A Rare disease: MPS III
San Filippo disease

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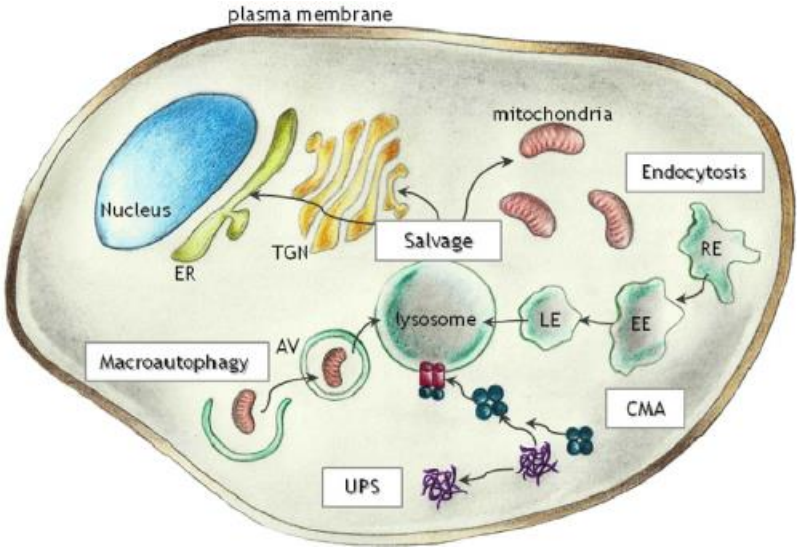
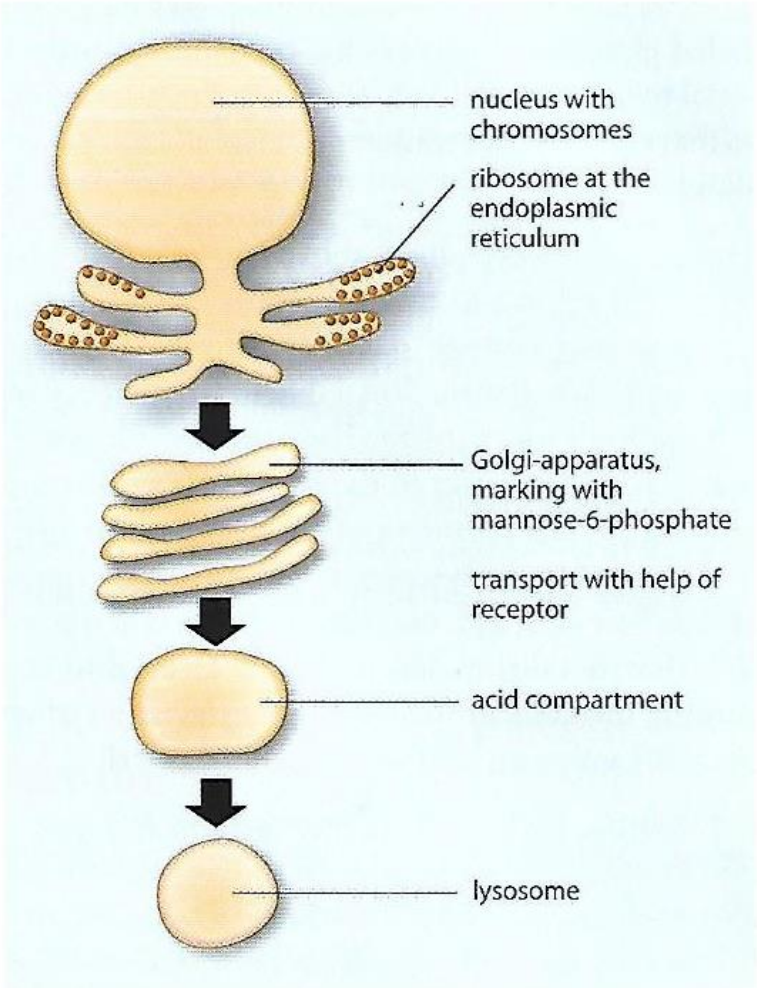
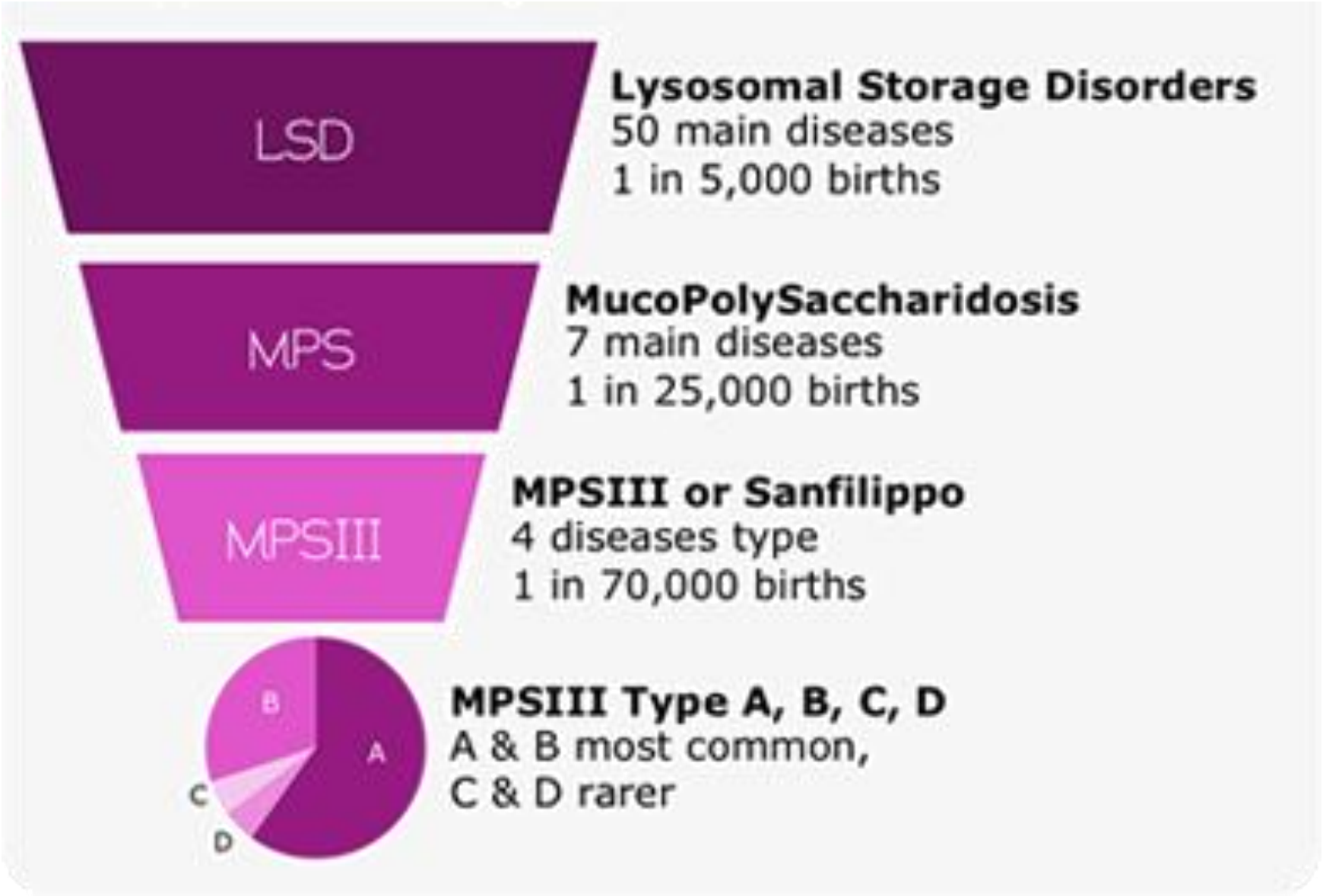
Recognition of rare diseases

- Stop unnecessary testing
- Patient prognosis
- Support group
- Specific early treatment
- Genetic counseling

