# Therapeutic strategies in Inborn Errors of Metabolism (IEM)

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# When to think at an Inborn Error of Metabolism (IEM) ?

- IEM are congenital and genetic disorders of biochemistry
  (or the impossibility to convert food into energy)
- IEM can present at any age from fetal life to old age
  (for the same enzymatic defect : neonatal symptoms / late onset/ asymtomatic)
- Acute neonatal symptoms /symptoms after « free interval » without symptoms
  (from days to years)
- Chronic/progressive symptoms (failure to thrive, neurologic deterioration, ..)
- Specific symptoms (eyes, skin, liver, heart, kidney,..)
- Persistent and unexplained symptoms after initial treatment.
- Although most IEM are autosomal recessive disorders, majority of cases appear to be sporadic in a family.

**DON'T MISS A TREATABLE disorder !**

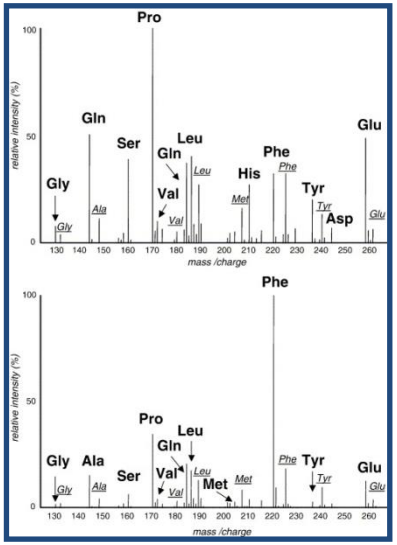
# Neonatal screening in IEM on Dried Blood Spot

Day 3-5 of life (heel prick)

Dried blood spot
(DBS) on filter paper


Neonatal Screening Laboratory

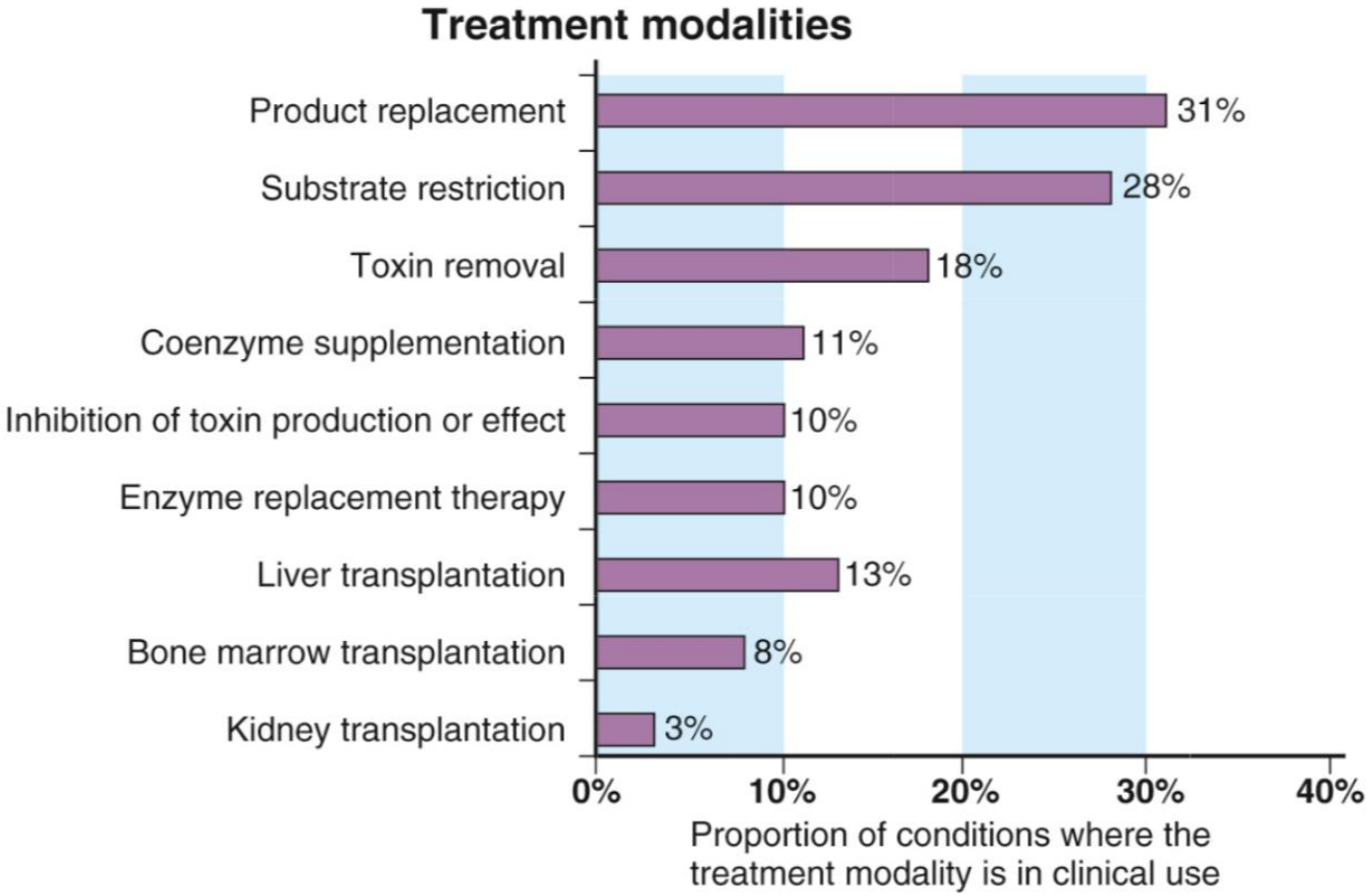
With Tandem Mass Spectrometry (MS/MS)




> 40 metabolites analyzed (amino acids, acylcarnitines, ..)

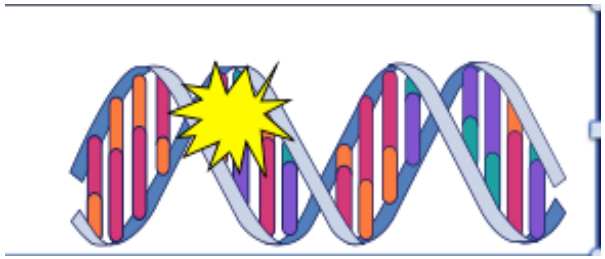
> 30 Inborn Errors of Metabolism screened after birth

# Lets talk … about Treatment modalities

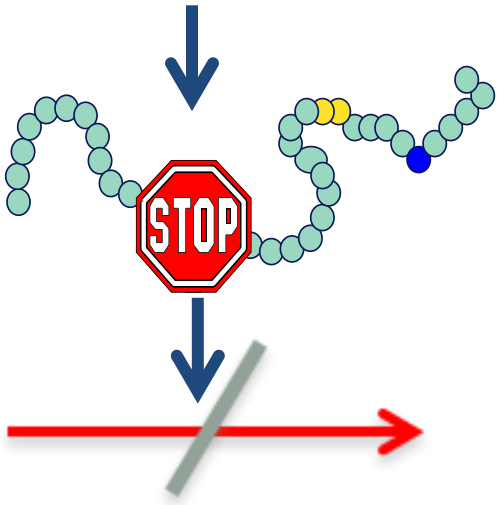


# Consequences of protein/enzyme deficiency

**> 5000 genes that encode enzymes**



**DNA mutation**




**Non functional/Absent of mutant protein/enzyme**

**A**

Toxic compounds Accumulation

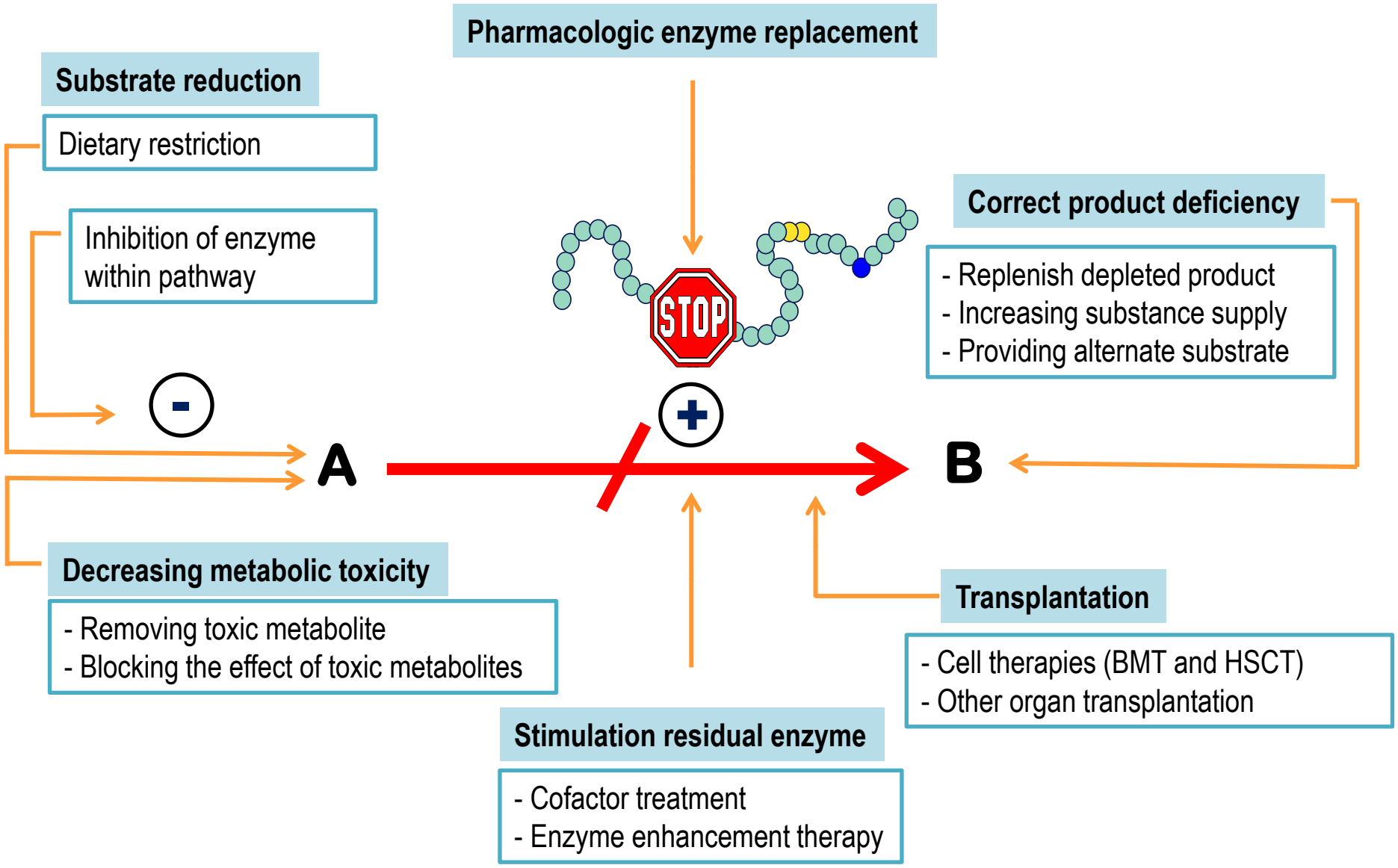
**B**

Substrate Deficiency

Absence of protein/mutant protein with no residual activity → **Severe phenotype**

Mutant protein with residual activity →**Milder phenotype**
Treatment will try to increase the residual function of the enzyme

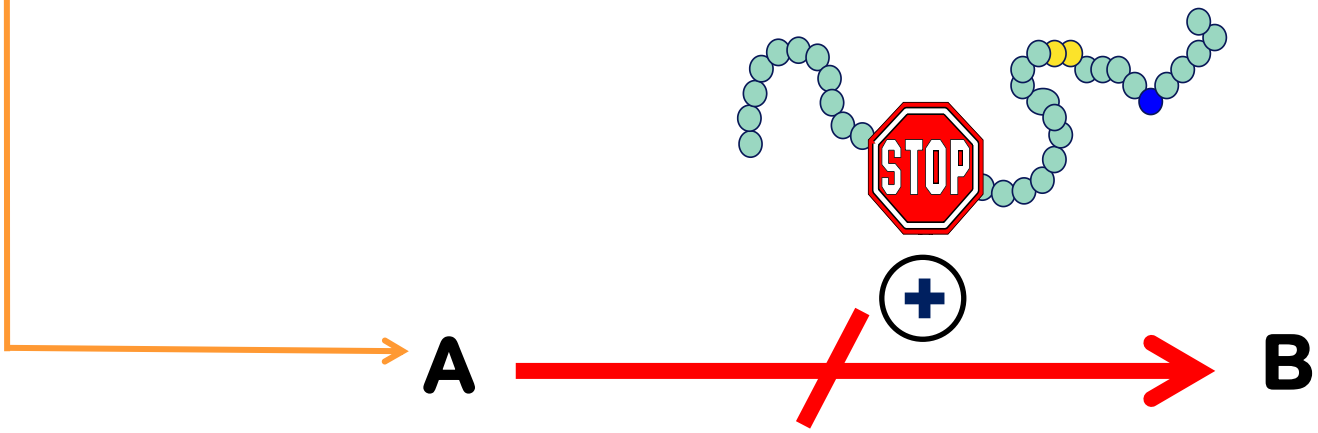
# Therapeutic strategies



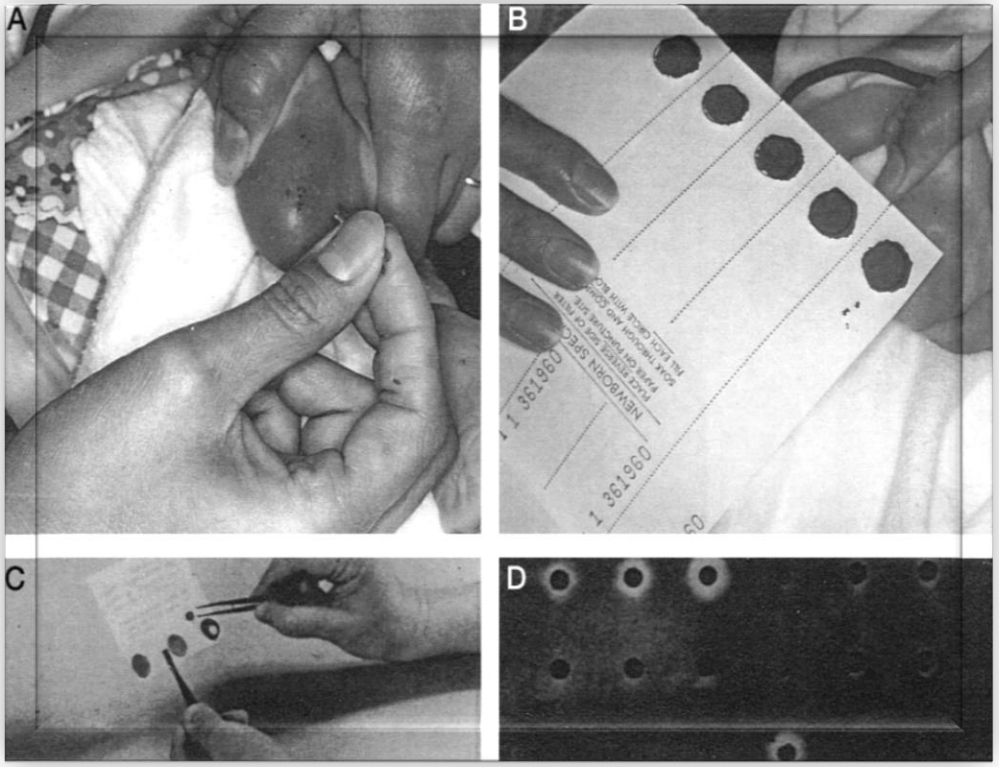
# Therapeutic strategies

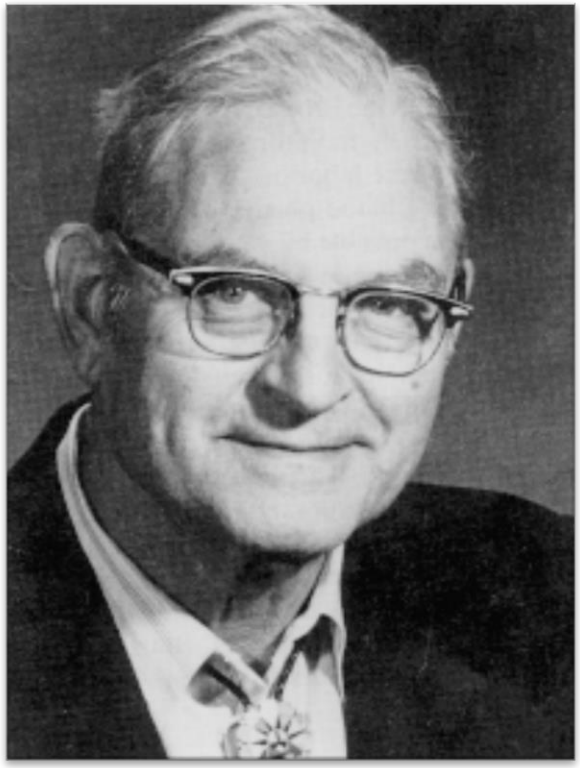
**Substrate reduction**

Dietary restriction



# Phenylketonuria = first metabolic disease detected through Neonatal Screening



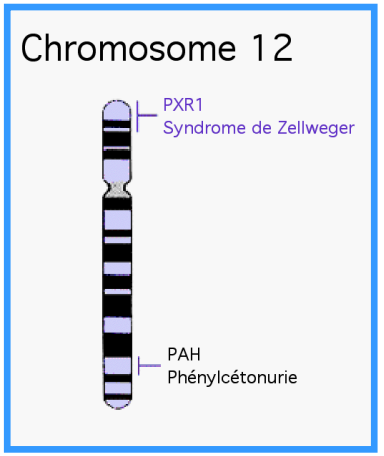
Robert Guthrie in early 1960s

Dried blood spot on filter paper : Guthrie card

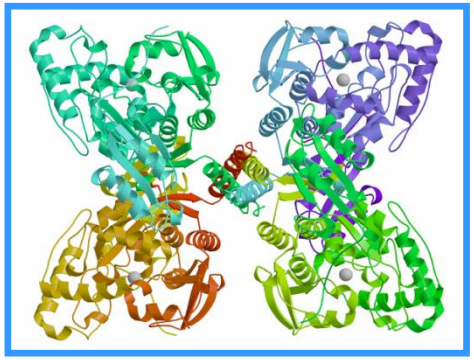
Bacterial inhibition assay : the amount of bacterial growth is measured as the diameter of the colony and is roughly proportional to the amount of Phenylalanine in the serum

