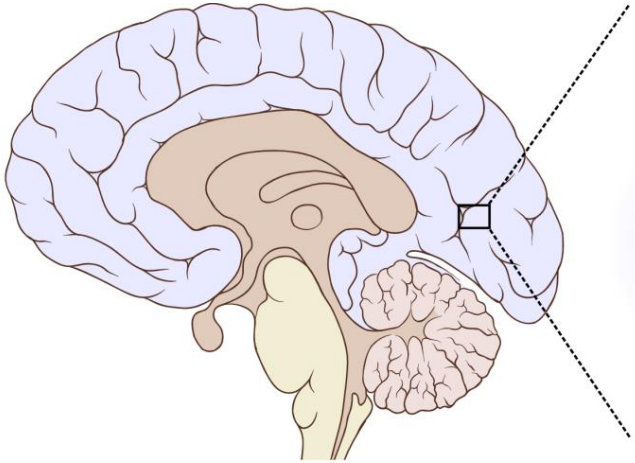


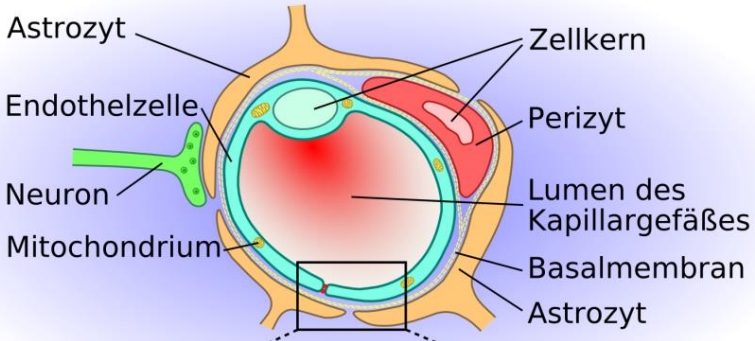
Hendriksz, CJ et al. J Inherit Metab Dis (2014)

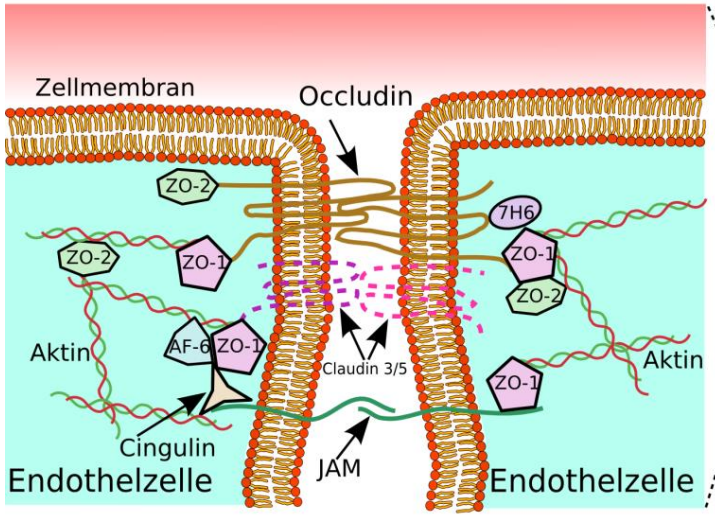
Grenzen der Enzymersatz-Therapie

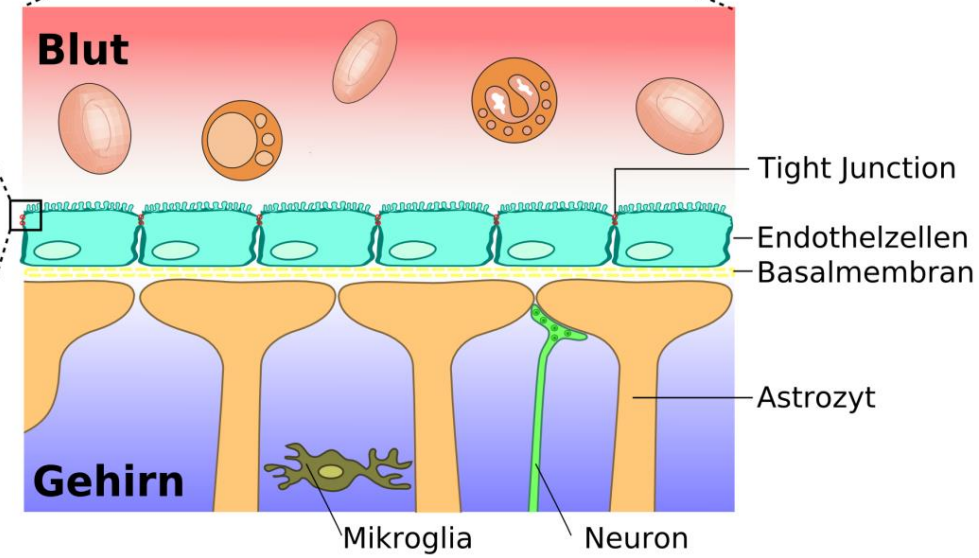
- Skelett-Deformitäten bestehen bereits in der frühen Kindheit
- Geringe Blutperfusion in den Gelenken
- **Bluthirnschranke**