Lysosomal Storage disease







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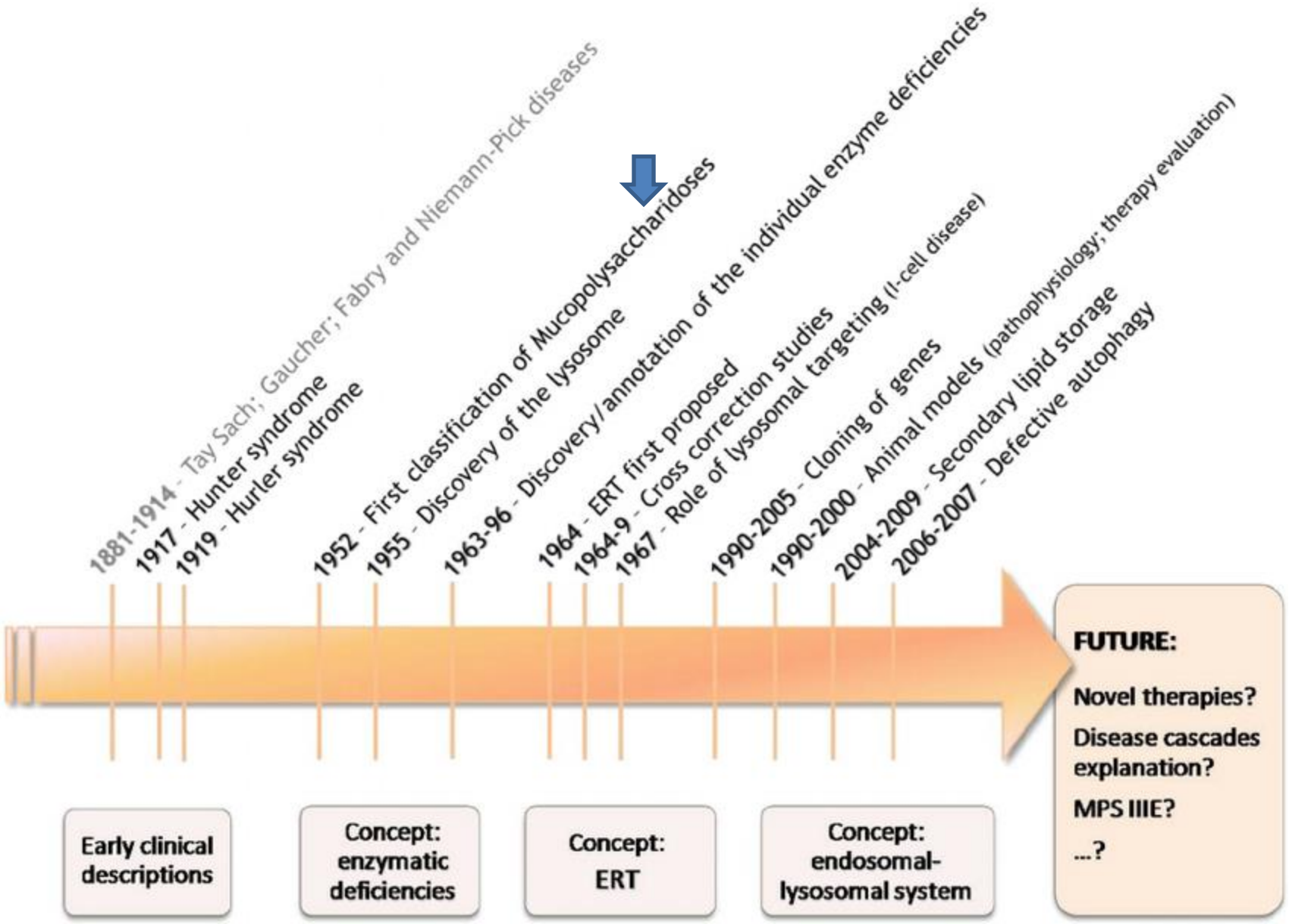
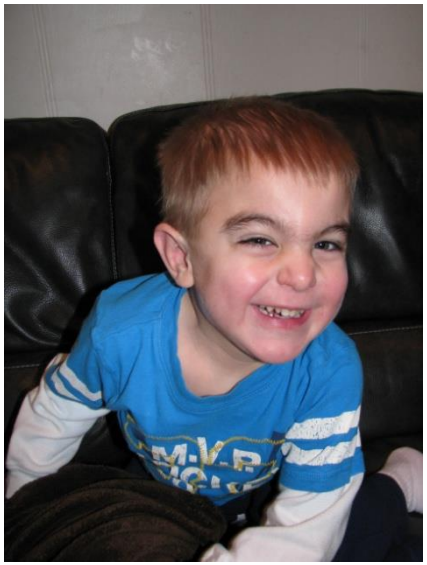

1881-1914 - Tay Sach; Gaucher; Fabry and Niemann-Pick diseases
1917 - Hunter syndrome
1919 - Hurler syndrome
1952 - First classification of Mucopolysaccharidoses
1955 - Discovery of the lysosome
1963-96 - Discovery/annotation of the individual enzyme deficiencies
1964 - ERT first proposed
1964-9 - Cross correction studies
1967 - Role of lysosomal targeting (I-cell disease)
1990-2005 - Cloning of genes
1990-2000 - Animal models (pathophysiology; therapy evaluation)
2004-2009 - Secondary lipid storage
2006-2007 - Defective autophagy
FUTURE:
Novel therapies?
Disease cascades explanation?
MPS IIIE?
...?
Early clinical descriptions
Concept: enzymatic deficiencies
Concept: ERT
Concept: endosomal-lysosomal system

- 1958 Meyer & Hoffmann: mention MPS III (biochemical paper)
- 1963: Sylvester Sanfilippo (Clinical description)
- 1971:Hans Kresse Enzyme deficiency MPS III
- 1990: genes identification
- MPS III : Autosomal recessive inheritance

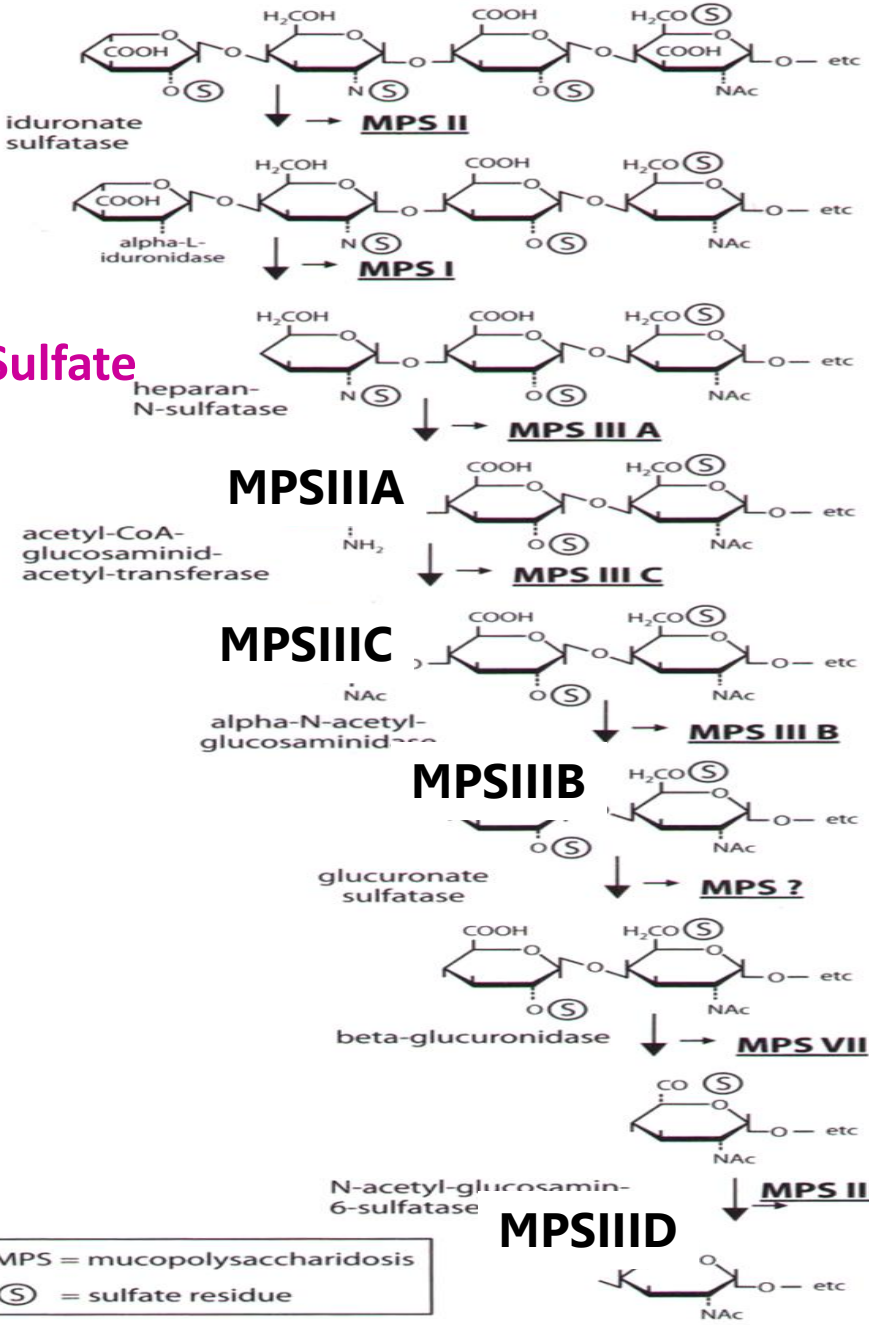

Classification of MPS

MPS Type	Diseases 7	Enzyme Deficiency 11	GAG Affected
MPS I	Hurler Hurler-Scheie Scheie	α-L-iduronidase	DS,HS DS,HS DS,HS
MPS II	Hunter	iduronate sulfatase	DS,HS
MPS III	**Sanfilippo A** **Sanfilippo B** **Sanfilippo C** **Sanfilippo D**	**heparan N-sulfatase** **α-N-acetylglucosaminidase** **acetyl CoA:α-glucosaminide acetyltransferase** **N-acetylglucosamine-6-sulfatase**	**HS** **HS** **HS** **HS**
MPS IV	Morquio A Morquio B	N-acetyl-galactosamine-6-sulfatase β-galactosidase	KS,CS KS
MPS VI	Maroteaux-Lamy	N-acetylgalactosamine-4-sulfatase (arylsulfatase B or ASB)	DS
MPS VII	Sly	β-glucuronidase	DS,HS,CS
MPS IX	Hyaluronidase Def.	Hyaluronoglucosaminindase-1	HA

