Organelle Diseases: The Lysosome The Peroxisome

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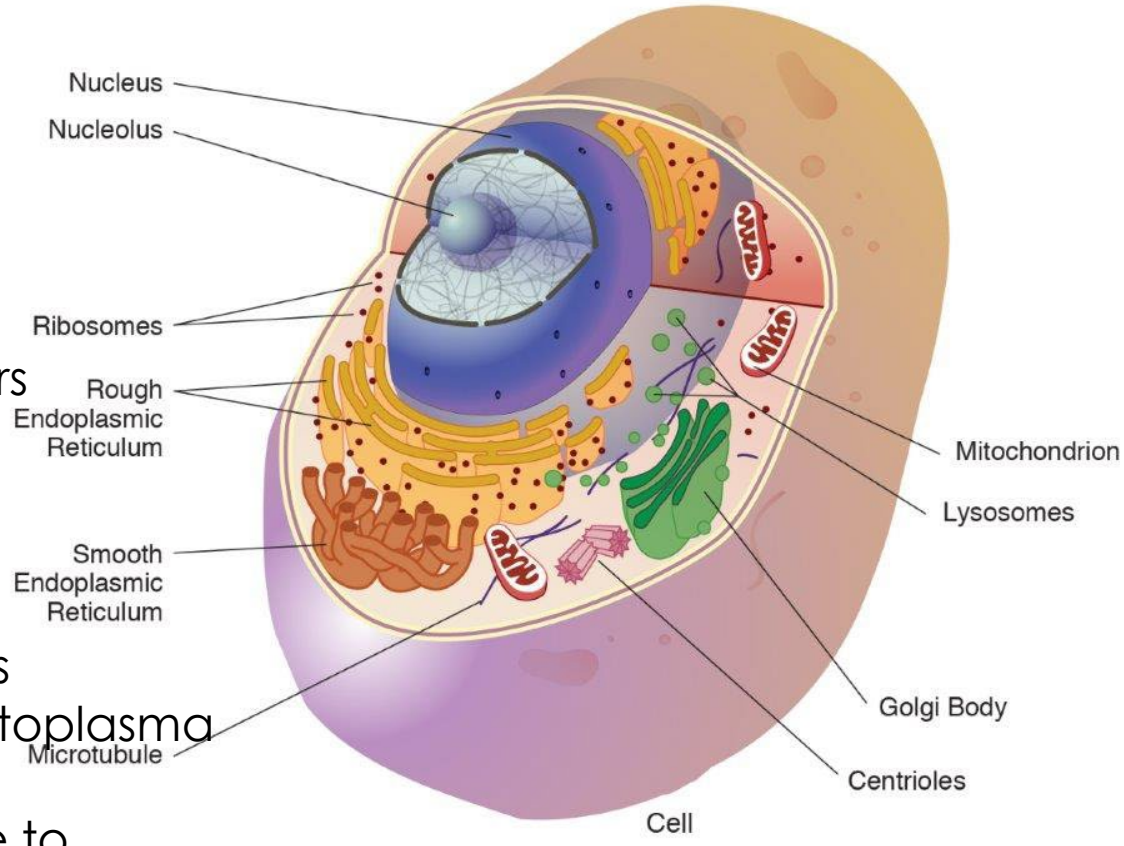
European Reference Network
for rare or low prevalence complex diseases
Network Hereditary Metabolic Disorders (MetabERN)

A biochemical pathway takes place in a cellular compartment/organelle

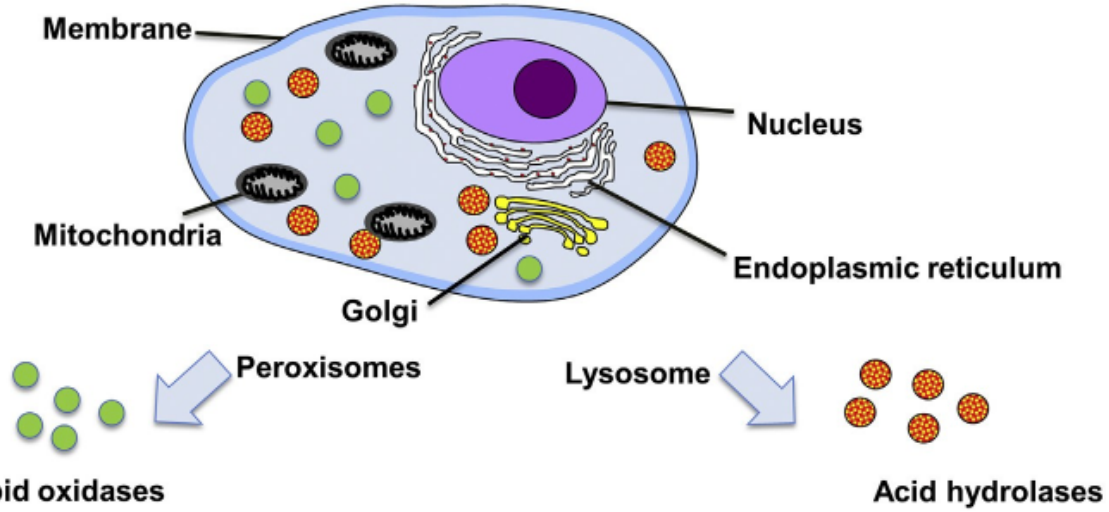
Membranes/transporters

Interactions between organelles; metabolic pathways involving different compartments e.g. mitochondrium/cytoplasma

DNA mutations give rise to tissue-specific expression



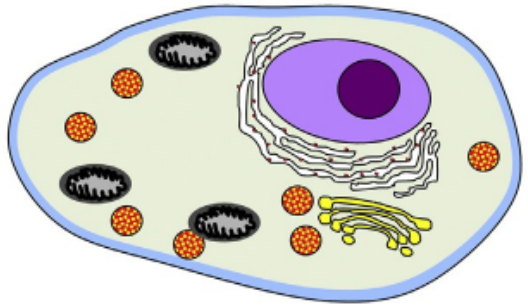
A



B

Severe Peroxisome Biogenesis Disorders

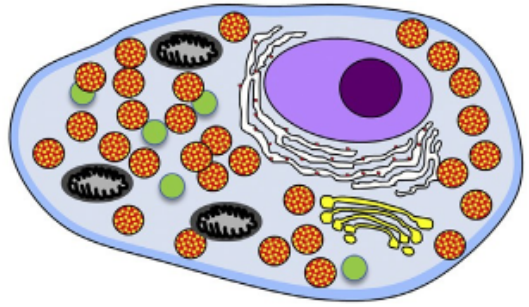
Lack of peroxisomes (or "empty" peroxisomes)



Clinical Patterns
Liver dysfunction
Hypotonia, seizures, retinopathy, hearing loss

Severe Lysosomal Storage Disorder

Accumulations within the lysosome

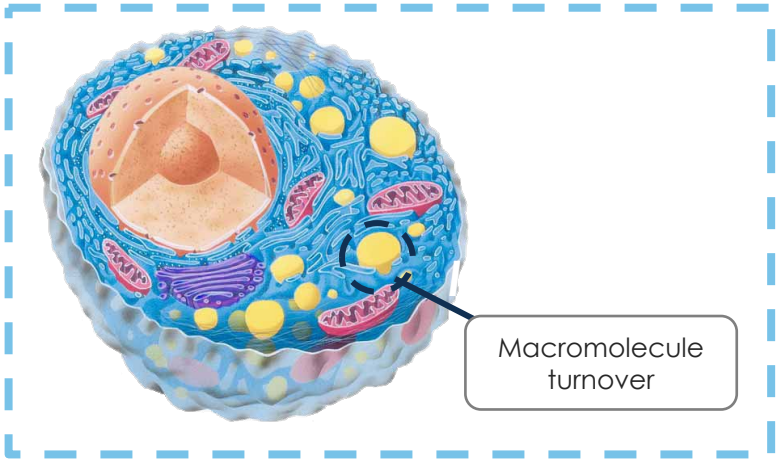


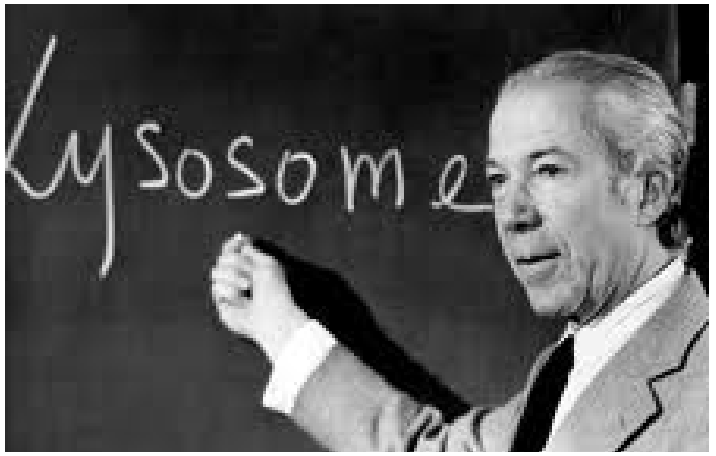
Clinical Patterns
Organomegaly
Neurological symptoms
Coarse features, dysostosis multiplex

The lysosome

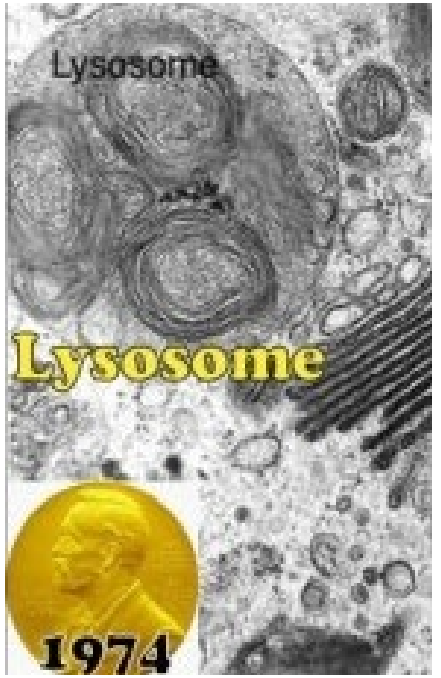
Lysosomes: recycling ‘bodies of cleavage’

Acid organelles with hydrolases





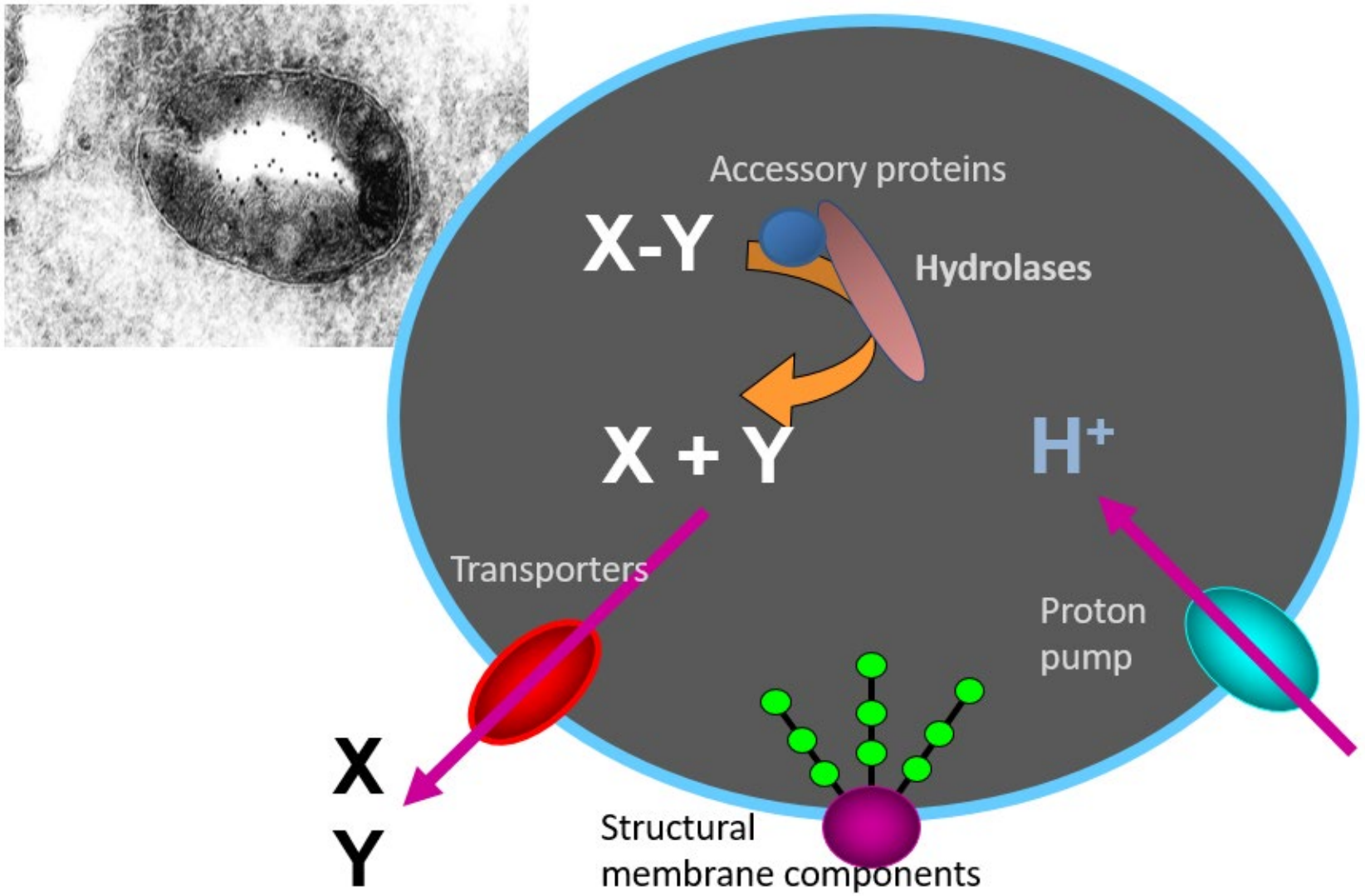
Christian de Duve



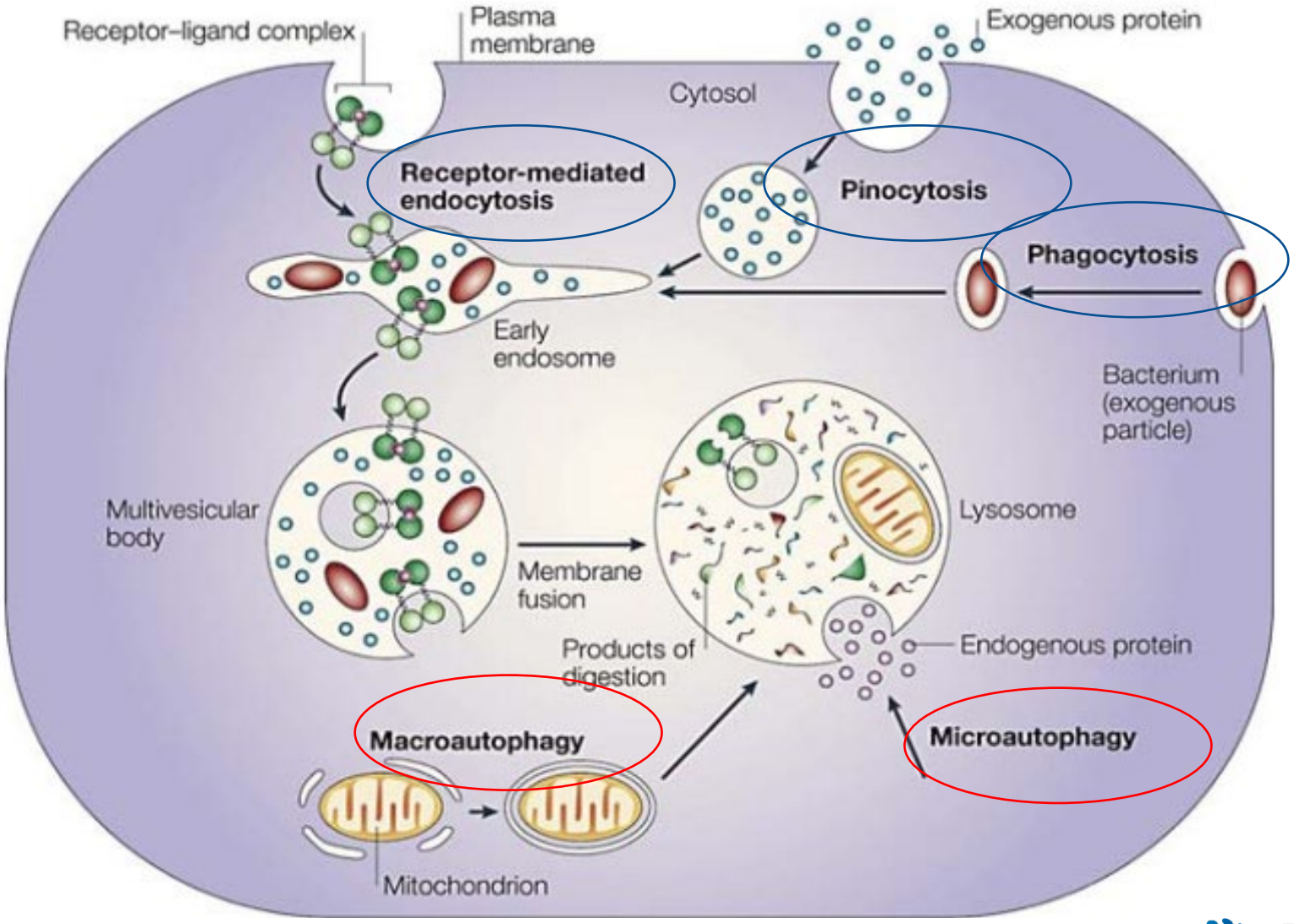
Nobel Prize
Medicine

Appelmans, F., Wattiaux, R. and De Duve, C. (1955). Tissue fractionation studies. The association of acid phosphatase with a special class of cytoplasmic granules in rat liver. Biochem. J. 59, 438–445.