Bluthirnschranke









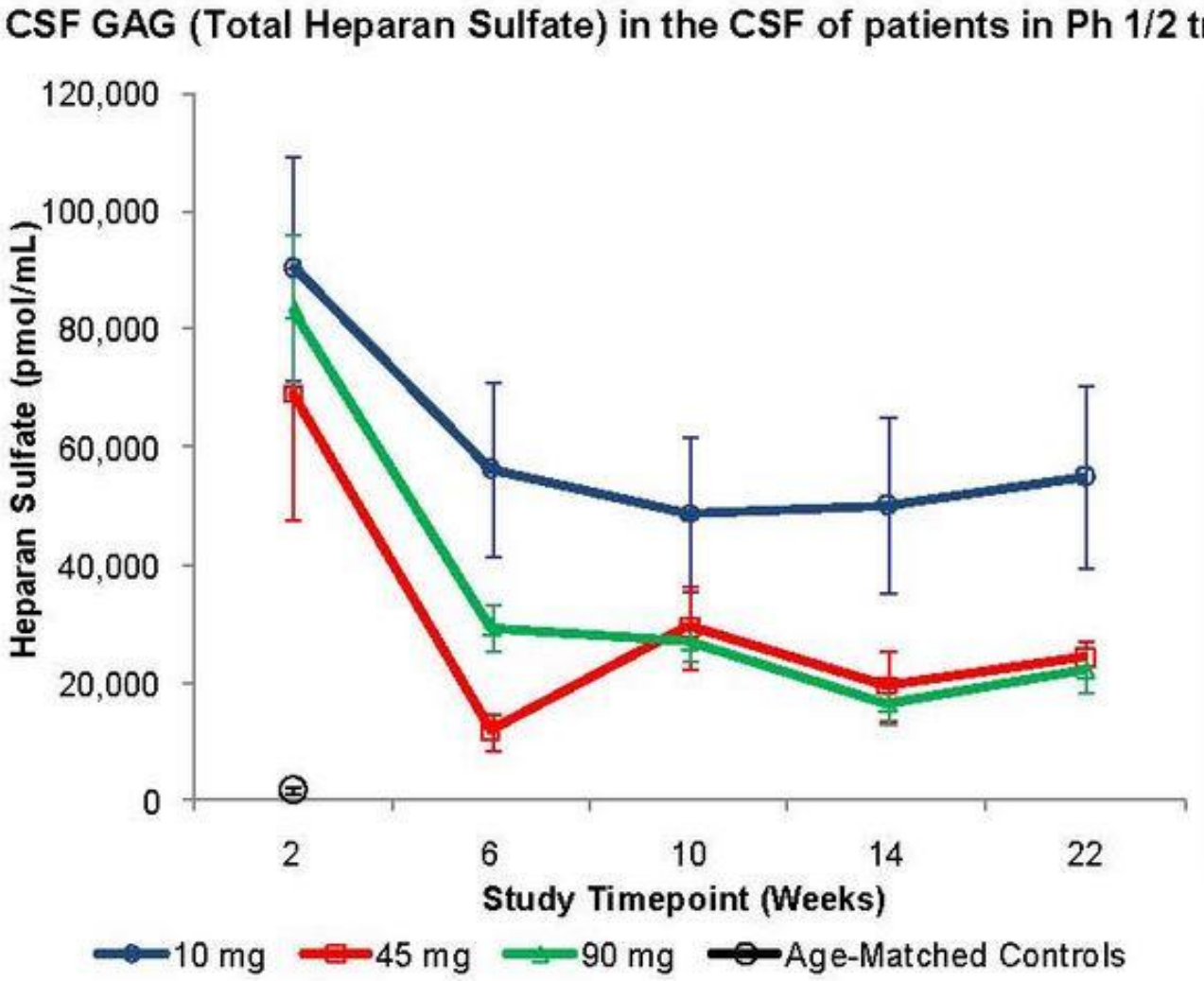
Wie können die Grenzen der Enzymersatz-Therapie überwunden werden ?

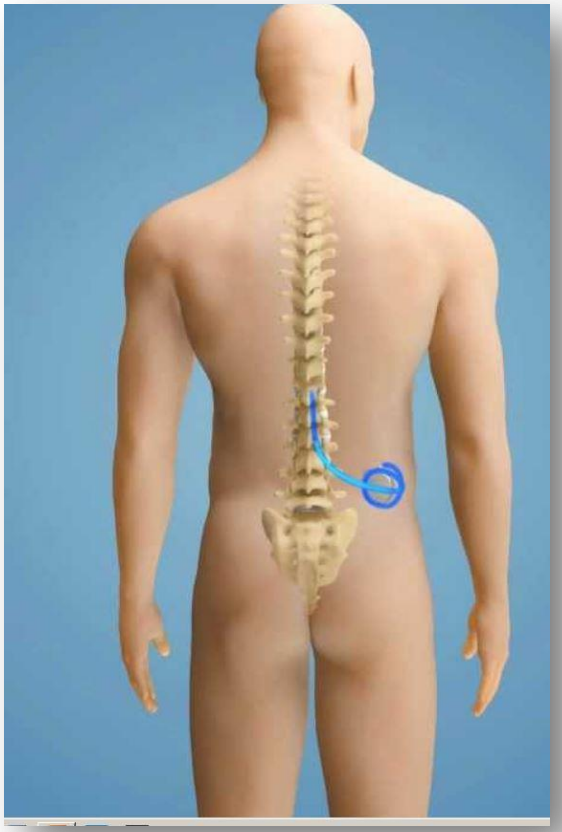
Intrathekale Applikation

(MPS I, MPS II, MPS IIIA, MPS VI)

HGT1410 Sanfilippo A Phase 1/2 Studie

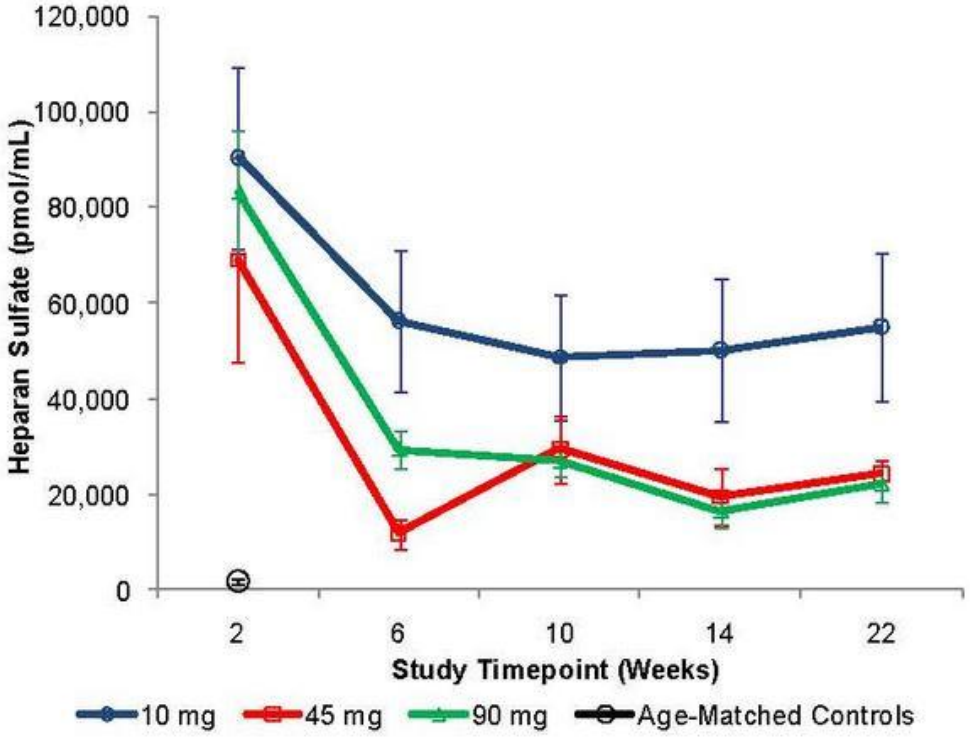
12 Patienten (> 3 Jahre), kein Effekt auf die geistige Entwicklung