# Substrate reduction - Dietary restriction

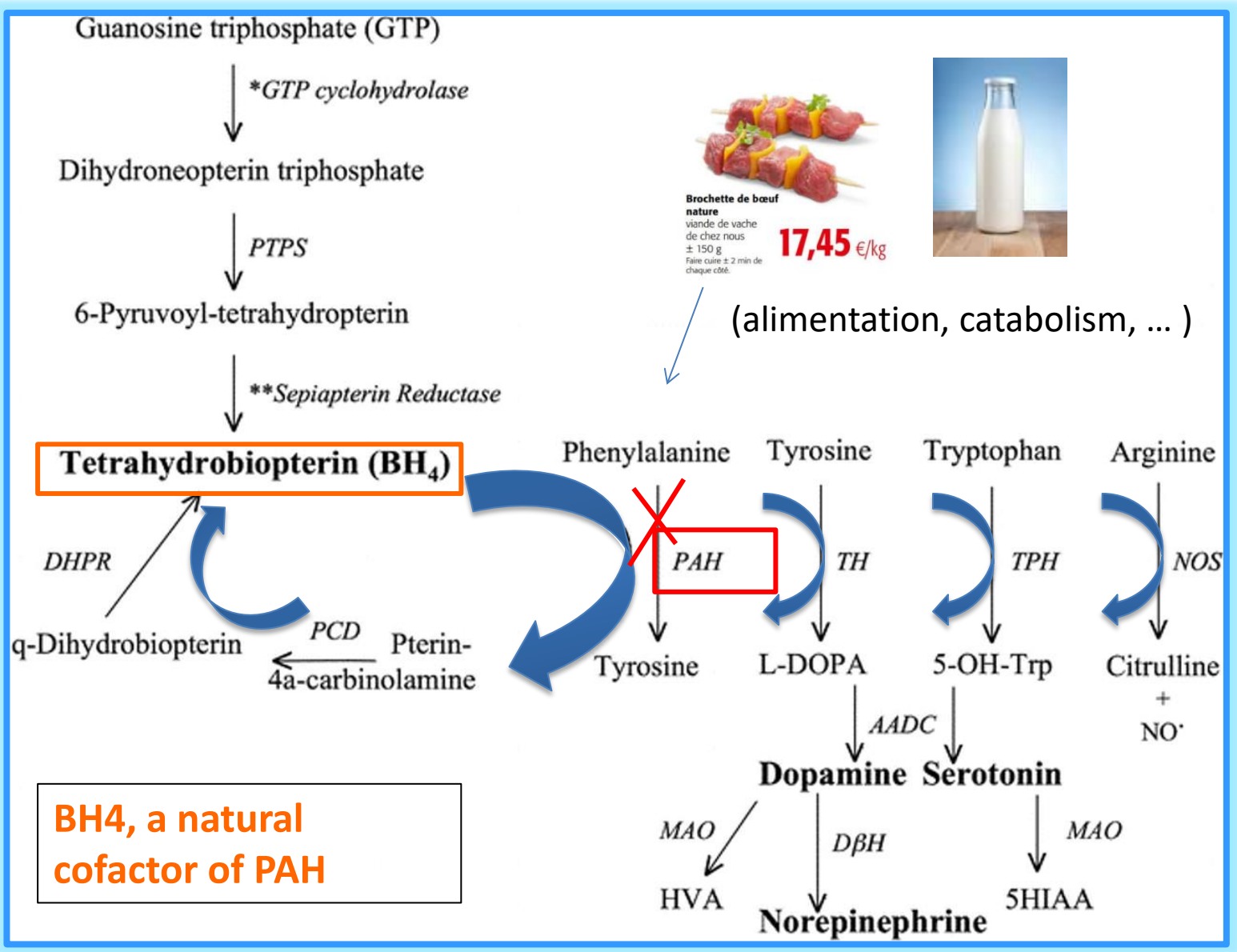
## Phenylketonuria (PKU)




- Autosomal recessive disease
- 1 / 10 000 birth
- PAH gene (chromosome 12)
- Classic PKU is caused by a complete (or near-complete) phenylalanine hydroxylase activity (PAH) deficiency in liver.
- PAH has a tetrameric structure
- PAH deficiency results in intolerance to dietary intake of phenylalanine (an essential amino acid)

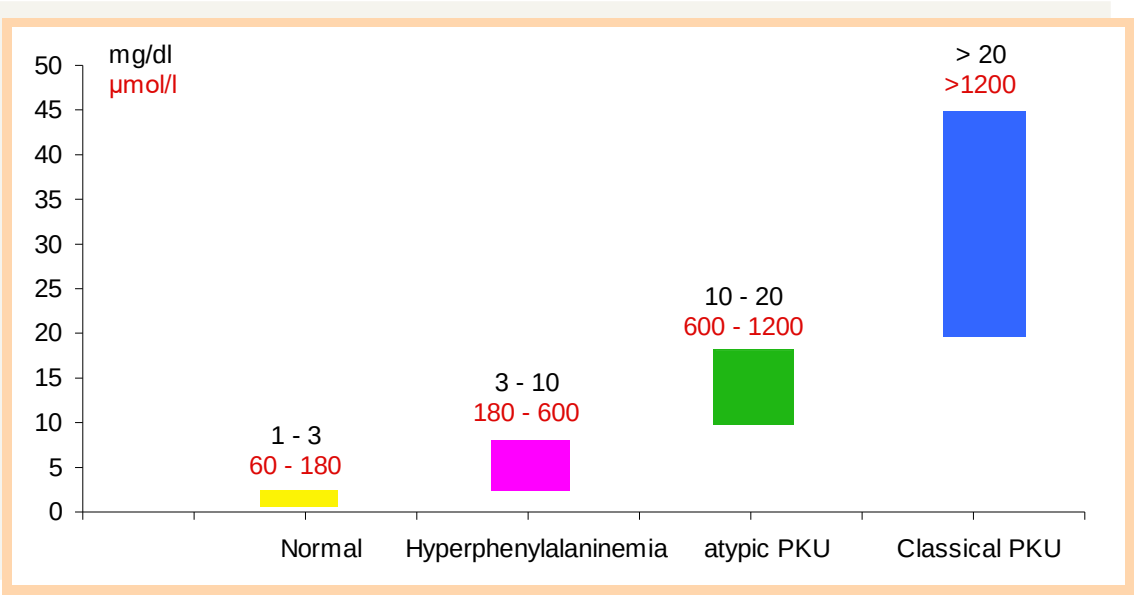


# Phenylketonuria and the Phenylalanine Hydroxylase (PAH) system



# Phenylalanine plasmatic levels and PKU classification

**Phenylalanine (PHE)**




| | PAH activity | PHE level without treatment | Daily PHE tolerance in food |
|---|---|---|---|
| **Classical PKU** | 0-1 % | > 20 mg/dl<br>> 1200 µmol/l | 200 – 350 mg |
| **Variant PKU or Atypical PKU** | 1-3 % | 10 - 20 mg/dl<br>600-1200 µmol/l | 350 - 850 mg |
| **Non-PKU Hyperphenylalaninemia** | 3 - 5 % | 3 – 10 mg/dl<br>180-600 µmol/l | > 850 mg |

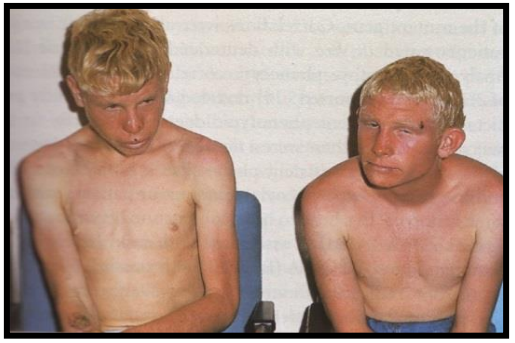
# Untreated classical PKU

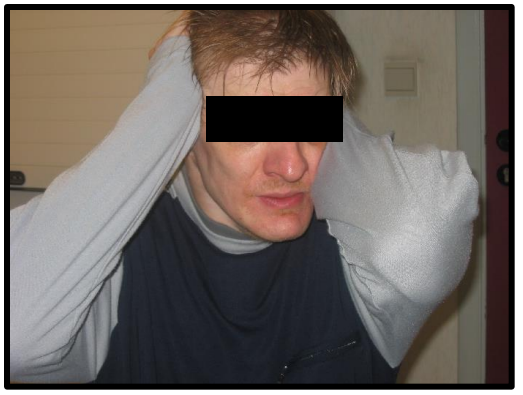
- Mild to severe mental retardation

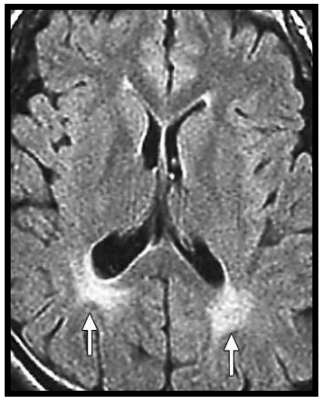
- Neurologic symptoms
  - Microcephaly
  - Gait instability, tremor
  - Epilepsy
  - Autistic behavior
  - Auto and hetero aggressivity

- Structural brain changes on MRI
  (white matter abnormalities)
- Decreased skin and hair pigmentation
  (Blond hair, blue eyes)

- Eczema/prurigo
- Musty body odor (typical)







# First dietetic treatment for an IEM

**Horst Bickel (1953)**

**Influence of phenylalanine (PHE) intake on phenylketonuria**

**Phenylketonuria can be treated with a phenylalanine restricted diet**

## Principle of a phenylalanine restricted diet

- Control of natural protein intake according to patient's PHE tolerance
- Avoidance of high protein food
  (milk, dairy products, meat, fish, chicken, eggs, beans and nuts,...)
- Phenylalanine-free formula (amino acids mixture with vitamins and oligoelements)
- Low protein food (manufactured hypoproteic bread, pasta, biscuits, ...)
- But ….. No control of 'protein-free' food


*Lancet, 1953; 2, 812-813*

+ PHE-free Amino acid supplements
+ Hypoproteic food

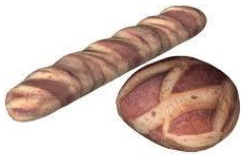


Allowed

Forbidden

# PKU Phe-restricted diet

Controlled natural
Protein intake



# Correlation between Phe metabolic control and IQ

Meta-analyses of within-study correlations: intelligence quotient (IQ) and concurrent[a] blood phenylalanine (Phe) level

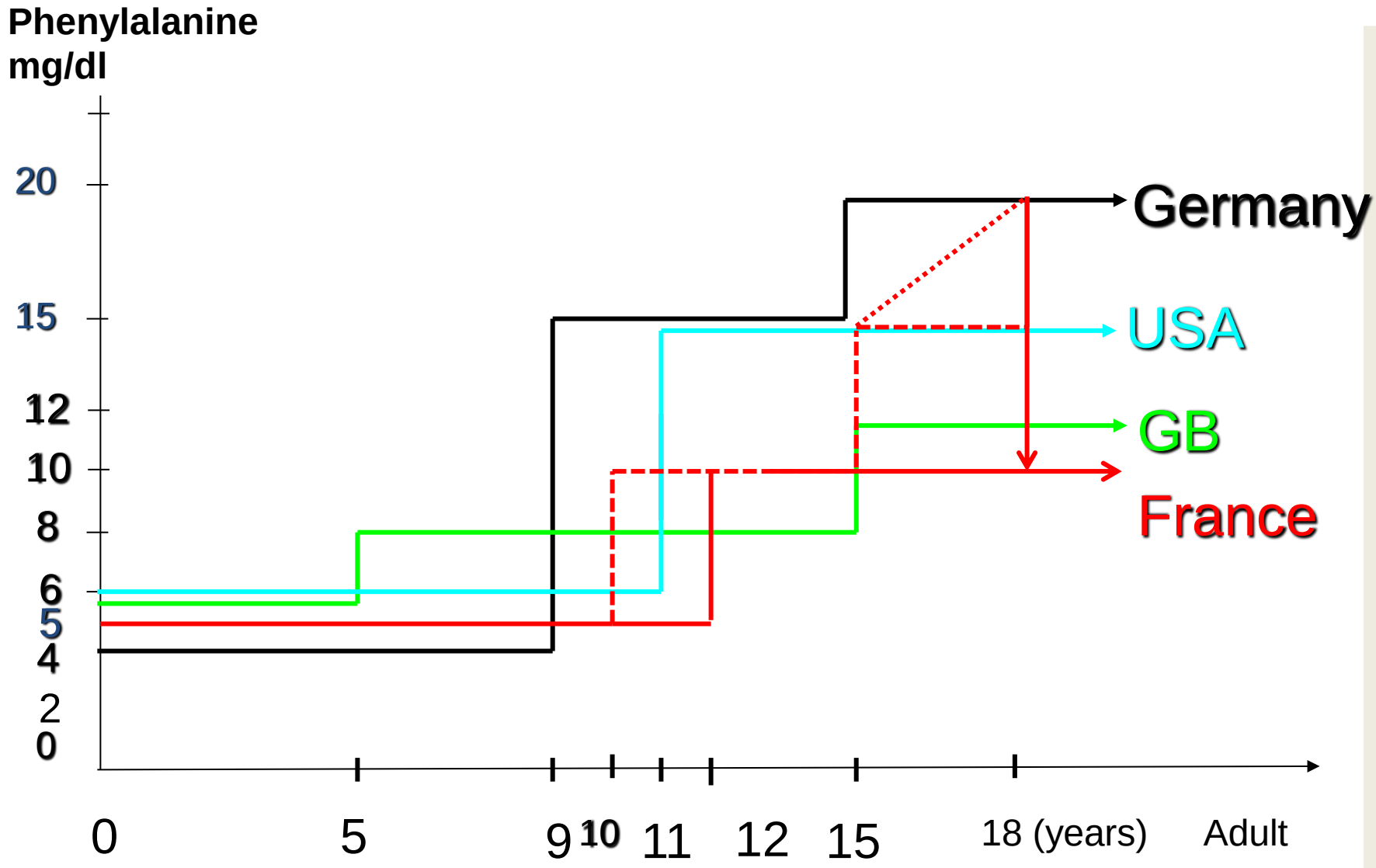
| PKU population | *t* | *n* | *r* (95% CI)[b] |
|---|---|---|---|
| Early treated | 29 | 666 | **−0.31 (−0.41, −0.20)*** |
| Classic | | | |
| Total | 23 | 499 | **−0.23 (−0.32, −0.14)** |
| Early treated | 21 | 473 | **−0.25 (−0.34, −0.15)** |
| Mixed treatment history | 3 | 32 | 0.04 (−0.35, 0.42) |
| Mixed/unspecified | | | |
| Total | 14 | 310 | **−0.29 (−0.48, −0.07)*** |
| Early treated | 9 | 219 | **−0.42 (−0.60, −0.19)*** |
| Mixed treatment history | 5 | 91 | 0.02 (−0.27, 0.31) |
| Mild | 1 | 8 | −0.28 (−0.82, 0.53) |
| Hyperphenylalaninemia | 1 | 16 | −0.08 (−0.55, 0.43) |

**0-12 years** : Each **100 µmol/l** Phe increase predicted a **1.3 to 3.1 IQ** point reduction

**→PHE level is a predictive IQ indicator**
**Stronger association was observed between Phe levels during early childhood and later IQ.**

*Mol Genet Metab (2007),92:63-70*

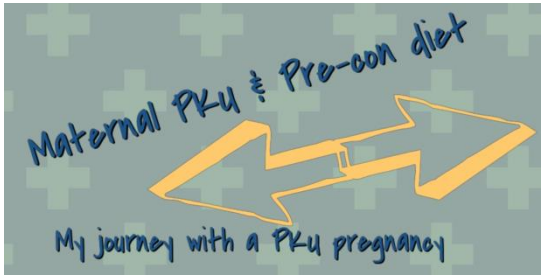
# International recommendations for PHE control according to age and country – no universal consensus



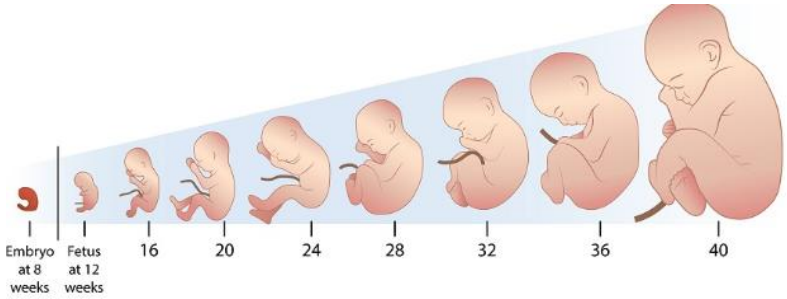

- **Lifelong low phenylalanine diet** (in males and females) to prevent : decreased IQ scores, eczema, behavioral problems, seizures, decreased executive functioning, depression, irritability, headaches, impairment of short term memory, … .

- Important **in Females** who are willing to be pregnant, keep them on a **controlled diet**

- Recommandation to start a strict low PHE diet
  at least **3 months before planned conception**
  **and**
  **throughout** pregnancy because of
  teratogenic effects of Phenylalanine



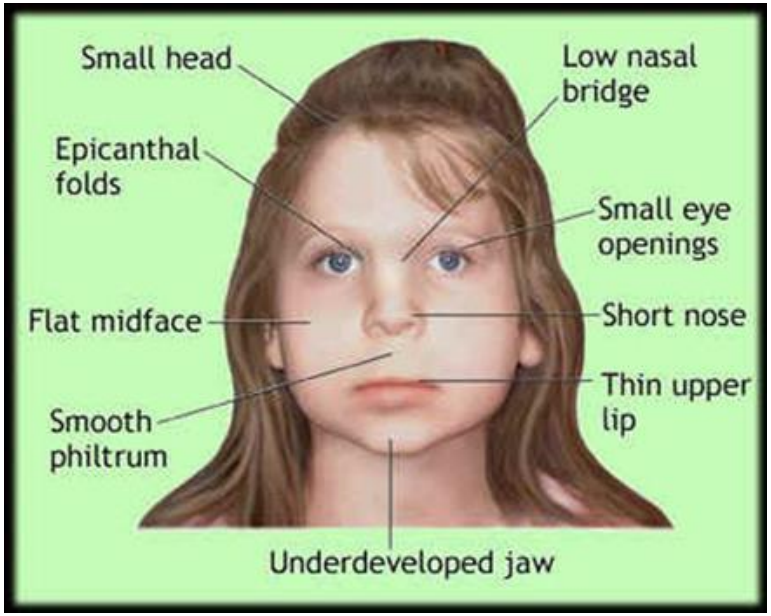
# Maternal Phenylketonuria
# The toxic effects of Phenylalanine on fetus




**MATERNAL PKU : RISKS TO FETUS**

**LACK OF DIET OR POOR DIET CONTROL** → **May cause in fetus**

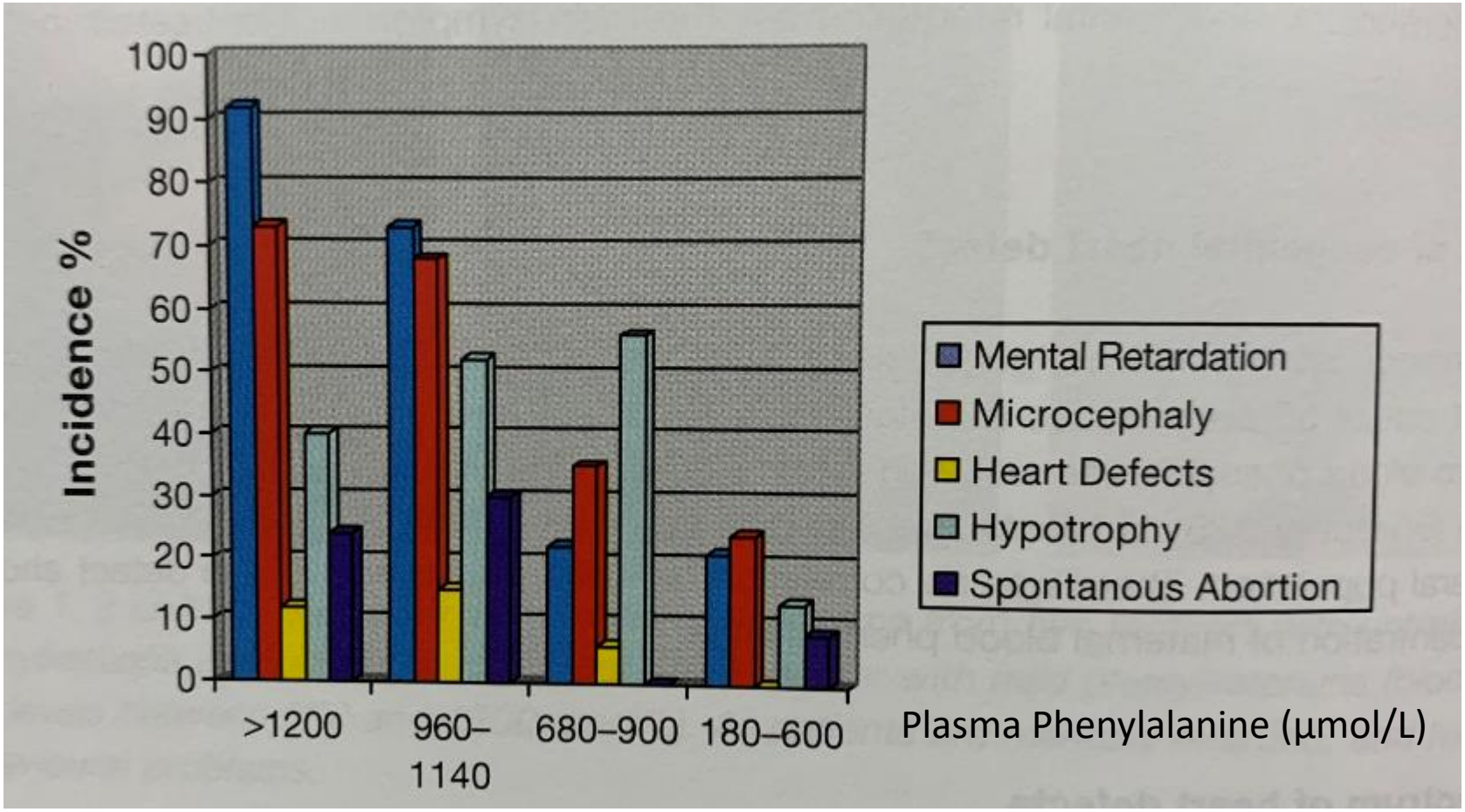
- **Congenital heart disease**
- **Microcephaly (small head size)**
- **Low birthweight**
- **Mental retardation**
- **Slow development**
- **Language deficit**