Lysosomes – general components

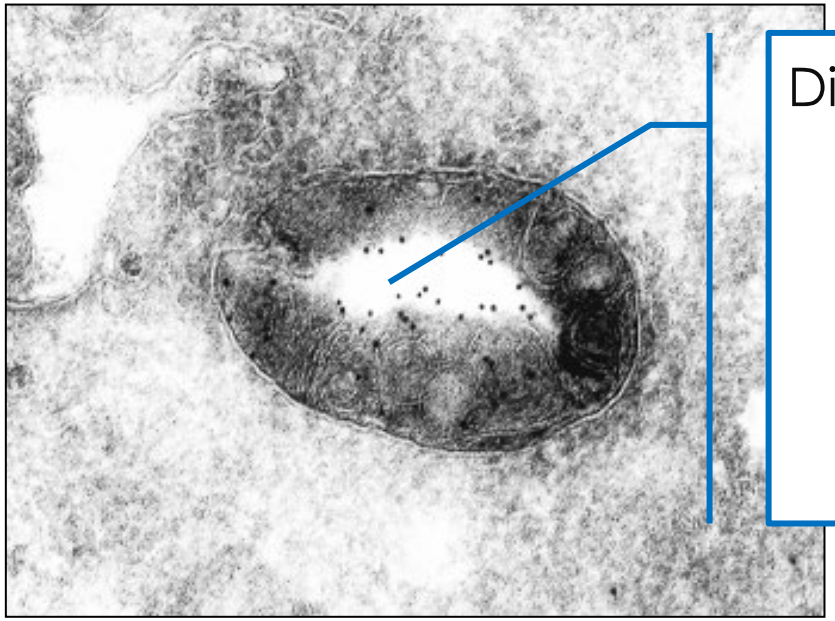


Entry of substrates by endocytosis and autophagy



Lysosomes: recycling stations for breakdown of macromolecules

Acid organelles with hydrolases



Digestive enzymes (~ 60):
- proteases
- glycosidases
- nucleases
- lipases
- phosphatases
- sulfatases

- Breakdown of macromolecules
- Release of nutrients to cytosol

Functions and pathologies associated with lysosomes

Recycling of endogenous macromolecules to maintain cell function and viability

- Inherited lysosomal storage disorders (LSDs)
- **Neurodegenerative diseases (Alzheimer, Parkinsonism)**

Nutrient release to cytosol

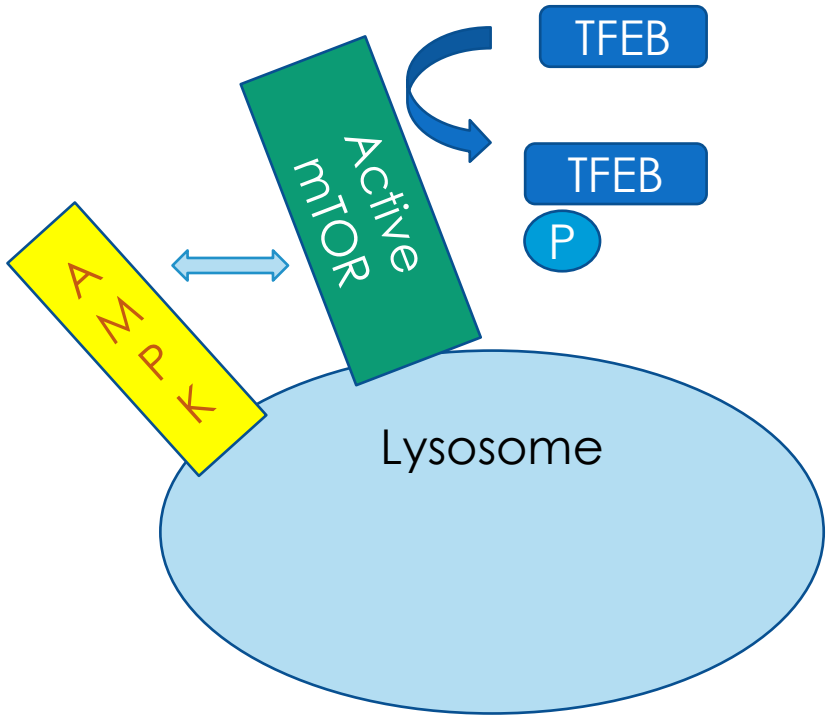
- Atherosclerosis (foam cells)

Special functions in specific cells

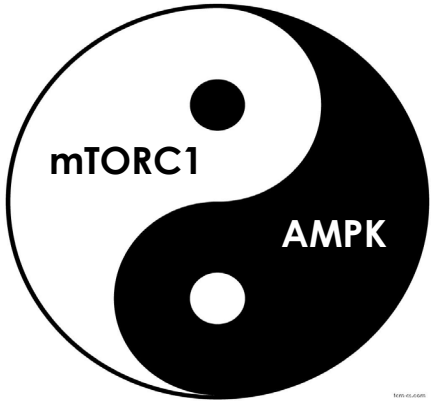
- Degradation pathogens (macrophages)
- Increased susceptibility for infections (tuberculosis)
- Bone remodelling (osteoclasts)
- Pycnodysostosis (Toulouse-Lautrec Syndrome)

Regulation of metabolism by lysosomes

Key regulators metabolism



Nutrient and Energy Regulation



Excess:
Anabolism, consumes nutrients & energy

Shortage:
Catabolism, generates nutrients & energy

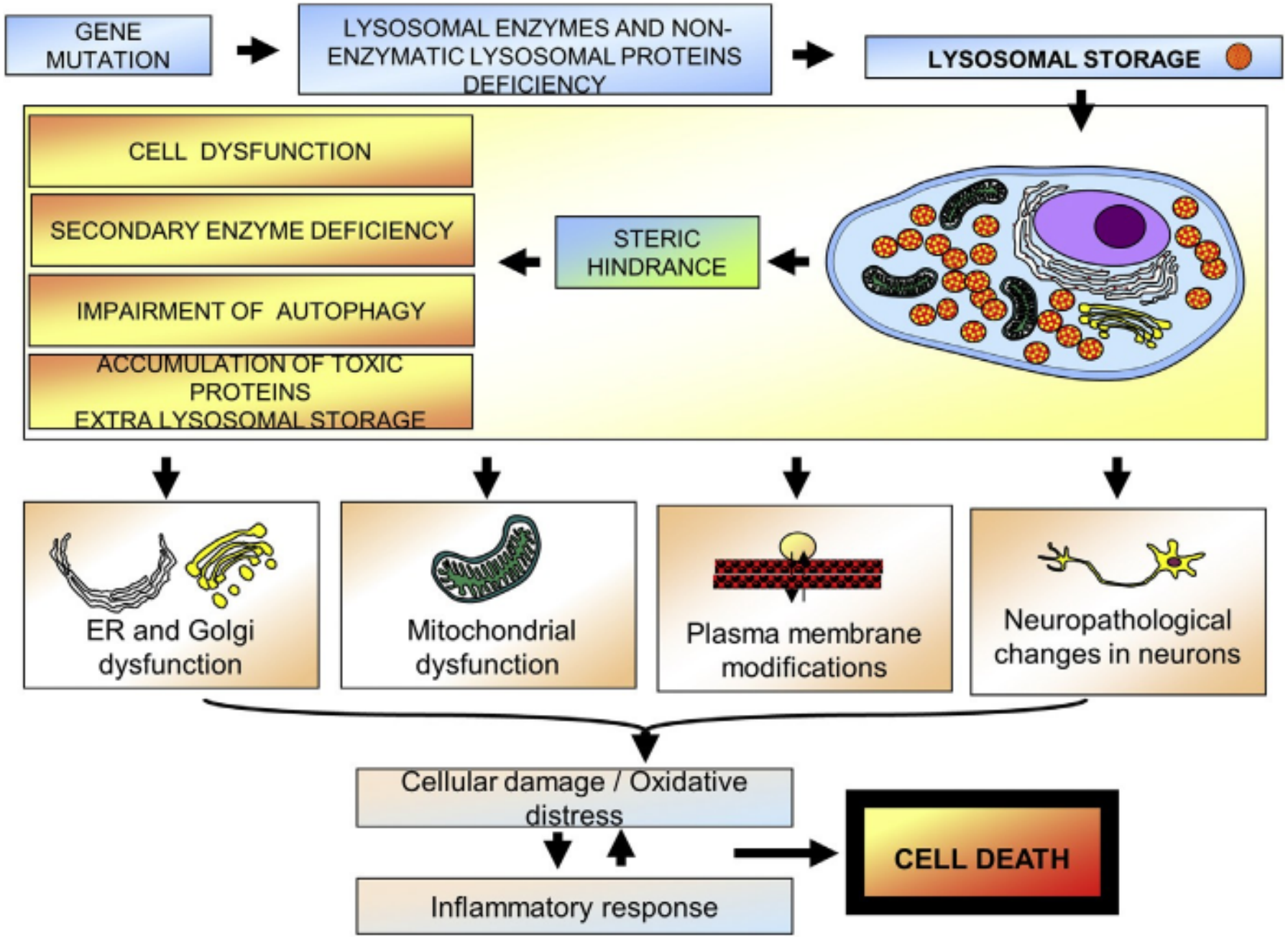
Active AMPK (during nutrient and energy shortage) replaces mTOR at lysosomes:
→ TFEB-induced lysosome biogenesis and autophagy

Lysosomal storage diseases (LSDs)

More than 70 discrete inborn errors:

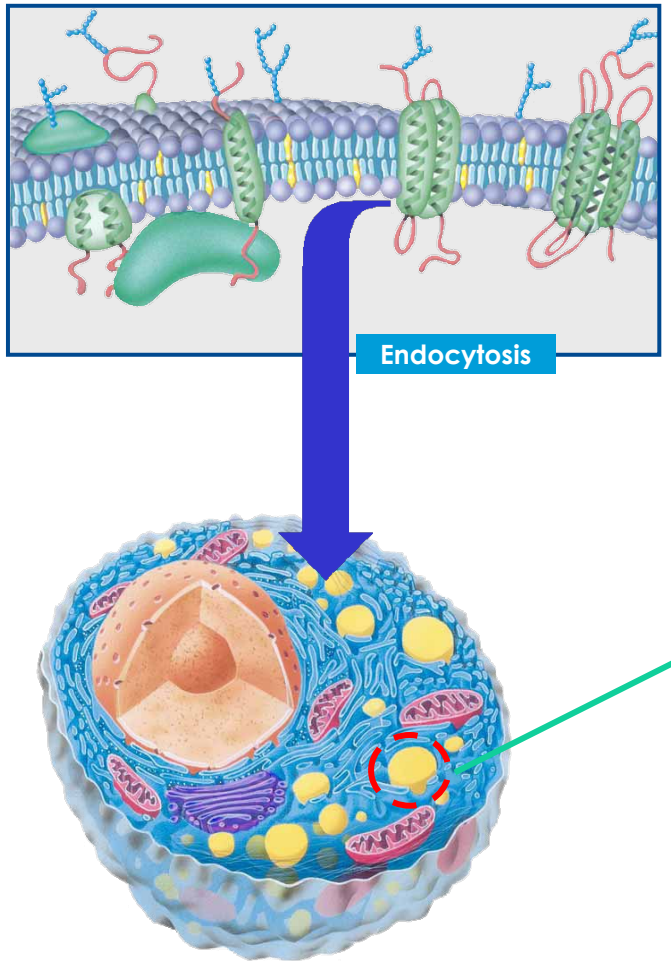
- Major part of inborn errors of metabolism;
- Total incidence symptomatic LSDs: 1 in <3000;
- Total frequency carriership for LSD: 1 in <20.

Enormous heterogeneity in clinical manifestations of LSDs contributing to limited knowledge with general public and even clinicians.


GENE MUTATION
LYSOSOMAL ENZYMES AND NON-ENZYMATIC LYSOSOMAL PROTEINS DEFICIENCY
LYSOSOMAL STORAGE
CELL DYSFUNCTION
SECONDARY ENZYME DEFICIENCY
IMPAIRMENT OF AUTOPHAGY
ACCUMULATION OF TOXIC PROTEINS
EXTRA LYSOSOMAL STORAGE
STERIC HINDRANCE
ER and Golgi dysfunction
Mitochondrial dysfunction
Plasma membrane modifications
Neuropathological changes in neurons
Cellular damage / Oxidative distress
Inflammatory response
CELL DEATH

The lysosomal degradation of sphingolipids

Glycosphingolipids – Ongoing intralysosomal fragmentation

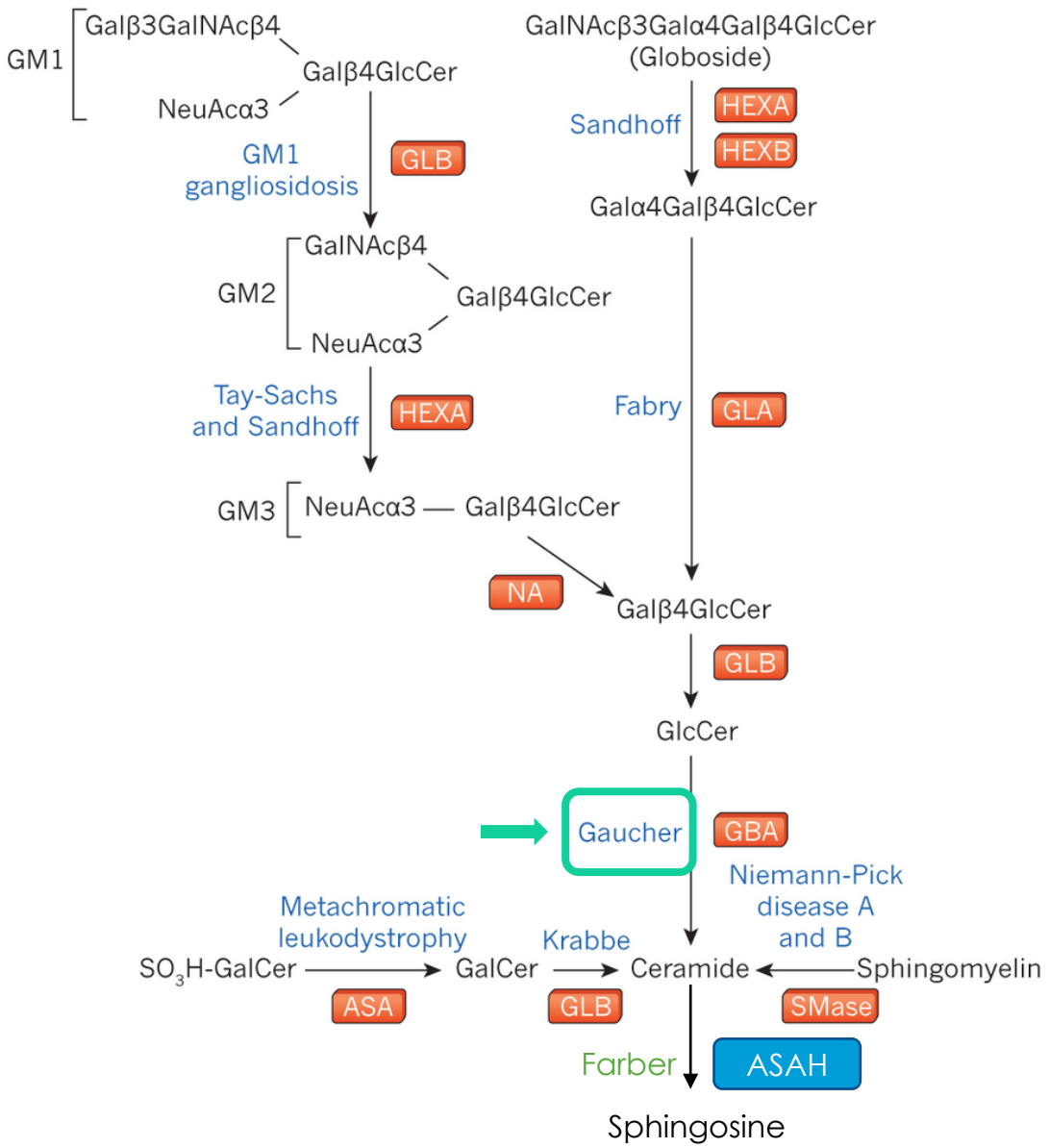


Glycosphingolipids are prominent in the outer leaflet of the plasma membrane where they largely reside in lipid rafts.

Glycosphingolipids are internalized to lysosomes and recycled by sequential action of glycosidases and ceramidase.

Free sugars,fatty acid and sphingosine

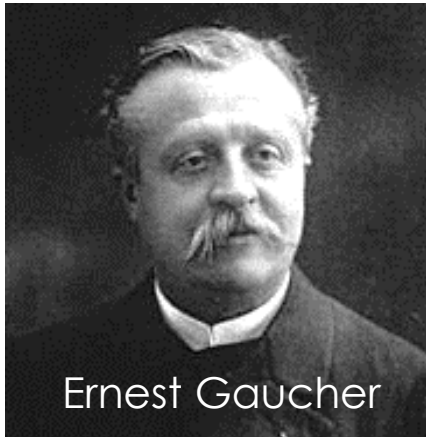
Inherited lysosomal glycosphingolipid storage disorders

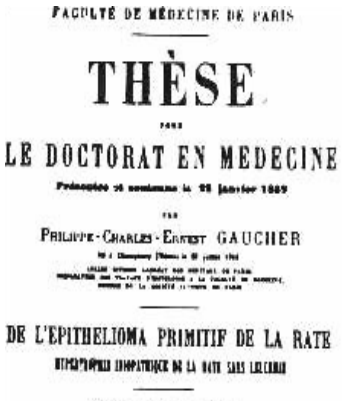


Sphingolipidosis	OMIM	Locus Gene	Gene product	Storage
Farber	228000	8p22 ASAH	Acid ceramidase	Cer
Fabry	301500	Xq22 GLA	α-Galactosidase A	GB3
Gaucher	606463 230900 231000 230800	1q21 GBA	Glucocerebrosidase	GlcCer
GM1 gangliosidosis	230500 230600	3p21 GLB1	β-Galactosidase	GM1
Tay-Sachs	272800	15q23 HEXA	β-Hexosaminidase α-subunit	GM2
Sandhoff	268800	5q13 HEXB	β-Hexosaminidase β-subunit	GM2
Tay-Sachs AB variant	272750	5q32 GM2A	GM2 activator protein	GM2
Krabbe	245200	14q31 GALC	β-Galactosyl-ceramidase	GalCer
Metachromatic leukodystrophy	250100	22q13 ARSA	Arylsulfatase A	Sulfatide
Prosaposin deficiency **Saposin B deficiency** **Saposin C deficiency**	176801 249900 610539	10q22 PSAP 10q22 PSAP 10q22 PSAP	Prosaposin Saposin B Saposin C	Multiple lipids Sulfatide GlcCer
Niemann-Pick types A and B **ASMD**	257200 607616	11p15 SPMPD1	Acid sphingomyelinase	SM

Defect in the degradation of glucosylceramide by deficient enzymatic activity of glucocerebrosidase

Gaucher Disease: a prototype of glycosphingolipidosis


Ernest Gaucher


FACULTÉ DE MÉDECINE DE PARIS

THÈSE

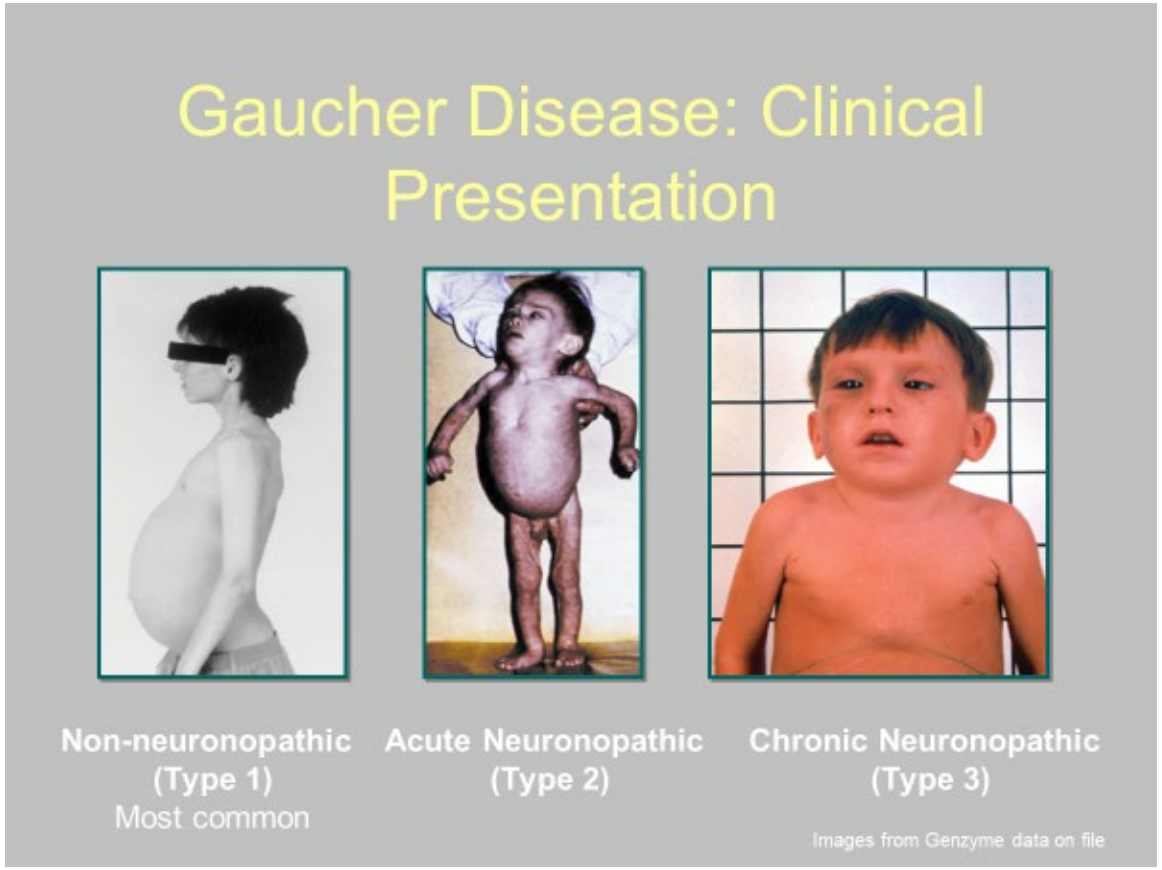
POUR

LE DOCTORAT EN MEDECINE

PHILIPPE-CHARLES-ERNEST GAUCHER

DE L'EPITHELIOMA PRIMITIF DE LA RATE

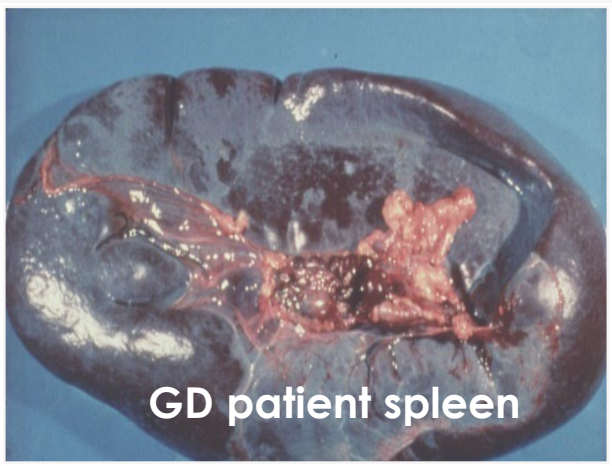
Gaucher PCE: De l'epithelioma primitif de la rate, hypertrophie idiopathique de la rate sans leucemie. Faculte de Medecine (1882), These de Paris.