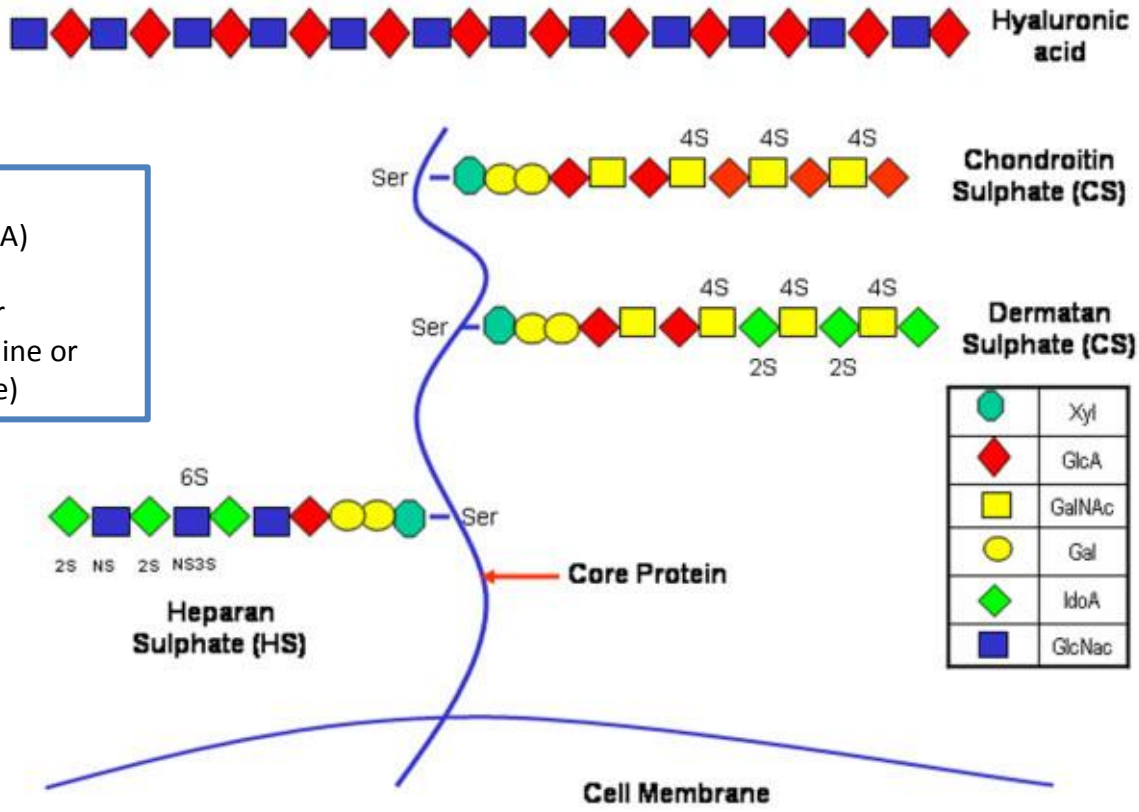
DS = dermatan sulfate, HS = heparan sulfate, CS = chondroitin sulfate, KS = keratan sulfate, HA = Hyaluronan

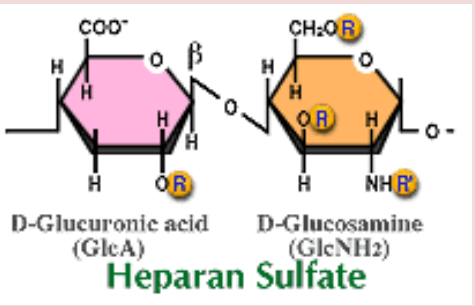


Heparan Sulfate

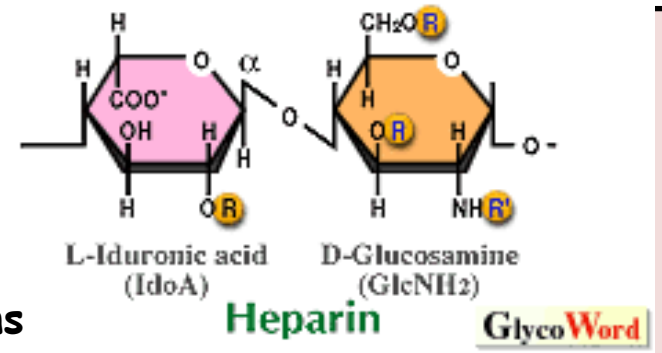


Mucopolysaccharides = Glycosaminoglycans (GAGs) are polysaccharide chains





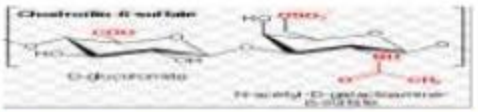
Glucosaminoglycans

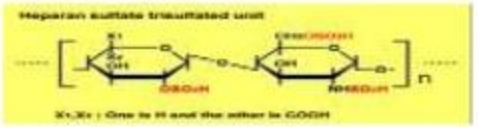


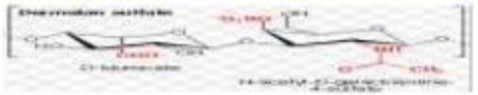
Glycosaminoglycans(GAGs)

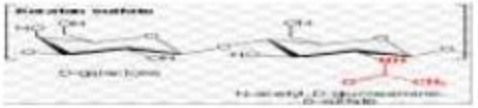
The major GAGs are:

1. Chondroitin -4- sulfate
2. Chondroitin -6- sulfate
3. Heparan sulfate
4. Dermatan sulfate
5. Keratan sulfate
6. Hyaluronan



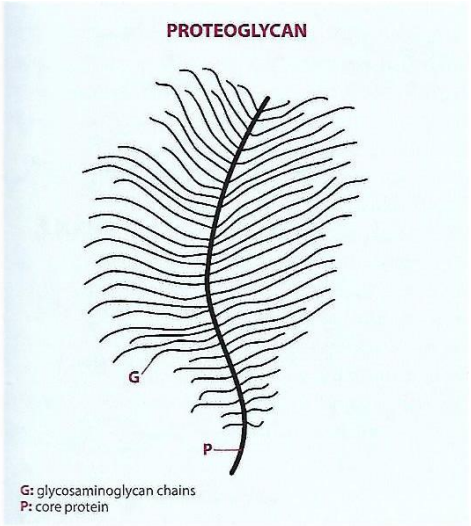


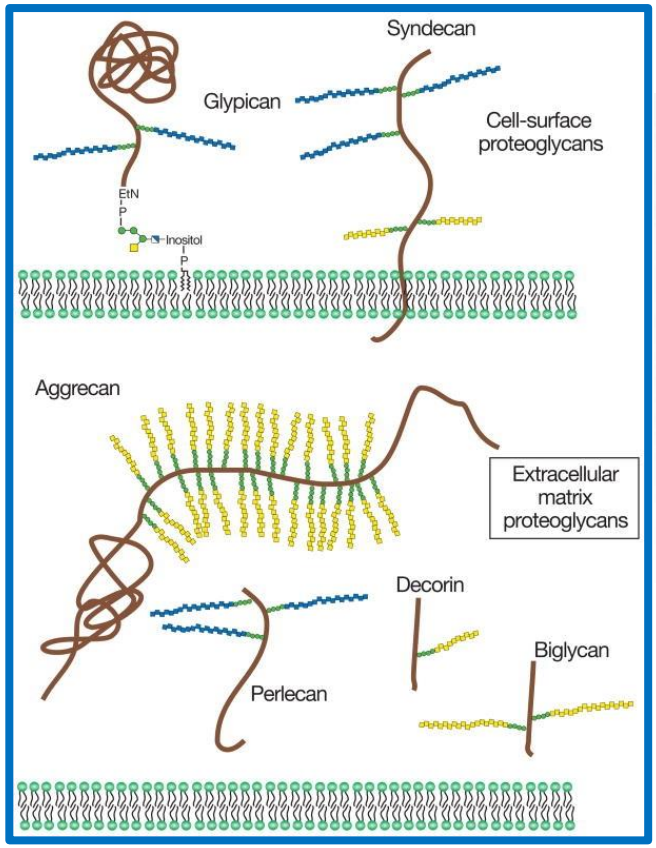




GAGs are a major component of connective tissue

- Widely distributed throughout the body
- Basic substance of skin, cartilage, bone
- A component of lubricating fluid in joints
- Regulate multiple processes, including cell-cell adhesion