<u>Maternal PKU Syndrome after birth :</u>

- Dysmorphism
- Microcephaly 73 %
- Developmental delay 92 %
- Mental retardation 75-90 %
- Congenital hart disease 12 %
- Low birth weight 40 %

# Maternal Clinical picture in untreated maternal Phenylketonuria

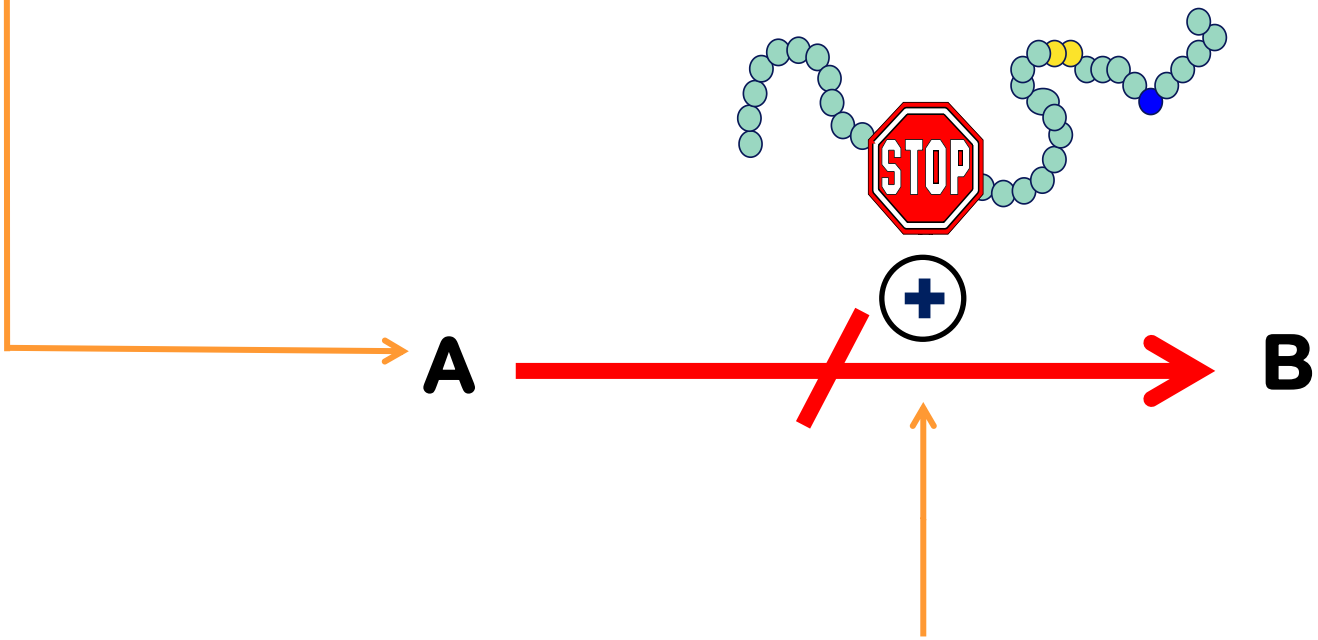



Clinical consequences at different phenylalanine levels

# Therapeutic strategies

**Substrate reduction**

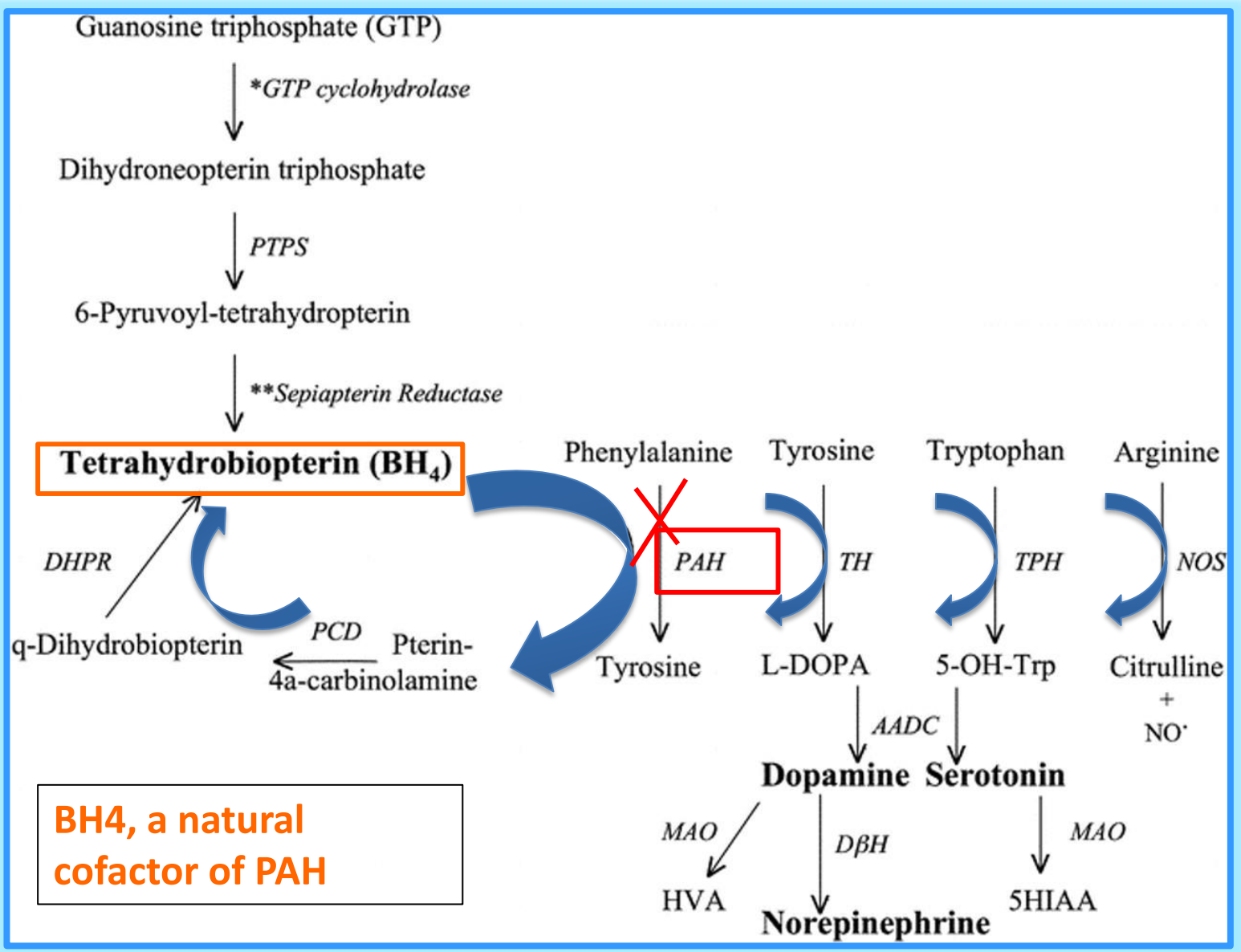
Dietary restriction




**Stimulation residual enzyme**

- Co-enzyme treatment
- Enzyme enhancement therapy or « chaperone therapy »

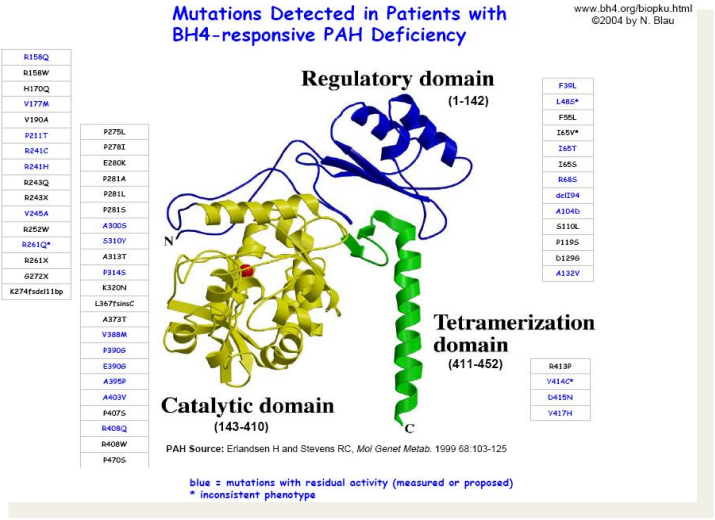
# Phenylketonuria and the Phenylalanine Hydroxylase (PAH) system



# PAH gene – Importance of missense mutations

~ 500 mutations worldwide

| Mutation Type | N° | Graph | |
|---|---|---|---|
| Missense | 308 | | 61,85 % |
| Deletion | 66 | | 13,25 % |
| Splice | 52 | | 10,44 % |
| Silent | 30 | | 6,02 % |
| Nonsense | 26 | | 5,22 % |
| Insertion | 8 | | 1,61 % |
| Sil./Splice | 3 | | 0,60 % |
| Splicing | 2 | | 0,40 % |
| Silent ? | 1 | | 0,20 % |
| Unknown | 1 | | 0,20 % |
| **Total** | **498** | | |

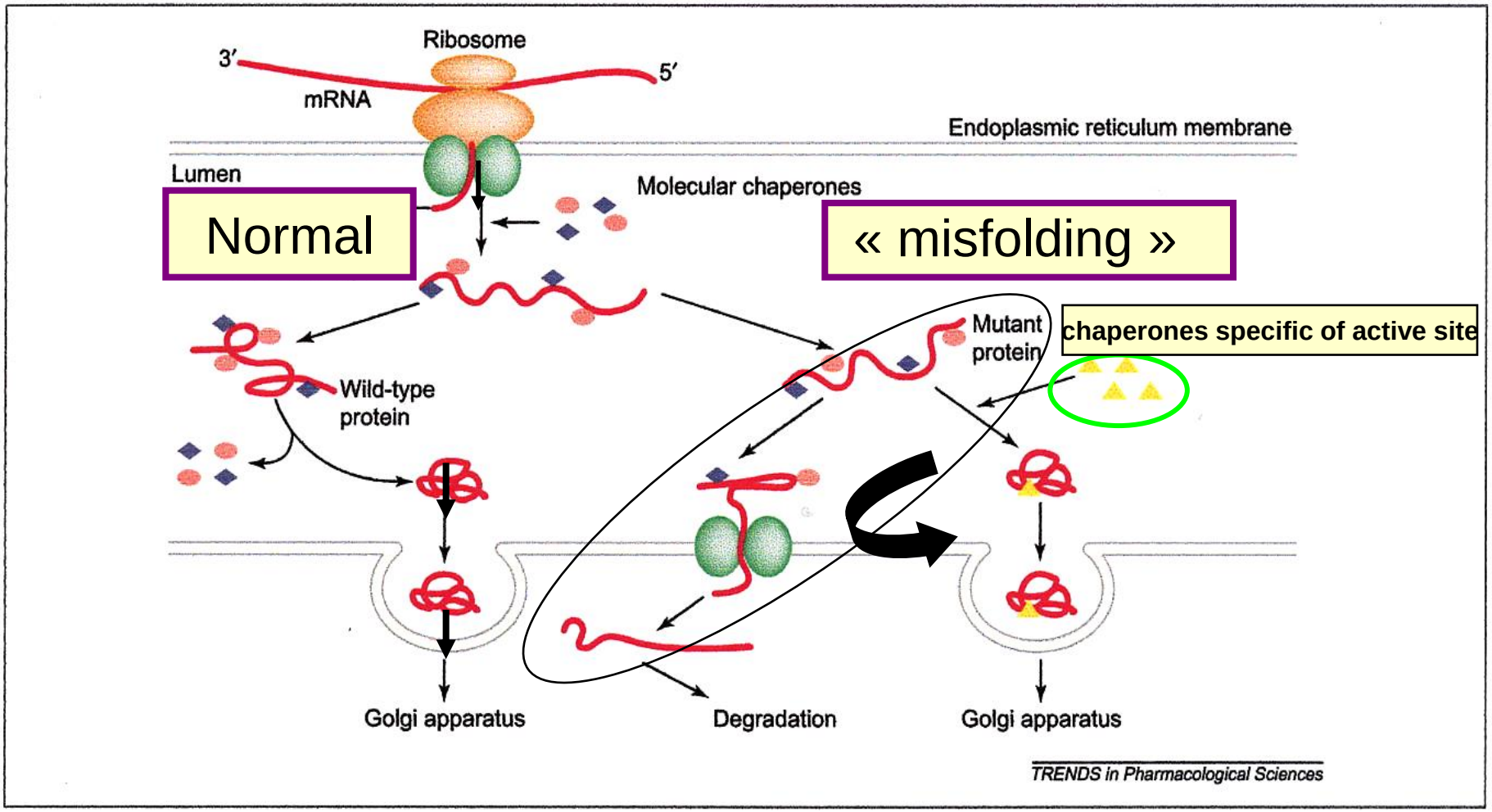



http://www.biopku.org

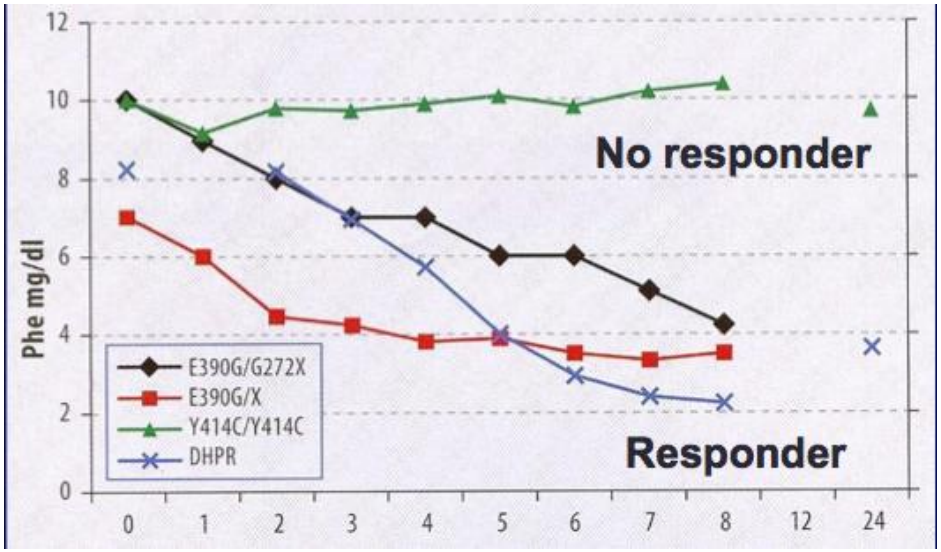
- Enzyme is synthesized but activity is null or decreased
- PKU as a model of « misfolding » enzyme ++

- **<u>BH4 = Natural cofactor of aromatic amino acid hydroxylases</u>**
- **Sapropterin (6R-BH4) synthetic form of tetrahydrobiopterin**
- Orphan drug (FDA and EMEA)
- Stabilization of the active tetramer forms of the mutant protein
- Protection from inactivation
- Acts as a « chemical chaperone », preventing misfolding

# Enzyme Enhancement Therapy
# or pharmacological «chaperone»

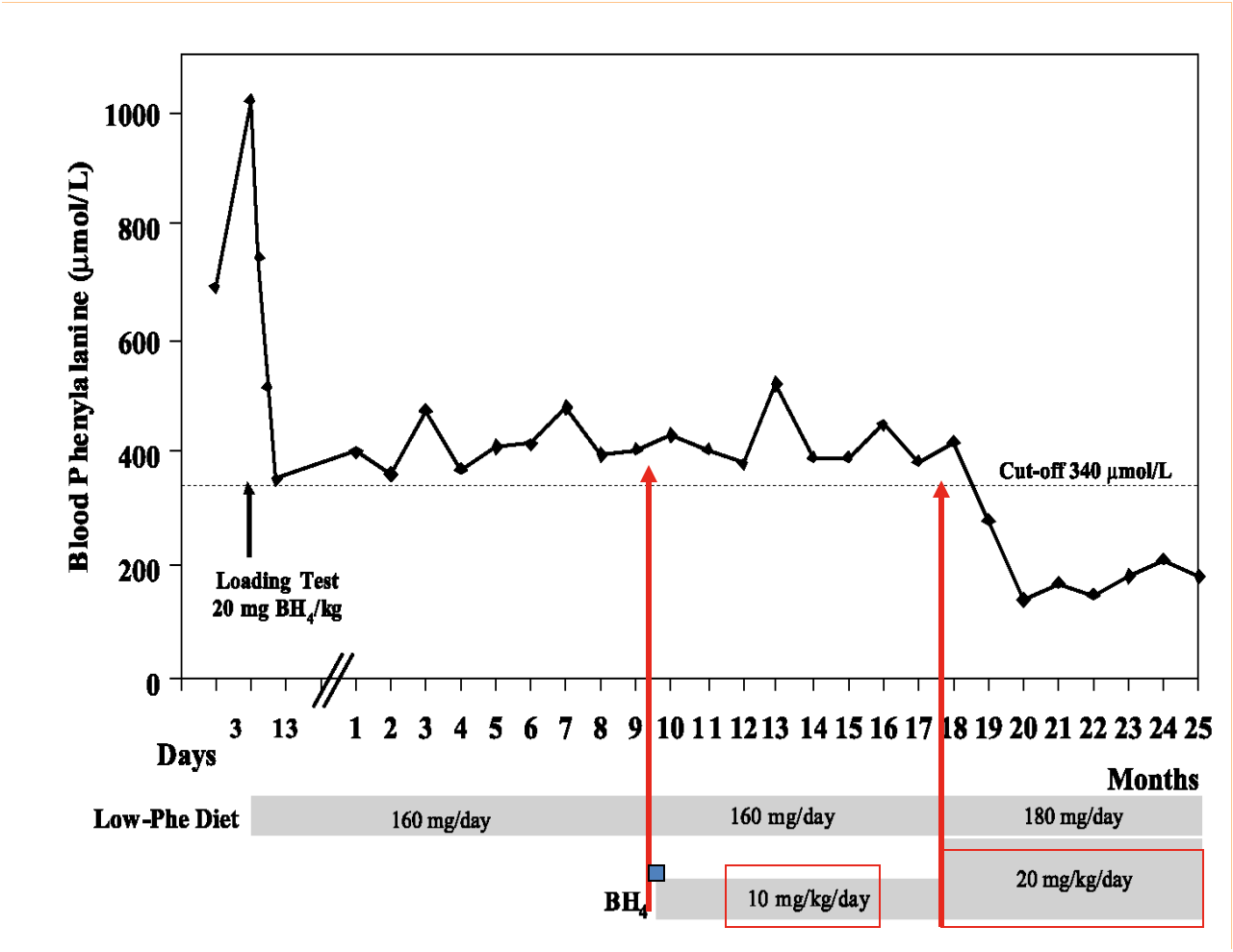


# Different responses to oral BH4 loading test (20mg/kg) according to genotype in PKU patients



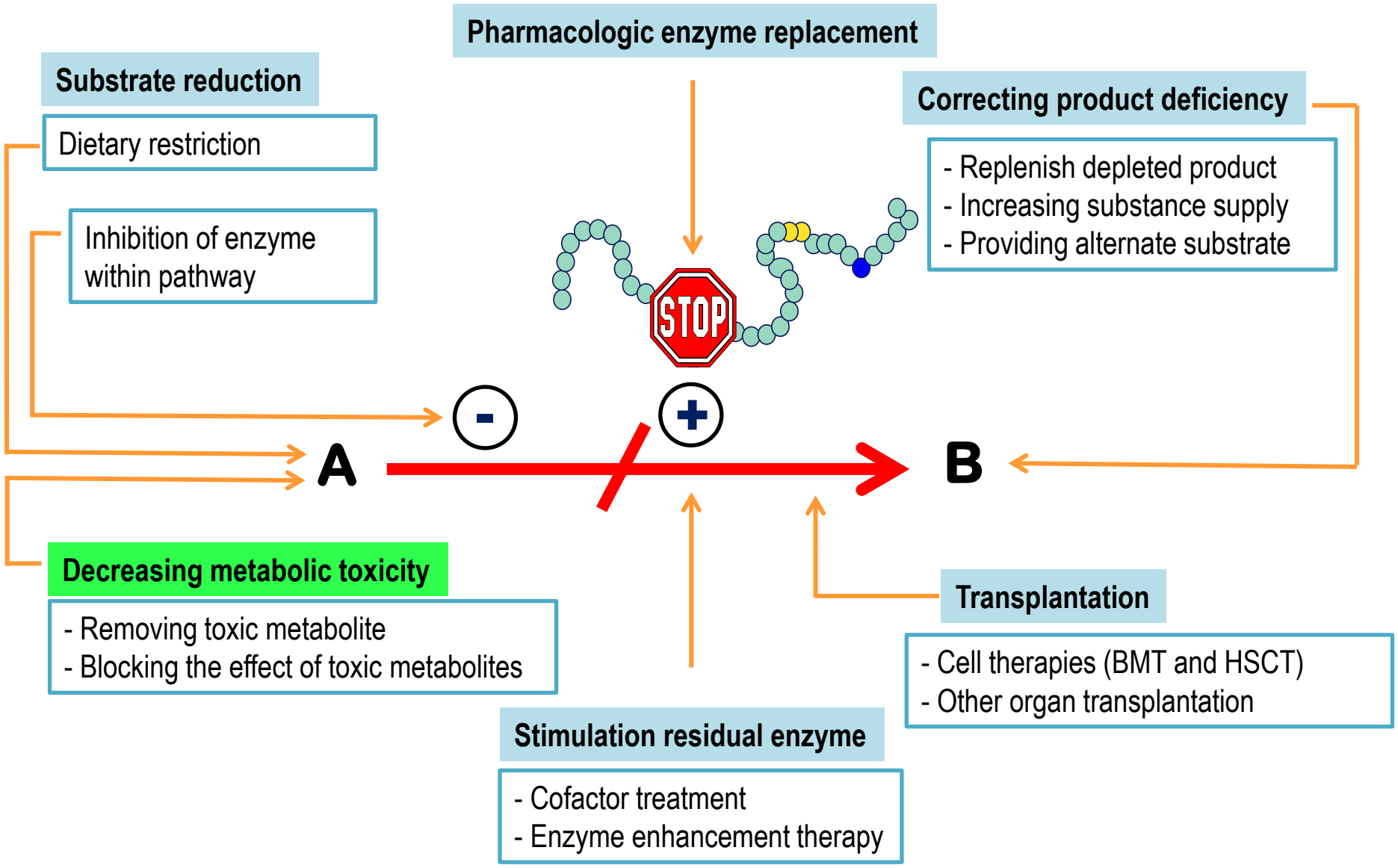

- About **70** % of <u>mild HPA and mild PKU</u> patients proved to respond to BH4 therapy (reduced Phe level after loading test > 30 %).
- About **10** % of <u>classical PKU</u> patient respond to BH4 (more severe mutations, null mutations)
- In PKU patients responsive to BH4, oral treatment could be used **<u>in addition</u>** to a restrictive low-phenylalanine diet to reduce blood phenylalanine and increase PHE tolerance, and might even replace the diet in some instances.