HGT1410 – Sanfilippo A Phase 1/2 trial top line data

CSF GAG (Total Heparan Sulfate) in the CSF of patients in Ph 1/2 trial

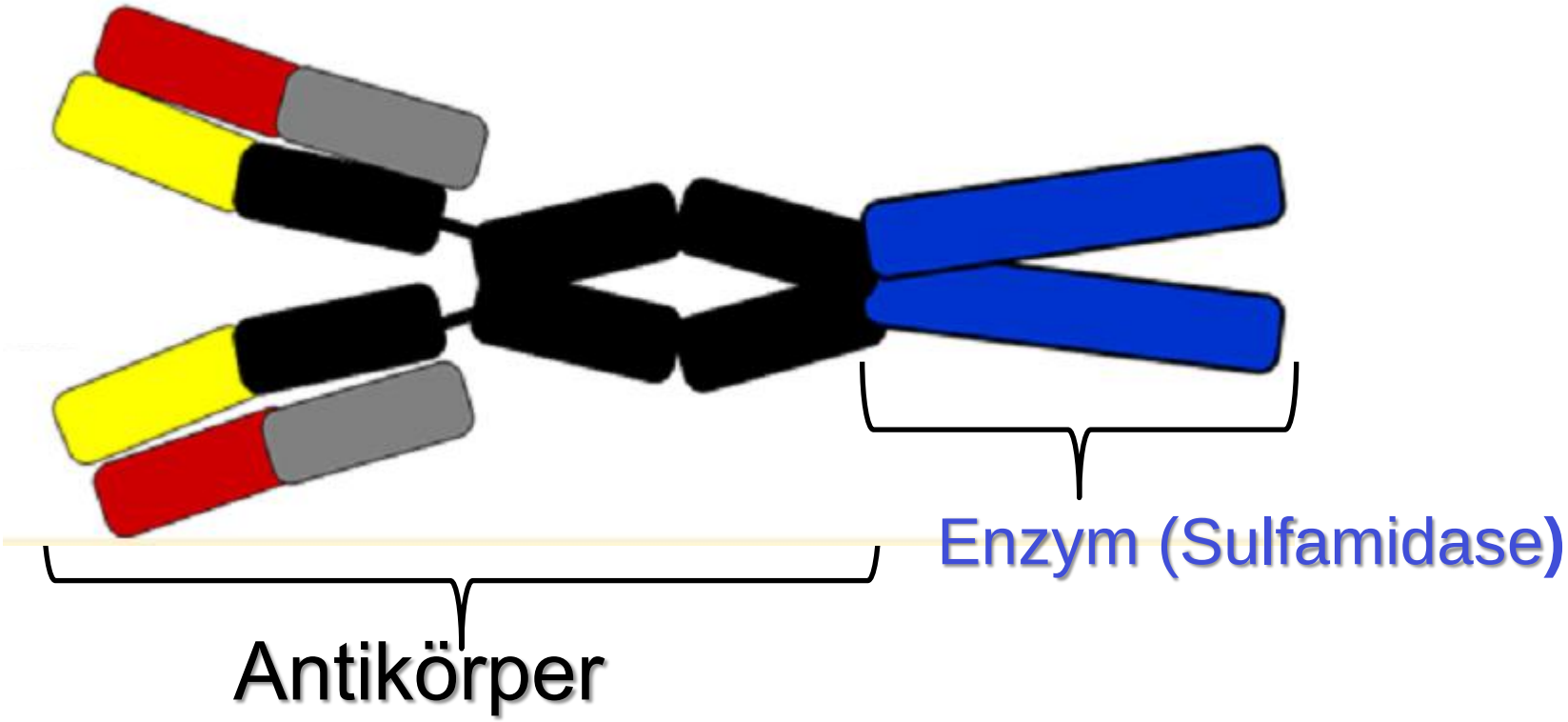


Trial design

- Multicenter, multiple dose, dose escalation study
- Evaluating safety and tolerability of 10, 45 or 90mg of HGT1410 administered monthly for 6 months
- Primary endpoints were safety & tolerability, exploratory endpoints included measures of cognition

- HGT1410 appears well tolerated at all 3 doses studied
- Pronounced, long lasting, dose dependent decline in CSF GAGs(1)
- Full results to be disclosed at ACMG(2) in March
- Aiming to initiate next clinical trial in H2 2013, designed to measure a clinical response
- Extension study ongoing