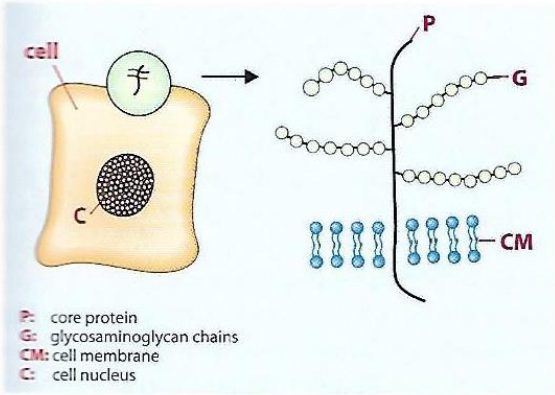
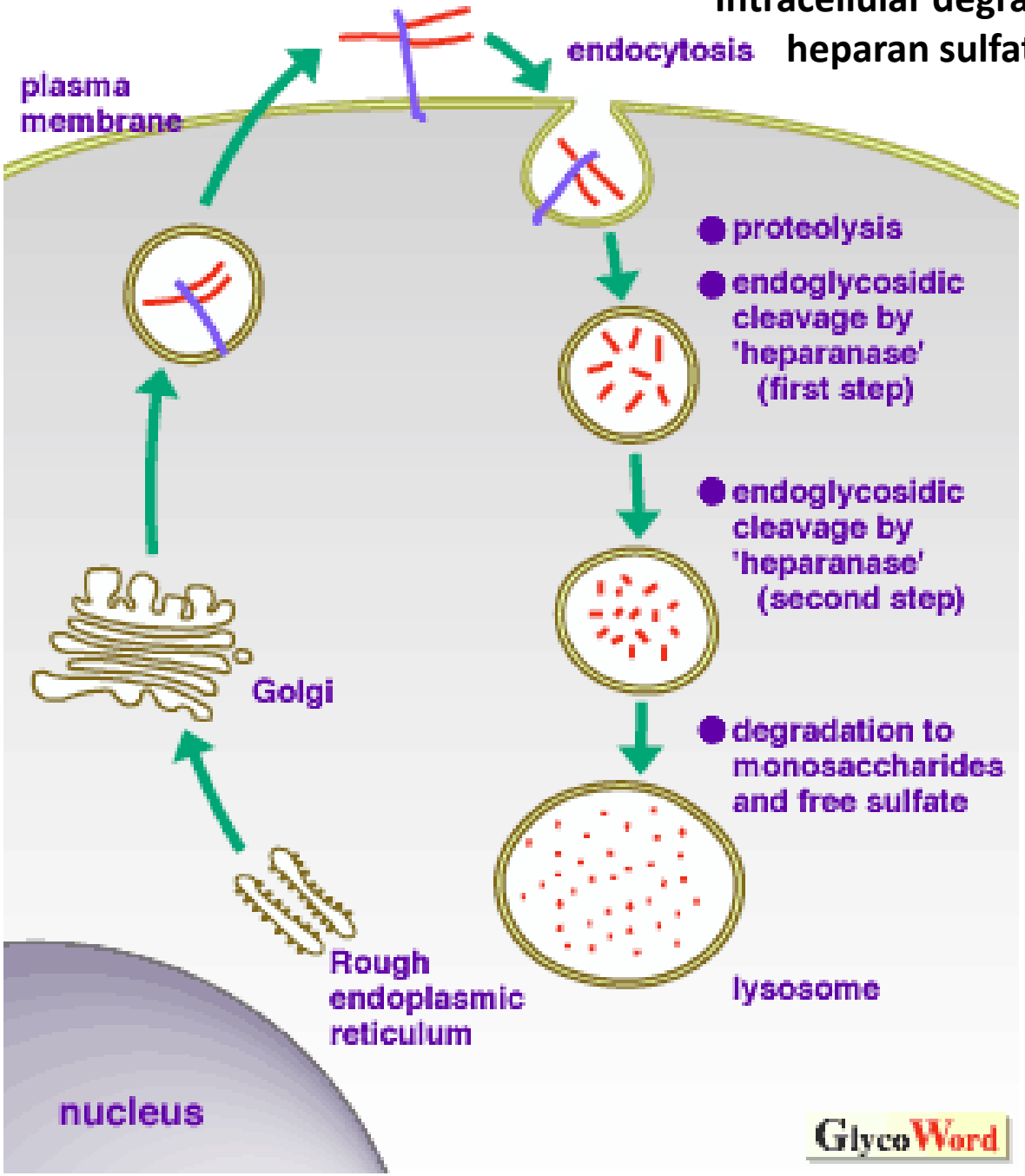


Figure 3.1: Functional structure of heparan sulfate inside the cell membrane.

Intracellular degradation of cell surface heparan sulfate proteoglycans.



Biological role of GAG

Biological function		Physiological processes/ potential roles in MPS
Cytokine binding	Chemokines (IL-8, IFN-γ, CD44, RANTES) Growth factors (FGF)	Cell proliferation Cell signalling pathways Inflammation Osteogenesis Neuronal function
Cell-surface-receptor binding	FGFR, BMPRs, TGF	Cell signalling and adhesion Osteogenesis Neuronal maturation
Specific protein binding	RANK-L	Osteoclast function
	Serpins (HCII, ATIII, PN1)	Regulation of proteinases Neuronal function
	Cathepsin K	Inhibition of collagenase Osteoclast function
	BMPs	Osteoblast development
	Osteopontin	Osteoclast function
	Elastin-binding protein	Elastogenesis
	Lysosomal hydrolases	Degradative pathways
Hyaluronan interactions[b]	Aggrecan and versican in cartilagenous tissue	Osteogenesis, arthropathy

Clarke LA , January 2008

A multisystemic disorder

- Coarse facial features
- Coarse hair
- Hirsutism
- Mild hepatosplenomegaly
- Delayed development
- Hyperactivity
- Aggressive behavior
- Anesthesia Difficulties\ danger

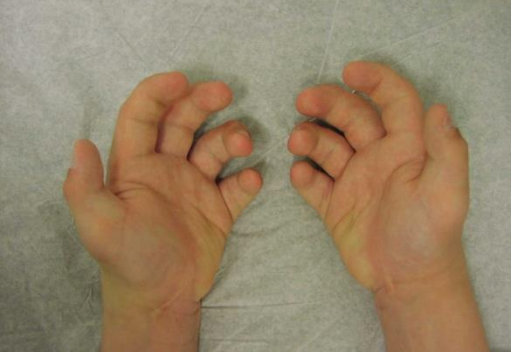
Delgadillo et al. Orphanet Journal of Rare Diseases 2013, 8:189