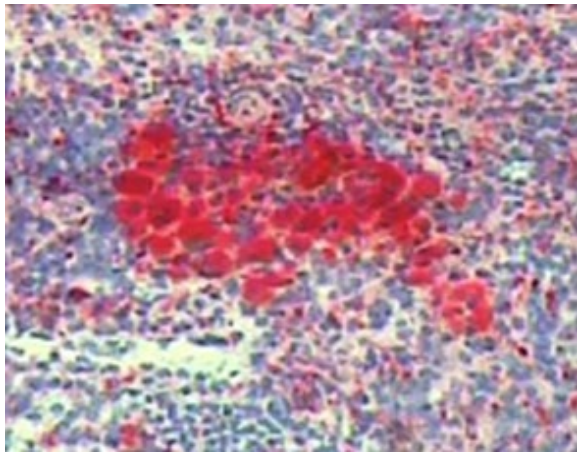


Gaucher patients and carriers of GBA mutations have increased risk for Parkinsonism and Lewy-body dementia.

Sidransky E, et al. N Engl J Med. 2009;361:1651-61; Baumann N, et al. J Neurol Neurosurg Psych 2001,1:133-4.

Gaucher Disease – Gaucher cells





Gaucher cells accumulate in spleen, liver and bone marrow

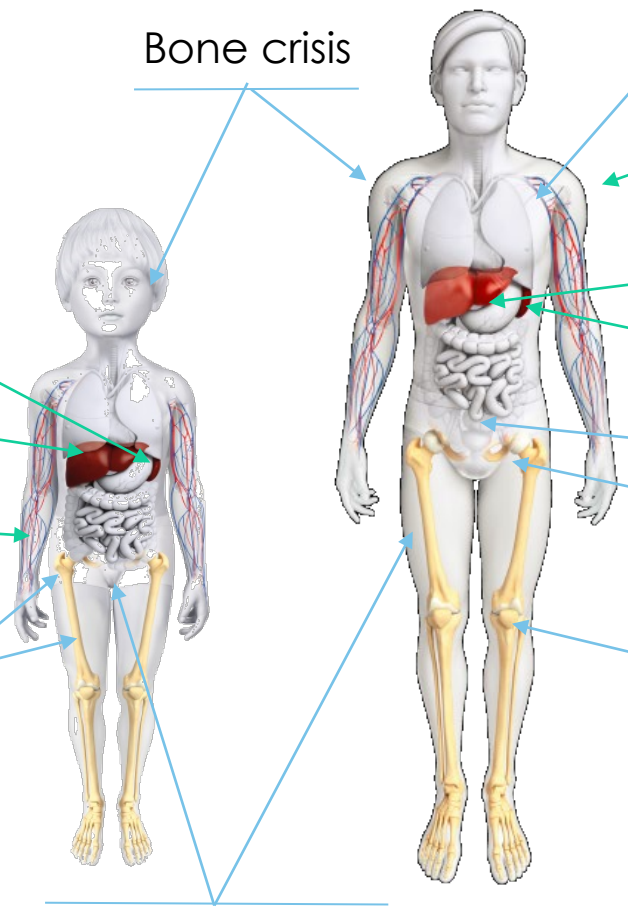
Lipid-laden Gaucher cells show features of alternatively activated (M2) macrophages, surrounded by smaller inflammatory macrophages (M1).

Gaucher cells in liver and spleen are associated with organ enlargement; their presence in bone marrow is thought to impair haematopoiesis.

Boven LA, van Meurs M, Boot RG, Mehta A, Boon L, Aerts JM, Laman JD. Gaucher cells demonstrate a distinct macrophage phenotype and resemble alternatively activated macrophages. Am J Clin Pathol. 2004 Sep;122(3):359-69.

Clinical presentation of Gaucher disease

Gaucher Disease: clinical manifestations in children and adults



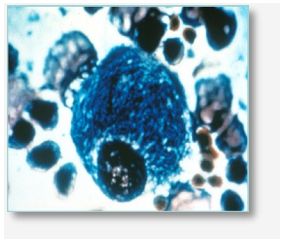
Growth retardation

Splenomegaly

Hepatomegaly

Anaemia/ Thrombocytopenia

Growth



Enlarged macrophages (Gaucher cell)

Bone crisis

Infiltration of macrophages in bone marrow

Pathological fracture

Anaemia/ Thrombocytopenia

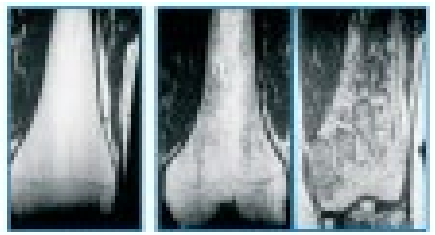
Hepatomegaly

Splenomegaly

Compression fracture

Osteonecrosis/ Osteopenia

Erlenmeyer deformity

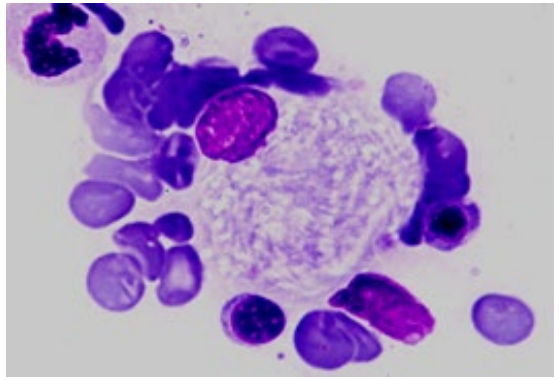


Normal Homogeneous
Heterogeneous

Cox TM Schafield JP Bailier's Clin Haematol. 1997:10:657-689

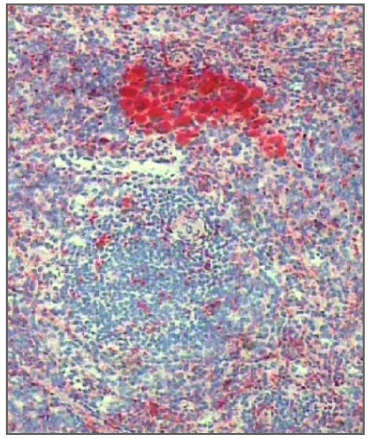
Diagnosis of Gaucher Disease

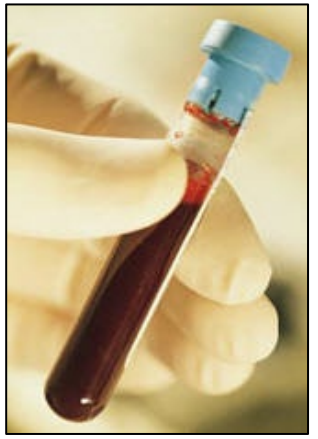
Gaucher cell-derived plasma biomarkers



Gaucher cells secrete specific proteins and lipids into the circulation that might serve as biomarkers (context, relation with disease manifestation).

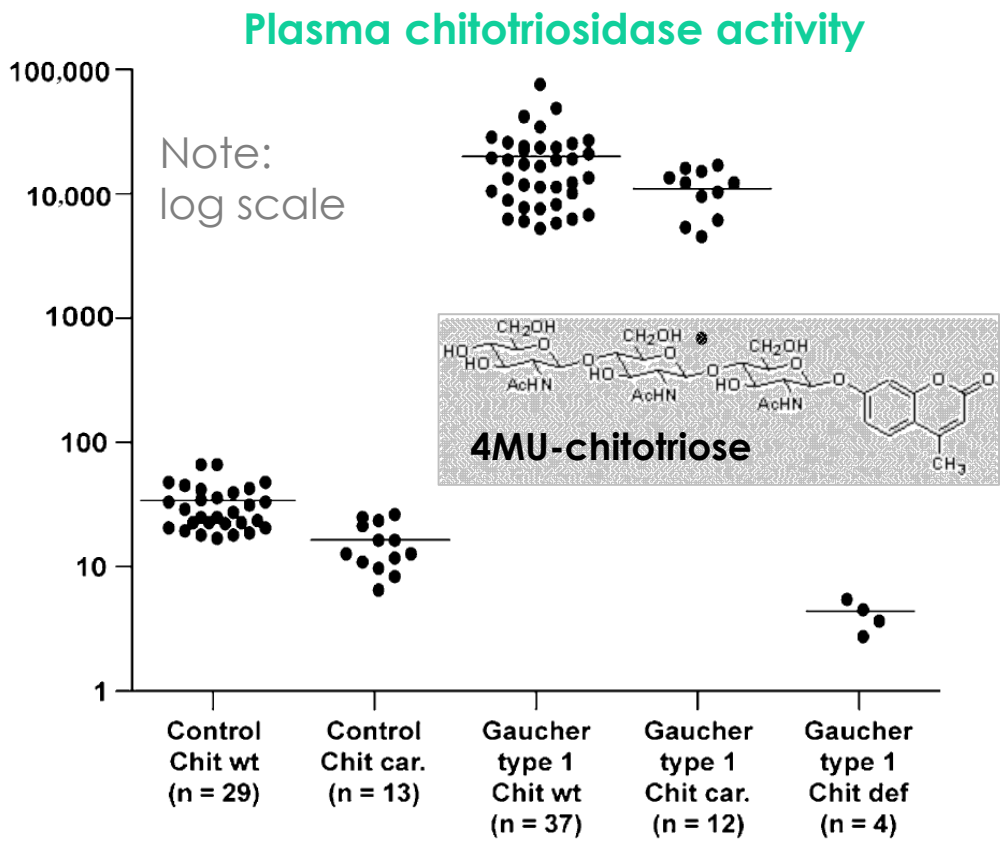
- Improved diagnosis
- Monitoring disease progression:
  - Initiation of costly therapy
- Monitoring therapy response:
  - Individualized dosing



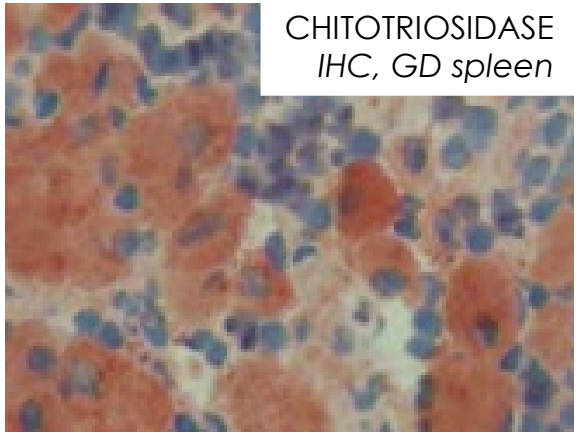


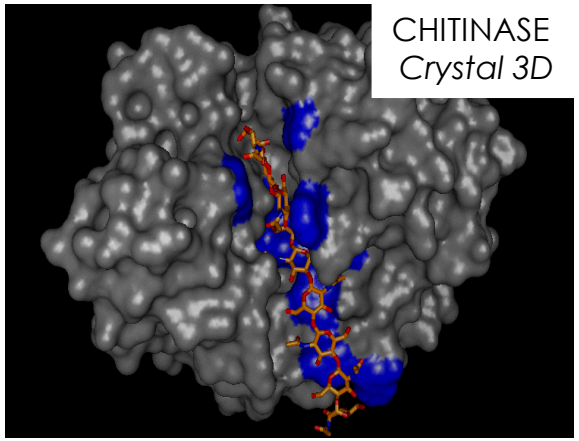
Chitotriosidase: first identified Gaucher cell biomarker

- Overexpressed and secreted by Gaucher cells;
- About 1000-fold elevated in plasma untreated GD.



Hollak CE, et al. J Clin Invest. 1994;93:1288-92





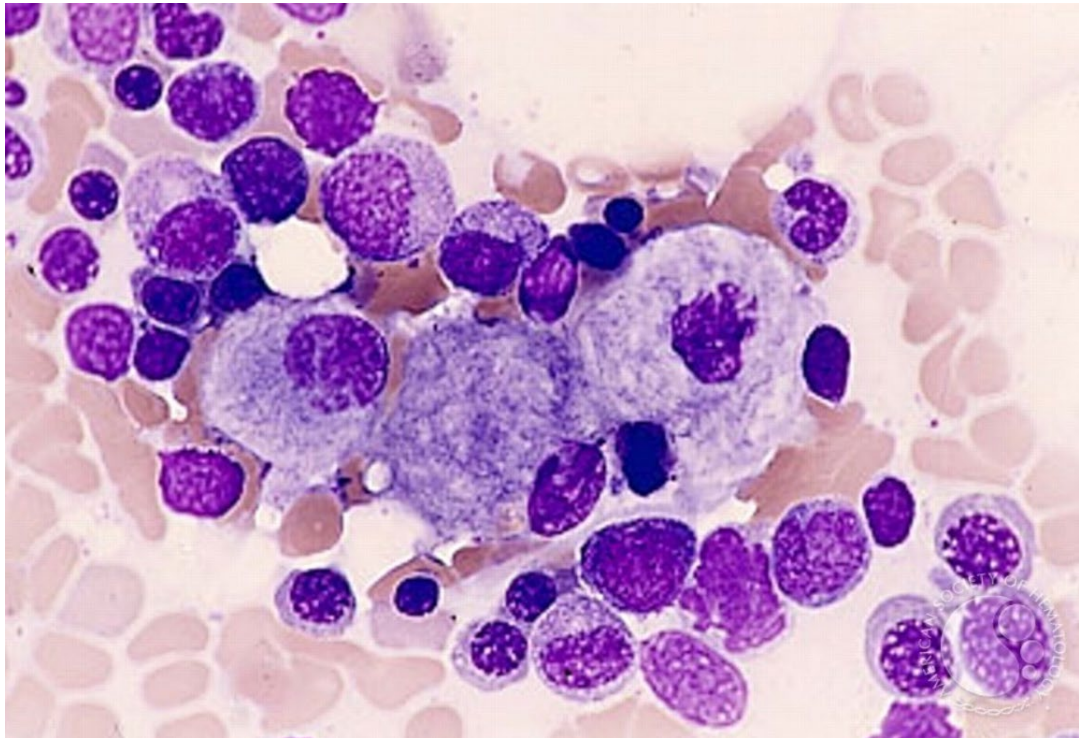
Ferraz MJ et al. BBA. 2014;1841:811-25

Confirmation of GD diagnosis

The case for using a specific marker of Gaucher cells as GD biomarker

- Presence of GCs is associated with visceral disease in GD patients;
- Removal of GCs (BMT, ERT) results in clinical improvements.

- Induction of GCs in mice causes cytopenia and organomegalies;
- Correction of GCs ameliorates visceral disease in GD mice.

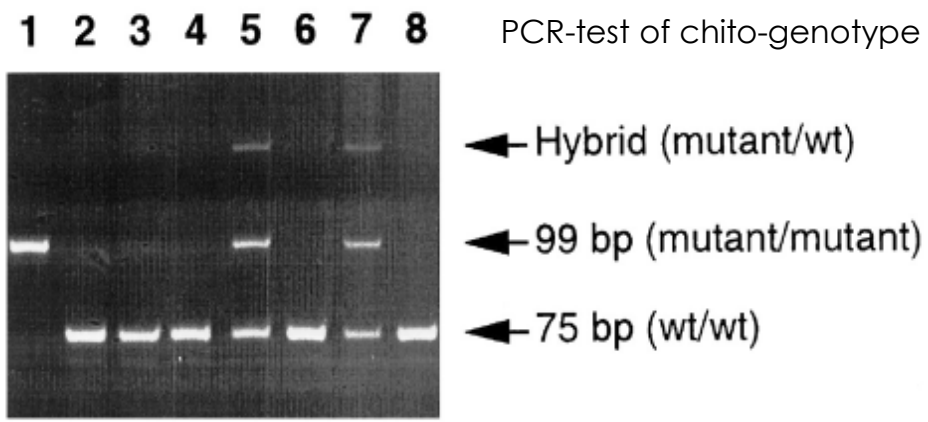


For a review on the topic, see: Aerts JMFG, Kuo CL, Lelieveld LT, Boer DEC, van der Lienden MJC, Overkleeft HS, Artola M. Glycosphingolipids and lysosomal storage disorders as illustrated by Gaucher disease. Curr Opin Chem Biol.2019;53:204-215.

Limitation of chitotriosidase: common inherited deficiency

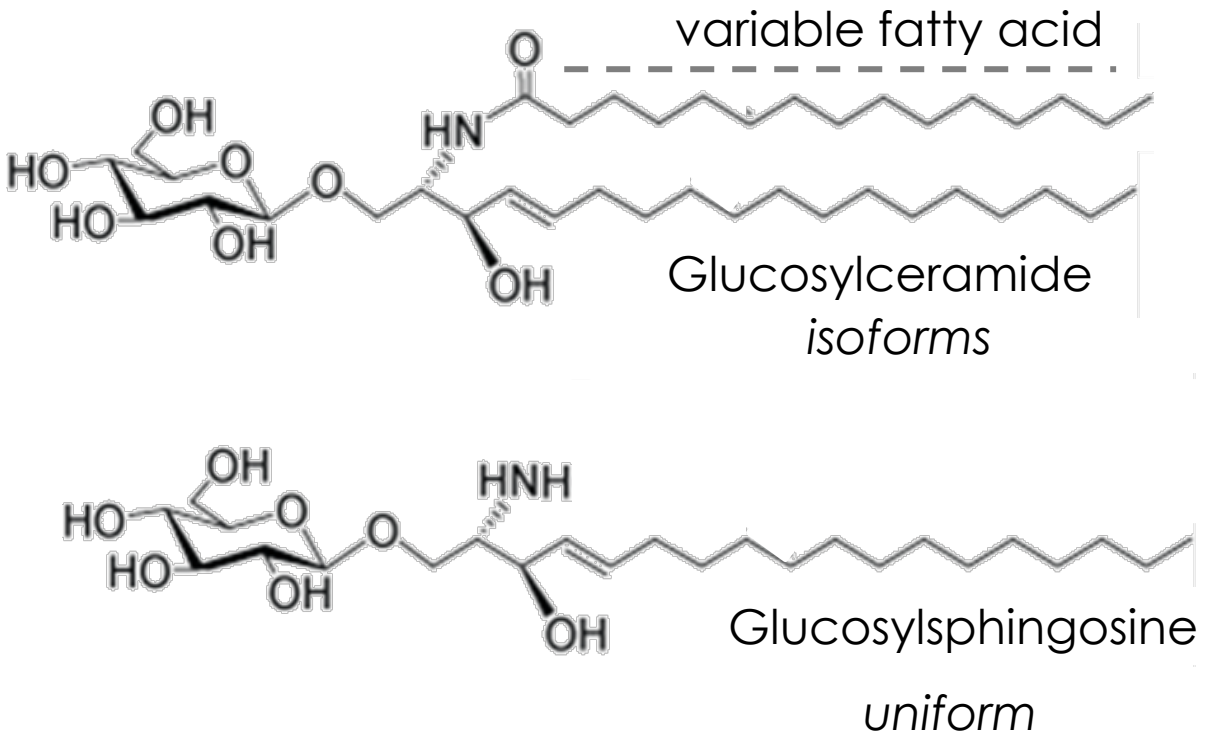
- Common occurrence of 24 BP duplication causing enzyme absence;
- Carriers show half normal plasma chitotriosidase activity (gene dosis effect).