Überwindung der Blut-Hirnschranke mit Hilfe des Fusions-Proteins



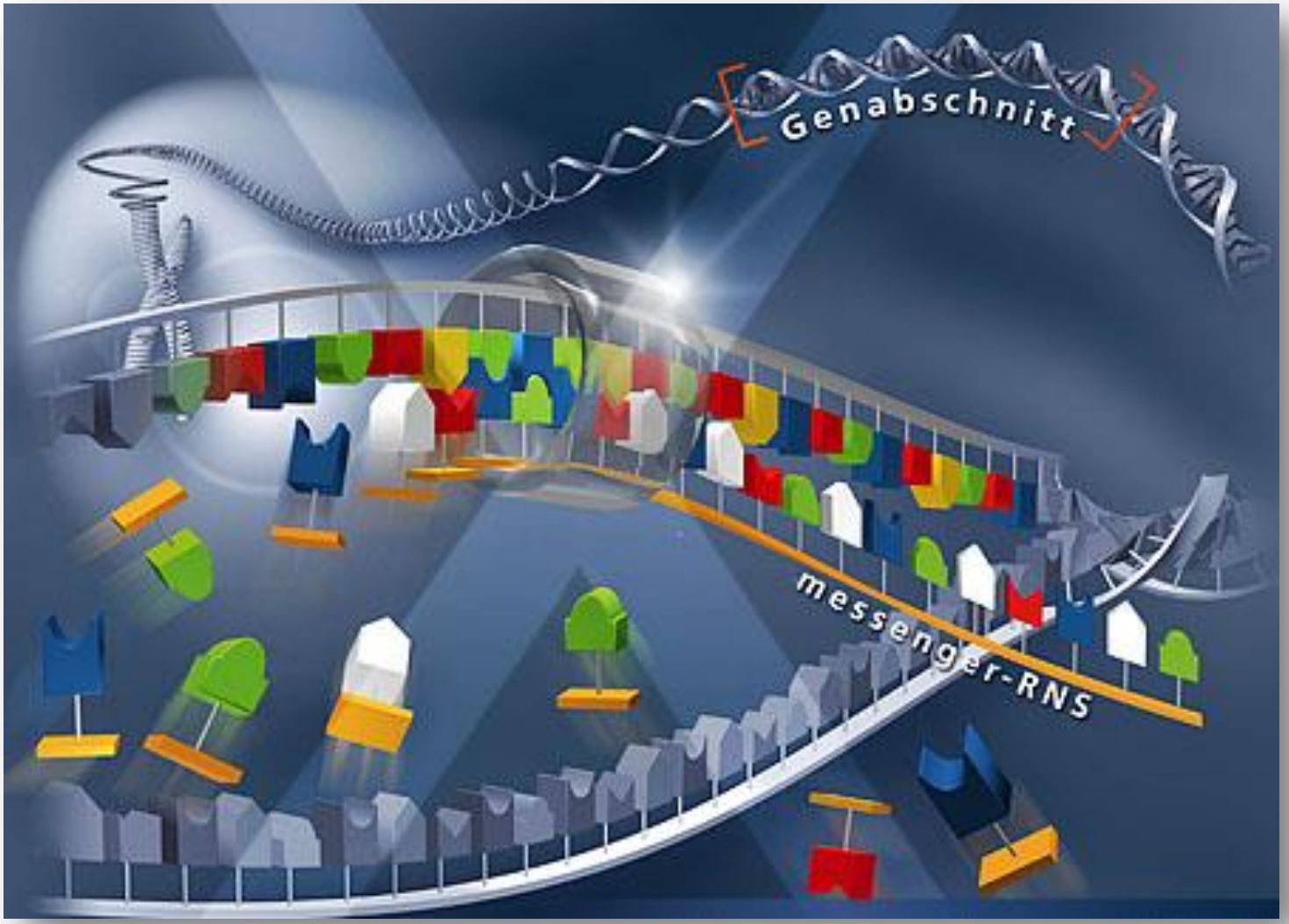
Boado, RJ et al. Mol Pharm (2014) 11: 2928

Überwindung der Blut-Hirnschranke (Rhesus – Affe)

ORGAN	ENZYM-AUFNAHME (& der Dosis)
Vorderhirn	0,81
Kleinhirn	0,60
Leber	16,2
Lunge	1,1
Herz	0,93
Muskel	0,31

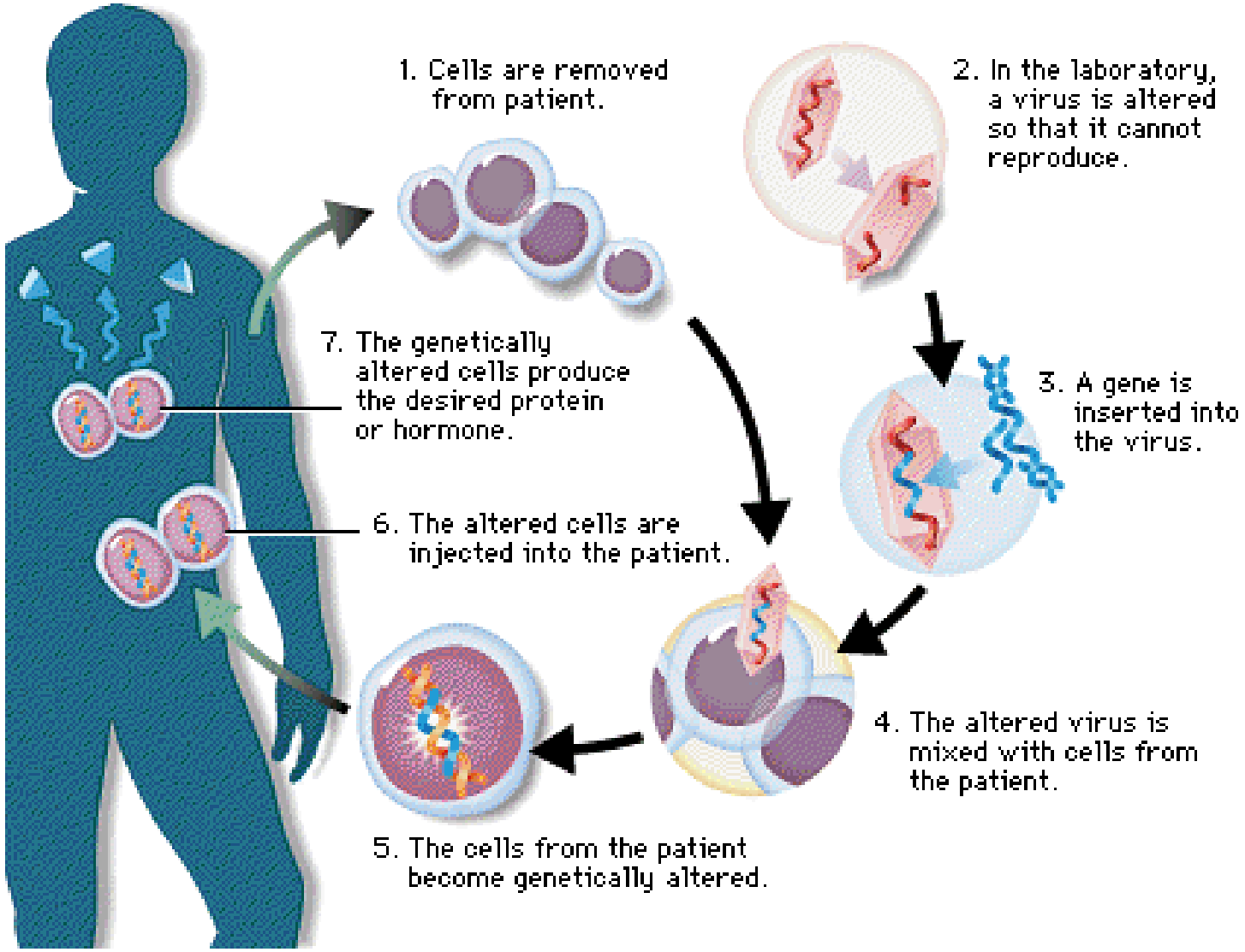
Boado, RJ et al. Mol Pharm (2014) 11: 2928