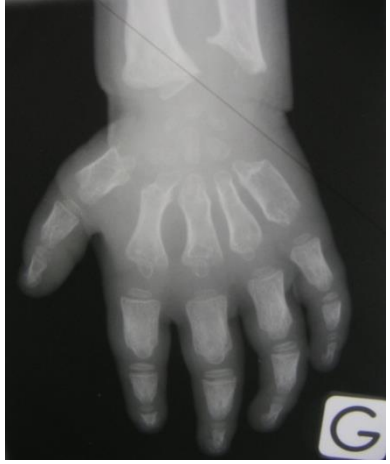
Progressive Disorders

Not all the patients have the characteristic features at a young age

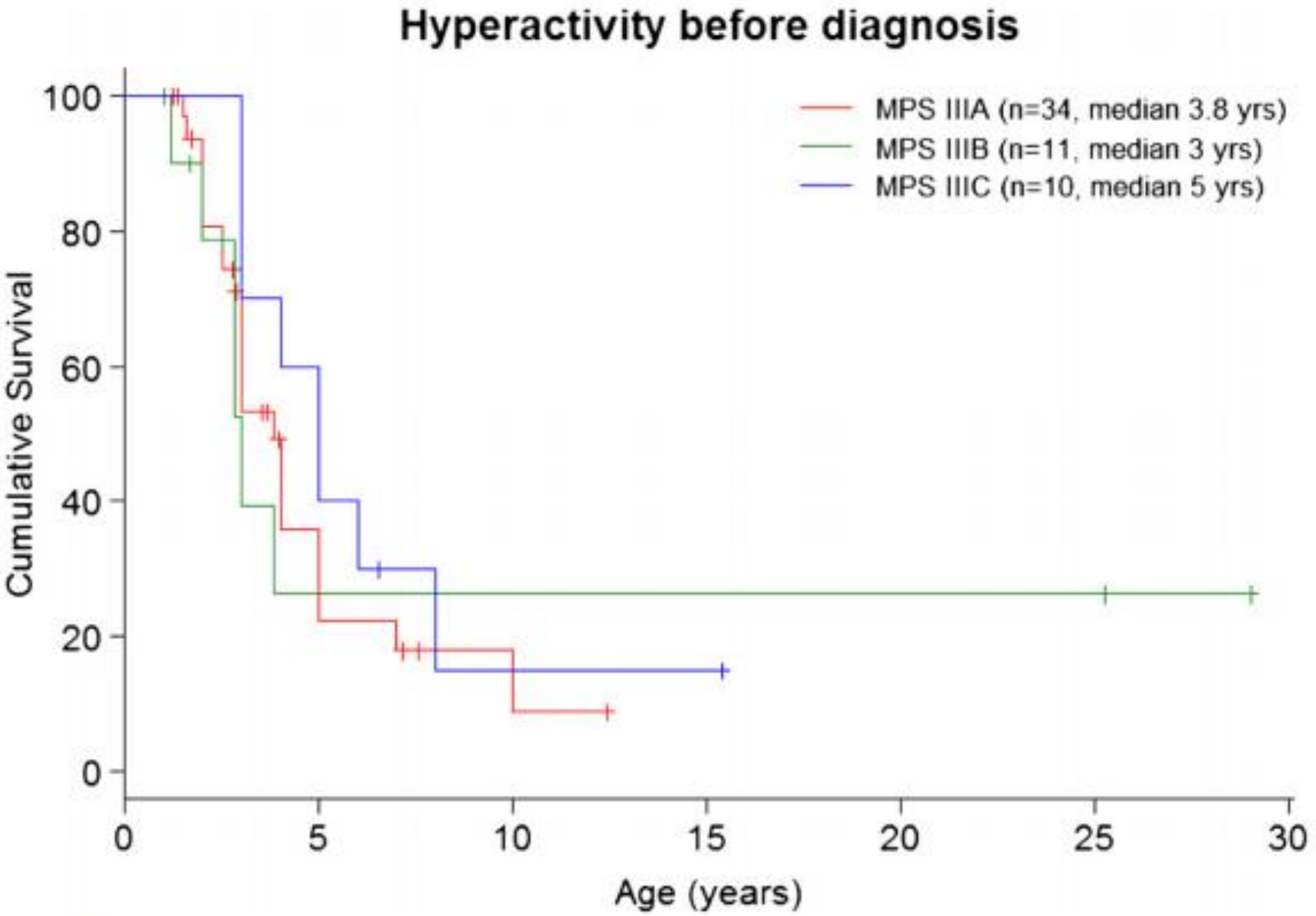
- Mouth and Teeth
- Heart:
  - valvular abnormalities;
  - systemic hypertension

- Airways and Respiration
  - Recurrent pulmonary infections
  - Obstructive airway disease
  - Enlarged tonsils & adenoids
- Eyes:
  - corneal clouding; glaucoma; retinopathy; optic nerve abnormality
- ENT & Audiology
  - Recurrent otitis media
  - Recurrent sinusitis
  - Hearing loss





- Bone and joint abnormalities
- Short, thickened fingers
- Fixed flexion
- Typical claw hand deformity
- Trigger finger abnormality
- Loss of dexterity



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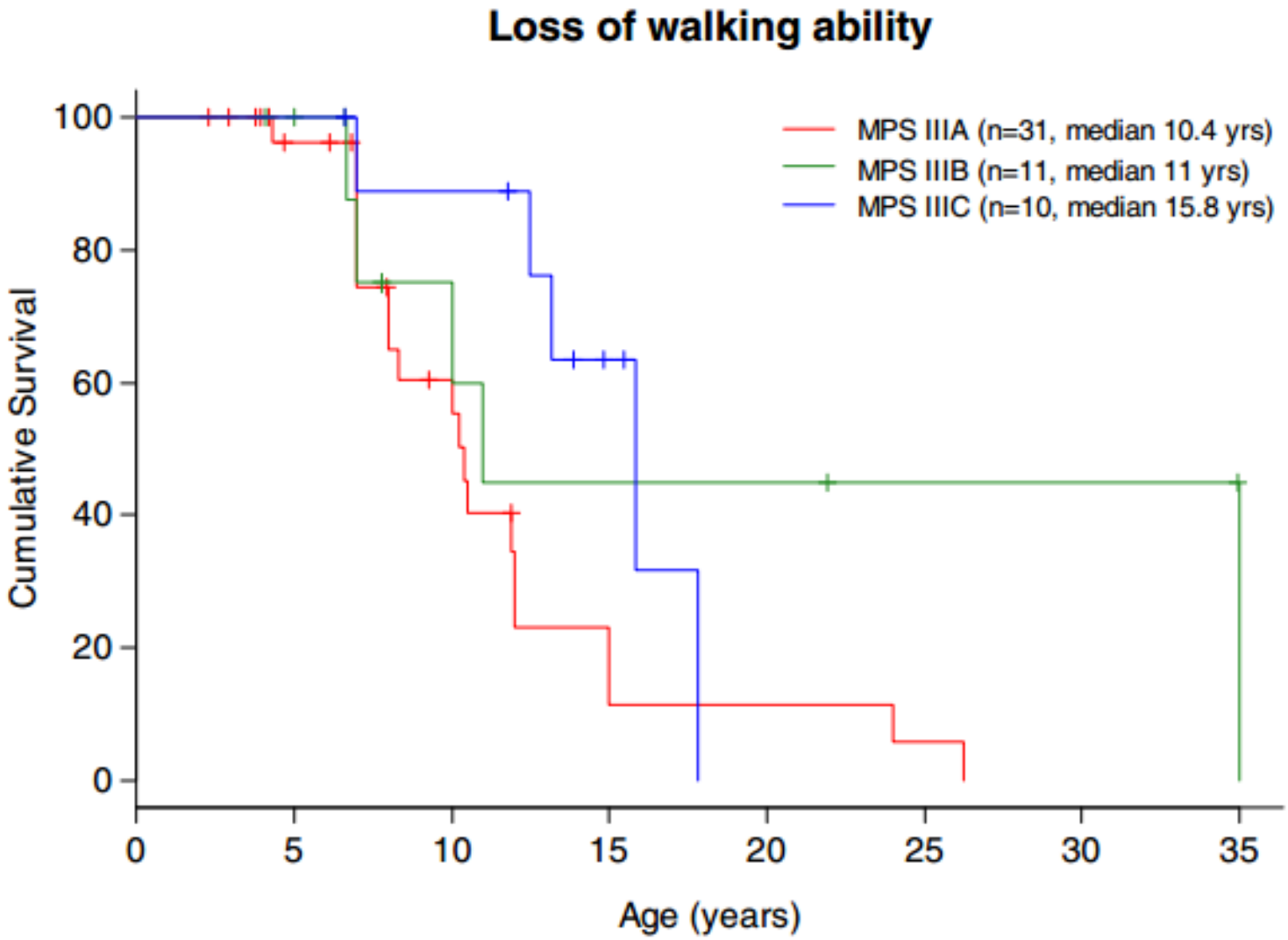

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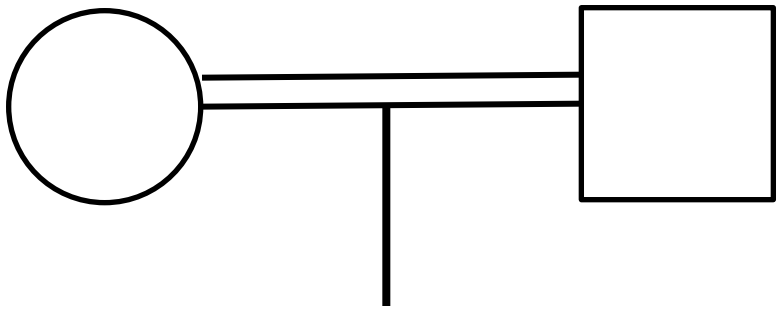