24 bp dupl. carrier frequency	
Europe	35%
Japan	38%
Indonesia	33%
Ashkenazi Jews	37%
African Americans	19%
Central Africa	10%



Boot RG, Renkema GH, Verhoek M, Strijland A, Bliek J, de Meulemeester TM, Mannens MM, Aerts JM. The human chitotriosidase gene. Nature of inherited enzyme deficiency. J Biol Chem.1998;273:25680-5.

Lipid abnormalities in Gaucher disease



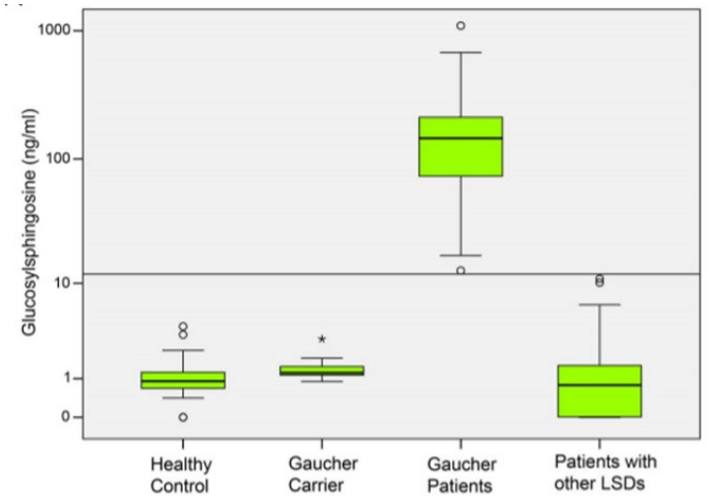
Raghavan, S.S.; Mumford, R.A.; Kanfer, J.N. Isolation and characterization of glucosylsphingosine from Gaucher's spleen. J. Lipid Res. 1974, 15, 484–490.
Nilsson, O.; Svennerholm, L. Accumulation of glucosylceramide and glucosylsphingosine (psychosine) in cerebrum and cerebellum in infantile and juvenile Gaucher disease. J. Neurochem. 1982, 39, 709–718.

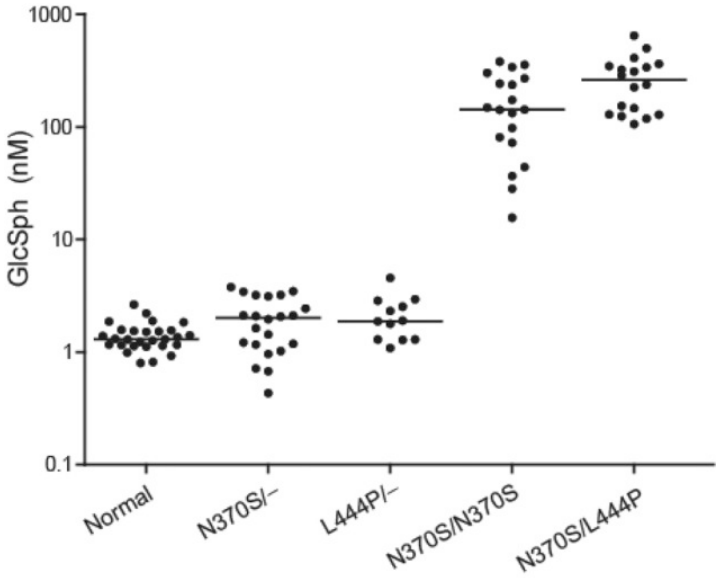
Elevated glucosylsphingosine in GD plasma

- Glucosylsphingosine is a highly sensitive and specific biomarker for primary diagnostic and follow-up monitoring in Gaucher disease in a non-Jewish, Caucasian cohort of GD patients.
  (Rolfs A, *et al.* PLoS One. 2013;8(11):e79732)

- Glucosylsphingosine is a key biomarker of Gaucher disease.
  (Murugesan V, *et al.* Am J Hematol. 2016;91:1082-9)

From: PlosOne 2013;8:e79732

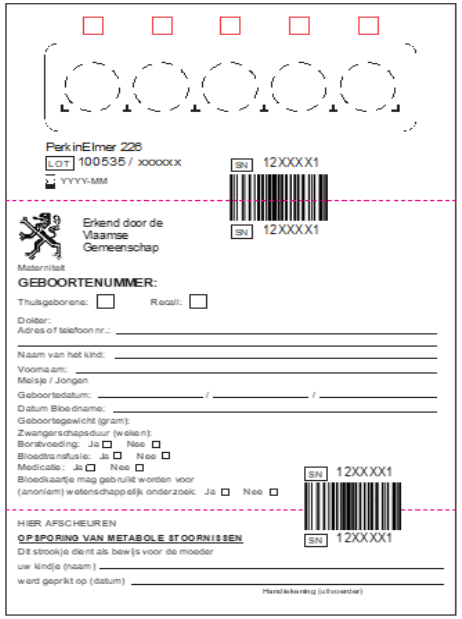




Elevated plasma glucosylsphingosine in Gaucher disease: relation to phenotype, storage cell markers, and therapeutic response.
(Dekker N, *et al.* Blood. 2011;118(16):e118-27)

Note: trend of slightly elevated GlcSph in GD carriers.

First stage: algorithm of screening and further diagnosis



DBS

- Screening

Enzymatic assay in DBS by MSMS; Biomarkers in DBS by MSMS

Blood

- Confirmation

Enzymatic assay in leucocytes

DNA

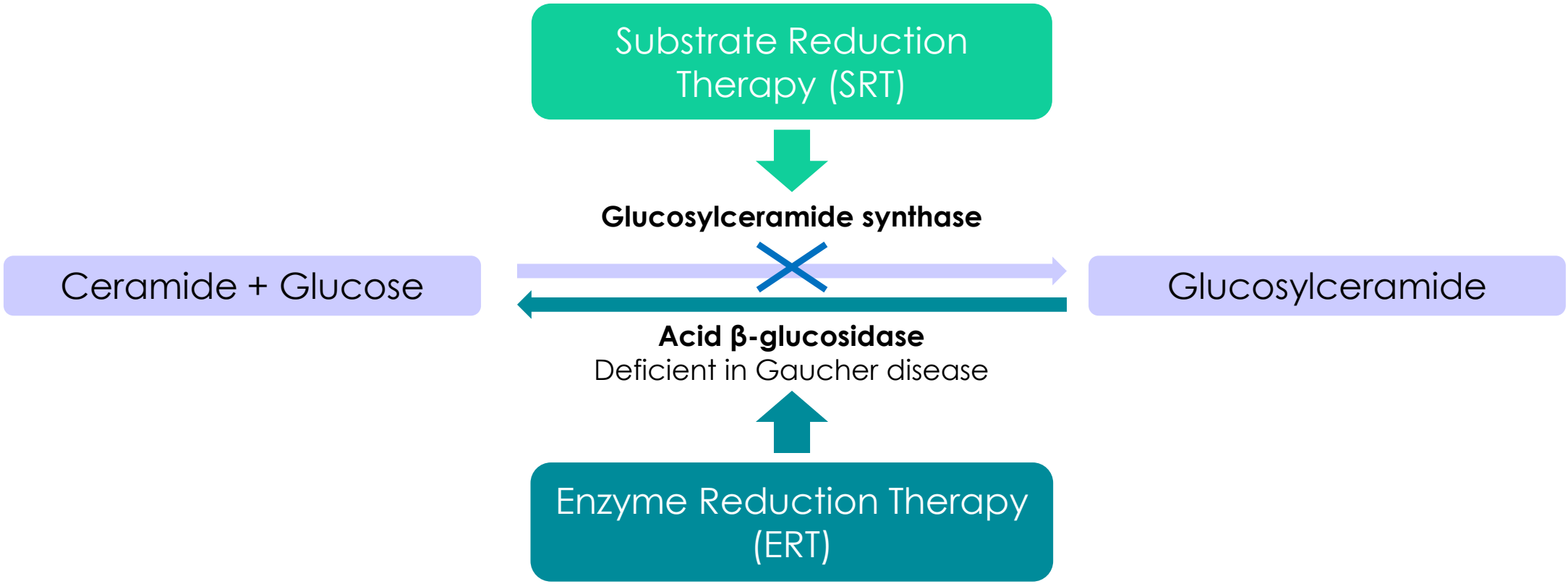
- Further diagnosis

GBA-gene mutation analysis

Therapy of Gaucher disease

Treatment options

- Since the 90s', enzyme therapy for Gaucher disease has been on the market. The deficient enzyme is administrered per infusion, so that the accumulated substrate can be broken down.
- Substrate reduction therapy is also available. This oral therapy inhibits the substrate synthesis.



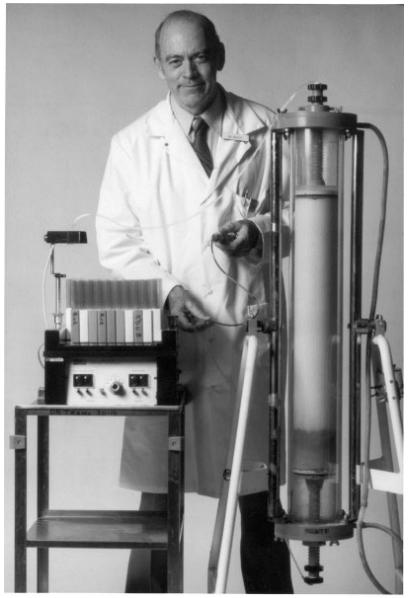
Therapy for type 1 Gaucher disease

Type 1 Gaucher disease: well defined therapeutic target
→ Glucocerebrosidase deficiency in macrophages

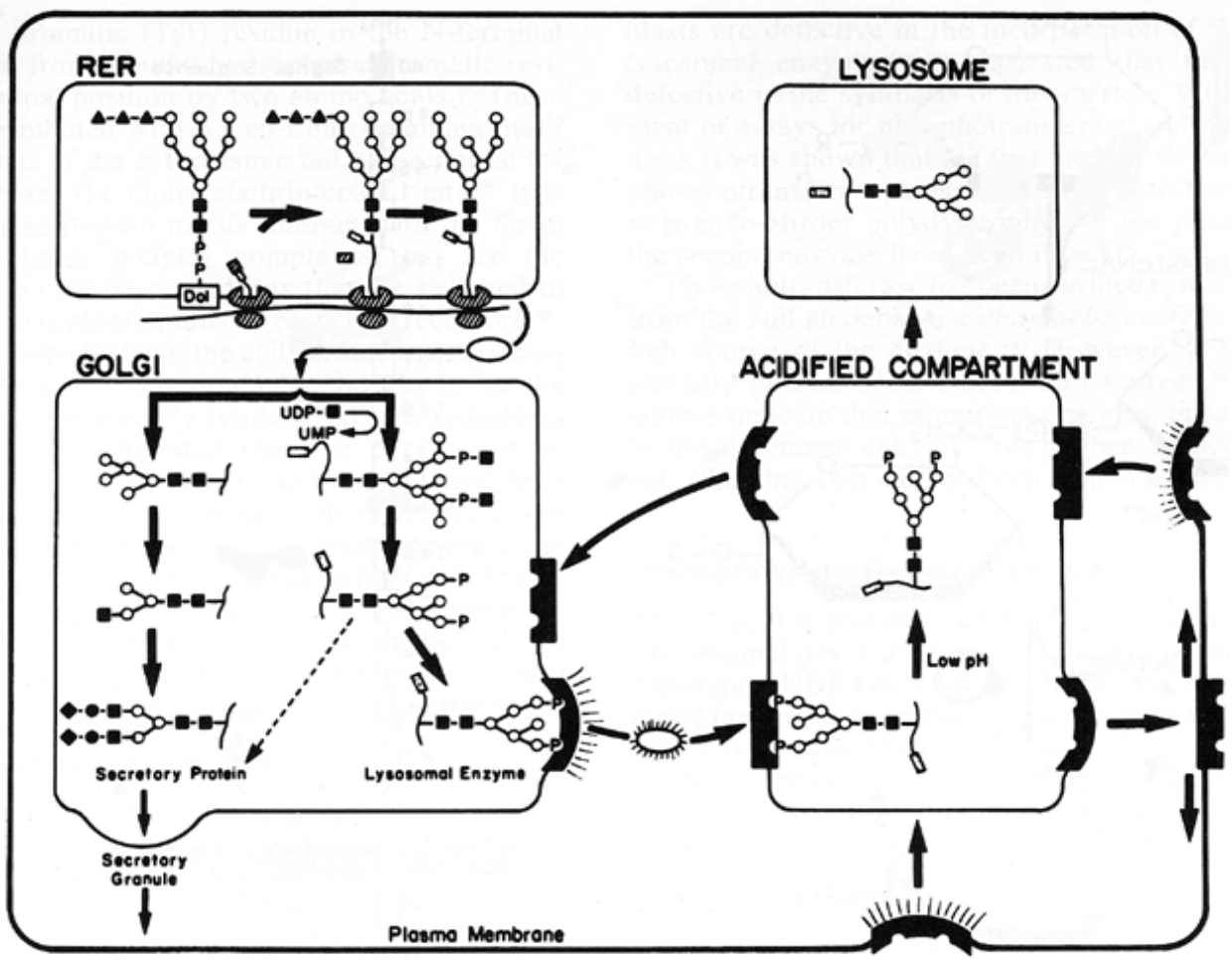
Enzyme replacement therapy (ERT): supplementing macrophages with glucocerebrosidase (Roscoe Brady, NIH, Bethesda)

Barton NW, Brady RO, *et al.* (1991)
Replacement therapy for inherited enzyme deficiency-macrophage-targeted glucocerebrosidase for Gaucher's disease.
N Engl J Med. 1991;324:1464-70.

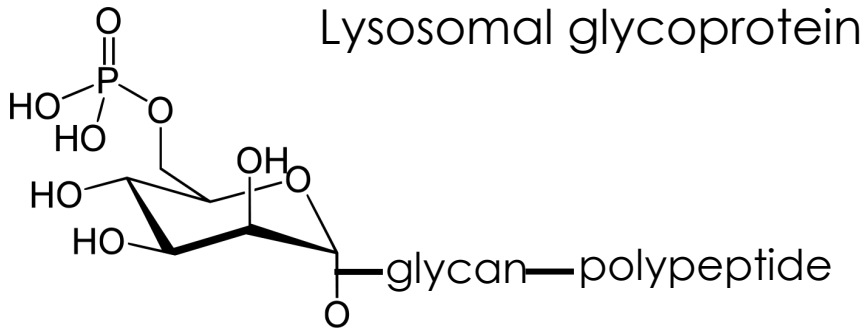
Pentchev P, Brady RO *et al.* (1973)
Isolation and characterization of glucocerebrosidase from human placental tissue
J. Biol. Chem. 248, 5256–61



Lysosomal glycoproteins: unique formation of ‘M6P recognition signal’ in glycans

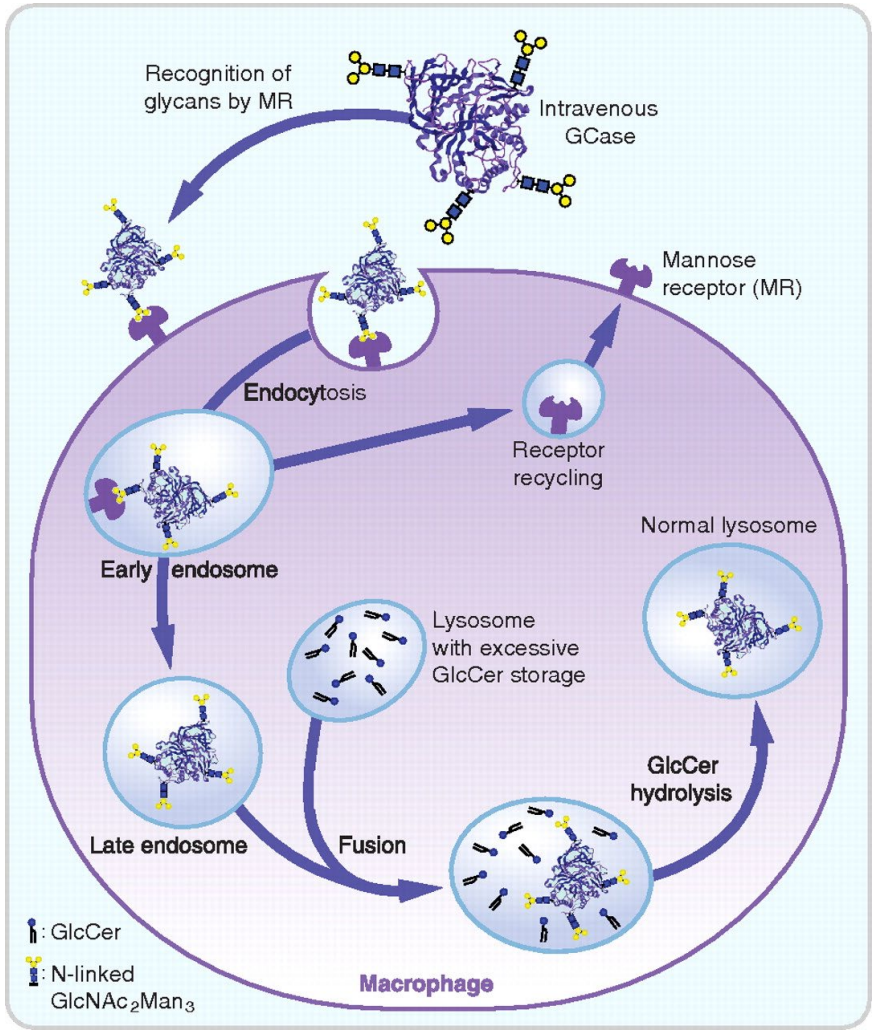


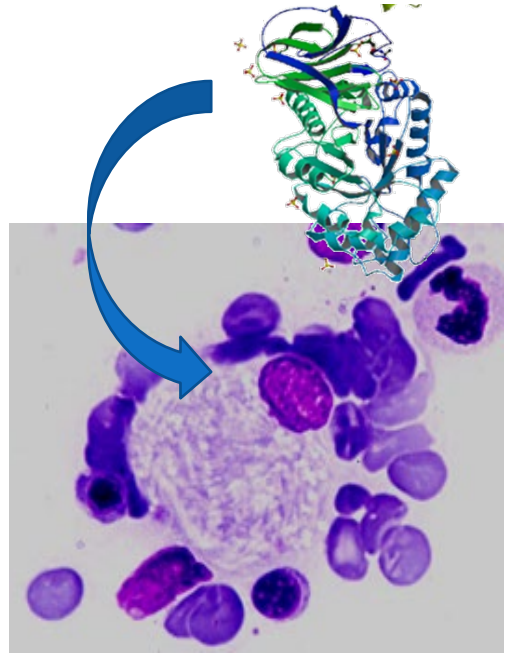
Mannose-6-phosphate (M6P) mediated sorting of components to lysosomes



- Lysosomal hydrolases are glycoproteins synthesized at ER.
- N-linked glycans acquire M6P recognition signals allowing bindng to M6P receptors in Golgi.
- Sorting of complex to acid late endosomes.
- Release of hydrolase and recycling of receptor.