GEN-THERAPIE

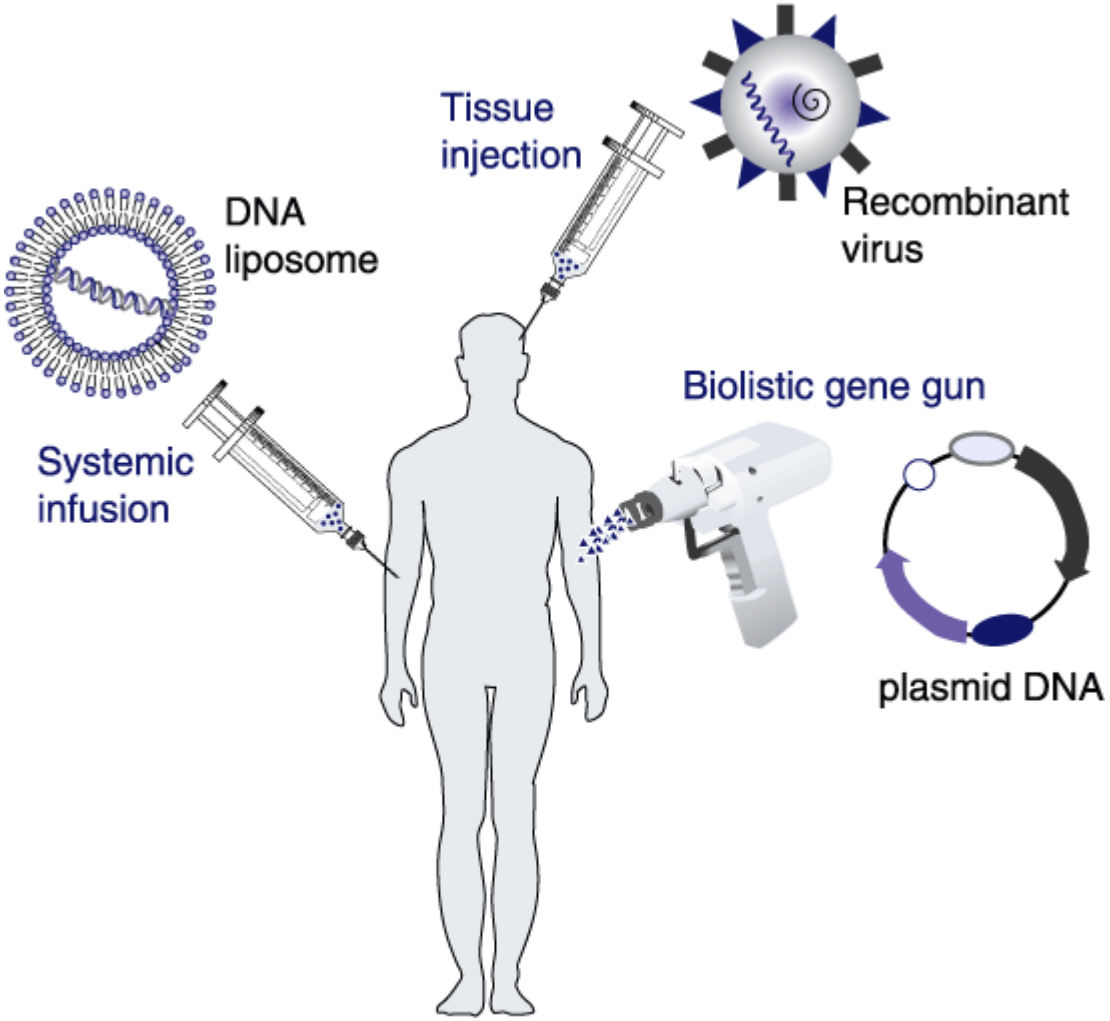


Ex-vivo – Gentherapie

Vorklinische Studien (Manchester)

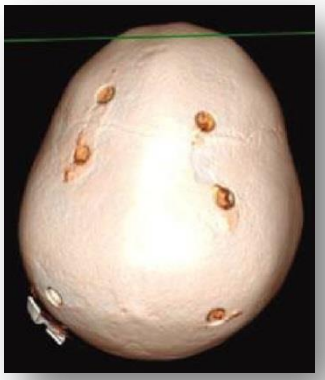


In-vivo - Gentherapie



Klinische Studie:

MPS IIIA (Paris)