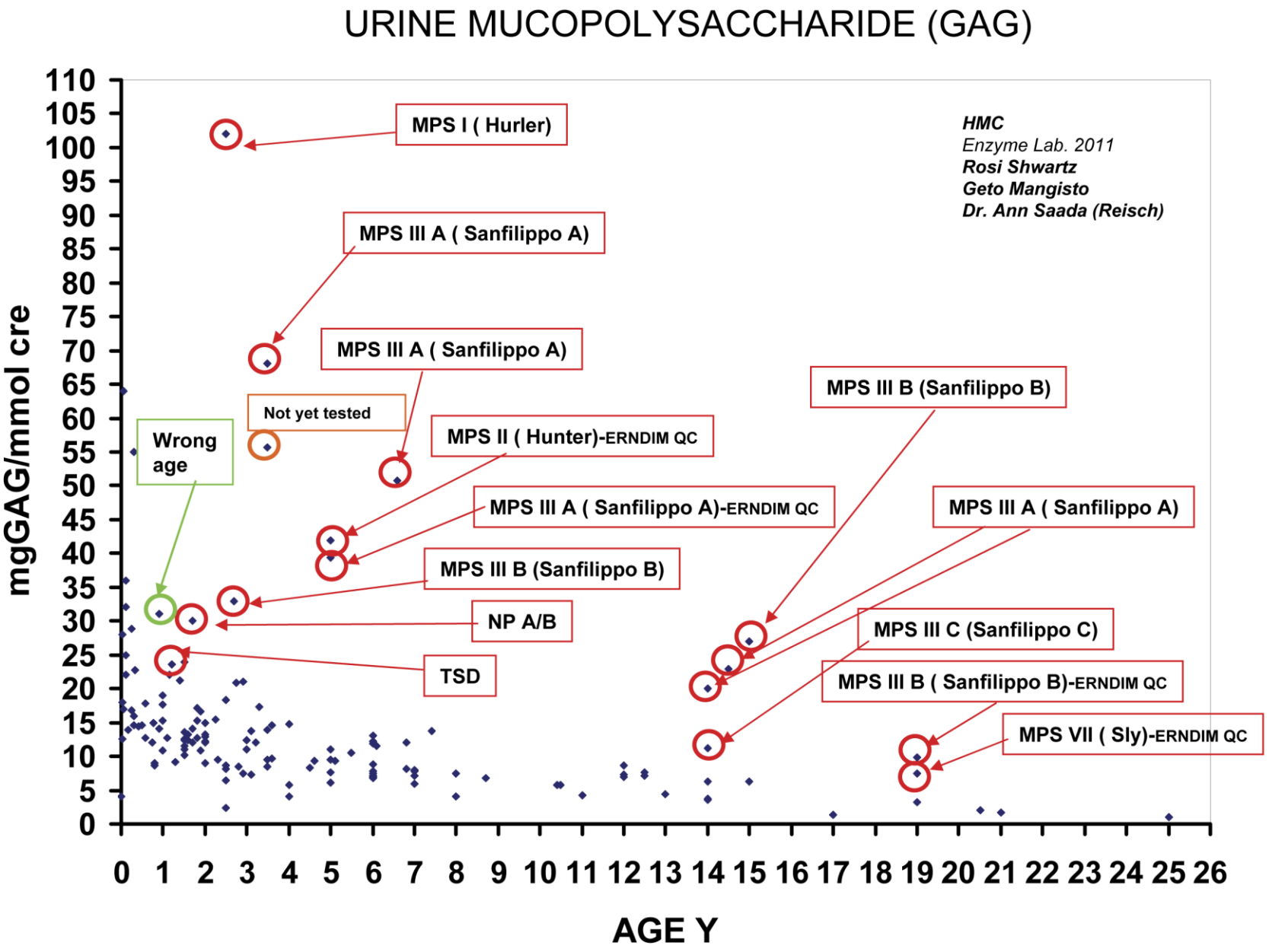
MPS III : San Filippo

No Therapy
Autosomal Recessive Risk
Carriers identification in the family
Prenatal diagnosis
Support group
Focus on the needs of the kid
Prevention of Complications: Anesthesia and more

Recurrent otitis media	Recurrent otitis media
Recurrent pneumonia	Recurrent pneumonia

Quantitative method

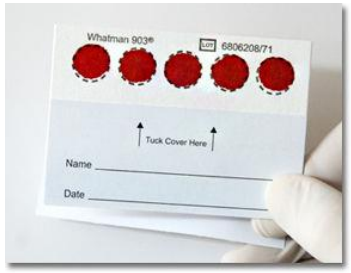
- **Spectrophotometric metod with DMB (Dimethyl-Methylene Blue)**
- The absorbance is correlated to urine creatinine and related to age

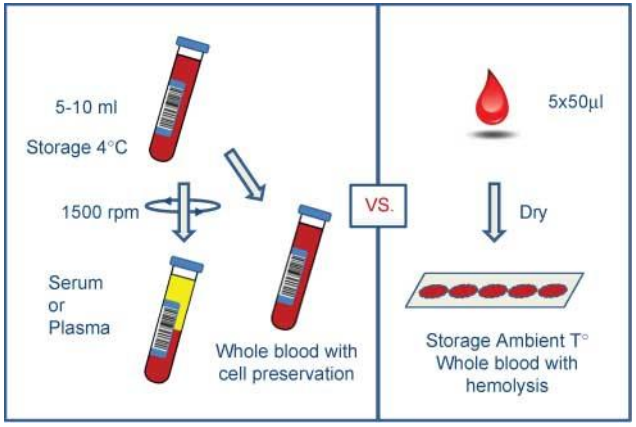


Dr Ann Saada Reisch; PhD;

Specific enzyme activity in white blood cells ,skin fibroblasts, Dried Blood spots

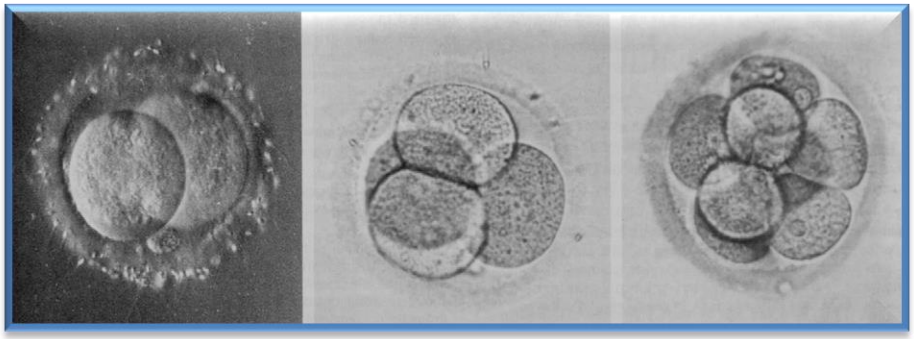
MPSIII	Enzyme		Location
A	Heparan-N-Sulfatase	SGSH	17q25.3
B	N-Acetyl-alpha-glucosaminidase	NAGLU	17q21.1
C	acetylCoA Alpha-glucosaminidine-N-Acetyltransferase	HGSNAT	8p11.1
D	N-acetylglucosamine-6-sulfatase	GNS	12q14

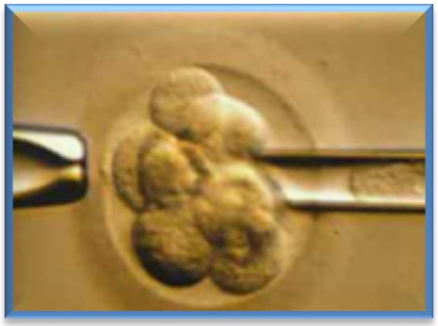




Definitive diagnosis

- **Mutation analysis:**
  - Identify carrier in the family
  - Prenatal diagnosis
  - Preimplantation genetic diagnosis





1983

A Social challenge


Daily News

1983

Congress Passes
Orphan Drug Act

1979 FDA Task Force on orphan diseases :

"Whenever a drug has been identified as a potentially life-saving or otherwise of unique major benefit to some patient, it is the obligation of **society**, as represented by government, to seek and to make that drug available to that patient"

Orphan Drugs Laws

Orphan drug:
product developed to treat or prevent
a specific rare disease

- 1983: USA
- 1991: Singapore
- 1997: Australia
- 1998: Taiwan
- 1999: Europe

Challenges

- Limited knowledge of epidemiology
- Limited knowledge of natural history
- Are treatments leading to changes in the disease progression? Quality of life?
- Effectiveness:
  - What are the outcomes?
  - What is a meaningful change ?