Type 1 Gaucher Disease: macrophage enzyme supplementation

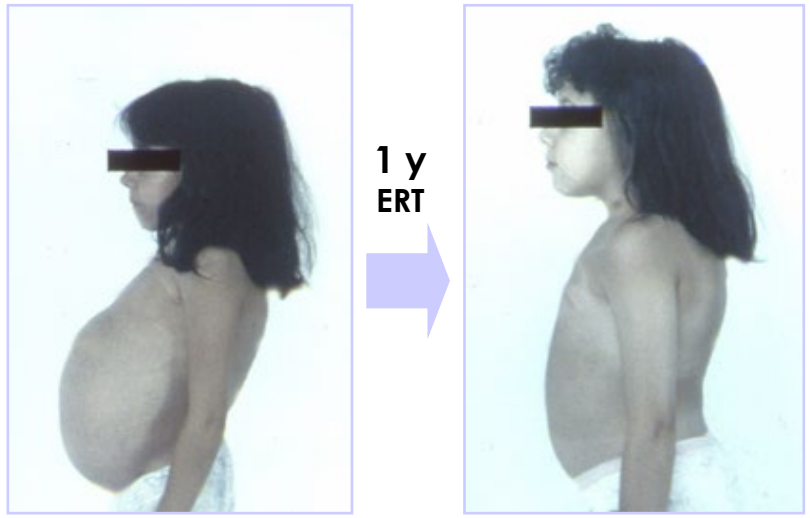




Therapy strategy:
Infusion with GBA containing N-linked glycans with terminal mannose moieties, favoring uptake and delivery to lysosomes of macrophages.

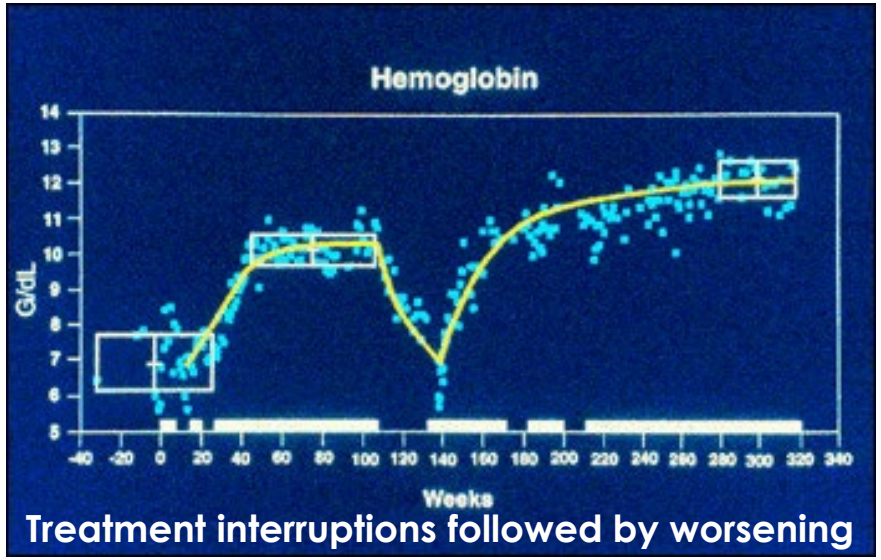
ERT of type 1 Gaucher disease: effective, but costly chronic therapy

Effective therapy for type 1 GD,
correcting major visceral manifestations.
Designed at NIH in the ‘80s.
Drug development by Genzyme Corp.



Characteristic response in type 1 GD child:
reduction organomegaly and growth spurt

First patient treated at NIH: anemia response

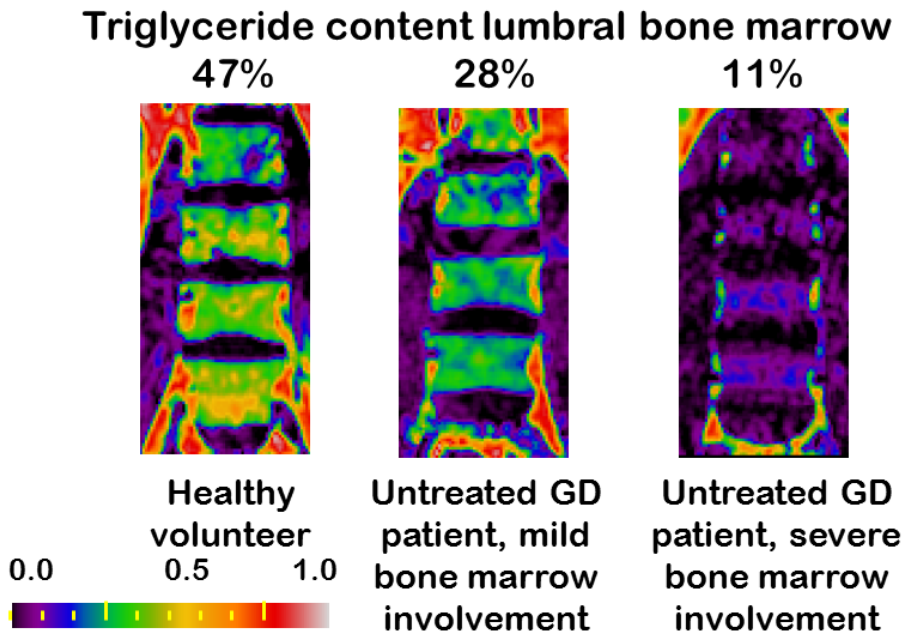


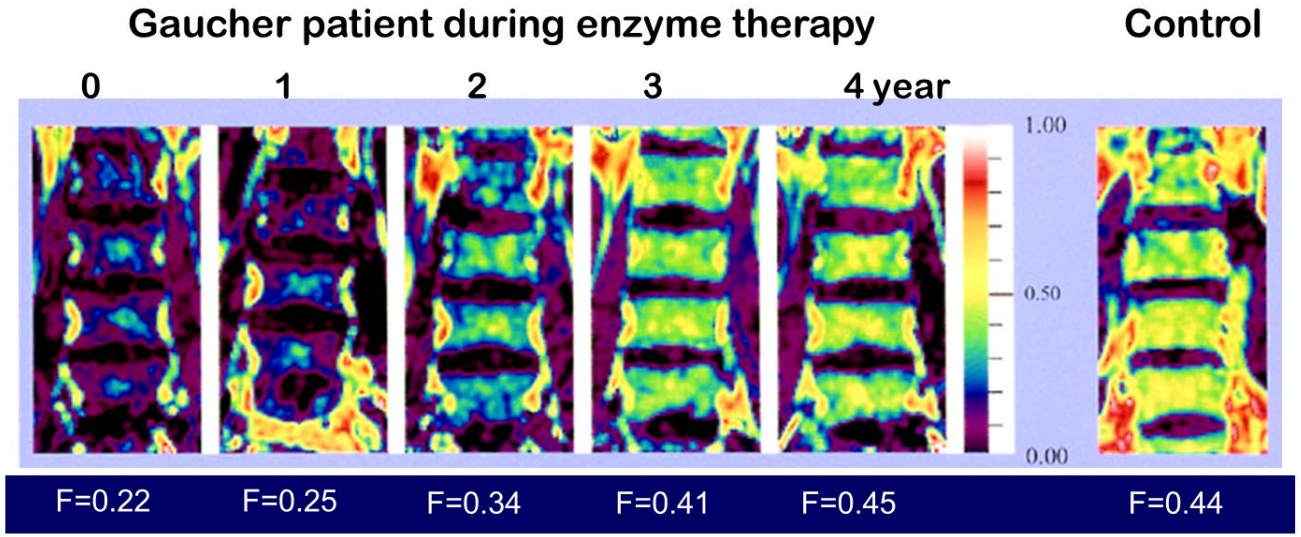
Initially required per adult patient/year:
enzyme isolated from 25,000 placentas.
Enzyme isolated with AMC-procedure.

High costs: > €200,000/adult patient/year

Major clinical responses to ERT in type 1 Gaucher patients

Abnormality in lumbar bone marrow quantified by QCSI (quantitative chemical shift imaging)





Bone marrow correction visualized by QCSI-NMR

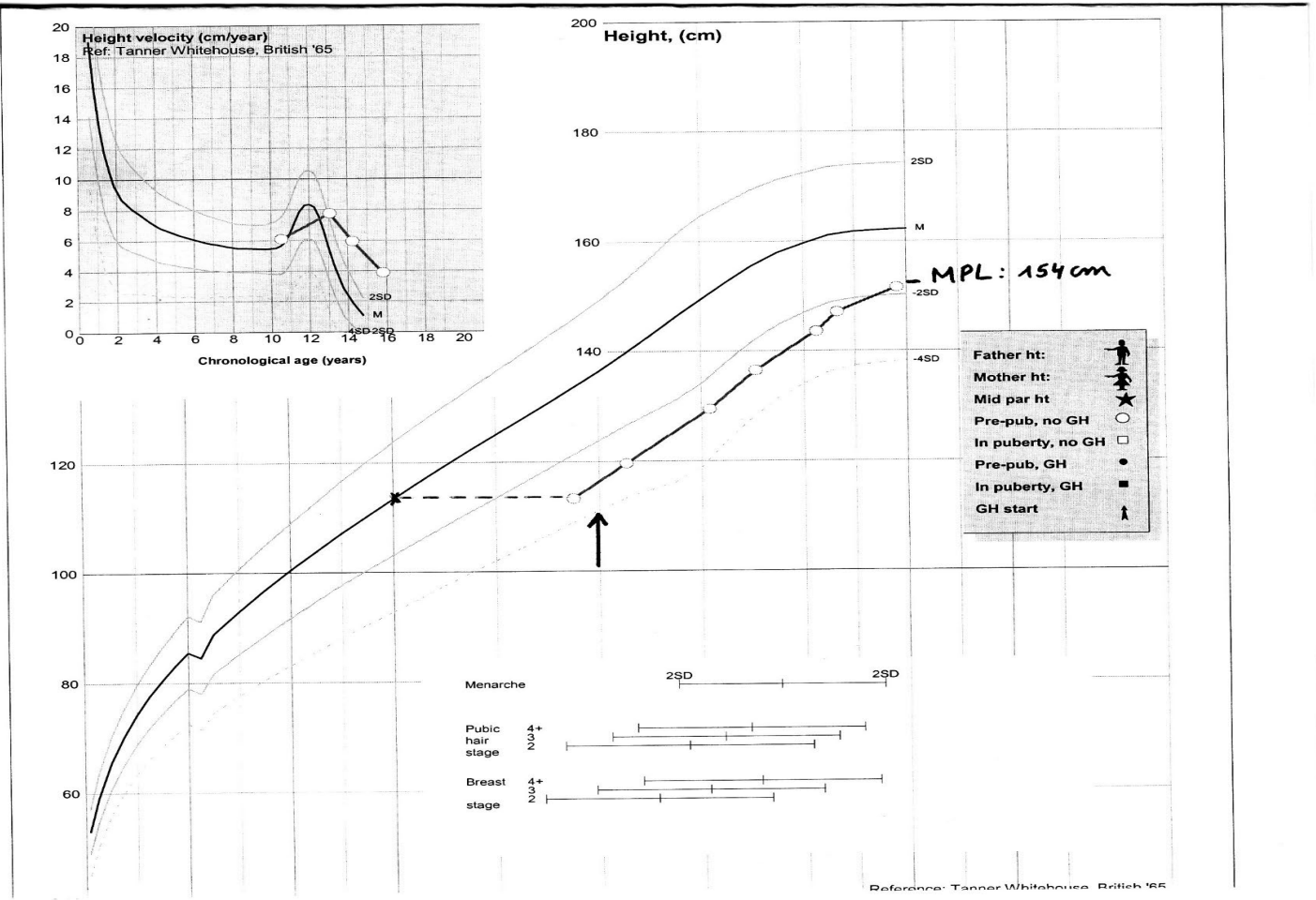
Maas M, Hollak CE, Akkerman EM, Aerts JM, Stoker J, Den Heeten GJ. Quantification of skeletal involvement in adults with type I Gaucher's disease: fat fraction measured by Dixon quantitative chemical shift imaging as a valid parameter. AJR Am J Roentgenol. 2002 Oct;179(4):961-5.

Bone Mass Density in Gaucher Disease

Age Group	Baseline DEXA Z-score ≤ -1 (Lumbar spine)	After 8 – 10 years of Cerezyme®
Children (n=19)	−1.38 (95% CI −1.73 to −1.03)	−0.73 (95% CI −1.25 to −0.21)
Adolescents (n=23)	−2.16 (95% CI −2.53 to −1.79)	−1.13 (95% CI −1.78 to −0.49)
Young adults (n=30)	−1.95 (95% CI −2.26 to −1.64)	−0.67 (95% CI −1.09 to −0.26)
Older adults (n=68)	−1.82 (95% CI−2.00 to−1.63)	−1.30 (95% CI−1.57 to −1.04)

Children (ages ≥5 years to <12 years), Adolescents (ages ≥12 years to <20 years), Young adults (ages ≥20 years to < 30 years) and Adults (ages ≥30 years to ≤50 years).

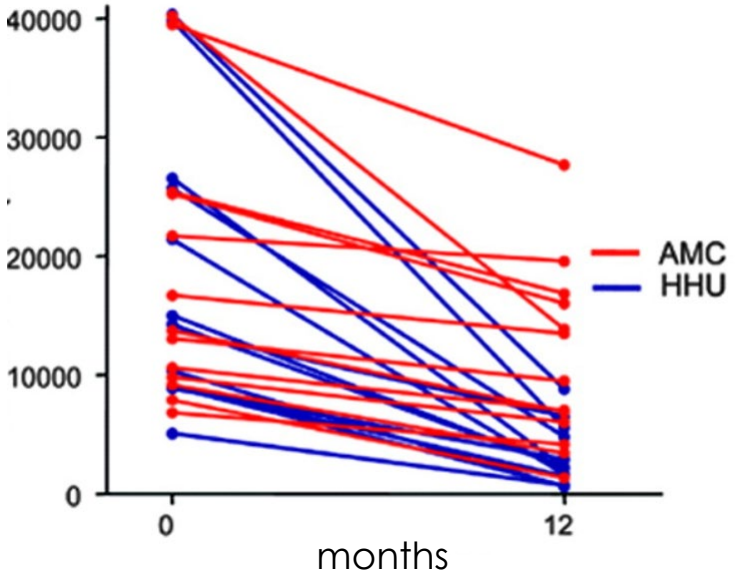
Mistry et al. Blood Cells Mol Dis, 2011, 46(1): 66-72



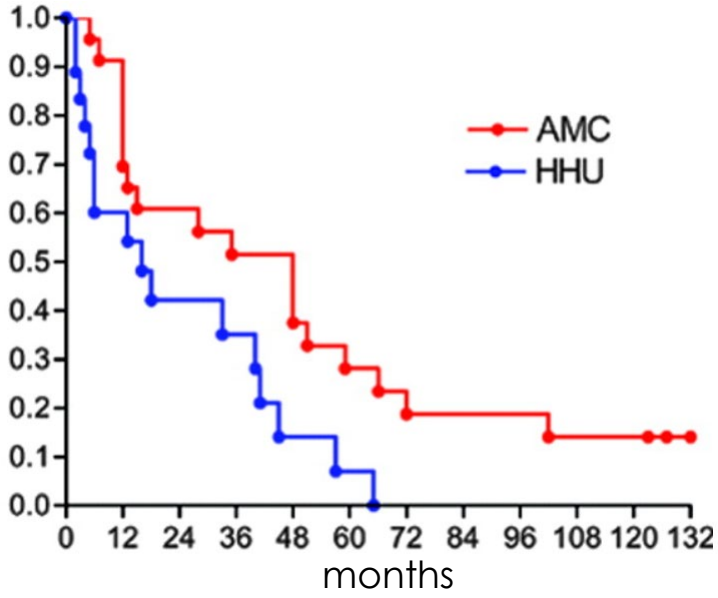
Impact of ERT dose on changes on plasma chitotriosidase activity

High dose (80 IU/kg/4 wks at HHU) *vs.* low dose (15-30 IU/kg/4 wks at AMC)

Plasma chitotriosidase:
baseline and after 12 months



Share of patients who reached a chitotriosidase <5000 nmol/mL/h



De Fost M, *et al.* Blood 2006;108:830-835

- Higher dosing on average reduces faster plasma chitotriosidase;
- Marked individual variation in chitotriosidase correction.

Efficacy of ERT for GD – limitations for type 2/3 GD

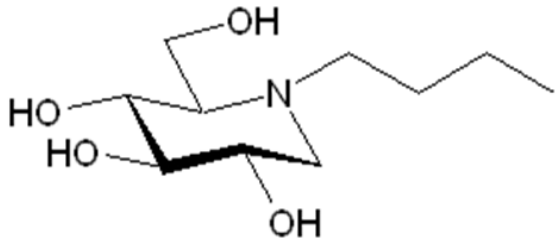
- ERT does not prevent neurological manifestations in type 2/3 GD patients (enzyme not passing blood brain barrier).
- Long-term complications occur during otherwise successful ERT:
  - Bone complications, multiple myeloma, hepatocellular carcinoma;
  - Amyloidosis, pulmonary hypertension, Parkinsonism.
- Likely these complications are not due to storage macrophages, but other cell types affected by GBA deficiency.

van Dussen L, *et al.* J Inherit Metab Dis. 2014;37:991-1001

Substrate reduction therapy

Oral inhibitors of GCS registered as **orphan drugs** for treatment of mild type 1 GD

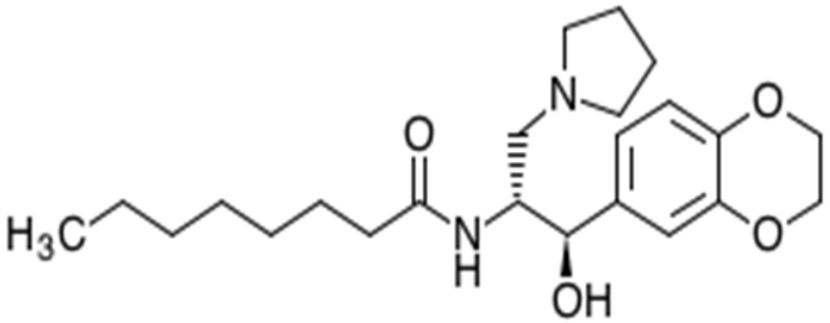
Miglustat, FDA registered 2001



Poor GCS inhibitor

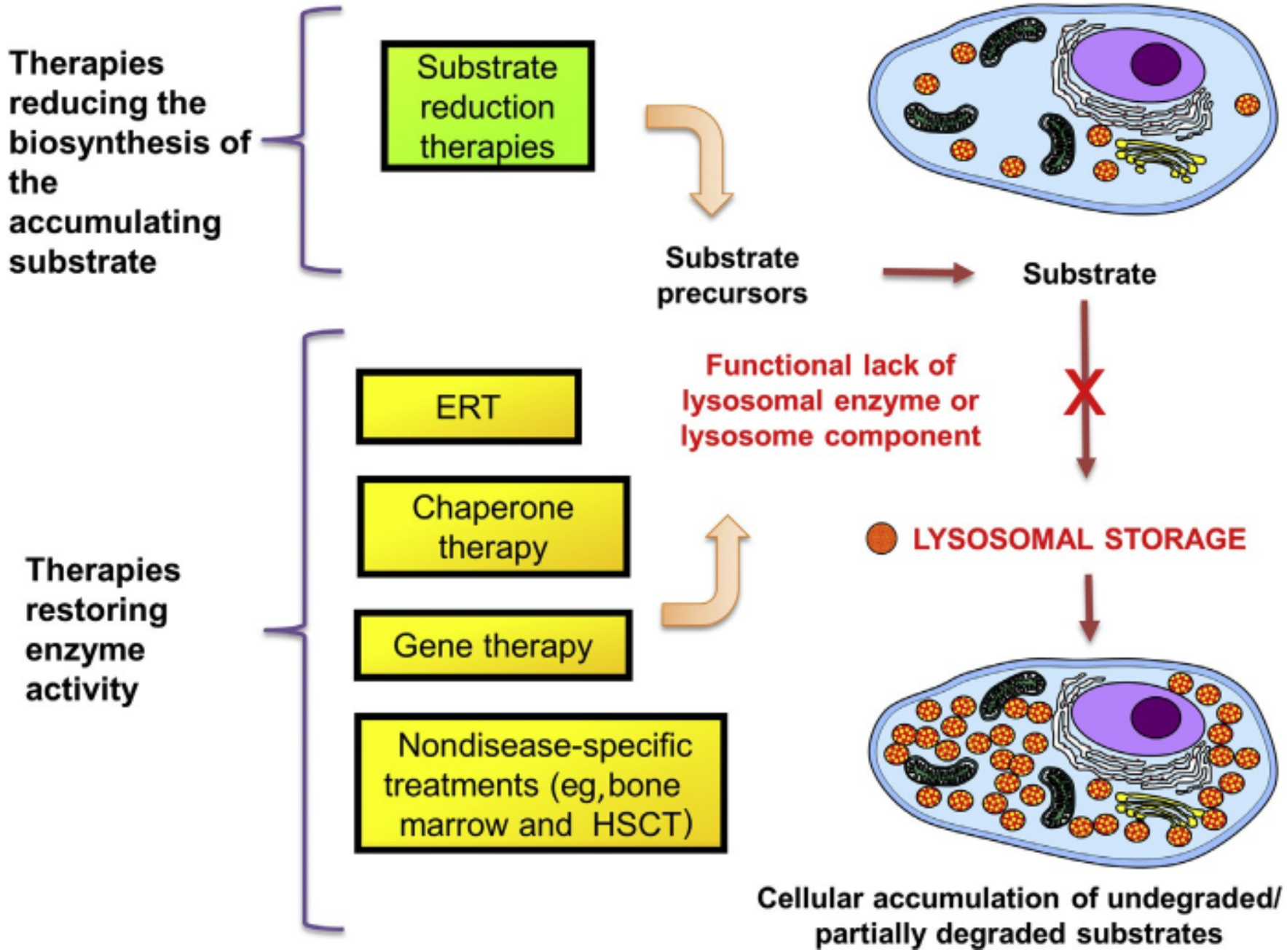
- poor (IC_{50} 25 uM),
- non-specific
- (intestinal glycosidases and GBA2)