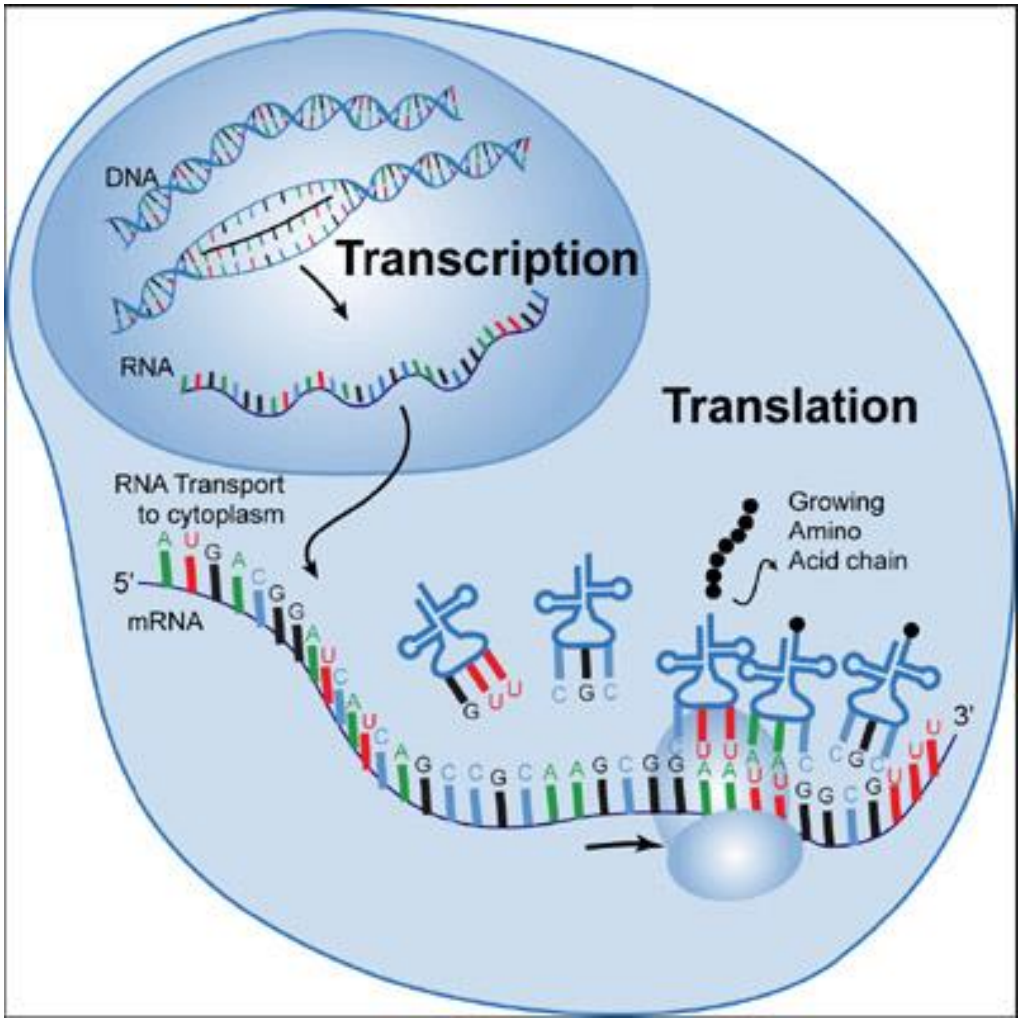


Tardieu, M et al.
Hum Gene Ther (2014) 25: 506

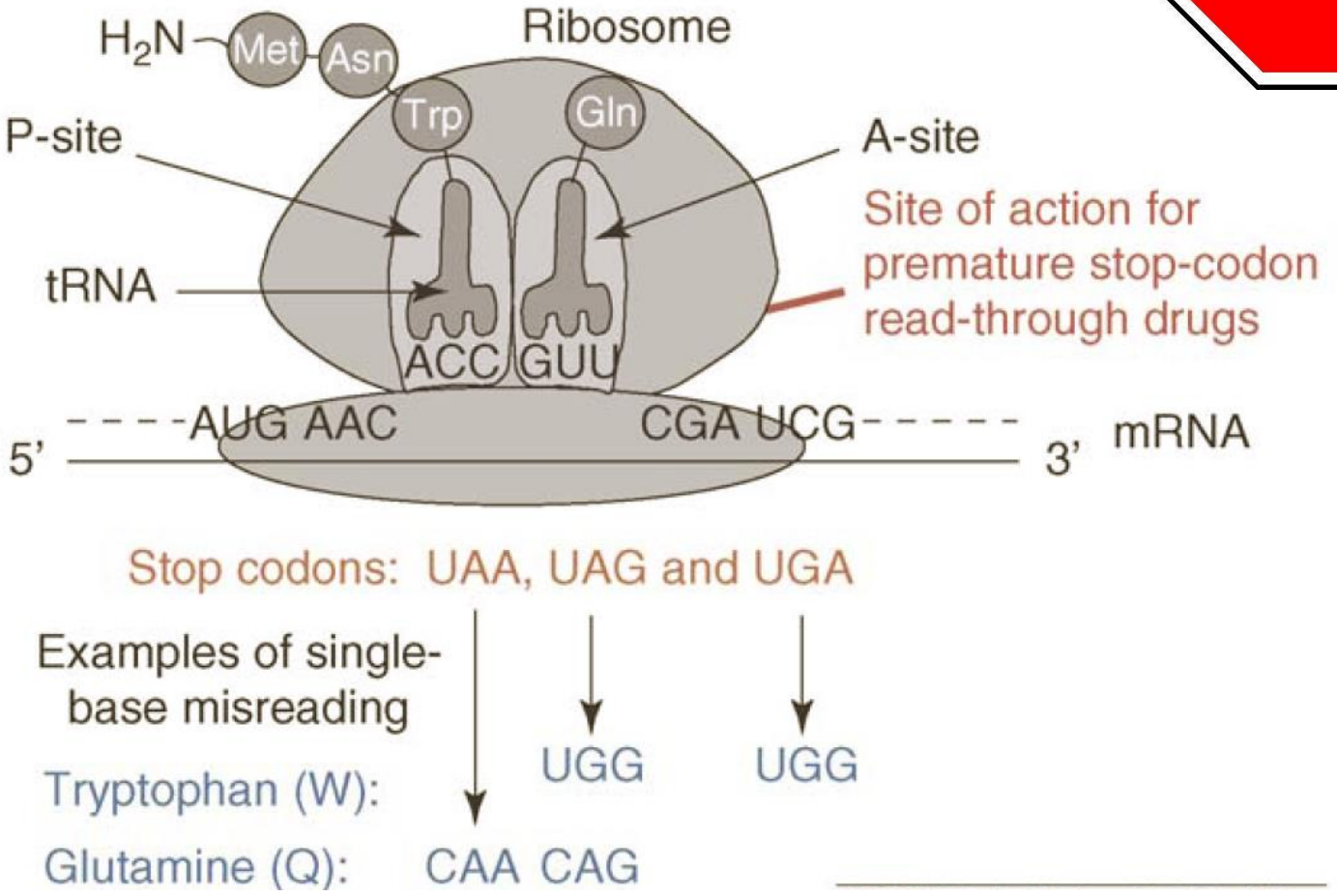
Maus-Modell:

MPS IIIC (Manchester)

Überwindung eines Stop-Codons



Korrektur eines Stop-Codons



Brooks DA (2006) *Trends in Molecular Medicine* **12**: 367

Häufigkeit von Stop-Codon Mutationen bei Mucopolysaccharidosen

MPS I (*IDUA*)	18.3% (17/93)
MPS II (*IDS*)	9.4% (29/309)
MPS IIIA (*SGSH*)	5.9% (4/68)
MPS IIIB (*NAGLU*)	8.7% (9/104)
MPS IVA (*GALNS*)	6.3% (6/96)
MPS VI (*ARSB*)	23.7%[f] (14/59)
MPS VII (*GUSB*)	14.3% (6/42)