# Long term treatment with oral BH4 increase in Phe tolerance




*R. Cerone et al. / Molecular Genetics and Metabolism 81 (2004) 137–139*

# Therapeutic strategies

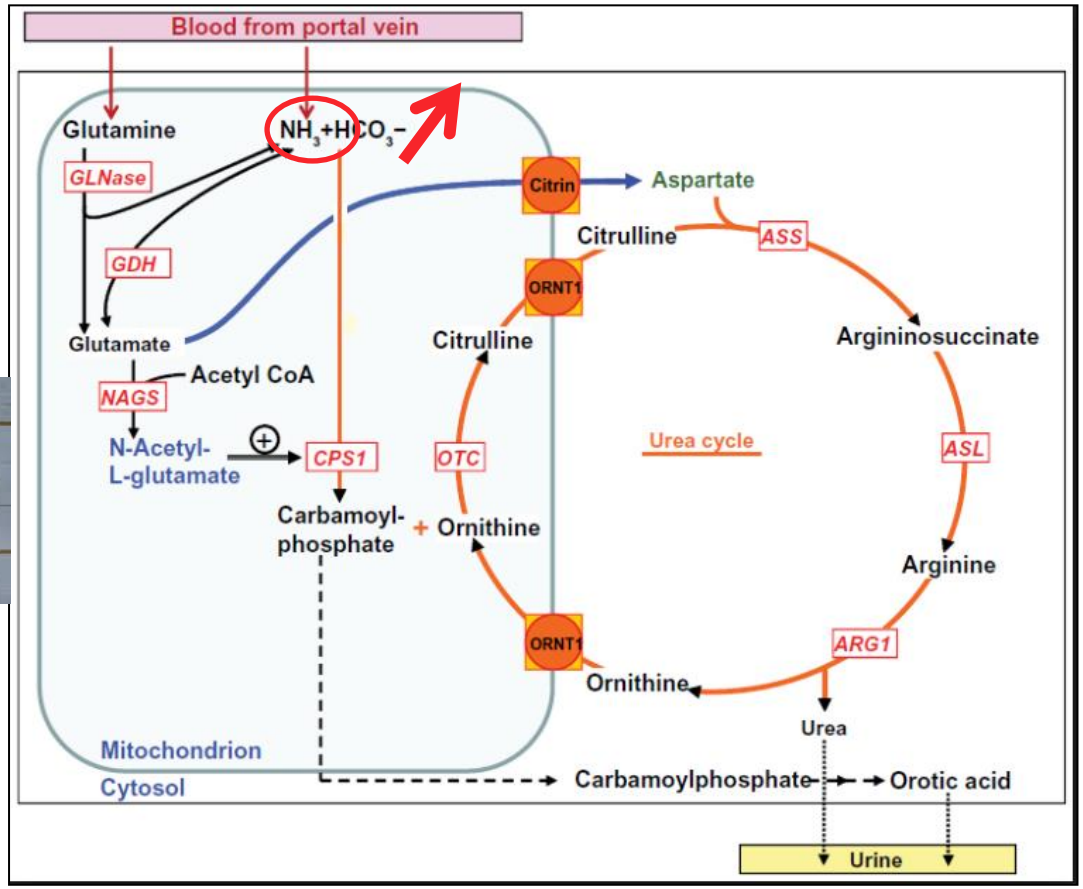


# Removing toxic metabolite

## Urea cycle defect (UCD)

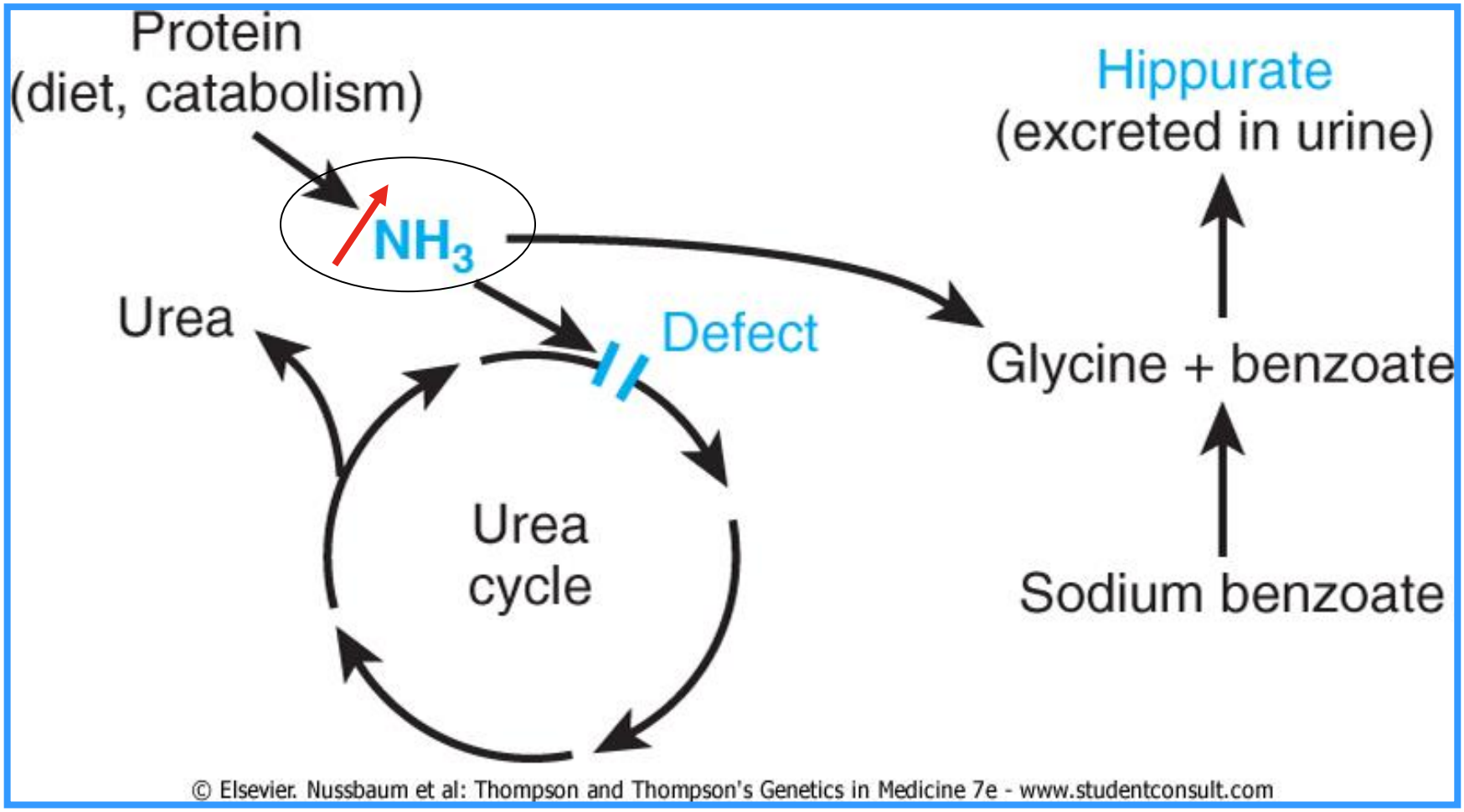
Amino acids

Proteins
(catabolism, diet)



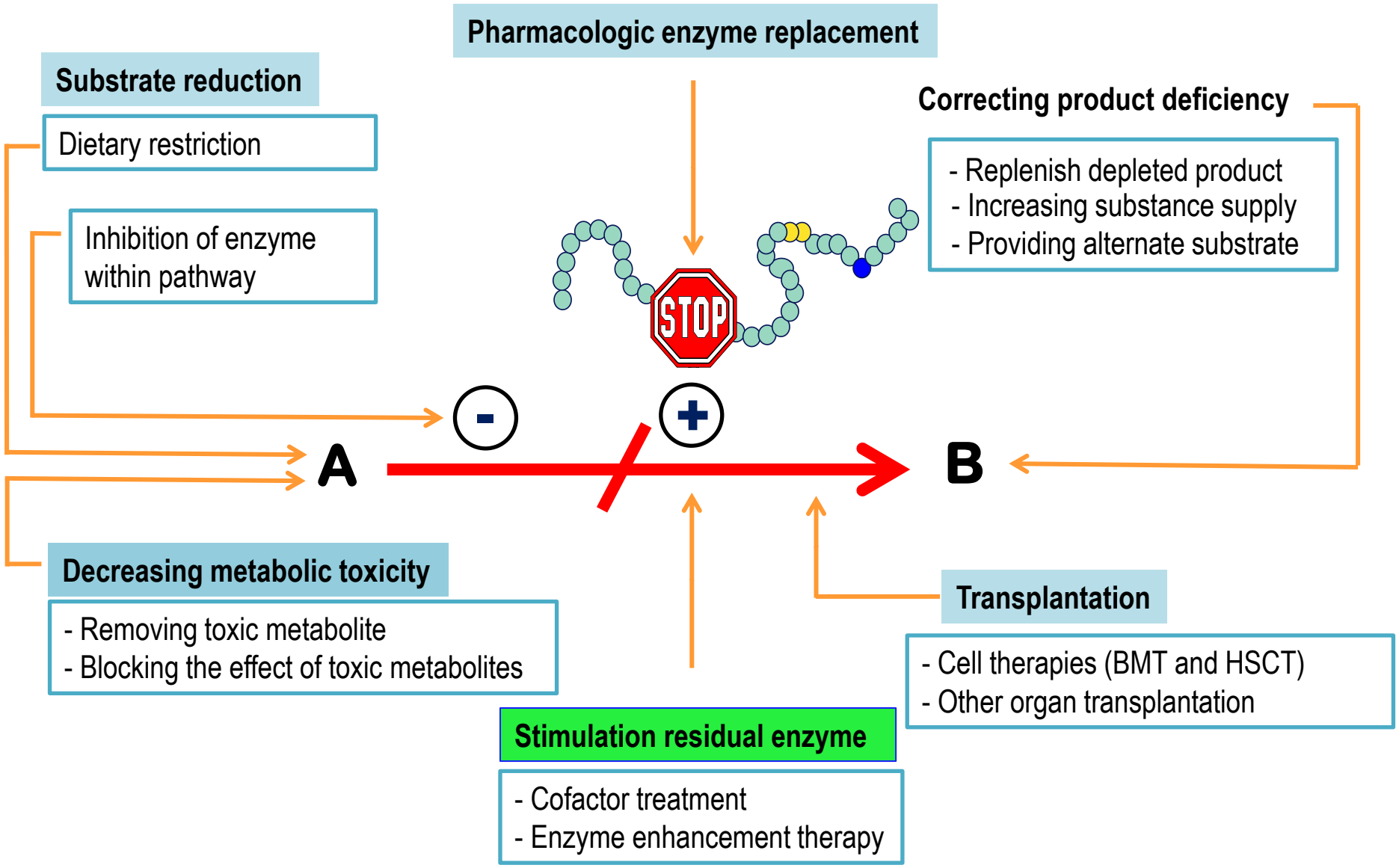

**Hyperammoniemia** is the hallmark of Urea Cycle Defect and responsible for severe brain damage

# UCD and nitrogen scavengers

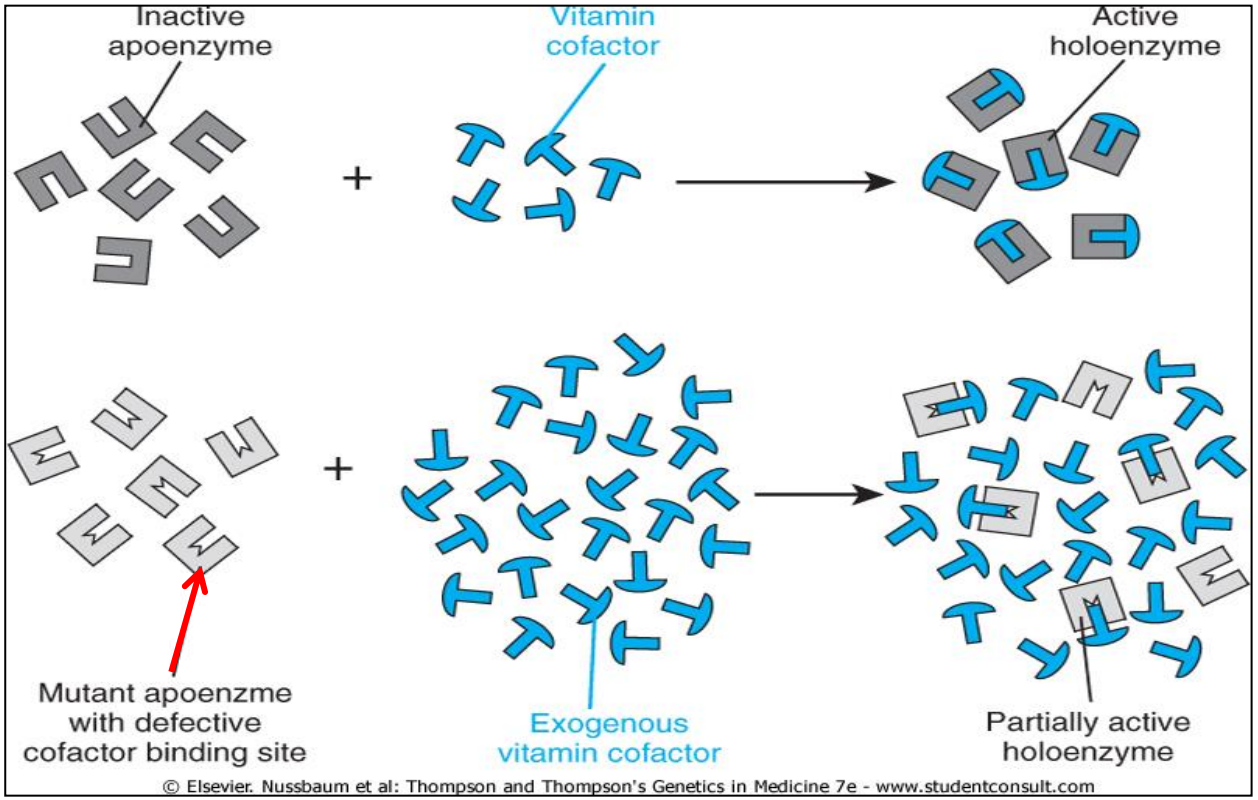



Administration of sodium benzoate diverts ammonia to glycine synthesis, and the nitrogen moiety is subsequently excreted as hippurate in urine (non toxic compound)

# Therapeutic strategies

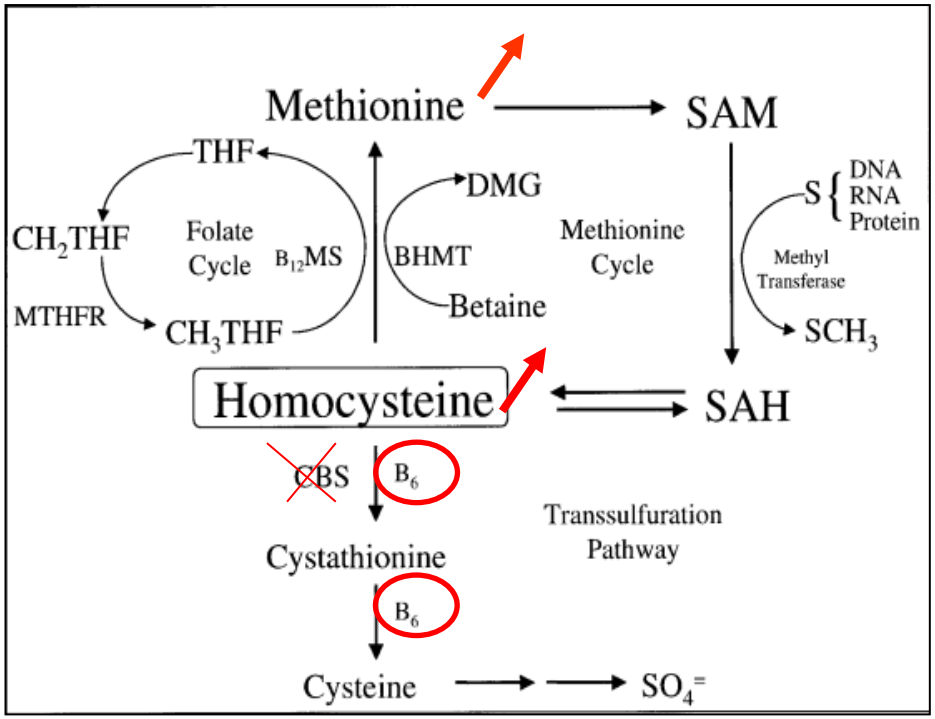


# Effects of High dose Cofactors or Vitamin-responsive effect

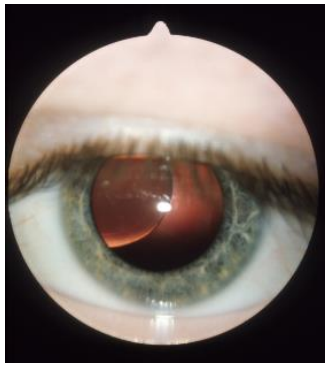



- Vitamin-reponsive enzyme defects are often due to mutations that reduce the normal affinity of the enzyme for the cofactor needed to activation