Eliglustat, registered 2014



More potent GCS inhibitor

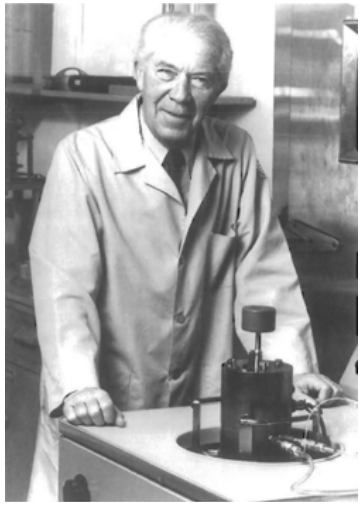
- high affinity (IC_{50} 20 nM)
- metabolism by CYP2D6
- not brain-permeable



Peroxisomal Biogenesis Disorders

THE PEROXISOME

- Small organelle
- Present in all eucaryotic cells
- One of the organelles discovered by C. De Duve, Belgian Nobel Price winner



Functions of peroxisomes:

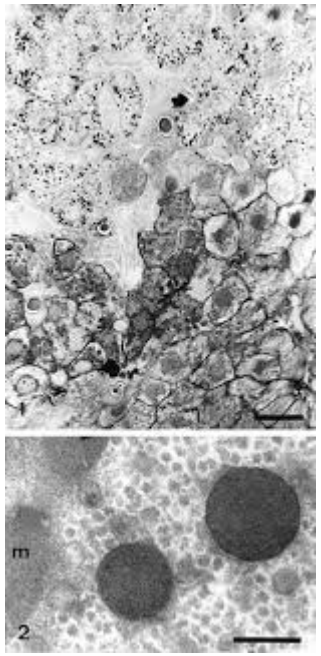
- Beta-oxidation of very long chain fatty acids
- Biosynthesis of ether lipids including plasmalogens
- Glyoxylate detoxification
- Pipecolate degradation
- Phytanic acid alfa-oxidation
- Biosynthesis of polyunsaturated fatty acids
- Hydrogen peroxide metabolism/catalase

- Unique biochemical functions
- Interaction with mitochondria and cytoplasmatic enzymes in different metabolic pathways

PEROXISOMAL DISORDERS

Assembly disorders: Zellweger spectrum diseases

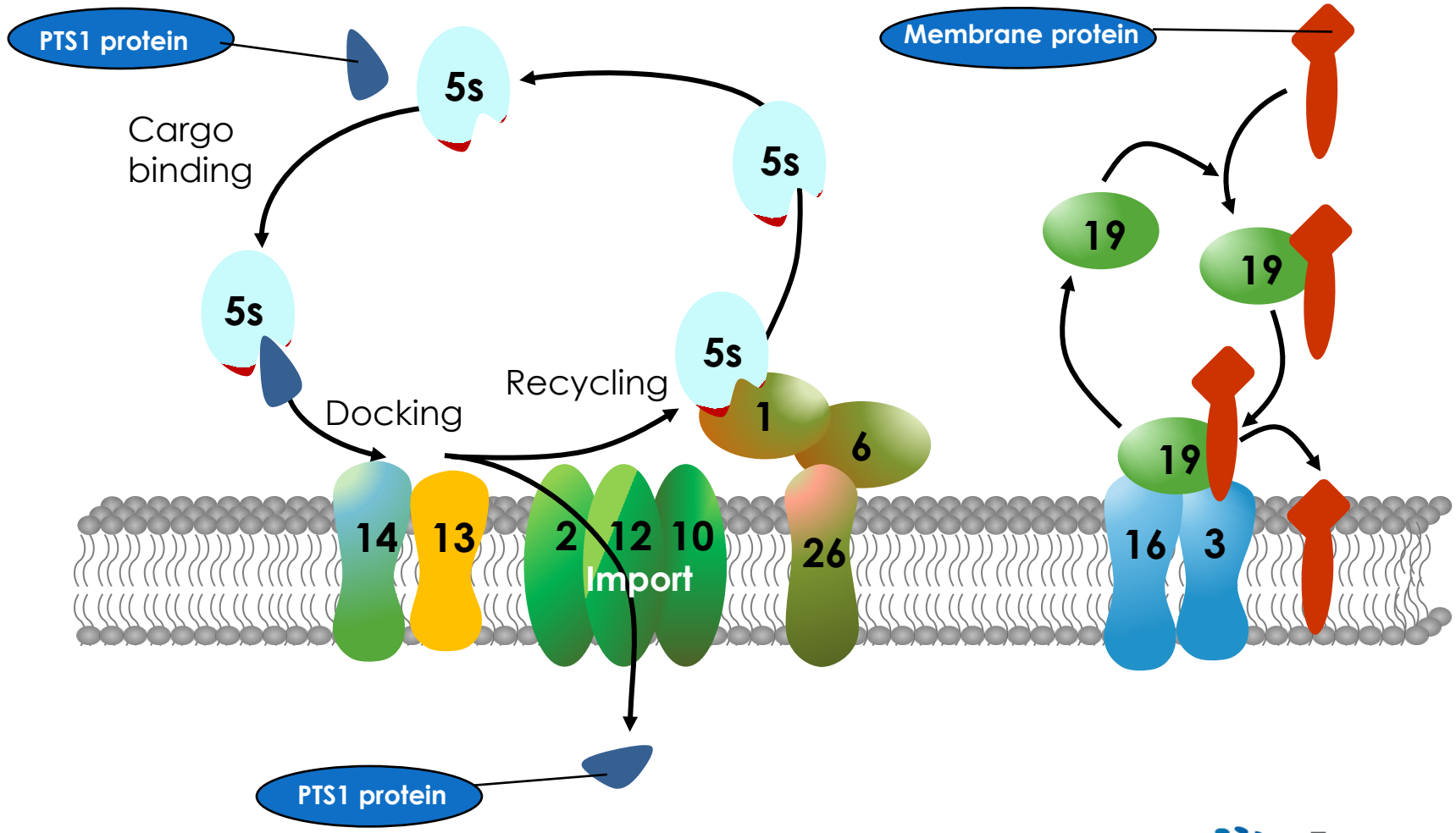
- "Empty peroxisomes"/Ghosts (EM picture by Prof. F. Roels, UZ-Gent)
- All enzymatic functions lost = biogenesis disorders

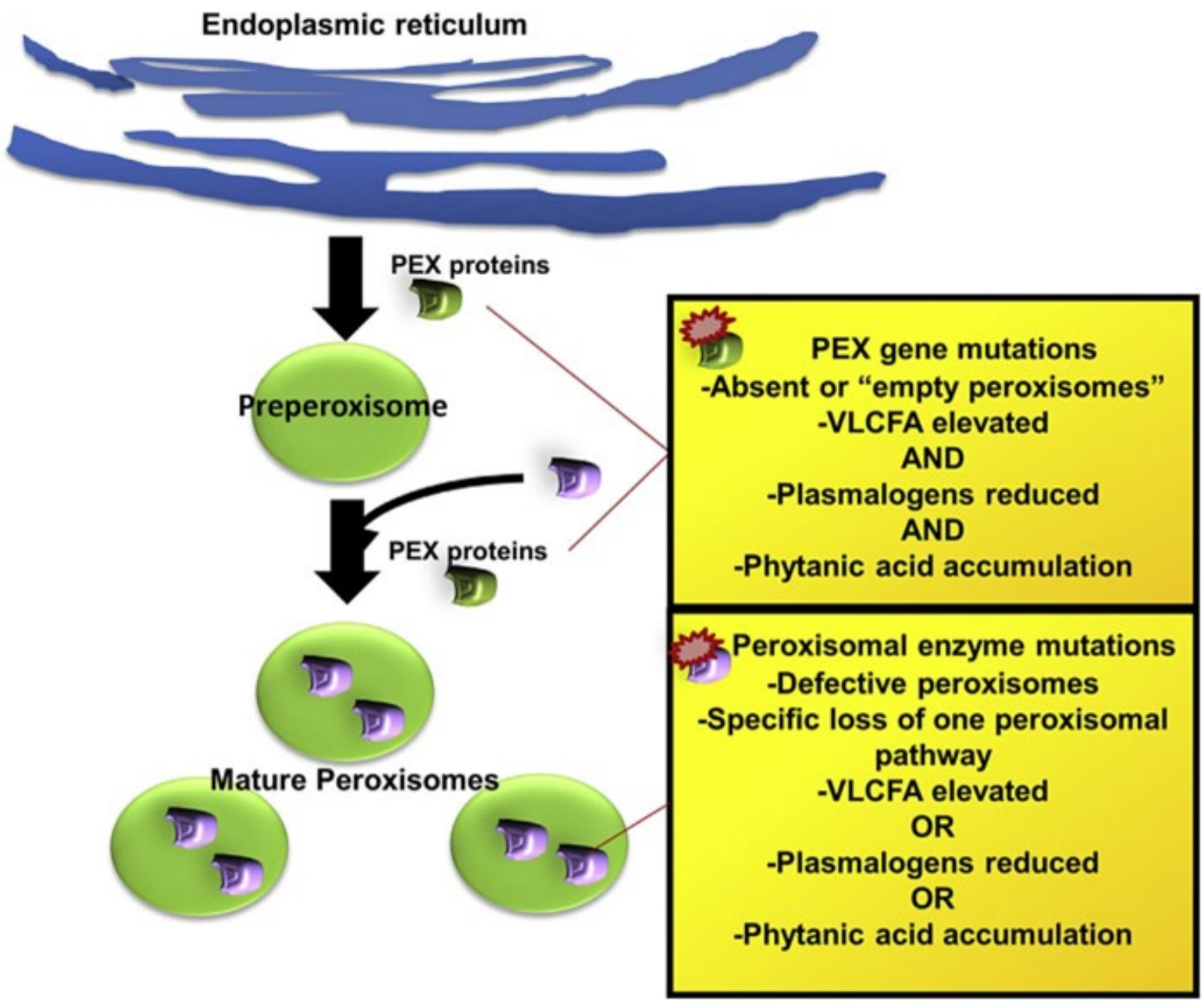


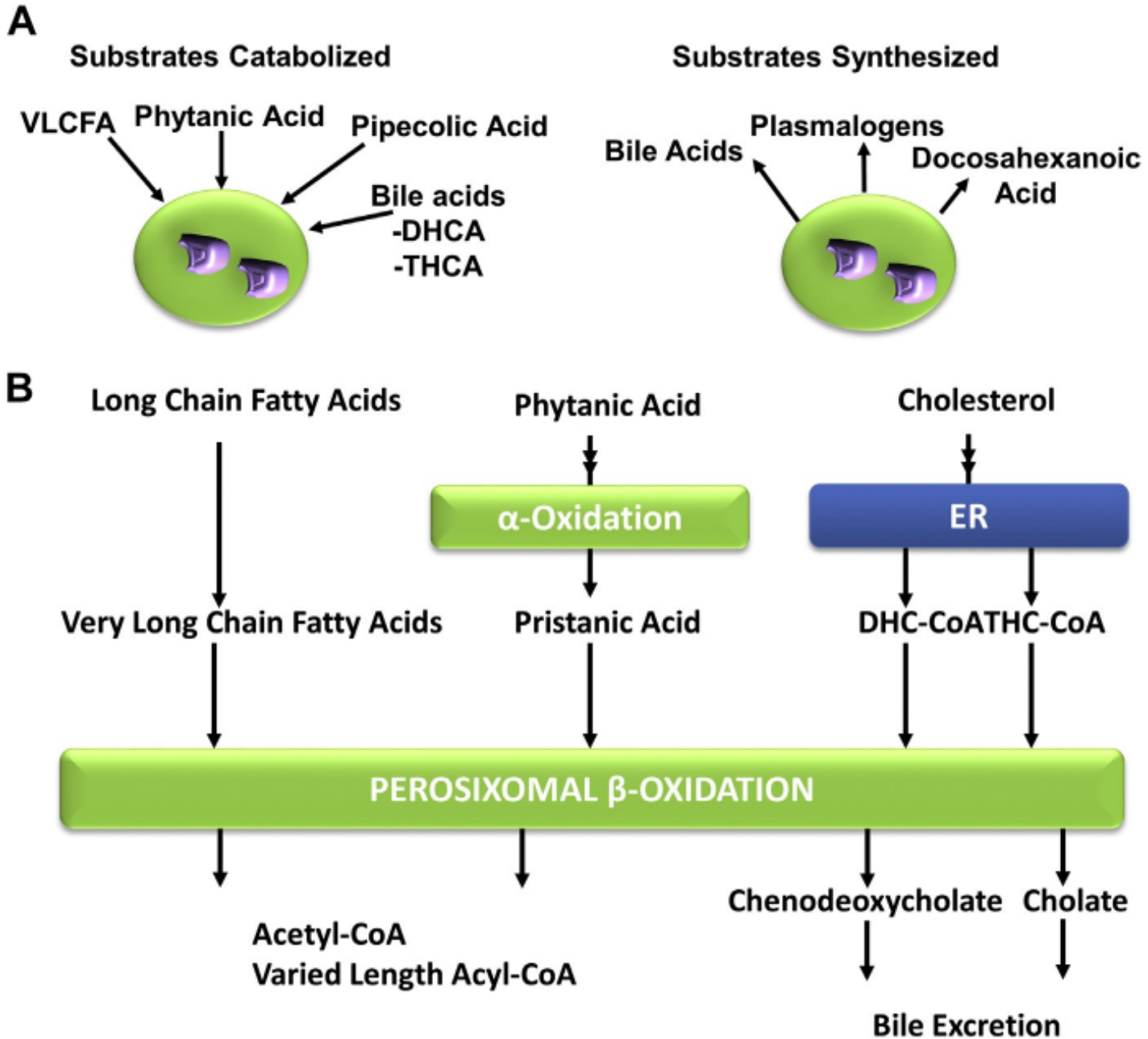
Others:
Single enzyme deficiencies:
e.g. X-Adrenoleucodystrophy
Multiple enzyme deficiencies
e.g. rhizomelic chondrodysplasia punctata

- Rare inherited metabolic disorders
- One X-linked, others autosomal recessive inherited

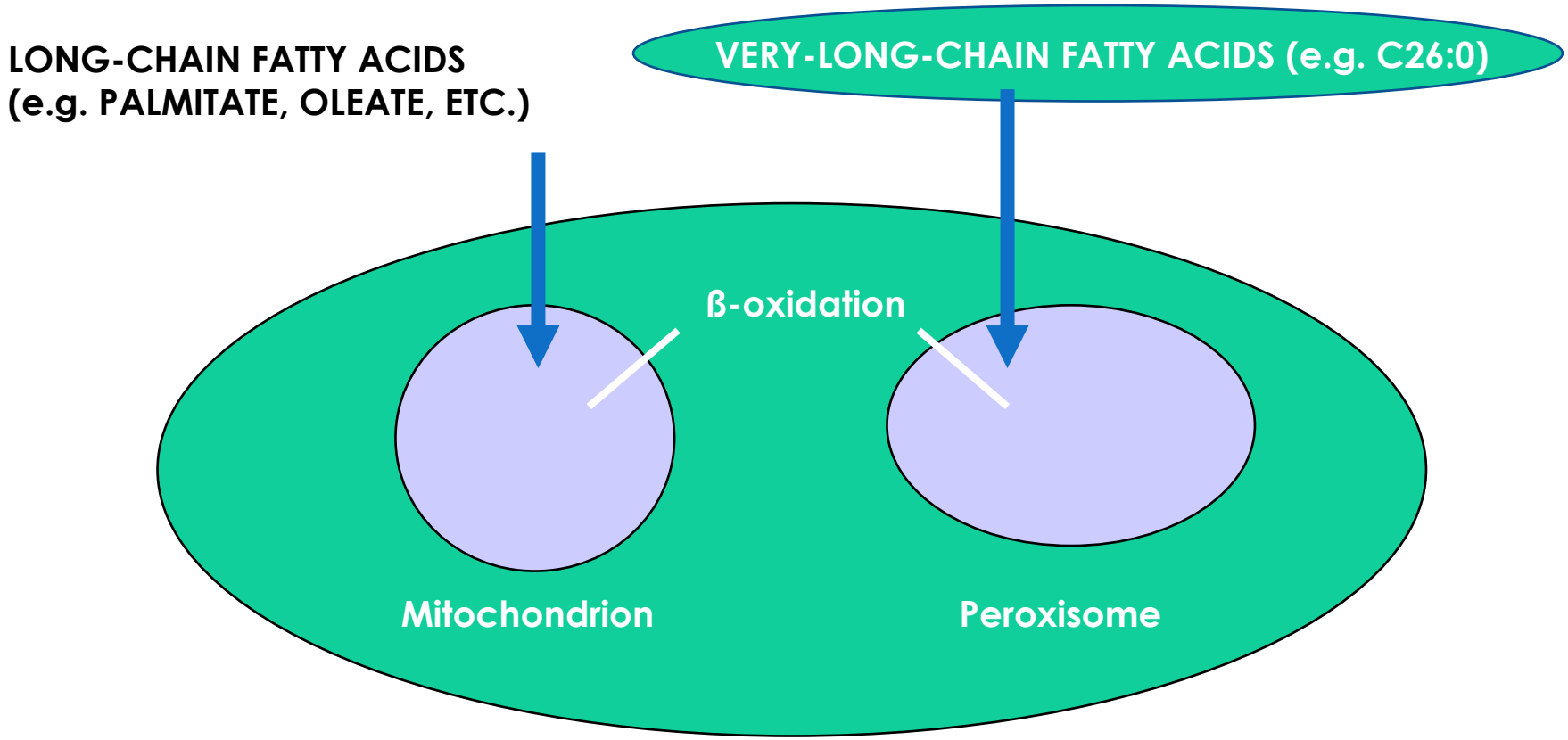
HUMAN PEROXISOME BIOGENESIS AND UPTAKE OF MATRIX & MEMBRANE PROTEINS FROM THE CYTOSOL