More on challenges

- Design studies which are feasible in a rare disease setting (few patients)
- Patients with rare diseases & their families are **experts** about health care needs
- Rare disease organizations are leading the way

Networks

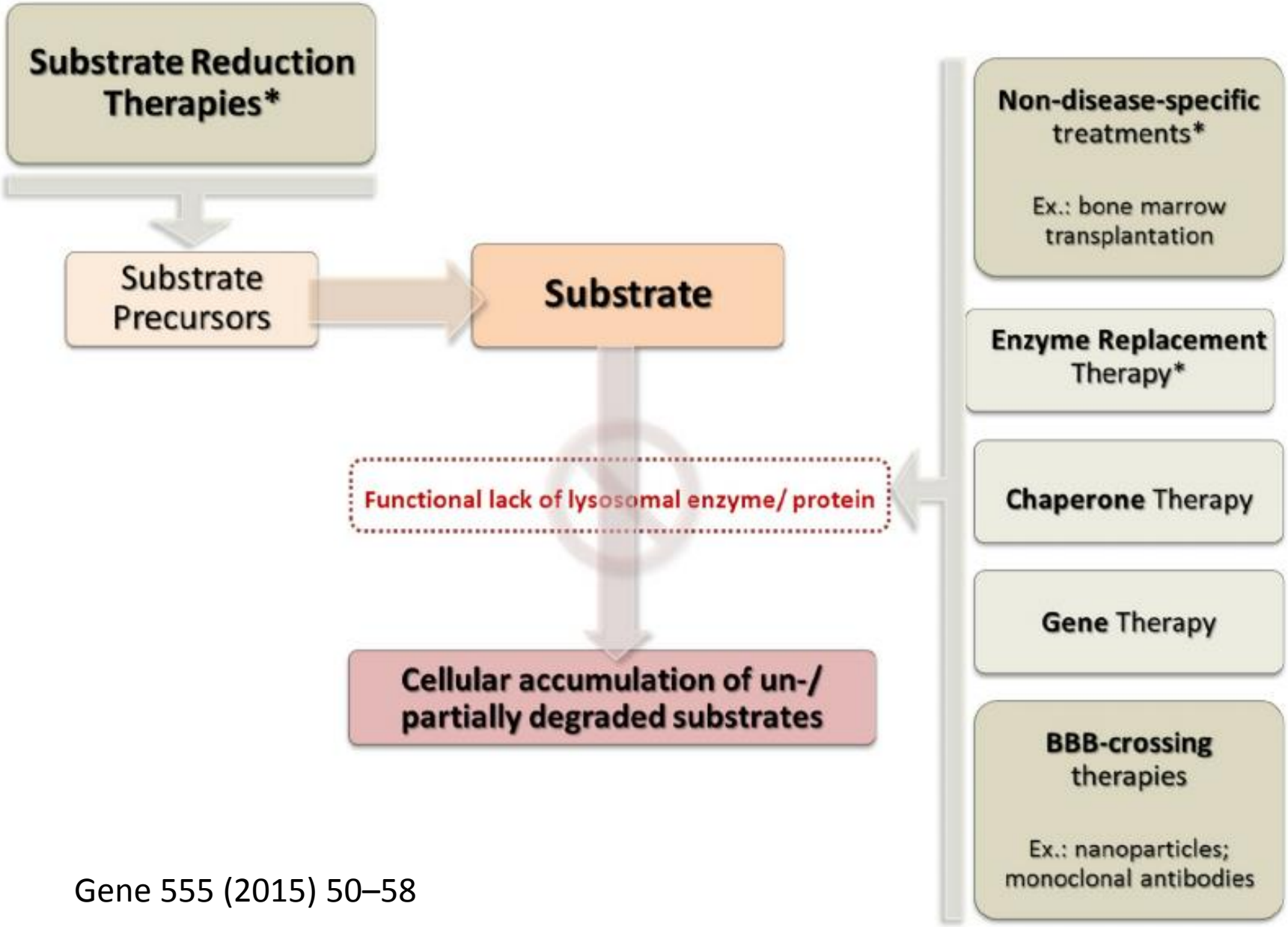
- Patients\ families
- Providers
- Policy-makers
- Researchers
- Stakeholder communities
- Across geographic boundaries

Difficulties for therapeutic trial

- Rare disease
- Heterogeneous phenotype
- Variable age of onset
- Variable symptoms
- Heterogeneous genetics
- Clinical progression occurs over years
- **GOAL: stabilization or delay of neurological disease**

Natural History & molecular analysis

- Observational study
- Parental questionnaire



Gene 555 (2015) 50–58

ERT

	MPS I	MPS II	MPS VI	MPS IVA
	Aldurazyme (Genzyme)	Elaprase (Shire)	Naglazyme (Biomarin)	Vimizim (Biomarin)
IV	0.58mg/kg	0.5mg/kg	1mg/kg	2mg/kg
Freq	weekly	weekly	weekly	weekly
Infusion time	3 - 4h	3h	4 h	3h

Genetics and Molecular Biology, 33, 4, 589-604 (2010)

LES AXES DE RECHERCHE

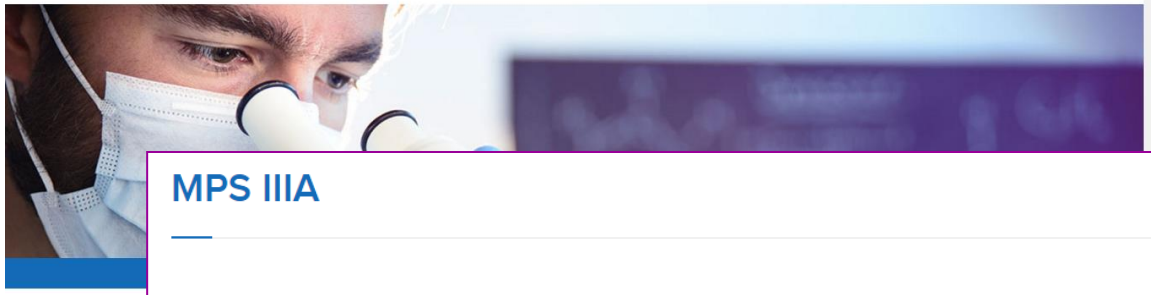
Conception de chaperons chimiques

Thérapie génique intracérébrale

Greffe de moelle osseuse

Modulation pharmacologique de l'activité lysosomale comme approche thérapeutique pour le traitement des MPS

Dév. d'inhibiteurs de la galactosidase β et de la



MPS IIIA

Long-term Follow-up of MPS IIIA Patients Treated by Intracerebral LYS-SAF301 Gene Therapy

What is the purpose of this study?

This is an open-label study evaluating the long-term safety and tolerability of intracerebral LYS-SAF301 previously administered to 4 patients with Sanfilippo type A syndrome. The primary objective is to collect additional safety and tolerability data on intracerebral LYS-SAF301 previously administered to 4 patients with Sanfilippo type A syndrome. The secondary objective is to further collect data to assess the effects of LYS-SAF301 on neurological and psychological status and potential biological markers

Trial at a glance

Clinical sites		
France		
End date	**Study identifier**	**Phase**

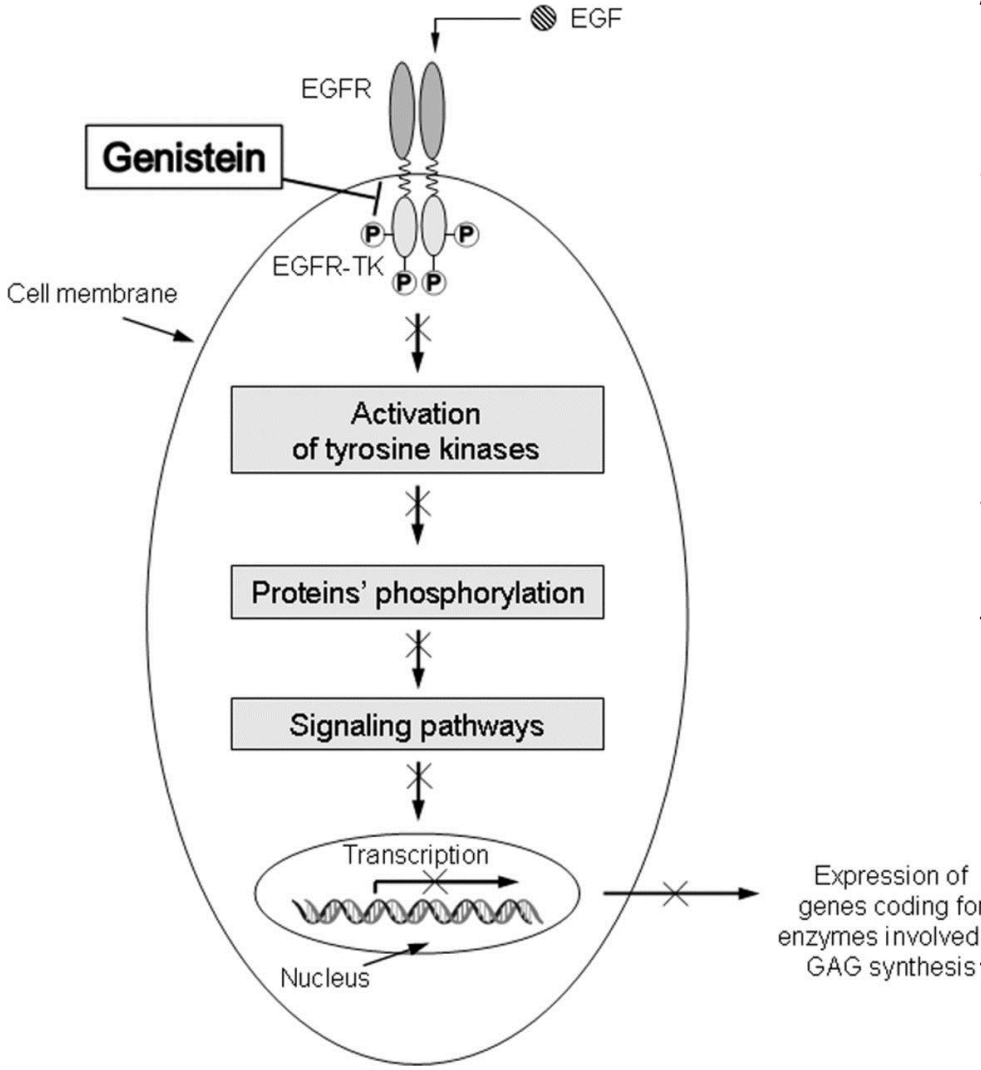
Observational study of patients with Mucopolysaccharidosis Type IIIA