# Classical Homocystinuria
# Cystathionine-β-synthase (CBS) deficiency

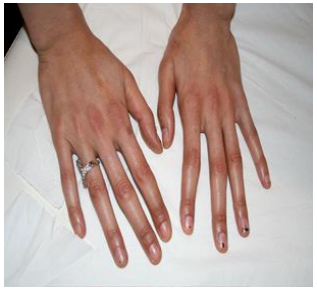



- High Homocysteine increases thromboembolic risks (stroke, myocardial infarctions), especially after 20 years



- Ectopia Lentis

- Marfanoid Habitus



- Arachnodactyly

**50 %** of patients with CBS deficiency are pyridoxine (vitamine B6) - responsive

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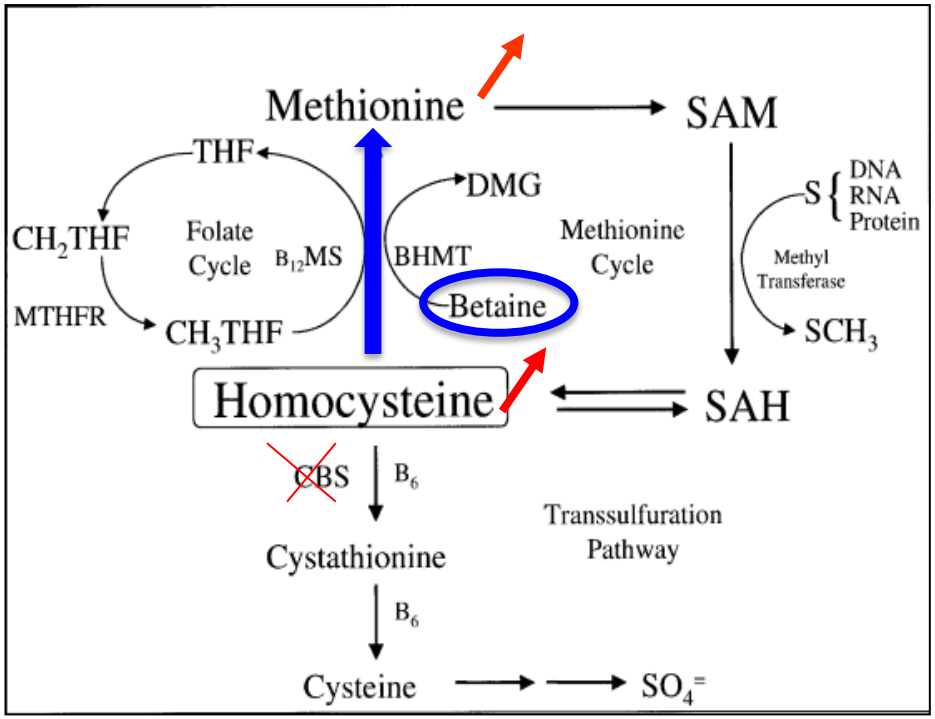


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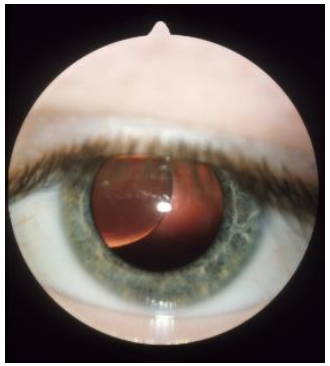

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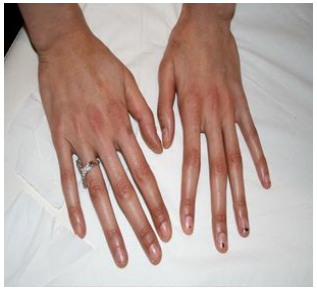

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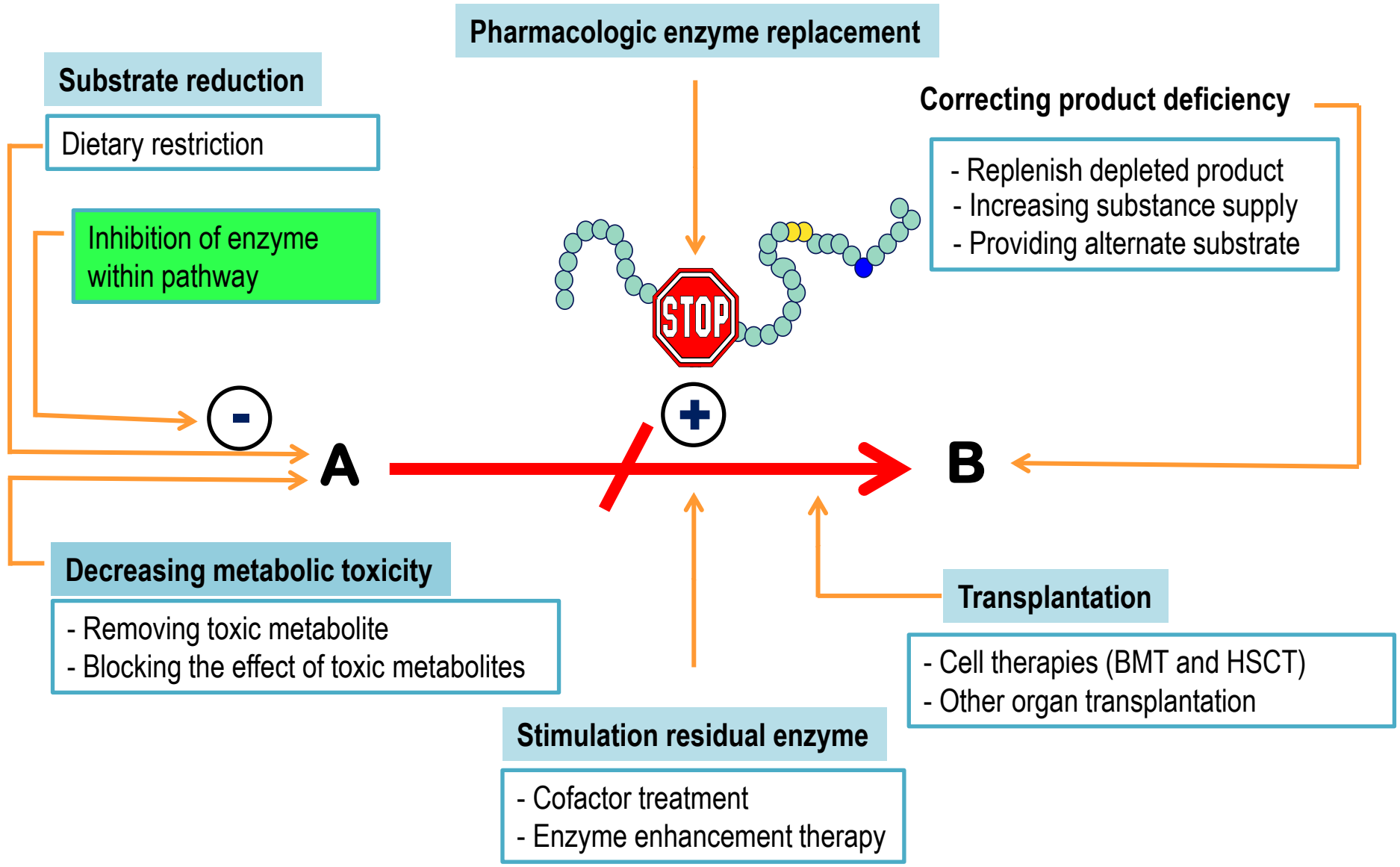
**50 %** of patients with CBS deficiency are pyridoxine (vitamine B6) - responsive

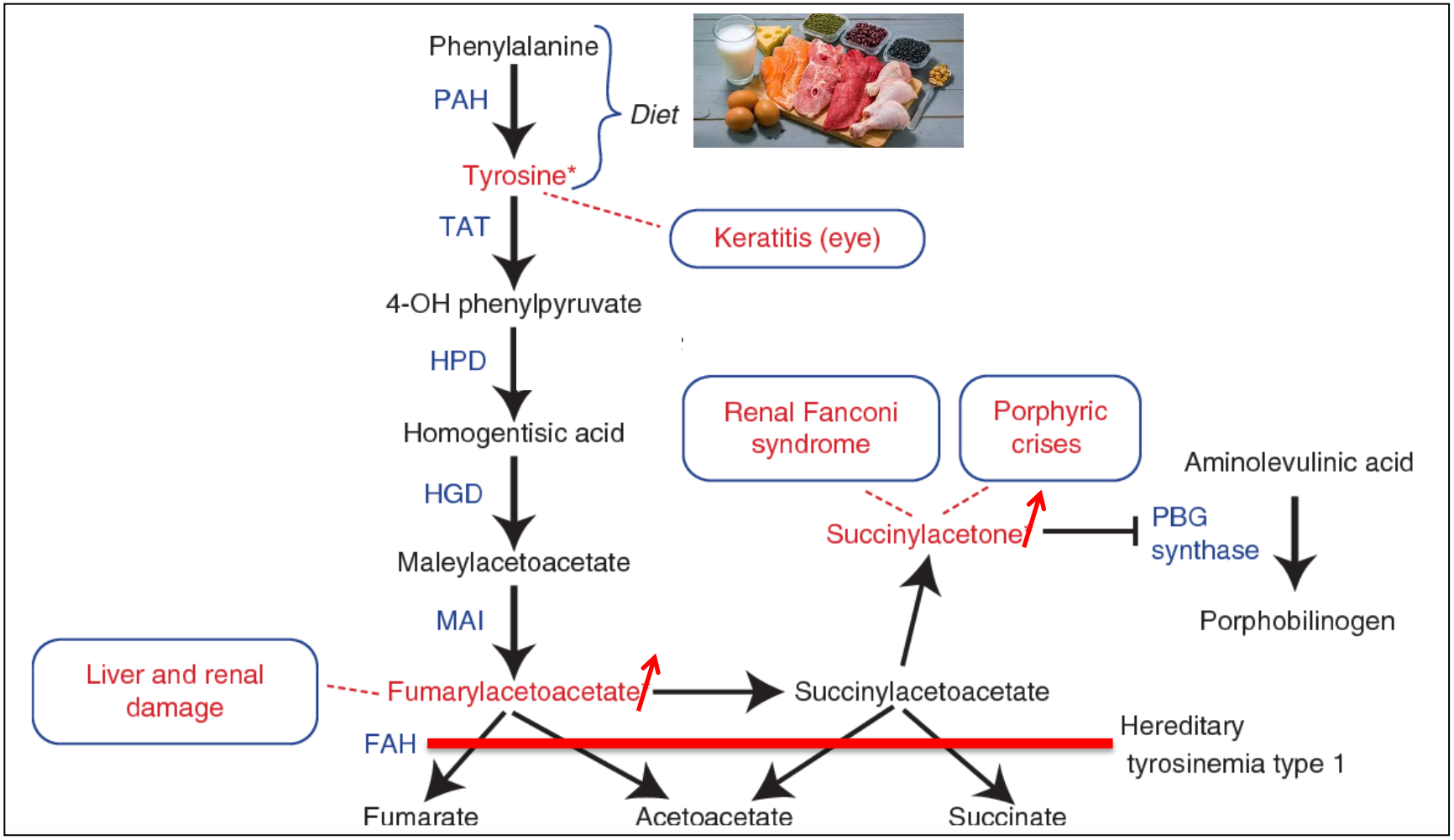
In B6 non-responsive patients, Betaine decreases Homocysteine levels

# Therapeutic strategies



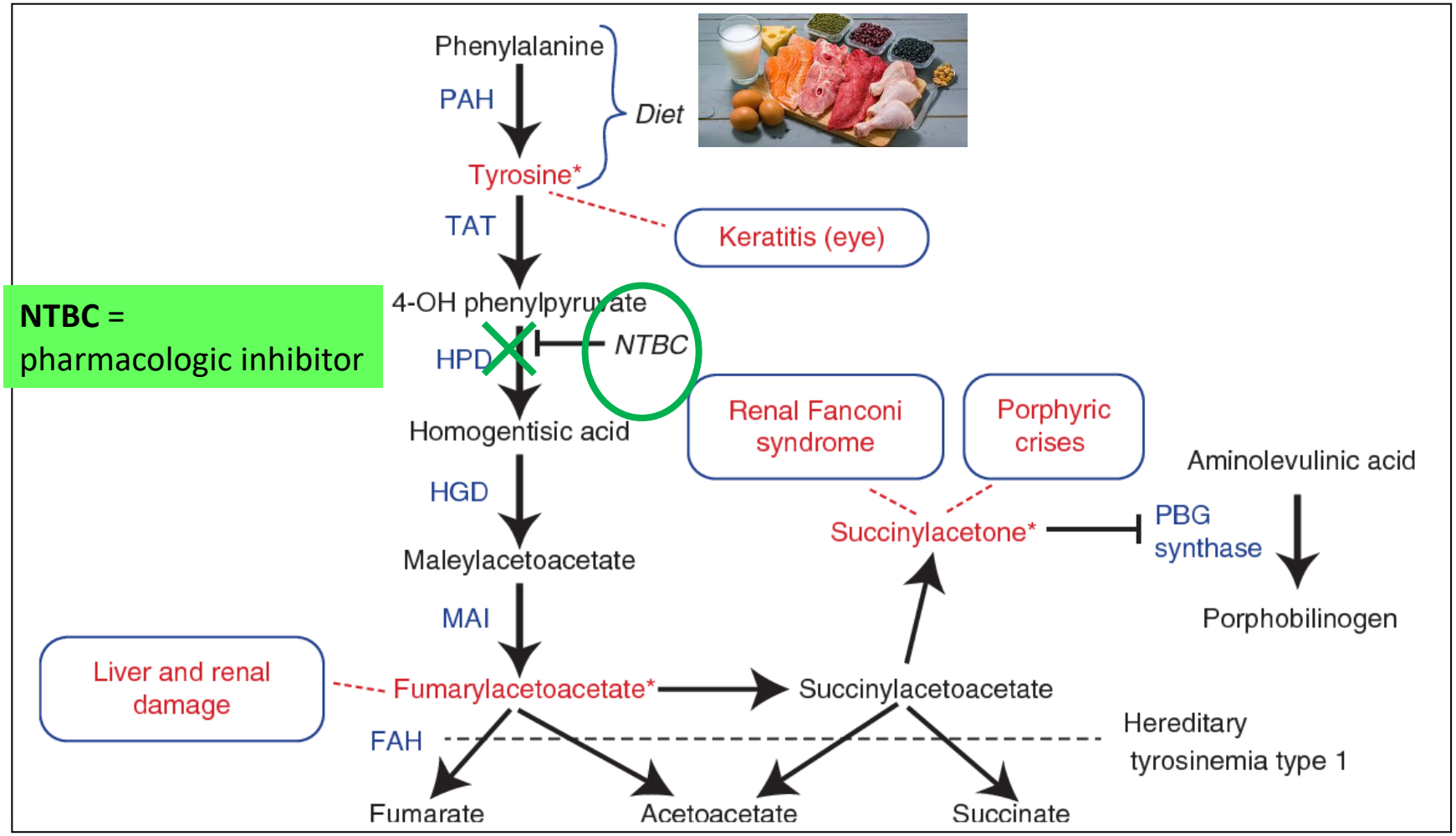
# Inhibition of enzyme within pathway

## Tyrosinemia Type 1



# Inhibition of enzyme within pathway

## How to transform a severe disease into a milder disease ?



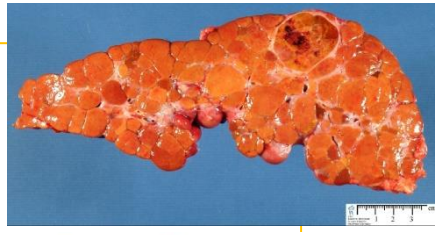

**NTBC** = pharmacologic inhibitor

Reducing the accumulation of toxic compounds, to transform **a severe disease (Tyrosinemia type I)** into a **mild disease (Tyrosinemia type II)**

# Inhibition of an enzyme within a pathway

## Tyrosinemia Type 1 = severe disease

- Autosomal recessive disorder, Europe 1/100.000 ; Quebec 1/1800
- Detected through Newborn screening on DBS (tyrosine level on DBS)



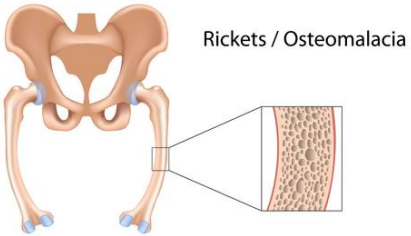
- Hepatic disease : Chronic hepatic insufficiency

→ cirrhosis

→ Hepatocellular carcinoma (HCC)

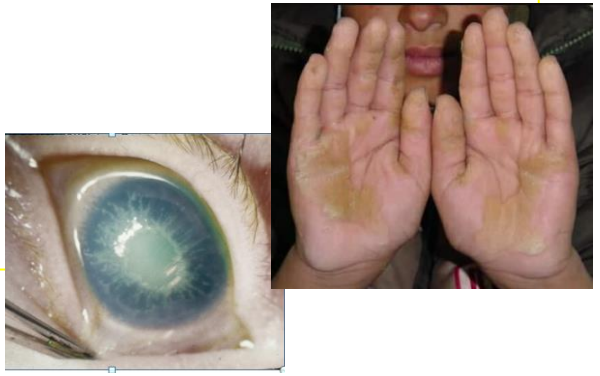
- Kidney disease :

Tubulopathy → Hypophosphatemic rickets

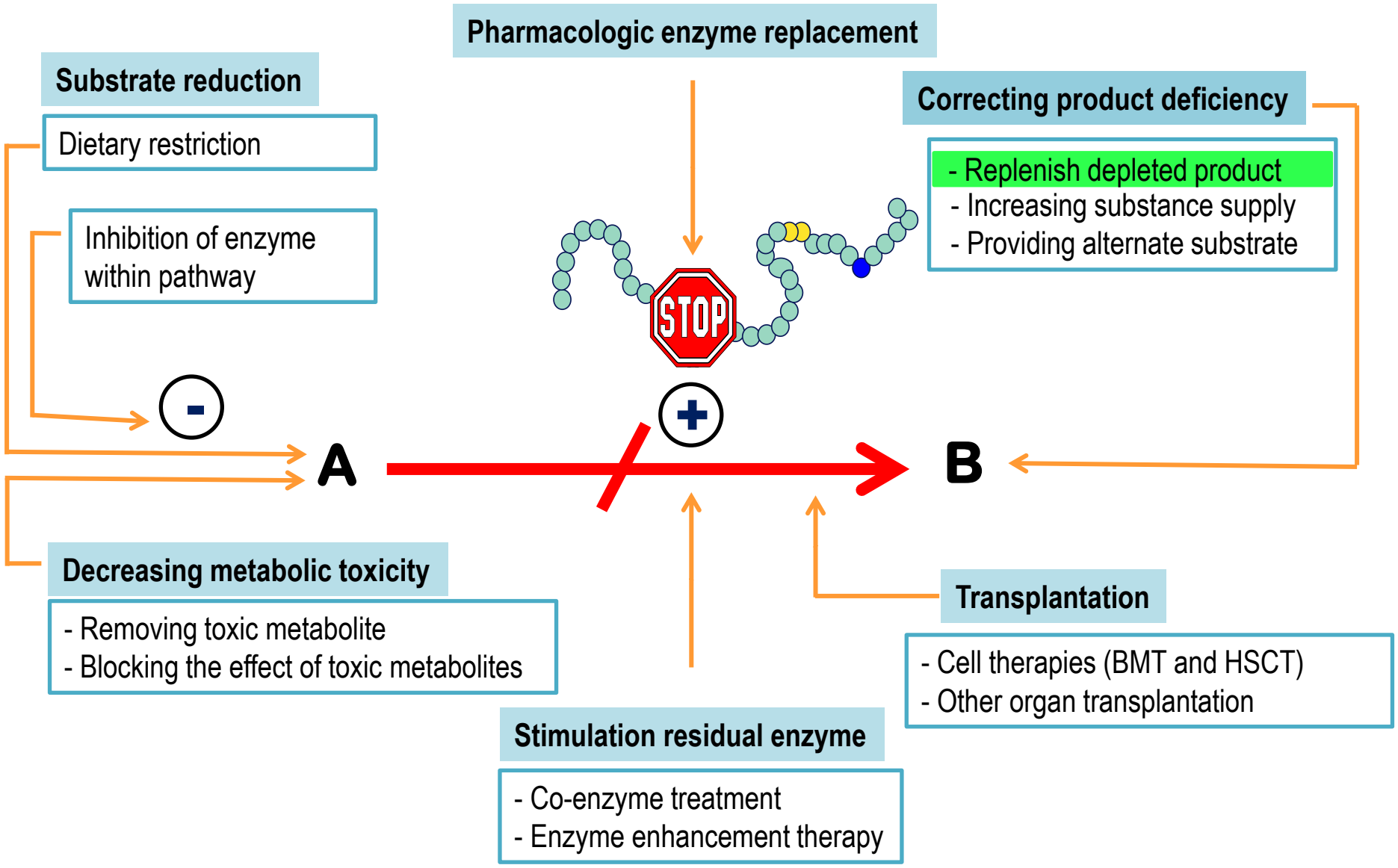



## Tyrosinemia Type 2 = milder disease

- Palmoplantar keratodermia, hyperhidrosis
- Corneal opacities
- Improved with a low phenylalanine and tyrosine diet
- Intellectual disability
- No liver or kidney disease