MITOCHONDRIAL AND PEROXISOMAL FATTY ACID ß-OXIDATION IN HUMAN CELLS



Peroxisomal defects

PEROXISOME BIOGENESIS DISORDERS

- Zellweger syndrome (ZS)
- Neonatal adrenoleukodystrophy (NALD)
- Infantile Refsum disease (IRD)
- Rhizomelic chondrodysplasia punctata (RCDP)

SINGLE PEROXISOMAL ENZYME DEFICIENCIES	**Pathway affected**
- X-linked adrenoleukodystrophy - D-bifunctional protein deficiency - Acyl-CoA oxidase deficiency - 2-Methylacyl-CoA racemase deficiency - Sterol carrier protein x deficiency - ABCD3 (PMP70) deficiency	**Beta-oxidation**
- DHAPAT-deficiency (RCDP Type 2) - Alkyl DHAP-synthase deficiency (RCDP Type 3) - FAR1 deficiency	**Plasmalogen biosynthesis**
- Refsum disease	**Alpha-oxidation**
- Hyperoxaluria Type 1 - Glycolate oxidase deficiency	**Glyoxylate metabolism**
- Acatalasaemia	**H_2O_2 metabolism**

Ron Wanders Metabolics.be meeting 2018

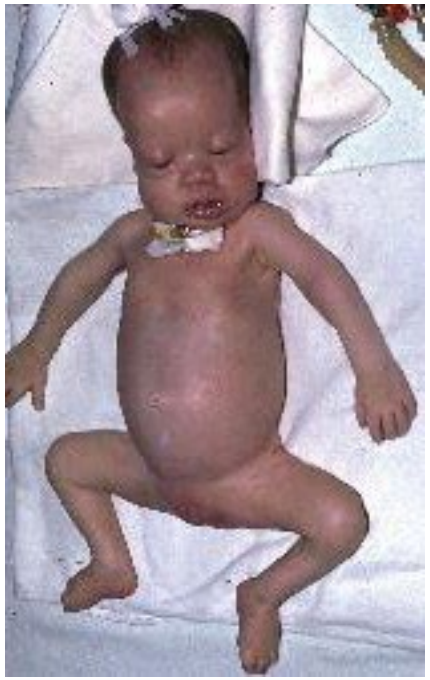
Clinical presentation of Zellweger Spectrum Disorders

ZELLWEGER SYNDROME PEROXISOMAL BIOGENESIS DEFECT: NEURONAL MIGRATION DISTURBANCES → HETEROTOPIA

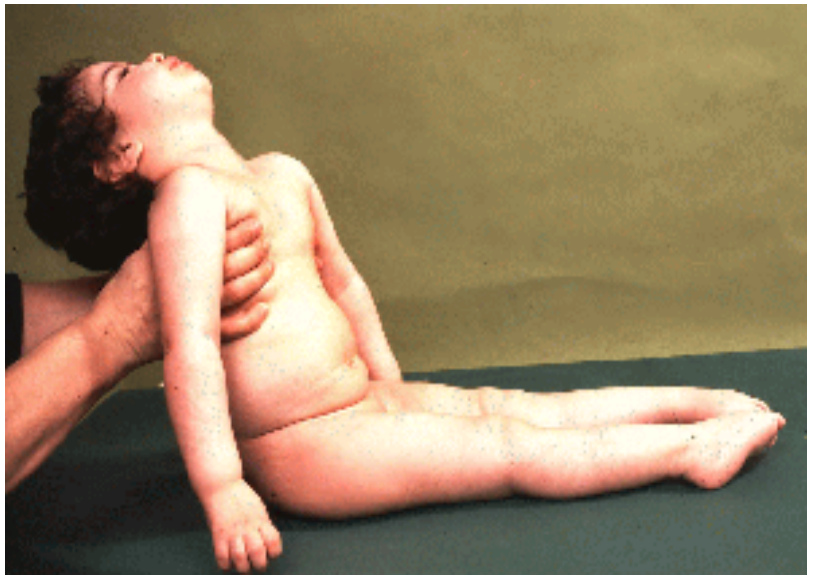
- Severe hypotonia
- Seizures
- Ocular abnormalities
- Dysmorphic
- Liver dysfunction
- Skeletal abnormalities
- Failure to thrive
- All peroxisomal fct are defect

ZELLWEGER SPECTRUM DISORDERS

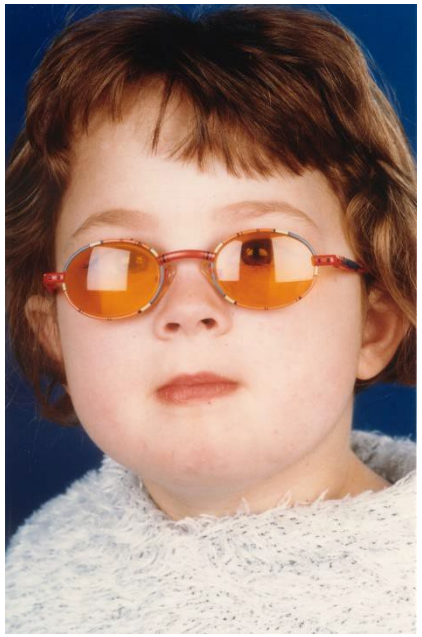
Peroxisome biogenesis disorders
"generalized peroxisomal disorders"



Zellweger syndrome



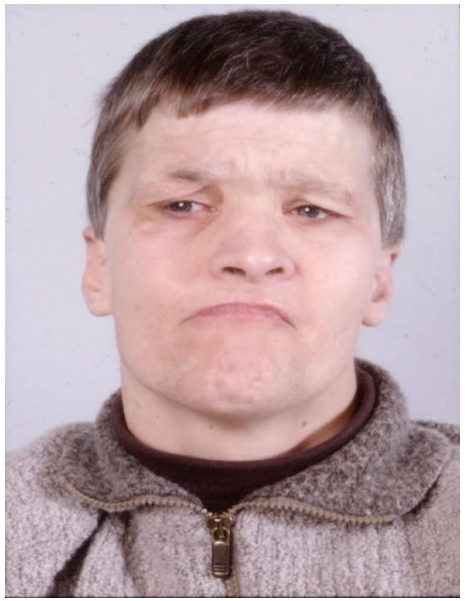
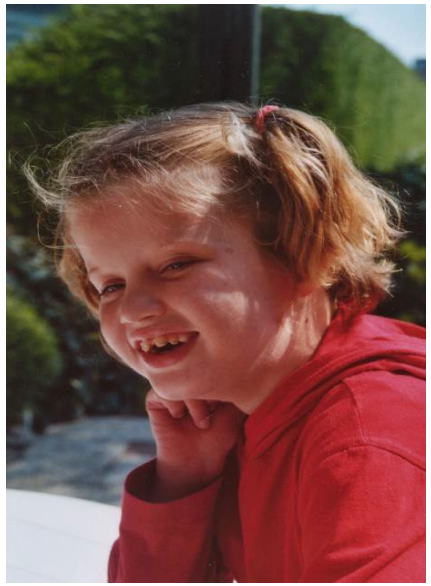
Neonatal adrenoleukodystrophy

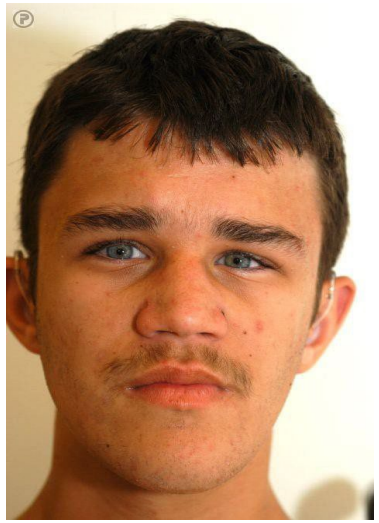
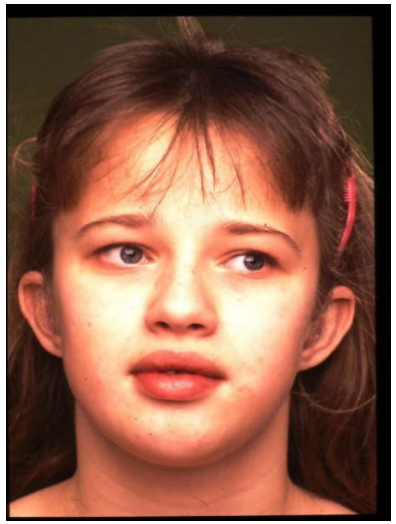


Infantile Refsum disease

Phenotype variants with overlapping clinical signs

ZSD: MILD PHENOTYPE

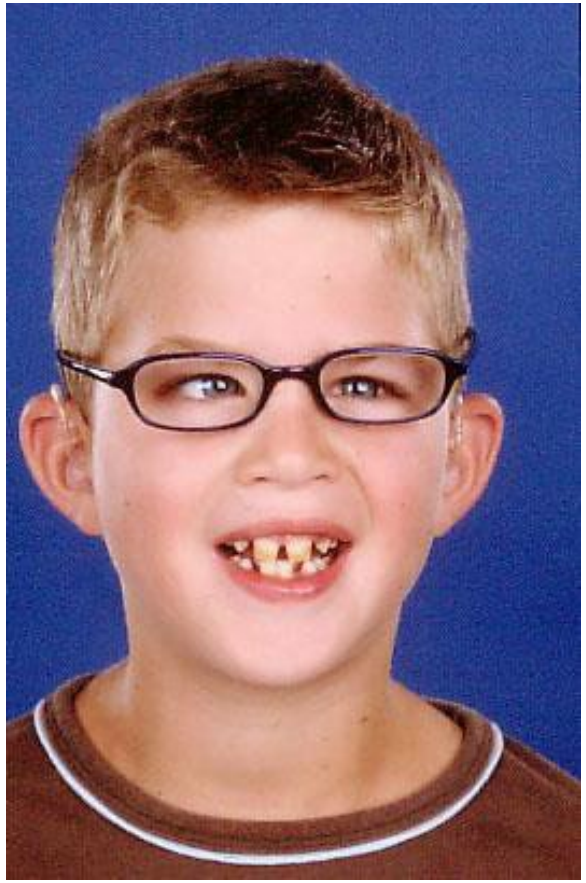




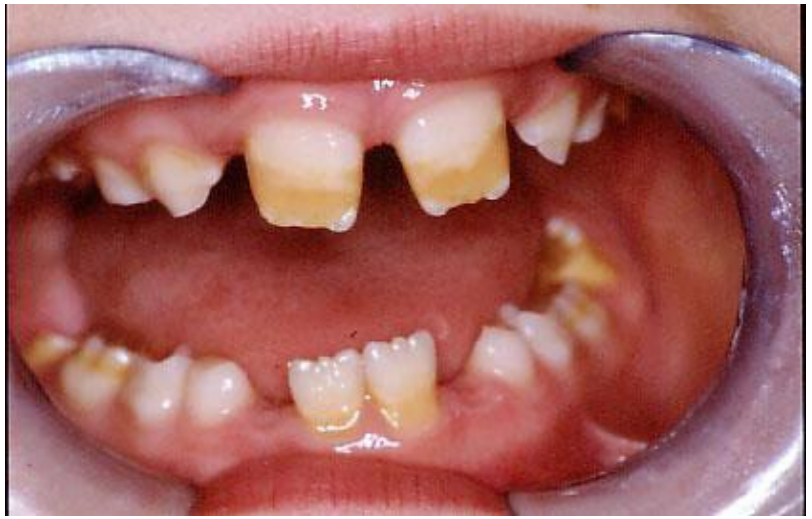



European Reference Network

MetabERN
European Reference Network for Hereditary Metabolic Disorders

TOOTH/ENAMEL ABNORMALITIES





CLINICAL PRESENTATION OF ZSD

Most frequent combination

- Cognitive and motor dysfunction
- Retinopathy
- Hearing defect
- Liver dysfunction

- Visual impairment/cataract
- cognitive impairment

- Ataxia
- Polyneuropathy

Jaundice; Hypoglycemia; Diarrhea; Osteoporosis; high serum iron+ TIBC; low cholesterol; ADEK vitamins deficiency

Diagnosis of peroxisomal disorders

ZSD: CHARACTERIZED BY THE ABSENCE OF FUNCTIONAL PEROXISOMES AND A DEFICIENCY OF MULTIPLE PEROXISOMAL METABOLIC PATHWAYS

Plasma

- ↑VLCFAs
- ↑Pristanic acid and phytanic acid (diet and age dependent)
- ↑DHCA and THCA (in most but not all patients)
- ↑Pipecolic acid

Erythrocytes

- ↓Plasmologens

Skin fibroblasts

- ↓ alpha and beta-oxidation
- ↑VLCFAs
- ↓DHAPAT activity
- Immunefluorescence microscopy with anti-catalase: absence of import-competent peroxisomes

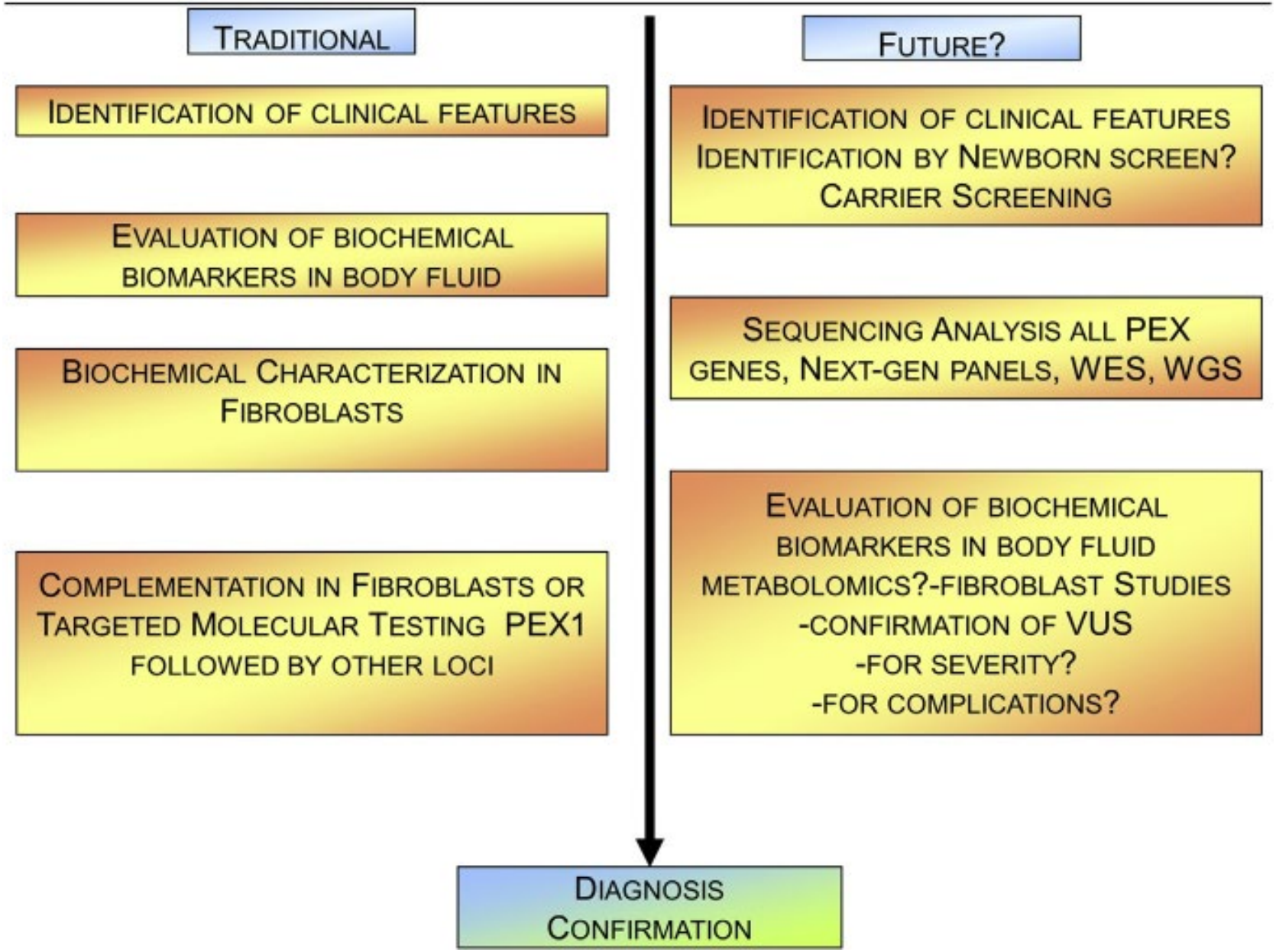
WHAT WE HAVE ALSO LEARNED THROUGH THE YEARS

Large biochemical variability with minimal to no abnormalities in peroxisomal biomarkers, at least in some patients.
Example: Zellweger Spectrum Disorders (ZSD)

VLCFA ↑
Bile acid intermediates ↑
Phytanic acid ↑
Pristanic acid ↑
Pipecolic acid ↑
Plasmalogens ↓

Normal

PBD-ZSD Diagnosis



Single Peroxisomal Enzyme Deficiencies

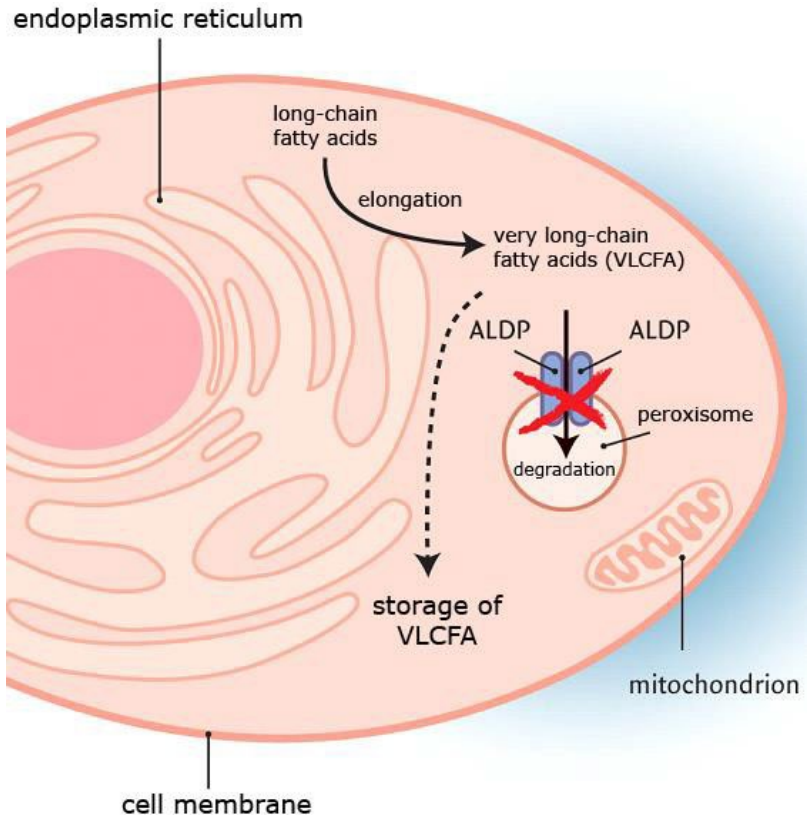
X-linked Adreno-leucodystropy (X-ALD)

Amsterdam UMC
University Medical Centers

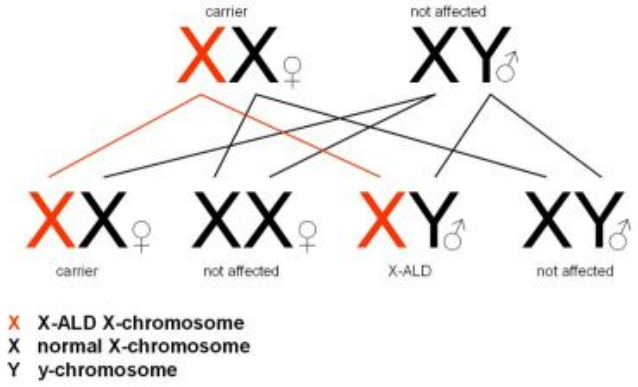
Emma Kinderziekenhuis
Amsterdam UMC

European Reference Network | MetabERN
European Reference Network for Hereditary Metabolic Disorders