What is the purpose of this study?

Lysogene has begun a multi-national observational study (SAMOS) as it prepares to initiate its pivotal clinical trial for the treatment of Sanfilippo Type A, also known as mucopolysaccharidosis IIIA (MPS IIIA). This is an observational study, so no experimental drug will be given. Patients enrolled will have access to regularly scheduled monitoring and follow-up visits. The information gained from this study will enable optimal trial design, greater understanding of disease progression and better predictions of future therapeutic effects.

Trial at a glance

Condition	Study type	Clinical sites	
MPS IIIA	Non interventional	France, UK, Germany, the Netherlands and Brazil.	
Enrollment	**Start date**	**End date**	**Study identifier**
Up to 25	May 2016	2018	ClinicalTrials.gov Identifier : NCT02746341



A mechanism for genistein-mediated impairment of expression of genes, whose products are involved in GAG synthesis

Stimulation of expression of genes coding for enzymes required for GAG production depends on EGF-mediated activation of its receptor, EGFR. The EGFR tyrosine kinase (EGFR-TK) activity causes phosphorylation of certain proteins involved in the cascade of kinases, which is the process of transduction of intracellular signals, leading to activation of transcription of specific genes in the nucleus. Inhibition of the EGFR-TK activity by genistein (thick blunt-ended line) results in impairment of the signal transduction and thus in a decreased expression of genes coding for enzymes involved in GAG synthesis. Therefore the secondary effect of this negative regulation is decreased efficiency of GAG production.

Health Care Professionals

Social System

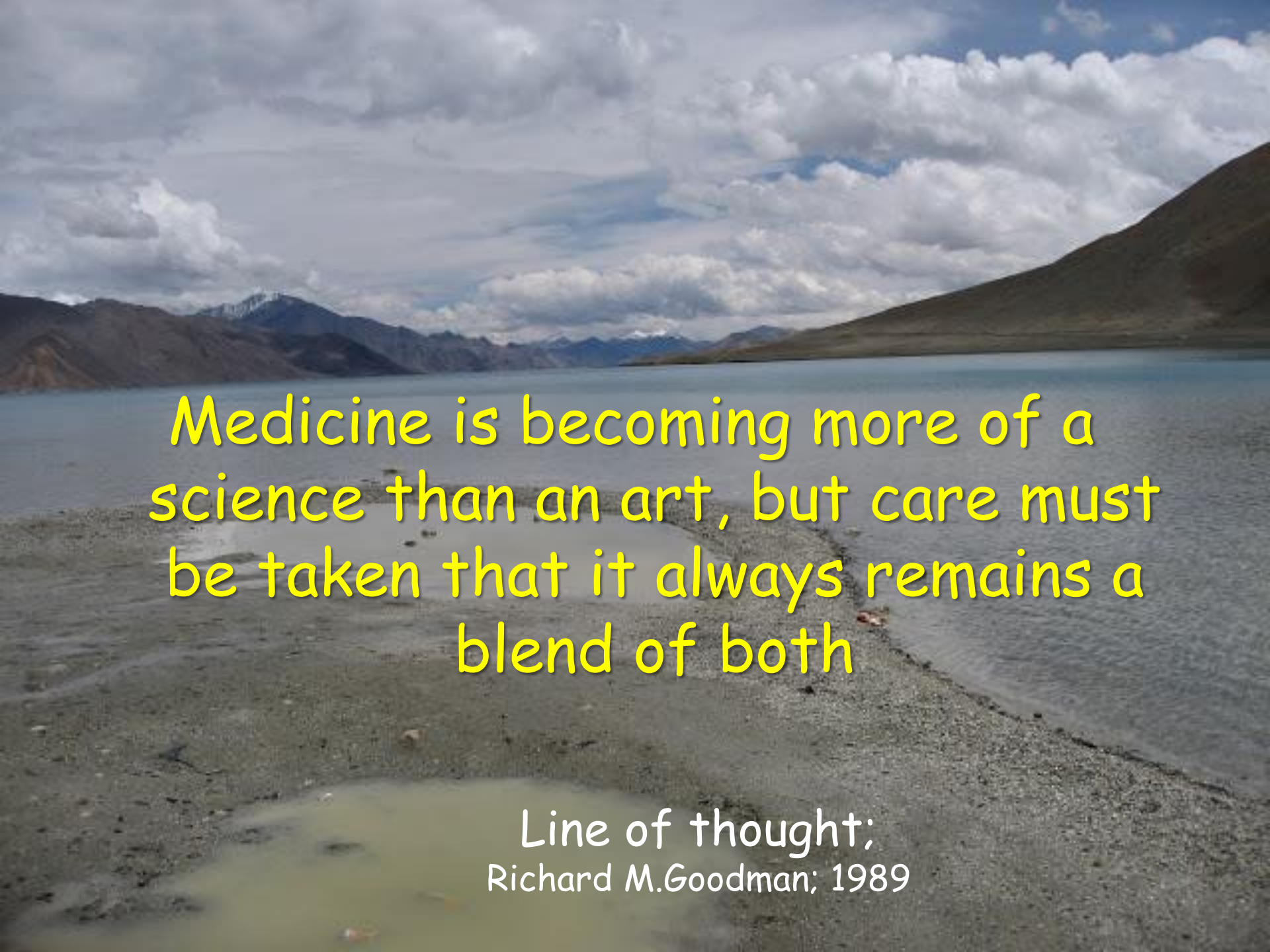
Diagnosis and Care

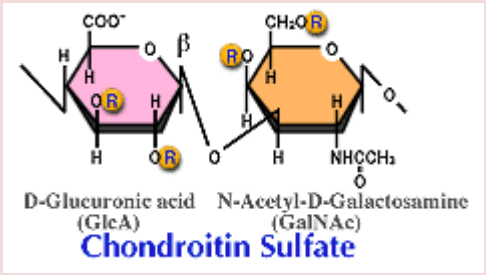
Patients and families

With rare diseases

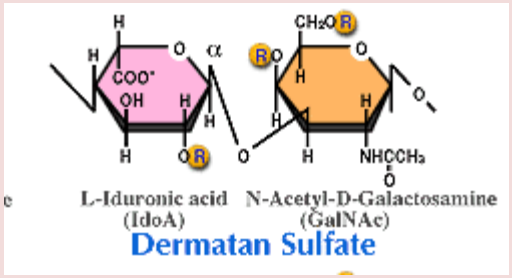
Patients Associations

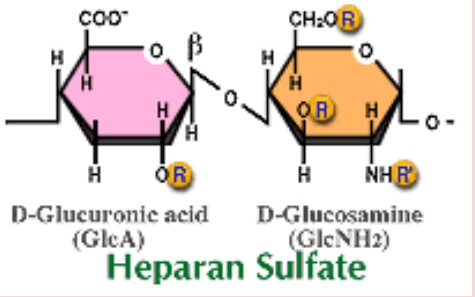
Economic system


Medicine is becoming more of a science than an art, but care must be taken that it always remains a blend of both
Line of thought;
Richard M.Goodman; 1989



Galactosaminoglycans





Glucosaminoglycans