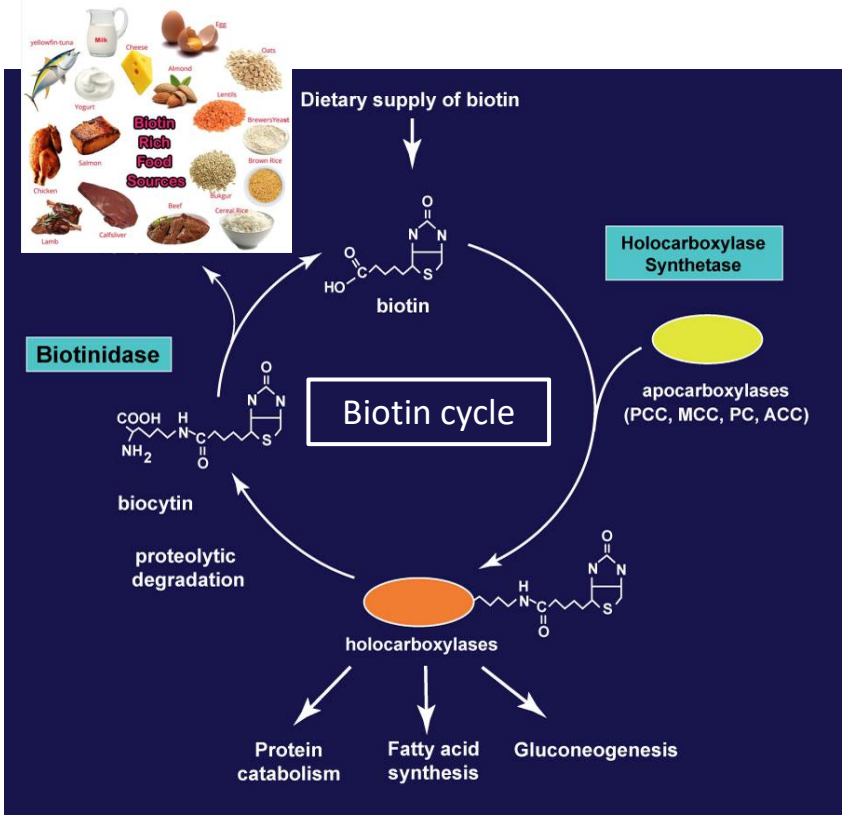


# Therapeutic strategies



# Correcting product deficiency

## Multiple Carboxylase Deficiency (Biotinidase, Holocarboxylase synthetase)



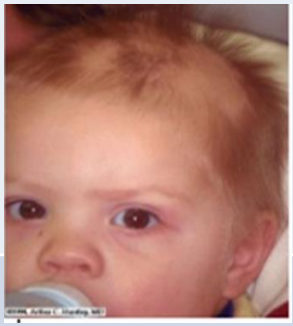

- Free biotine (B vitamine) is needed by biotine dependant carboxylases
- Profound biotinidase deficiency :
  < 10 % normal activity
- Partial biotinidase deficiency
  10-30 % normal activity
- *BTB* mutation causes Biotinidase deficiency must be ruled out in every child with unexplained neurologic symptoms even in absence of cutaneous or laboratory symptoms
- Improvement of most symptoms with treatment

**<u>TREATMENT</u> :**

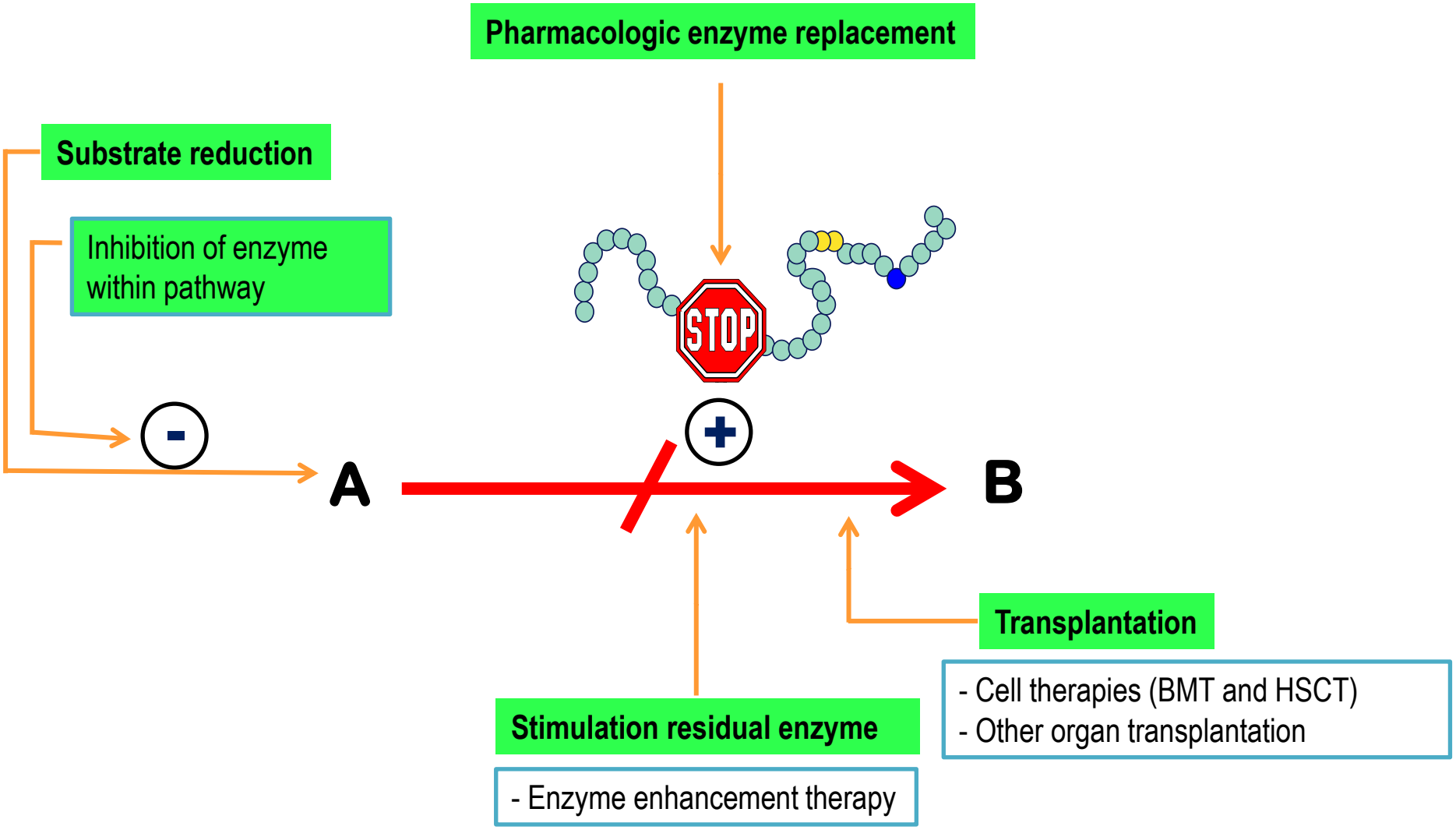
- Biotinidase deficiency : Biotin 5-10 mg/day (oral)
- HLCS : Biotin 10-20 (-40) mg/day

# Correcting product deficiency

## Multiple Carboxylase Deficiency (Biotinidase, Holocarboxylase synthetase)

| | Holocarboxylase synthetase (HCLS) | Biotinidase |
|---|---|---|
| First symptoms | First days of life | 1week till 10 years |
| | Hypotonia, coma, **Seizures,** hypothermia | Hypotonia, ataxia, **Seizures** |
| Cutaneous symptoms | **Alopecia, skin rash** | **Alopecia, scaly perioral/facial rash**<br>Periorificial eczema<br>pigmentation deficit (loss of hair color) |
| Complications<br>  | | Deafness and optic atrophy<br>Periventricular leucodystrophy<br>Or thalami abnormalities (MRI)<br>Spinal cord and progressive spastic paresis<br>Intellectual disability and developmental delay<br>Recurrent viral or fungal infections < immune dysfunction |
| | Severe **metabolic acidosis** | **Metabolic ketoacidosis**<br>Organic aciduria : propionylglycine, tiglylglycine, methylcitrate, 3-hydroxypropionique, 3-methylcrotonylglycine, 3-hydroxyisovalérique |
| Enzyme activity | Fibroblasts, lymphocytes | DBS or plasma |

# Therapeutic strategies in Lysosomal Storage Disease



# Treatment according to clinical phenotype in MPS I

**SEVERE FORM** — **ATTENUATED FORM**

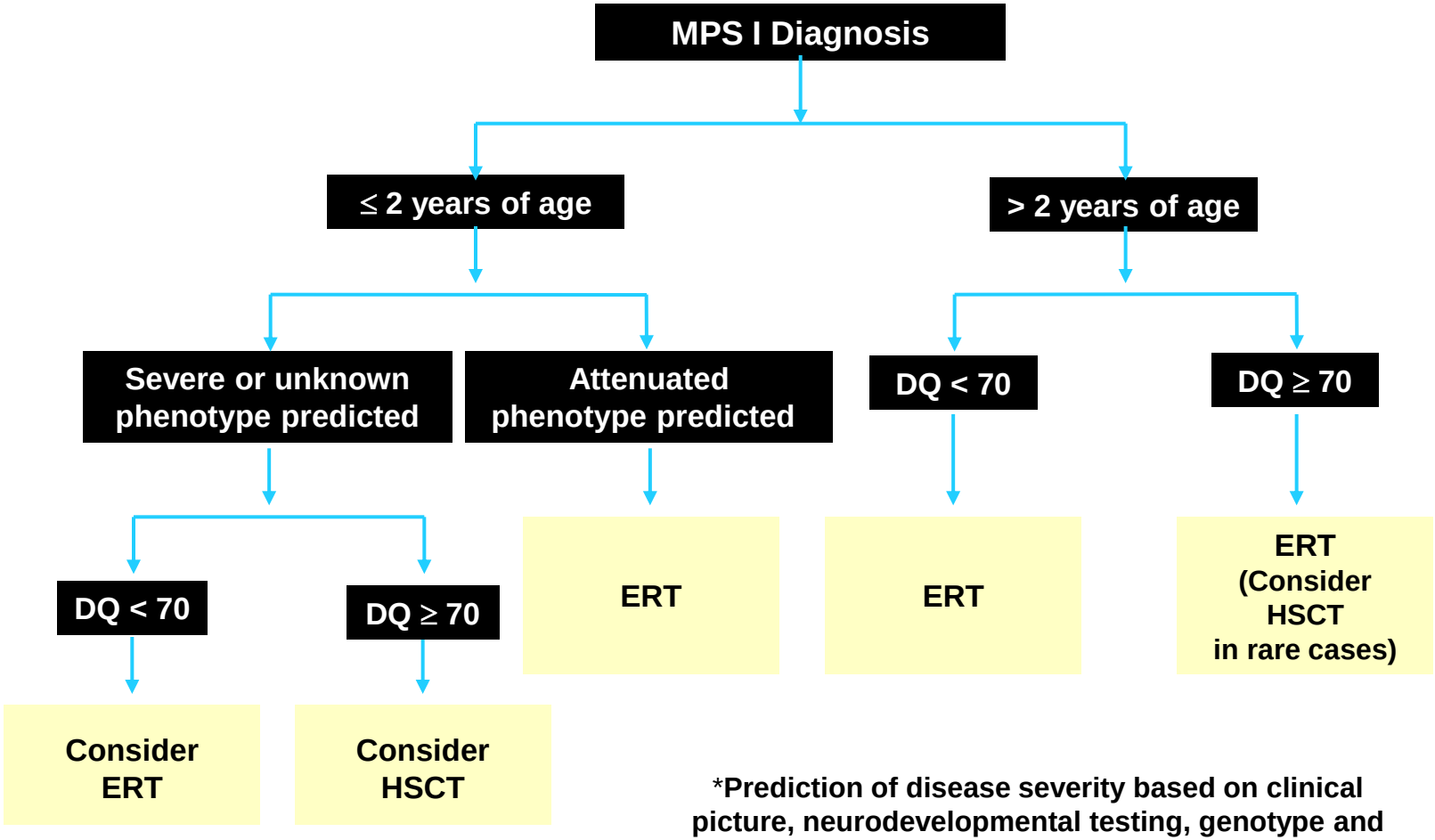
**HURLER** — **HURLER-SCHEIE** — **SCHEIE**

| | | | |
|---|---|---|---|
| Age at diagnosis | 0.2–7 years | 0.2–36 years | 2–54 years |
| Effect on cognition | Pronounced mental delay with loss of acquired skills | No/mild mental delay; learning disabilities | No impairment |
| Mean life expectancy (untreated) | 7 years | Approximately 20 years | Adulthood |
| Phenotype distribution* | ~65% | ~25% | ~10% |

**based on Moore et al. Orphanet J Rare Dis 2008;3:24 and MPS I Registry data*

# Treatment algorithm in MPS I

Treatment is adapted to phenotype




***Prediction of disease severity based on clinical picture, neurodevelopmental testing, genotype and other relevant information**

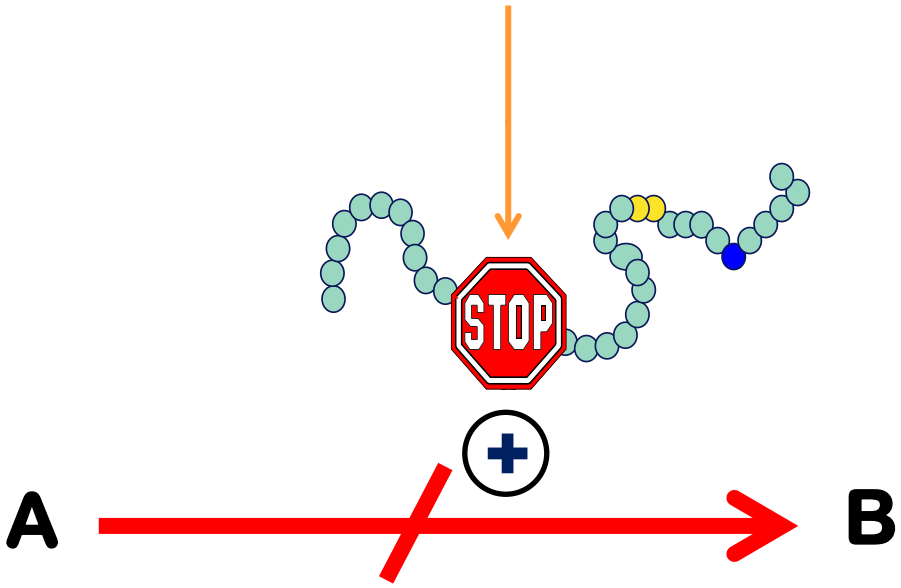
DQ = Developmental quotient

HSCT = Hematopoietic stem cell transplant

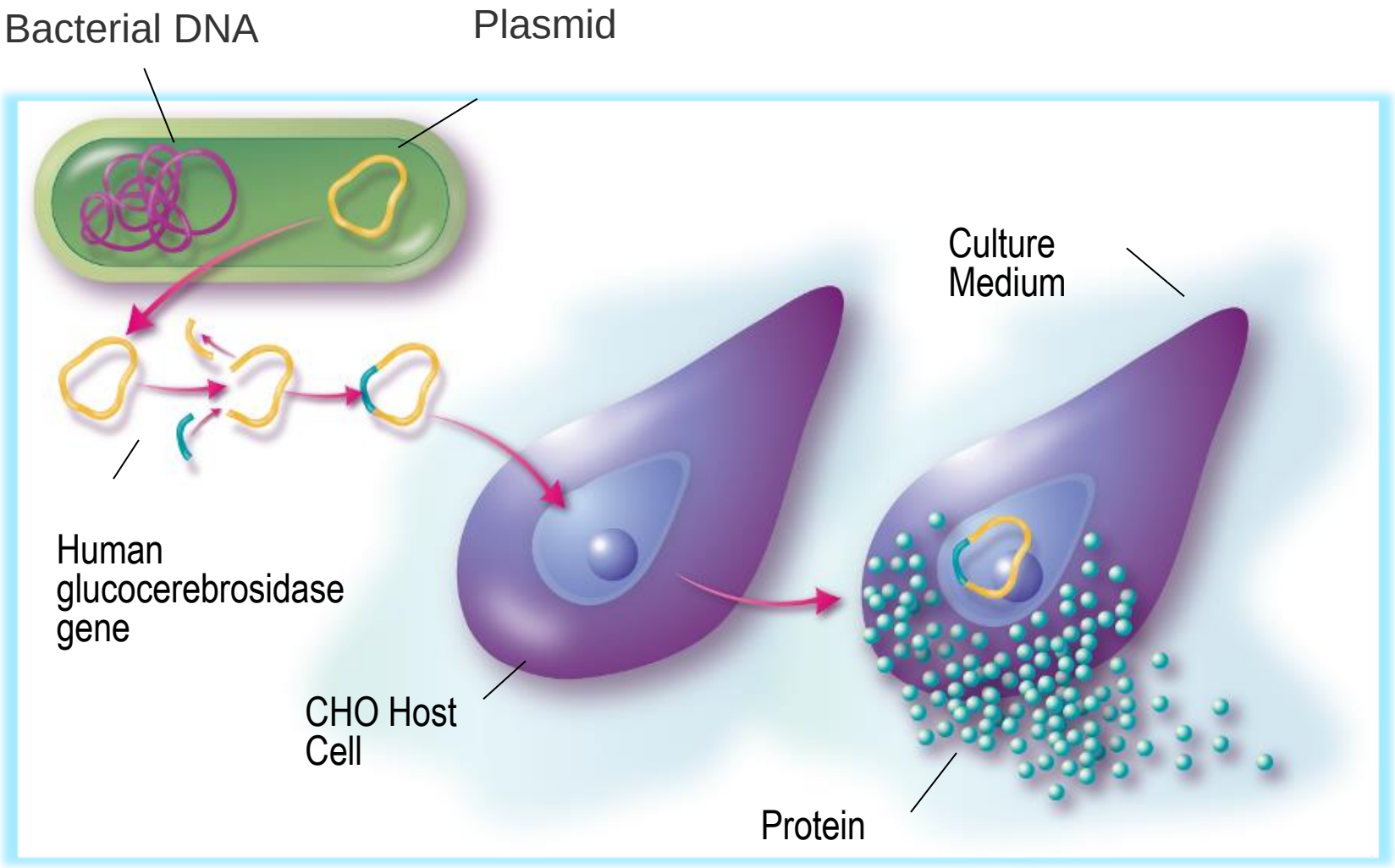
*Pediatrics 2009;123:19-29*

# Therapeutic strategies to IEM

**Pharmacologic Enzyme Replacement Therapy (ERT)**



# Recombinant DNA technology to manifacture ERT




CHO : Chinese Hamster Ovary

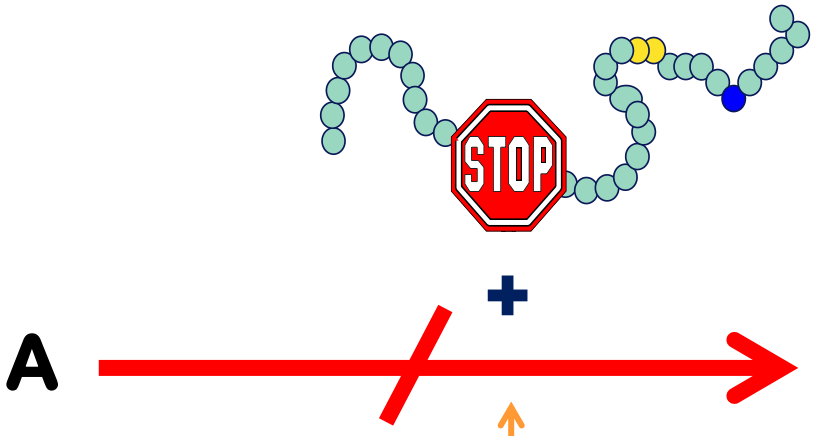
# ERT – Frequent immune response

| Disease | rh-enz | Nbr | % Ab | % patients with reactions |
|---|---|---|---|---|
| Gaucher | Cerezyme | 1322 | 15 % | 13,8 % |
| MPS I | Aldurazyme | 55 | 91% | 32 % |
| MPS II | Elaprase | | 11% | 55 % |
| MPS VI | Naglazyme | 10 | 100 % | 5 % |
| Fabry | Fabrazyme | 58 | 89 % | 52 % |
| | Replagal | 55 | 55 % | 10 % |
| Pompe | Myozyme | 3 | 66 % | 66 % |