Genetics and biochemistry of ALD



- Peroxisomal metabolic disease
- Mutation in *ABCD1* gene (X-linked)
- Accumulation of C26:0
- >10.000 patients in Europe
- Clinical spectrum
- Men and women affected



Biochemical defect

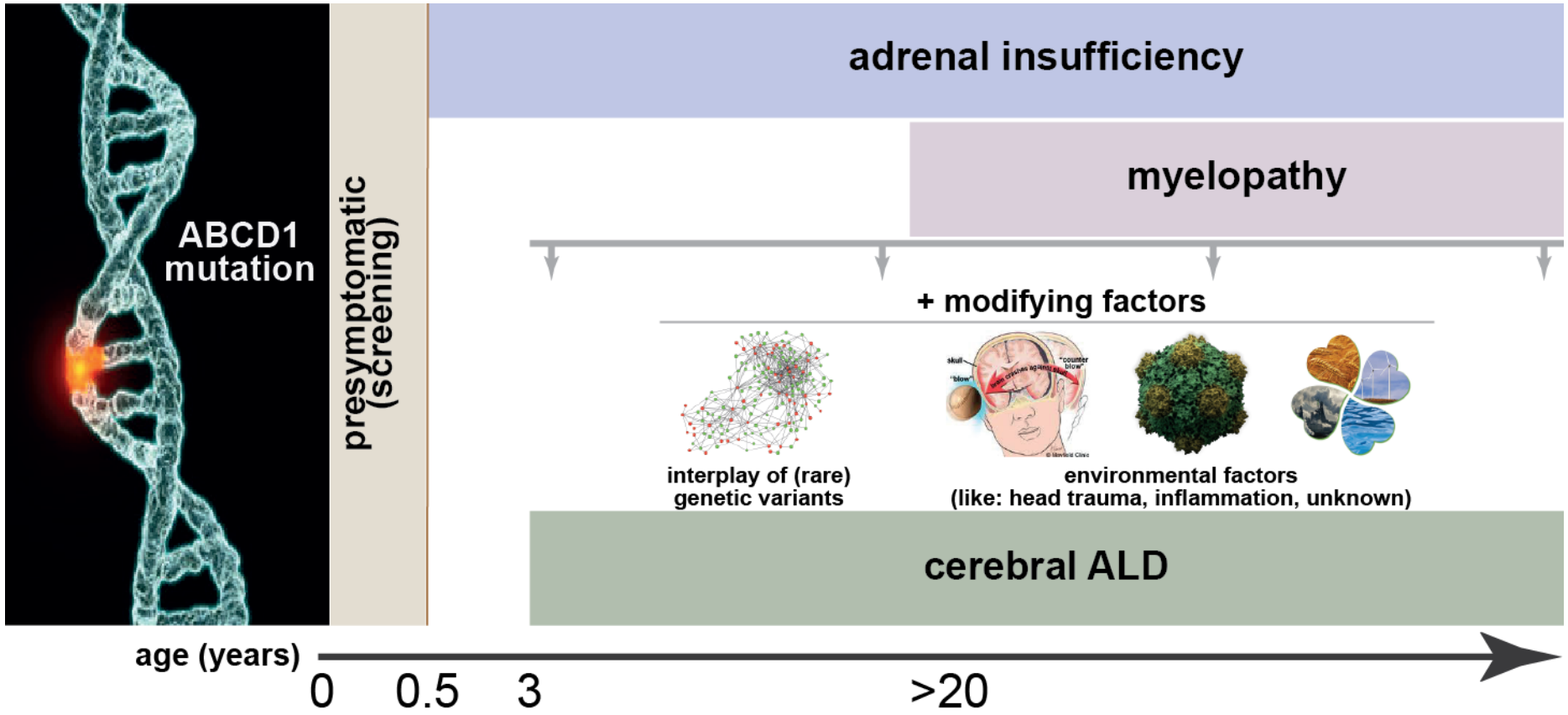
Peroxisomal membrane transporter of Very Long Chain Fatty Acids C26:0

X-linked *ABCD1* gene

VLCFA are metabolized by the peroxisomal beta oxidation pathway

Clinical Presentation of X-ALD

Clinical features

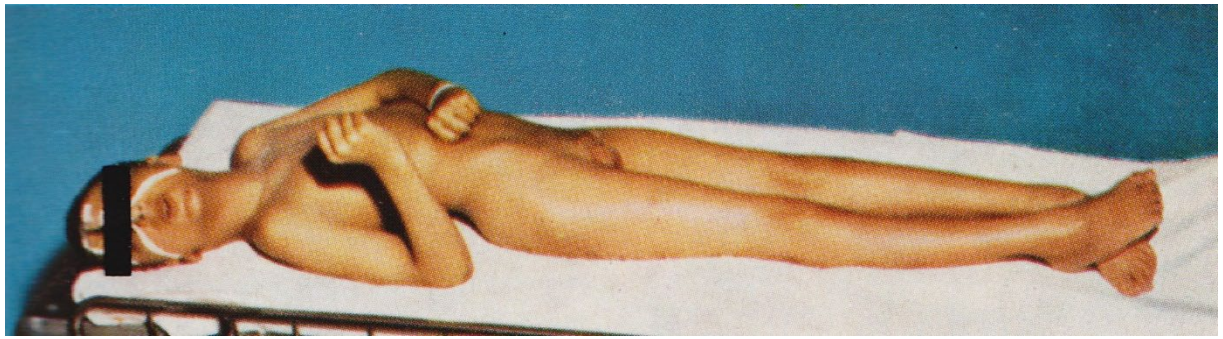


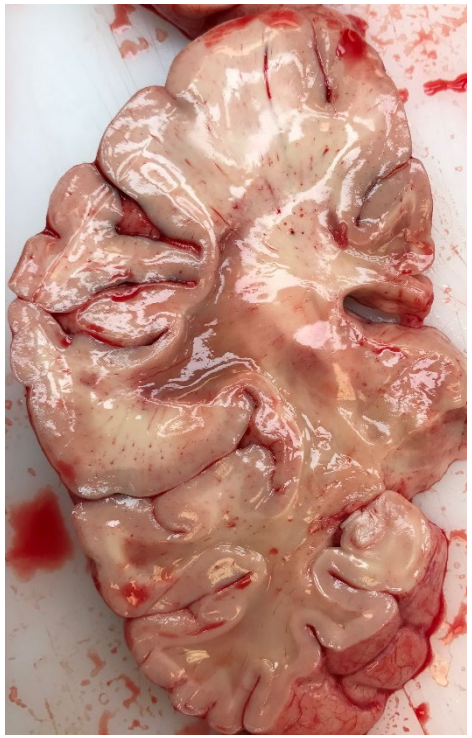
Kemp et al, Nature Reviews Endo, 2016

Clinical features: cerebral ALD

- Rapidly progressive leukodystrophy – months to years
- Onset after 3 years of age, peak before 10 years, lifetime prevalence 60%

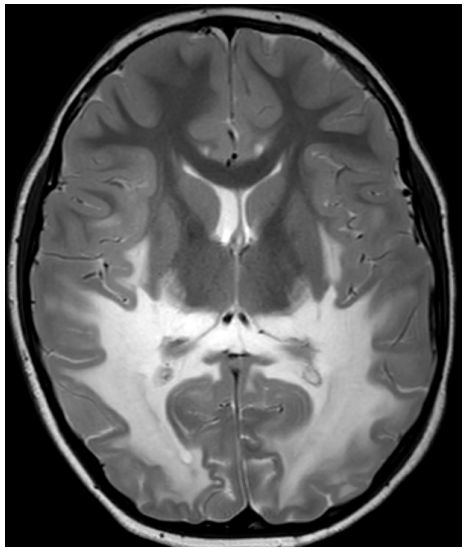
- Neuropsychological and psychiatric deficits
- Focal neurological deficits
- Seizures
- Untreated usually progressive

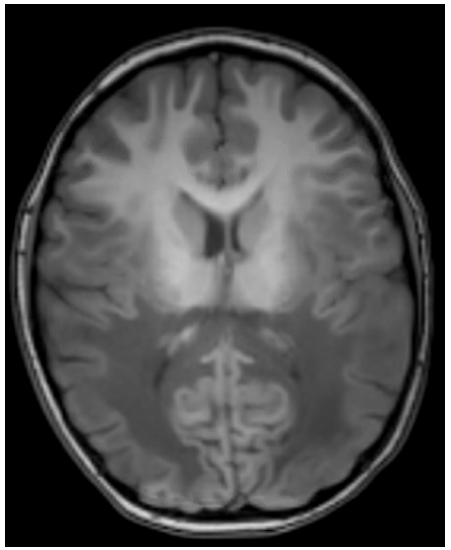


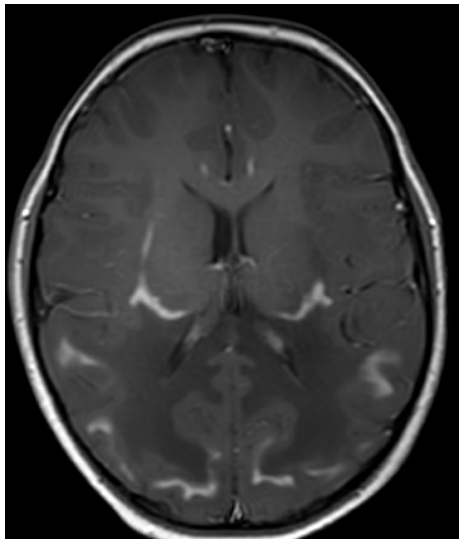


Engelen et al, OJRD, 2012; Powers et al, Clin Neuropathol, 1985

Clinical features: MRI



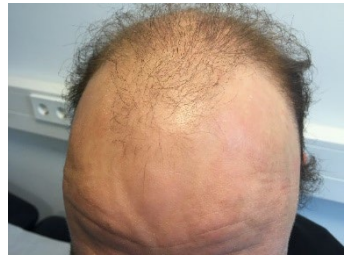


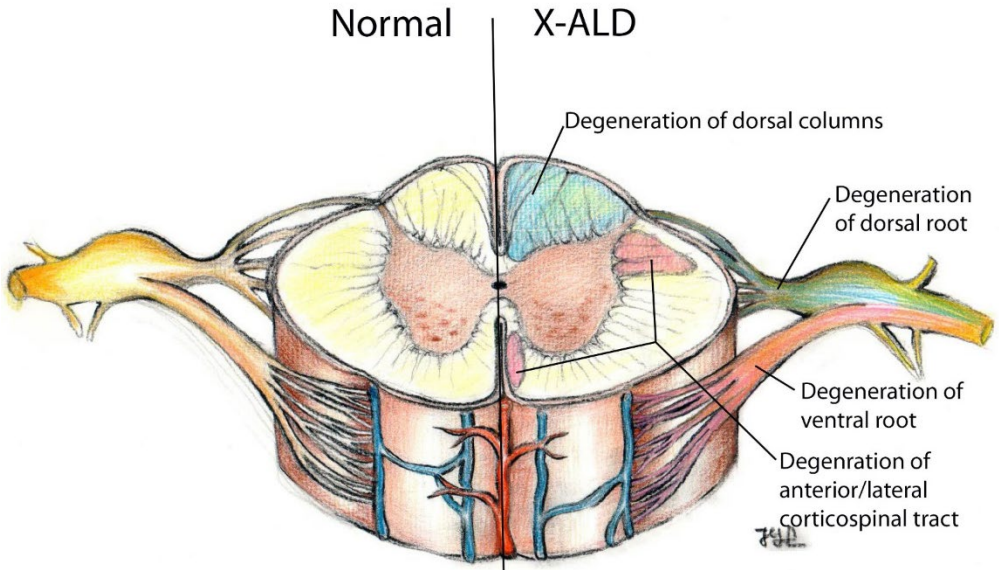


- 80% start in splenium and extends into occipital, parietal and frontal white matter
- Gadolinium enhancement in the lesion (just beyond the leading edge)

Clinical features

- Axonal degeneration in spinal cord and peripheral nerves
- All men and about 90% of women develop spinal cord disease
- "Core phenoype" in adulthood





Sensory ataxia

Spasticity

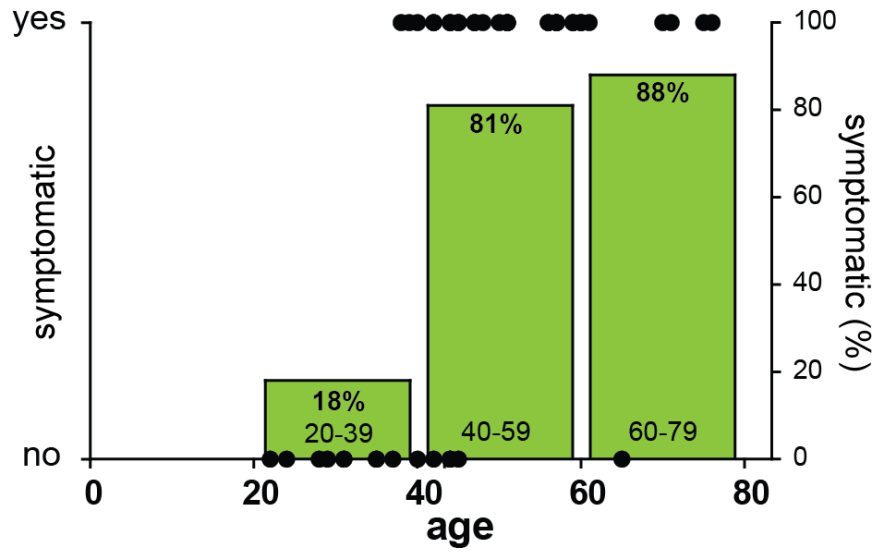
Gait disorder

Huffnagel et al, Brain, 2019

Clinical features of ALD

Women with ALD

- Myelopathy (prominent fecal incontinence)
- Peripheral neuropathy (clinically less relevant)
- Symptomatic status highly age-dependent
- Women are patients!

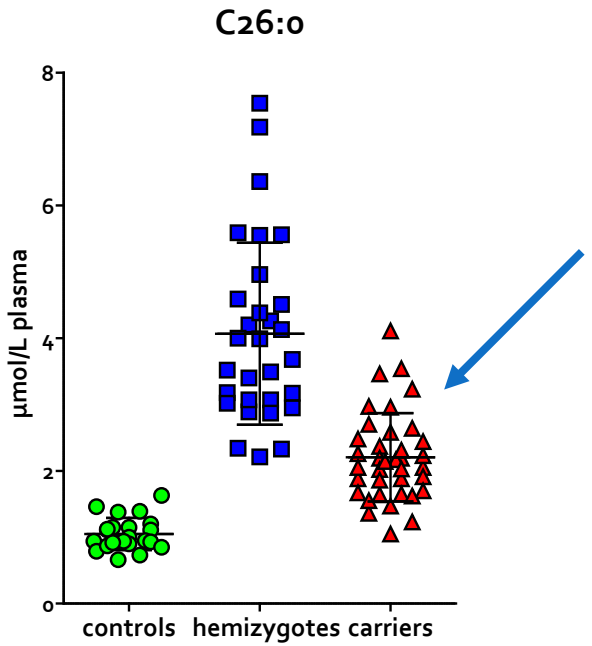


Diagnosis of X-ALD

Diagnosis

In men: plasma VLCFA (C26:0 and C26:0/C22:0 ratio).
Nowadays: C26:0-lysoPC

Confirmation by *ABCD1* mutation analysis



Diagnosis

In women: plasma VLCFA (C26:0 and C26:0/C22:0 ratio) normal in 15%! Nowadays: C26:0-lysoPC!

ABCD1 mutation analysis: however if VUS and VLCFA normal?

Diagnosis

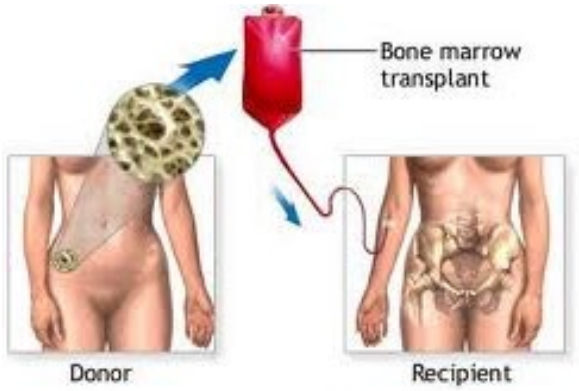
Newborn screening is implemented in part of the U.S., implementation study will start in the Netherlands

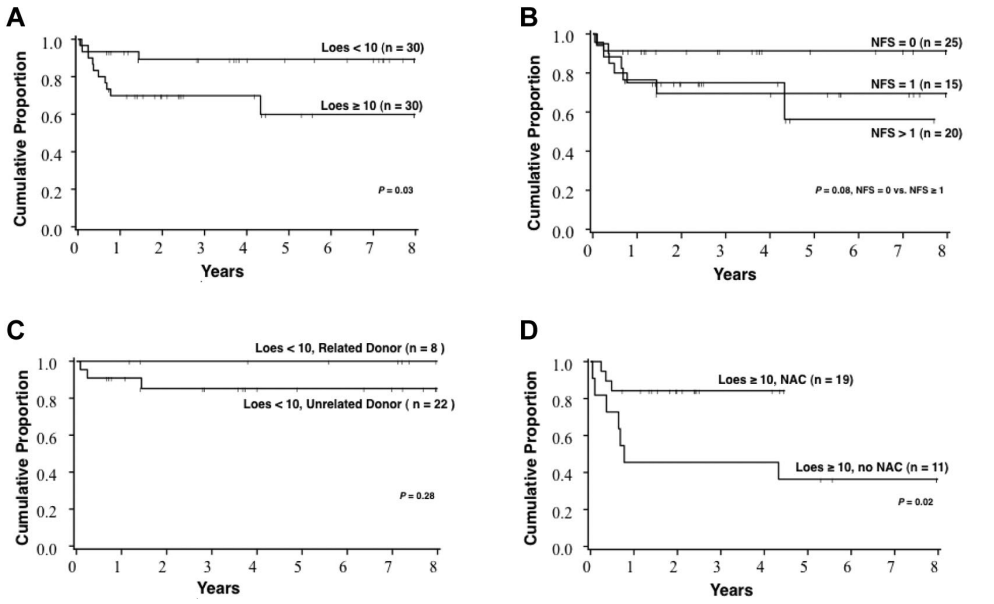
Only boys in NL! See http://www.scanstudie.nl

Follow-up from early age

Therapy and Follow-up of X-ALD

Follow-up and treatment





Survival estimates after HCT based on various patient and HCT characteristics. (A) All patients in the cohort stratified by Loes score at the time c

Prognosis (survival) poor if Loes score > 9
Modern insights: cognitive outcome poor if Loes score > 4.5

Miller et al, Blood, 2011; Pierpont, JAMA, 2017

Follow-up and treatment

- Only supportive care for the myelopathy of adulthood in men and women
- Suppletion of hydrocortisone (and sometimes fludrocortisone) by endocrinologist
- Progression over time (over years for men, decades for women)
- Many trials planned (and 1 ongoing) for disease modifying treatments

Engelen et al, OJRD, 2012

If you are interested in more of Inherited Metabolic Diseases

THE FIRST E-LEARNING PROGRAMME ON IMDs DEVELOPED BY METABERN MEMBERS

The **overall objective** of the DCTEP is to create and train a new class of professionals with a scientific background and interest in Inherited Metabolic Diseases (IMDs) and to provide them with expert knowledge and practical experience in the phenotypic spectrum, diagnostic work-up, treatment and long-term management of IMDs.

Learning Outcomes

- Provide diagnostic expertise for IMDs (recognize the red flags),
- Have knowledge of the available and appropriate diagnostic tests,
- Enhance the therapeutic thinking on a number of IMDs,
- Apply knowledge to recommend treatment where available,
- Manage difficult clinical cases and prescribe basic therapies.

Questions?

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