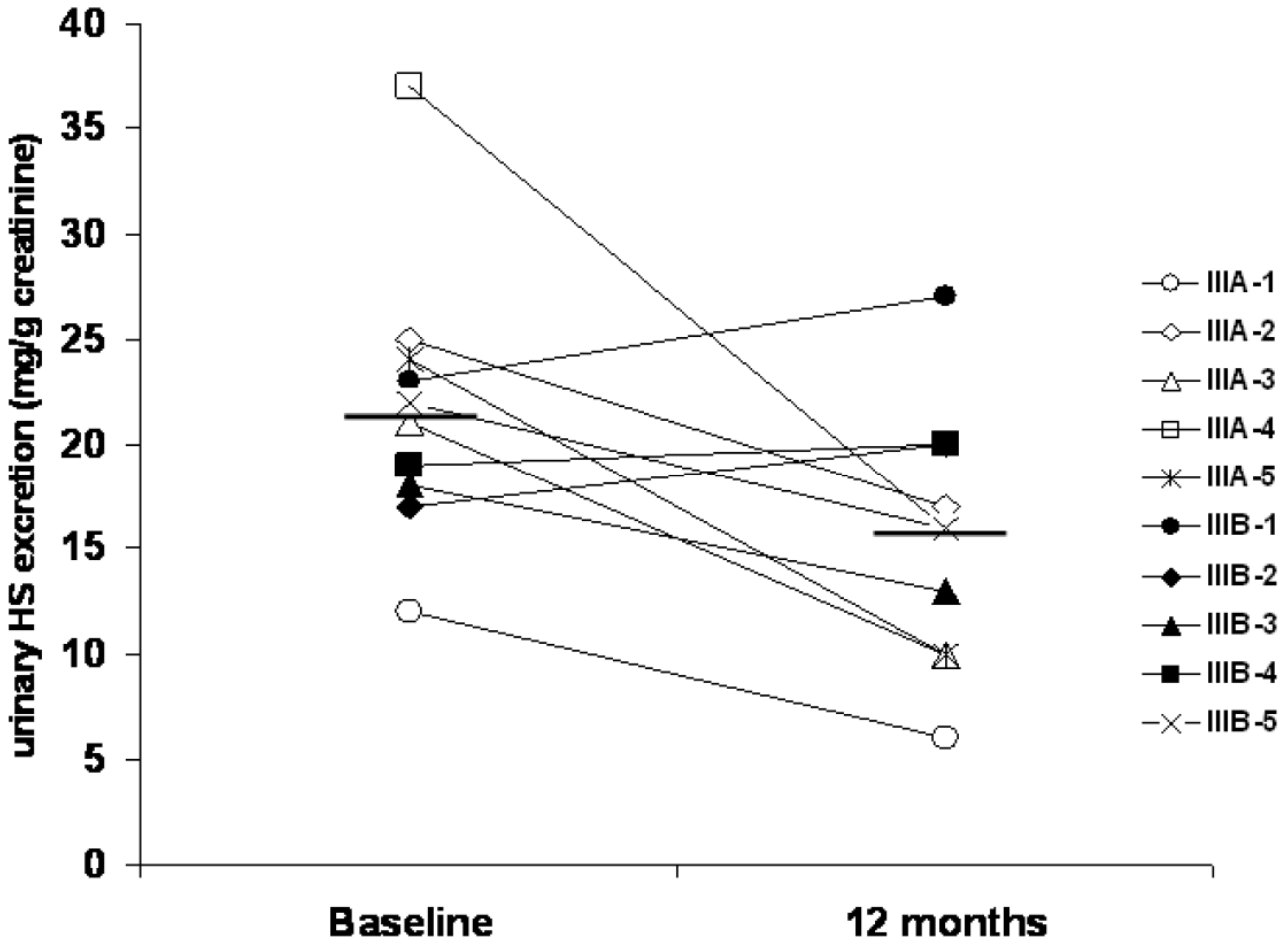
Brooks, DA et al. Trends Mol Med (2006) 12: 367

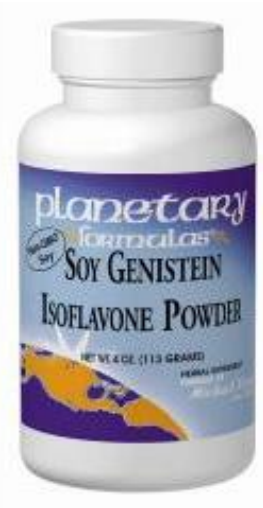
B) ÄNDERUNG DER KONZENTRATION DER SPEICHERSUBSTANZ

Hemmung der MPS- Synthese mit Genistein

- Genistein: Isoflavon aus der Soja-Bohne
- Genistein hemmt die MPS-Synthese

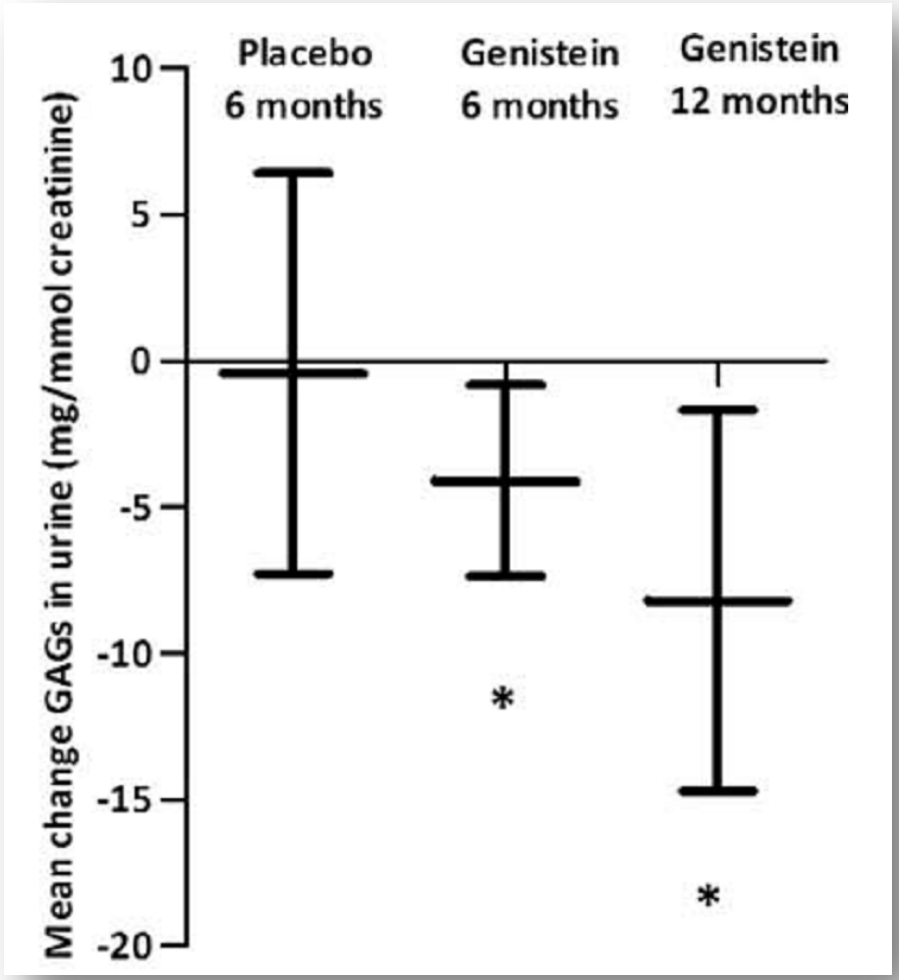
Effekt von Genistein auf die MPS-Ausscheidung