- Infusing **a foreign protein/enzyme** not synthesized by the mutant DNA bears the risk of immune reactions and/or enzyme activity inactivation
- **Increased IgG antibody** levels were detected during most treatments, but without correlation between the occurrence of severity of adverse events and the presence of high antibody titers
- **Neutralizing antibodies** were (most of the time) not associated with a reduction in efficacy of the enzyme preparation (or transient)
- Most **infusion-related reactions are mild** (fever, flush, tachycardia, ..)
- Hypersensitivity/anaphylactic reaction against the infused enzyme can be treated by slowing down the infusion rates and premedication with antihistamines and/or corticosteroids
- In an ongoing strong immune response**, tolerance induction by drugs** such as methotrexate or rituximab may become necessary (e.g.CRIM negative Pompe patients)

*Brooks et al. Trends Mol Med 2003, 9:450-3*

# Therapeutic strategies

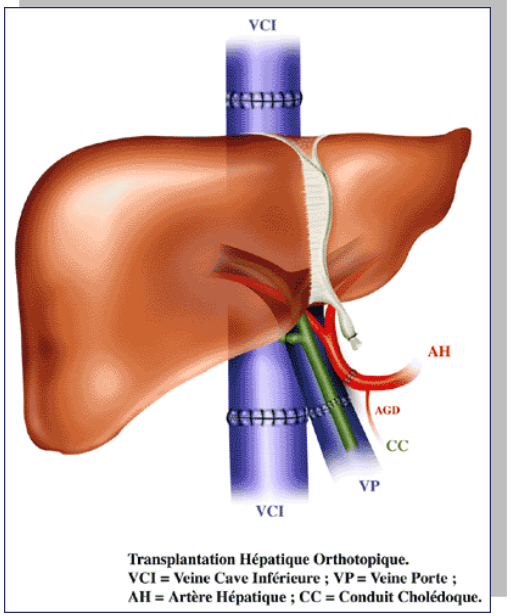



**Transplantation**

- Cell therapies (BMT and HSCT)
- Other organ transplantation

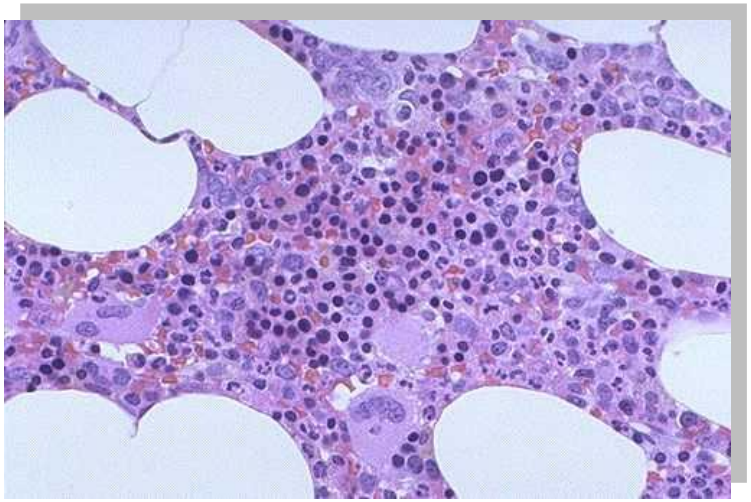
# *Modification of the somatic genome by transplantation*

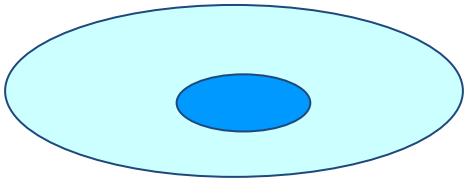
- Organs



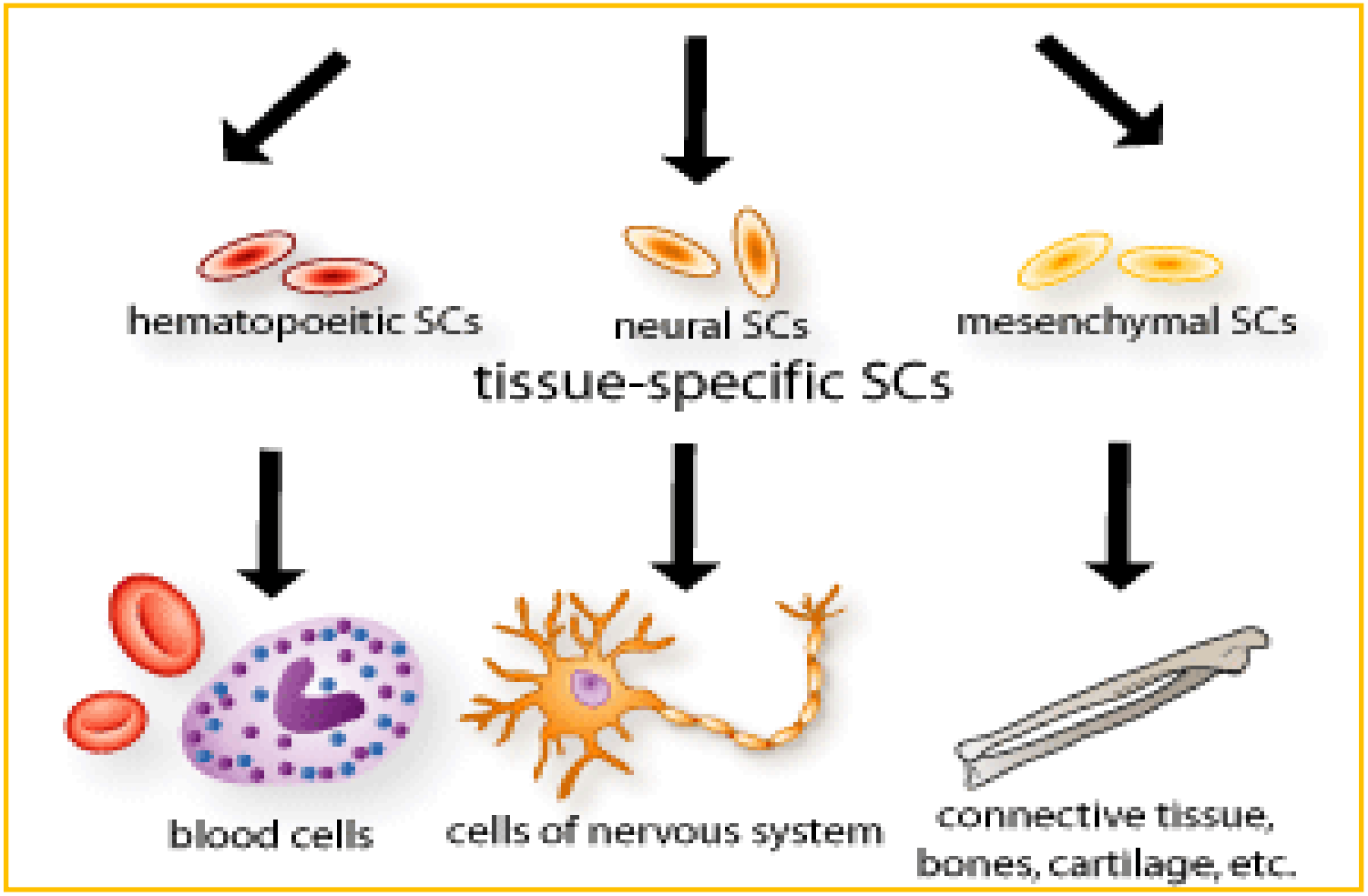

Transplantation Hépatique Orthotopique.
VCI = Veine Cave Inférieure ; VP = Veine Porte ;
AH = Artère Hépatique ; CC = Conduit Cholédoque.

- Cells





Stem cell


hematopoeitic SCs
neural SCs
mesenchymal SCs
tissue-specific SCs
blood cells
cells of nervous system
connective tissue,
bones, cartilage, etc.

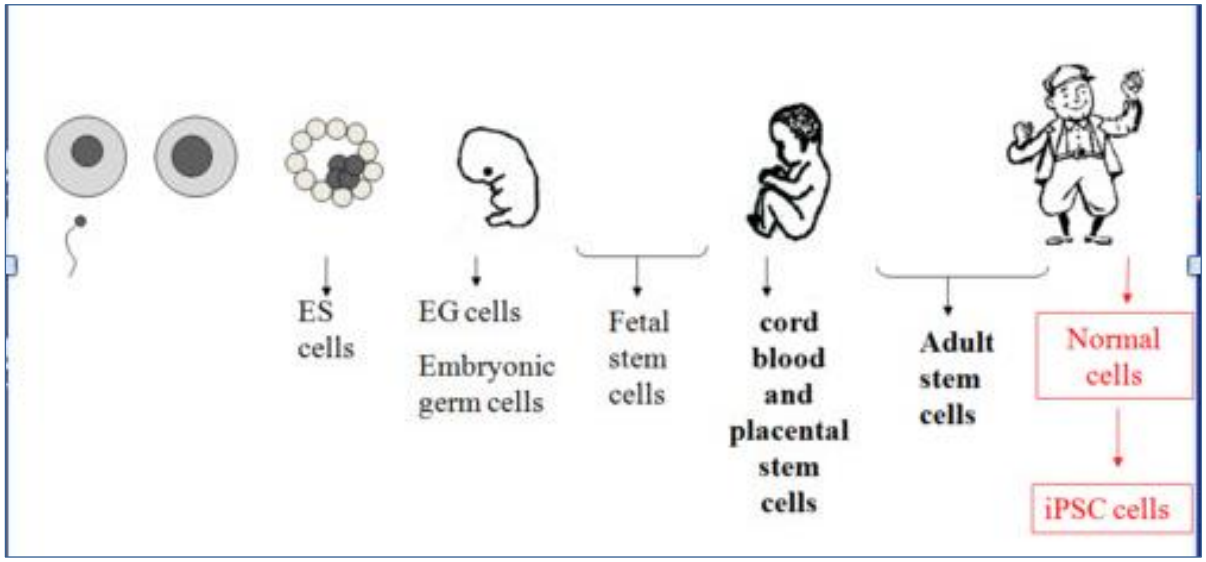
# Stem cell transplantation

Stem cells are self-renewing cells defined by 2 properties :

1. Ability to proliferate to form the differentiated cell types of a tissue in vivo

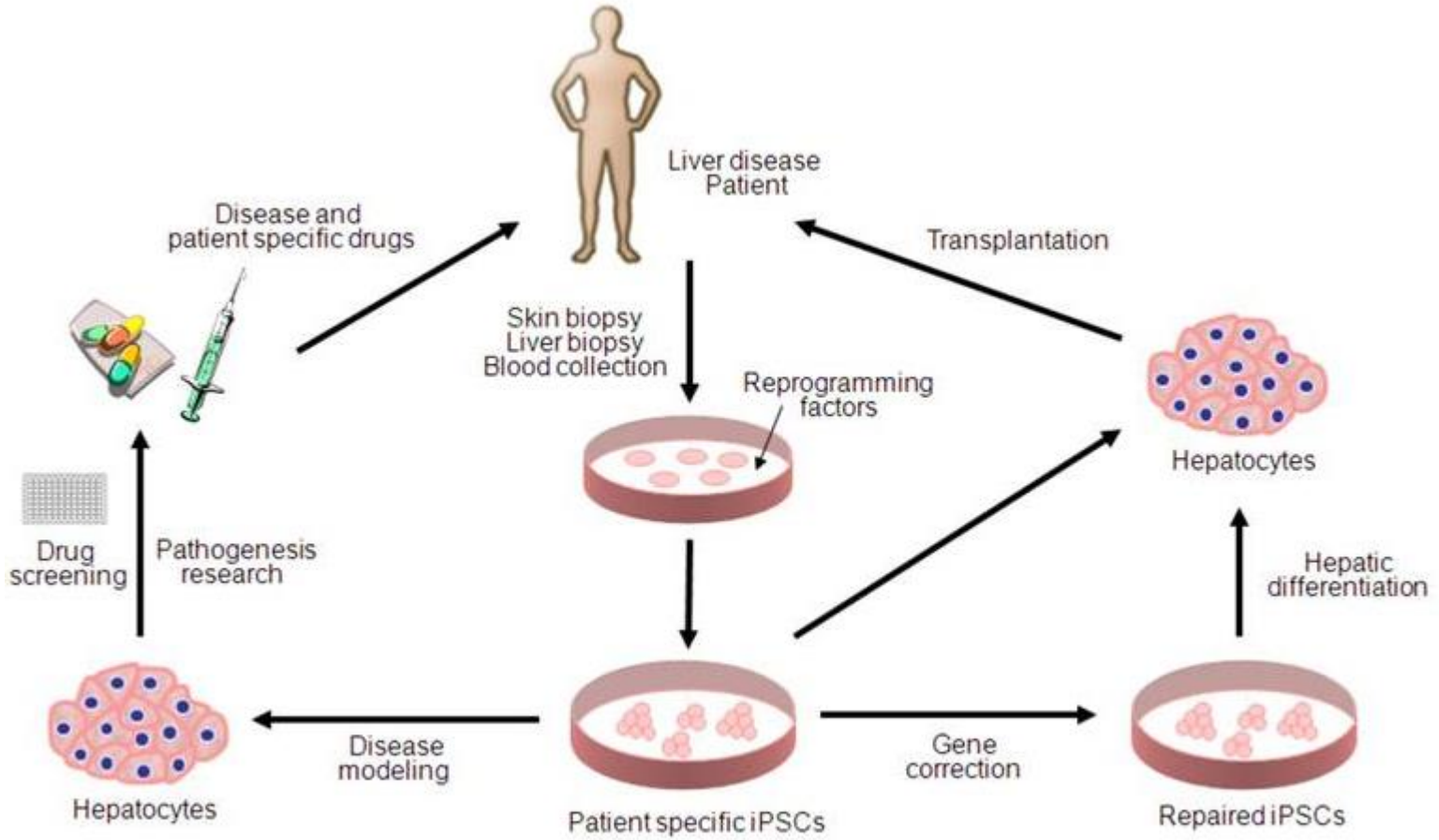
2. Ability to self-renew to form another stem cell

Origin : embryonic, fetal, cord blood, adult



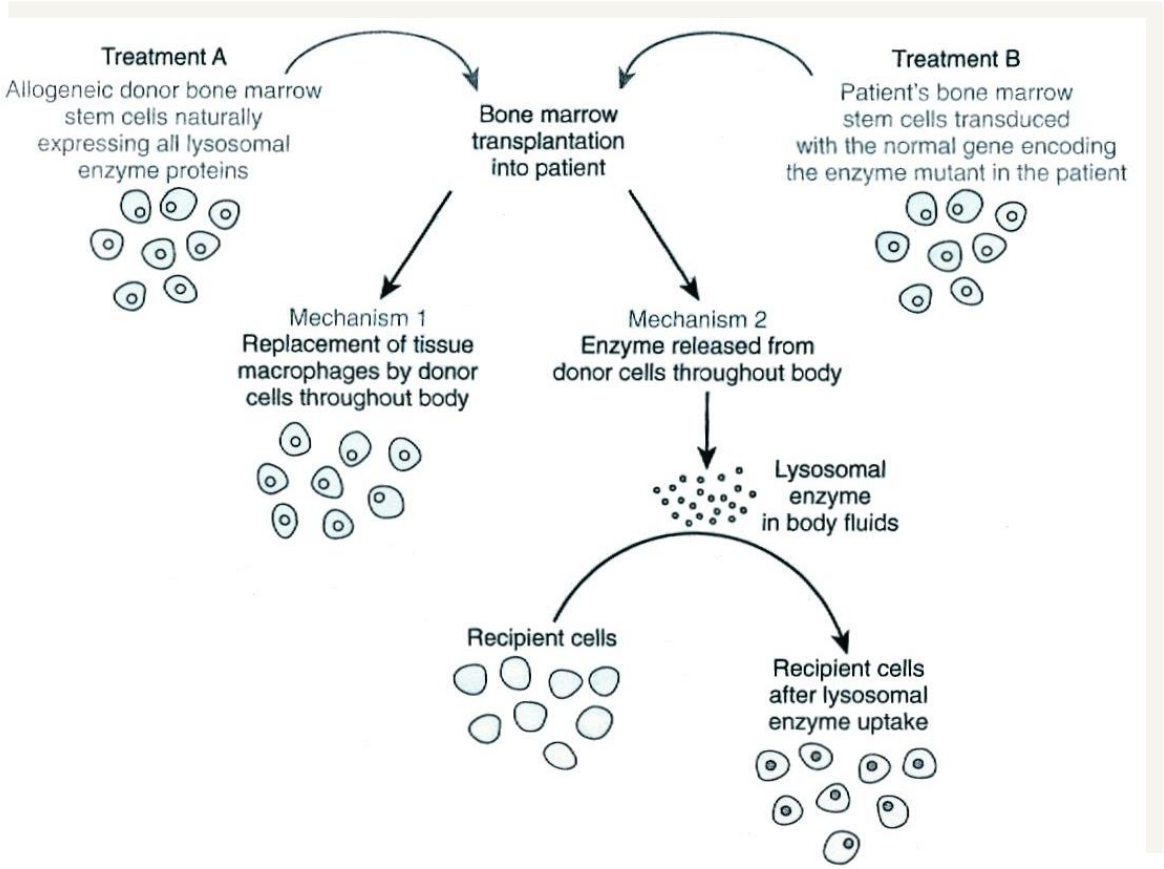

iPSC cells: Induced-pluripotent stem cells

# Potential applications of human iPSCs for liver diseases



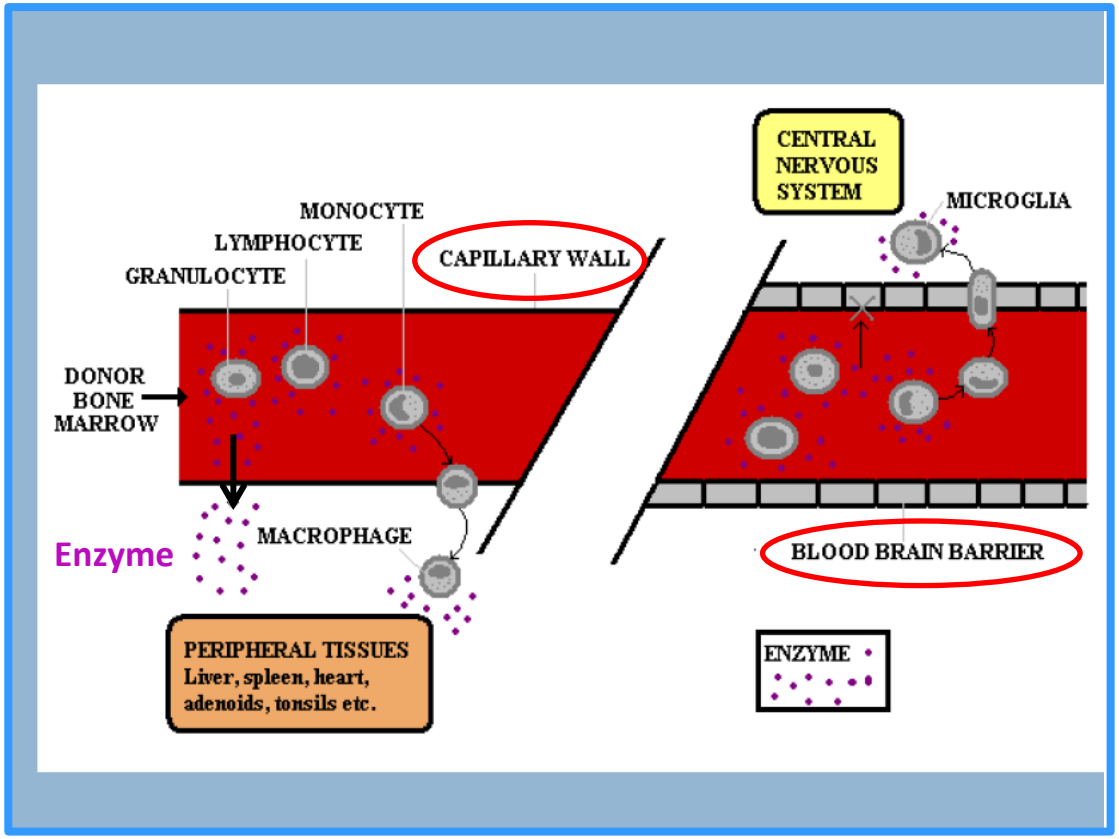
# Hematopoietic Stem Cell Transplantation (HSCT)-Principle