Piotrowska, E., et al., Current Therapeutic Research, 2008. **69**(2):166

MPS-Ausscheidung unter Genistein (30 Sanfilippo-Patienten)



de Ruijter, J et al. Ann Neurol (2012) 71: 110

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TABLE 6: Mean Scores of Behavior Changes Compared to Baseline Scores, Scored with the VOG Questionnaires

	Mean Changes of Behavior Scores: Crossover Study			Mean Changes of Behavior Scores: Extension Study	
Total Score and Subscales	**Placebo (SEM) (used 6 months)**	**Genistein (SEM) (used 6 months)**	***p***	**Genistein (SEM) (used 12 months)**	***p***
TPBS	−5.76 (2.96)	−2.18 (2.26)	0.25	−7.58 (6.11)	0.12
Self-absorbed	−2.80 (1.04)	−1.82 (0.90)	0.13	−3.00 (1.89)	0.07
Disruptive and antisocial	−0.77(1.52)	−0.14 (1.13)	0.49	−1.17 (2.79)	0.34
Communication disturbance	−1.03 (0.62)	−1.25 (0.56)	0.20	−1.42 (1.21)	0.13
Anxiety	−0.14 (0.43)	−0.04 (0.45)	0.28	−1.43 (0.73)	**0.04**
Social relating disturbance	0.13 (0.50)	0.86 (0.55)	0.25	0.92 (0.54)	0.06

Value in bold is p-value <0.05.
SEM = standard error of the mean; TPBS = total behavior problem score; VOG = Questionnaire on Development and Behavior.

de Ruijter, J et al. Ann Neurol (2012) 71: 110

Effekt von Genistein auf die MPS-Ausscheidung ?

Contents lists available at SciVerse ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

High dose genistein aglycone therapy is safe in patients with mucopolysaccharidoses involving the central nervous system

Katherine H. Kim [a,b], Charlotte Dodsworth [a], Andrea Paras [a,b], Barbara K. Burton [a,b,*]

- Patienten: 19 MPS III, 3 MPS II
- 1 Jahr Behandlung
- Dosis: 150 mg/kg/Tag
- Keine Reduktion der MPS-Ausscheidung
- Keine Besserung der kognitiven Funktion

Kim, KH et al. Mol Genet Metab (2013) 109: 382

ZUSAMMENFASSUNG

A) Erhöhung der Enzym-Aktivität

I. Enzym-Ersatz

II. Enzym-Modifizierung

Zielgerichtete Aufnahme durch spezifische Organe (Gehirn, Skelett)

III. Chaperone

IV. Gen-Therapie

V. Gen-Modifizierung („Read-through“)

B) Verminderung der Substrat - Menge

I. Miglustat (M. Gaucher, M. Niemann-Pick Typ C)

II. Genistein (Mukopolysaccharidosen) ?

Klinische Studien

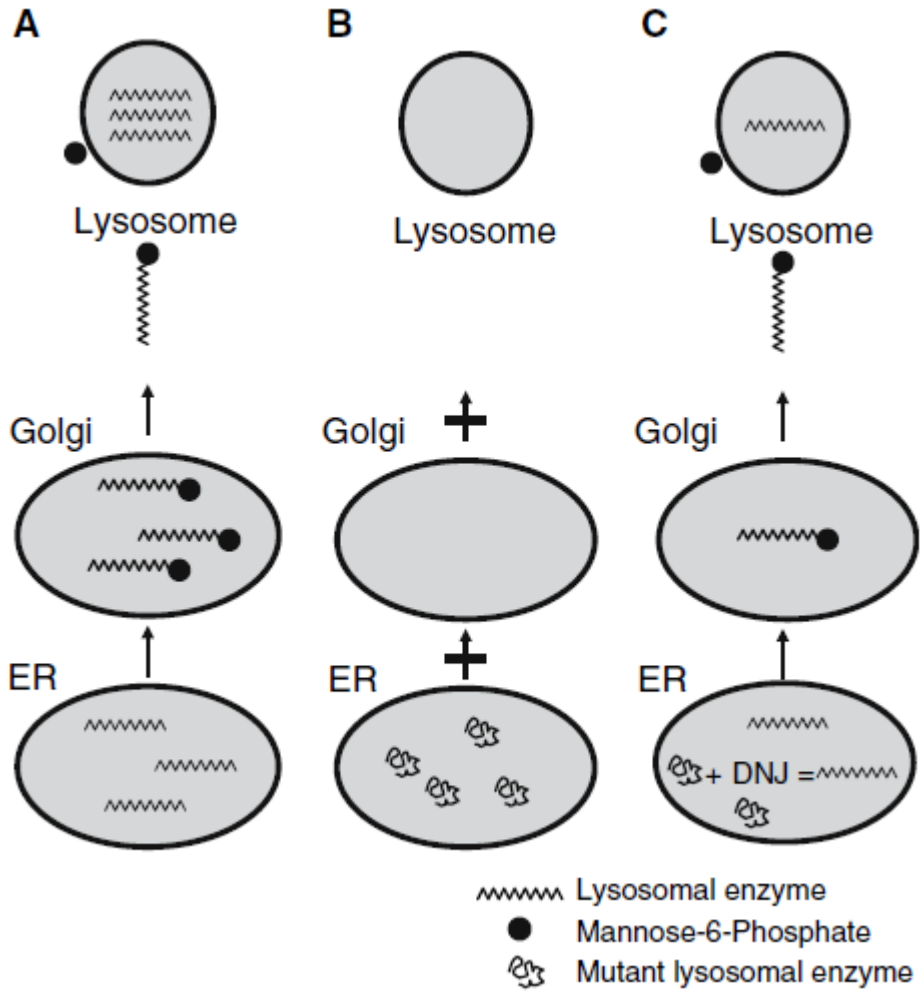
http://clinicaltrials.gov/

Suche nach: Sanfilippo Disease

Welchen Weg werden wir in Zukunft gehen ?

Enzyme Enhancement (Chaperones)

Chemical Chaperones



EXPERT OPINION

1. Introduction
2. Emerging therapeutic approaches
3. Expert opinion

Treatment of mucopolysaccharidosis type III (Sanfilippo syndrome)

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- MPS IIIB
- MPS IIIC ?

Meijer, OL et al. Expert Opinion on Orphan Drugs (2013) 1: 717