## a. Hematopoietic stem cells from **bone marrow**




**Two mechanisms by which bone marrow transplantation or gene transfer into bone marrow may reduce the substrate accumulation in LSD**

# Hematopoietic stem cell transplantation (HSCT)- principle



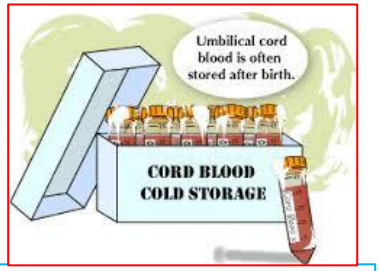

The goal of bone marrow or hematopoietic stem cell transplantation (BMT/HSCT) is to provide cells that produce the missing enzyme

- Enzyme deficiency corrected by donor cells
- Better response in some diseases

# HSCT-Evolution and limitations

## b. Hematopoietic stem cells from placental **cord blood**

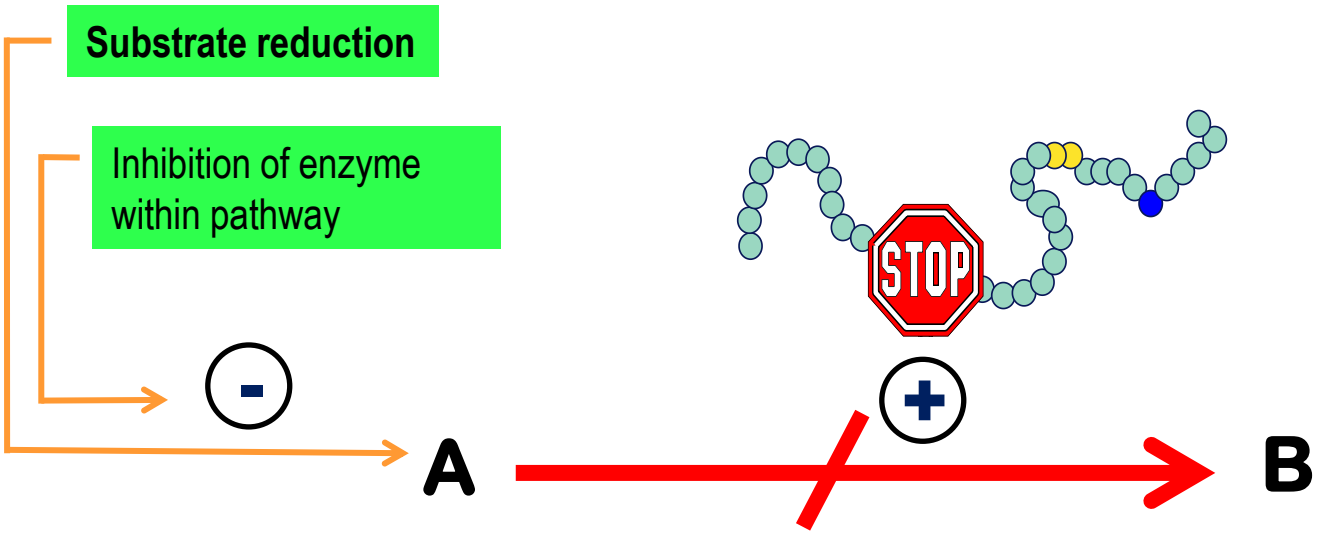
- Increased tolerance of histoincompatible donor cells
- Reduced risk of graft-versus host (GVH) disease
- Widely available (collected at birth in maternities)



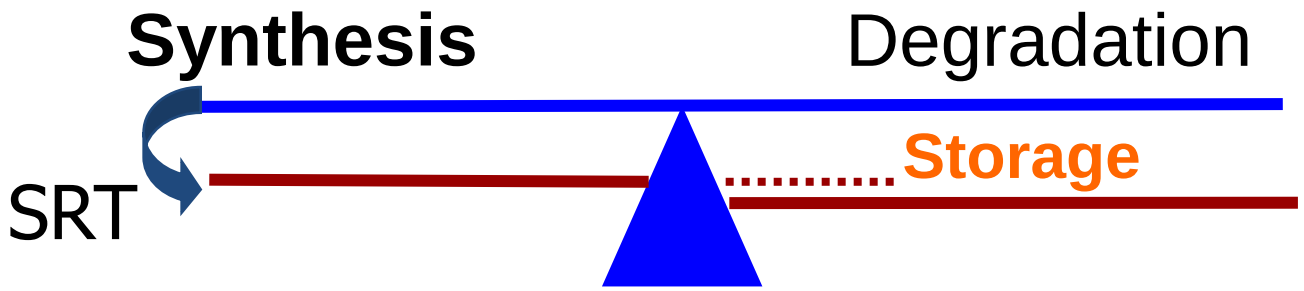

## Limitations

- Need an early diagnosis (before irreversible brain damage)
- Need of a Matching Donor (BM or CB)
- Effective for a limited number of LSD (approved option for MPS I, MLD, Krabbe ..)
- Despite progress, still significant procedure-related mortality and morbidity
- Long term outcome might not be favourable or limited in subsets of patients
- Variable results on brain and bone
- **Do not cure the disease .. but changes the natural history**

# Therapeutic strategies



# Substrate Reduction Therapy (SRT) in LSD - Principle

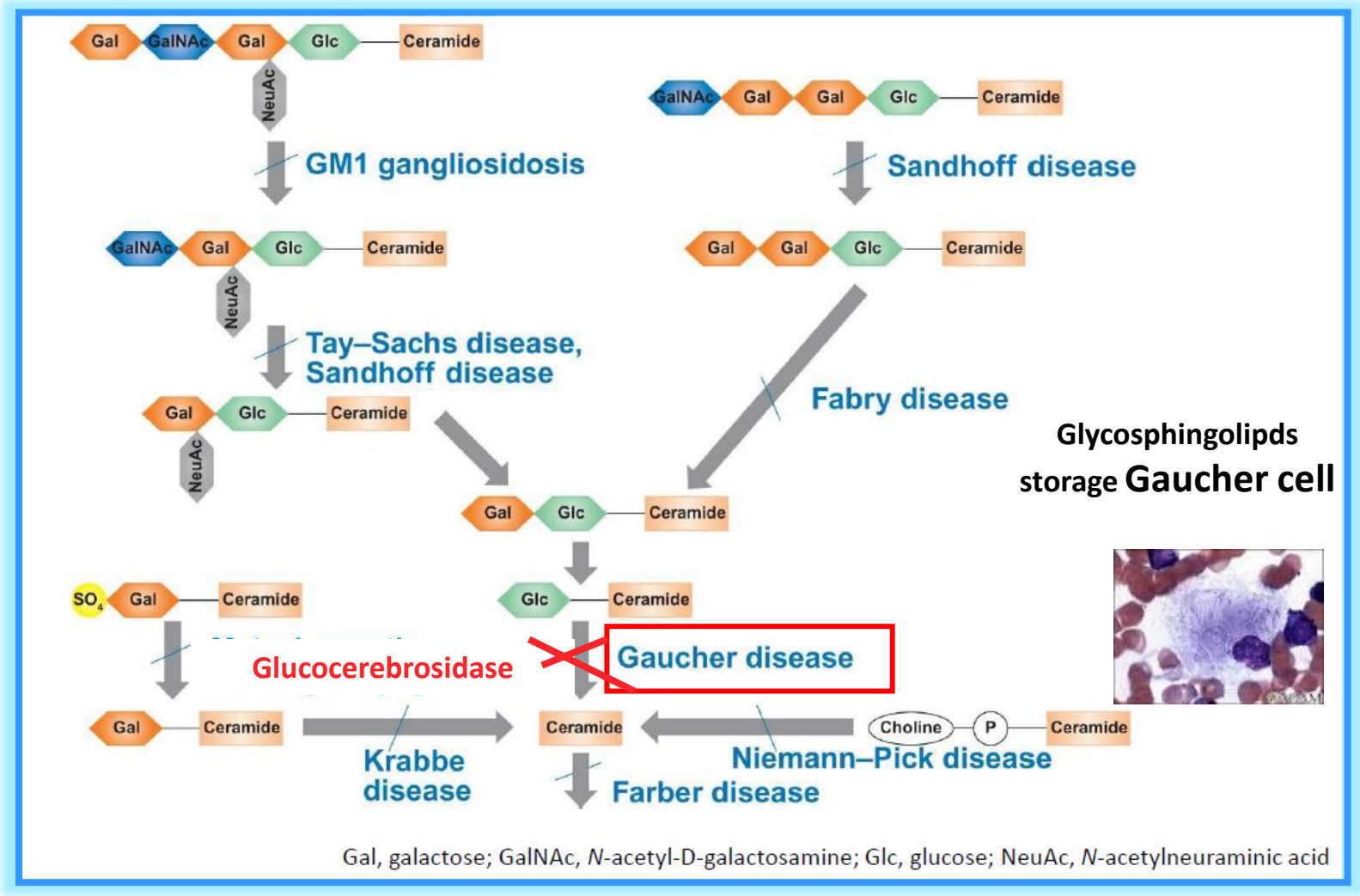



SRT are efficient if there is persistant residual degradation activity

to reduce residual storage

- **Possible application on glycosphingolipids metabolism**
- **Application with Gaucher disease**

# Gaucher disease = Sphingolipidosis
# Glycosphingolipids Catabolism




Sphingolipidosis, an heterogeneous group of diseases

# Multisystemic symptoms in Gaucher Disease

- Autosomal recessive LSD
- 1/450 Ashkenazi Jews
- 1/40.000 to 1/100.000 in other populations

**Heterogeneity in clinical presentation**

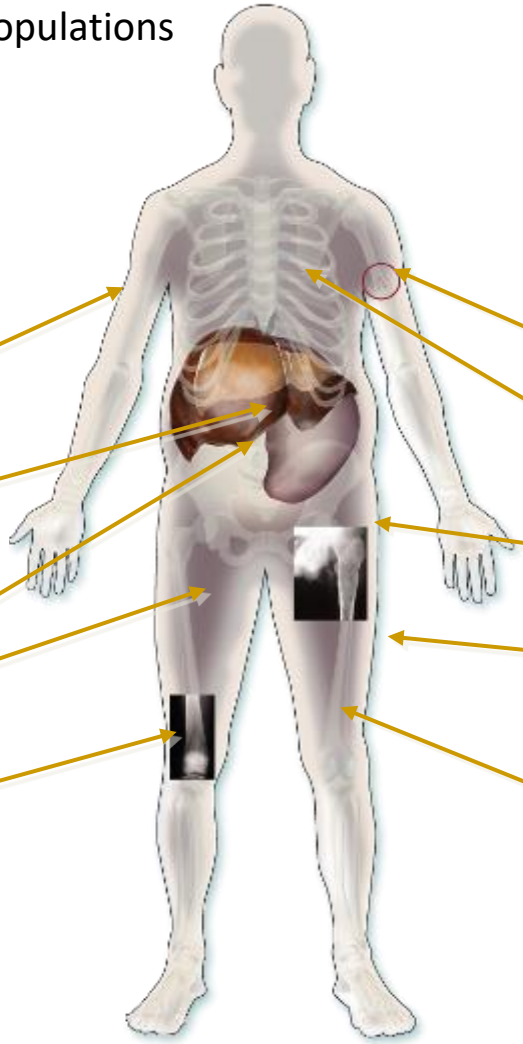
**Clinical diagnosis at every age**

Bone pain (63%)
Bone crisis (33%)

Hepatomegaly (79%)
Splenomegaly (87%)

Anemia (64%)
Thrombocytopenia (56%)

Erlenmeyer flask deformity (46%)



**General symptoms**

- Fatigue
- Easy bruising/bleeding
- Menorraghia
- Decreased appetite
- Abdominal pain
- Growth retardation
- Slow pubertal development

Pathologic fracture (15%)

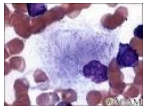
Interstitial Pulmonary fibrosis

Joint collapse (8%)

Osteonecrosis (25%)
Osteopenia (42%)

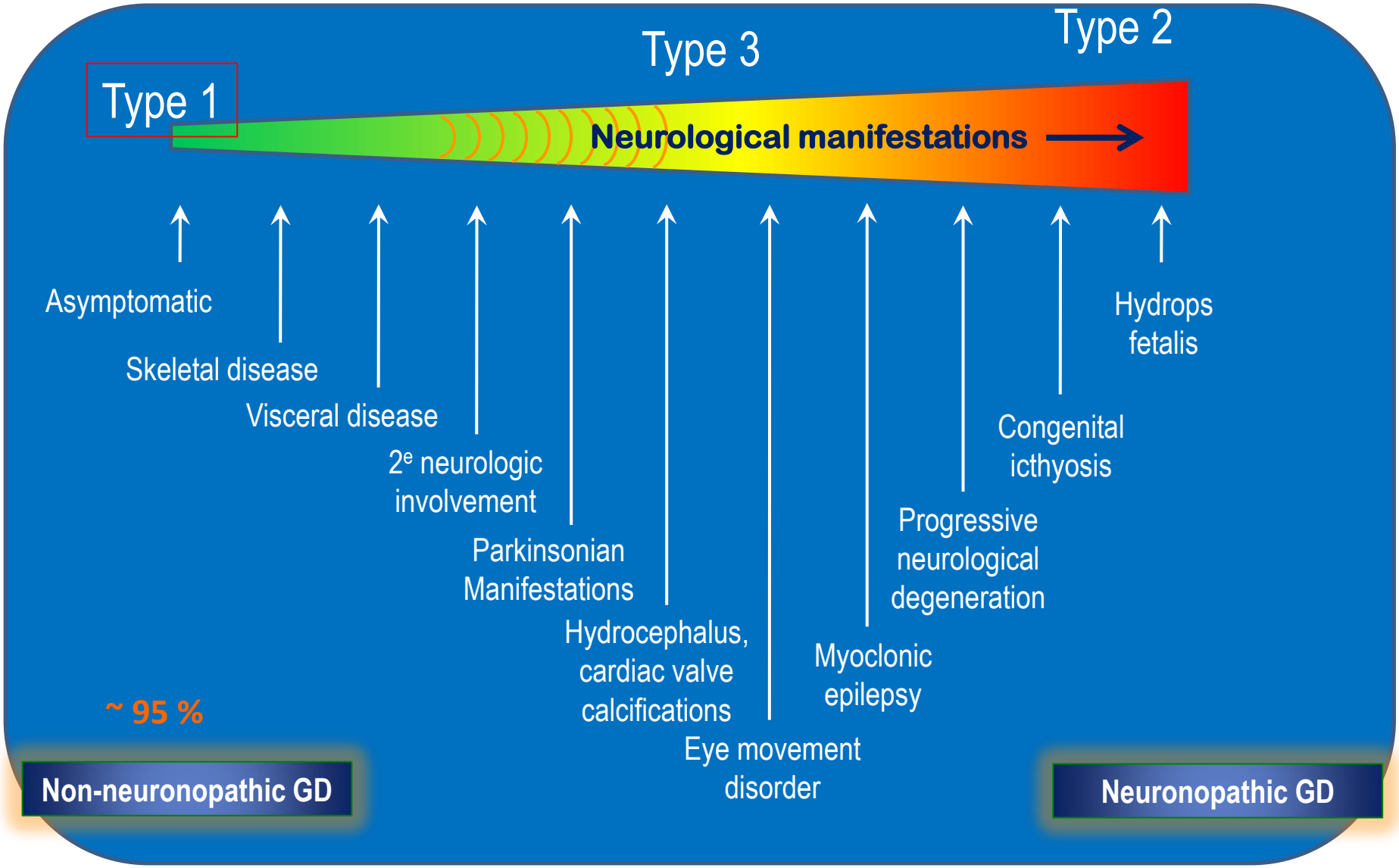
Bone marrow infiltration (40%) with

**Gaucher cell**
lipid laden macrophages

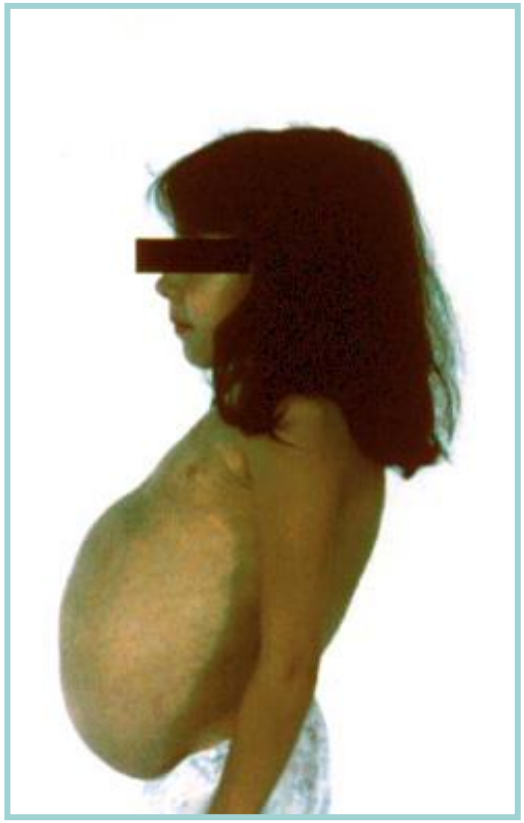


*Charrow J et al., Arch Intern Med 2000;160:2835.*

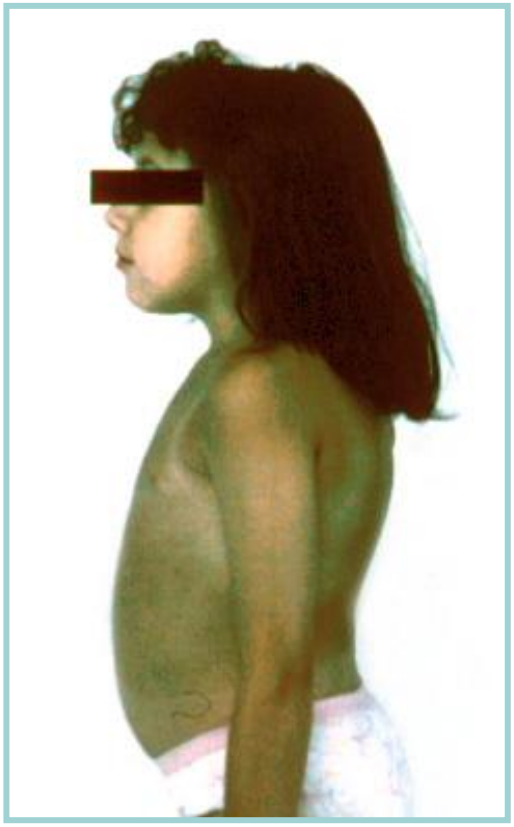
# Phenotypic continuum in Gaucher Disease



# Clinical Response to ERT in Gaucher Disease



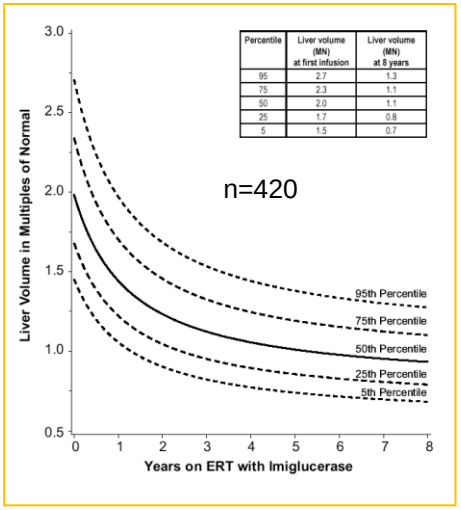
Before treatment
girl of 8 y and 8 months



After treatment
Girl of 10 y and 10 months

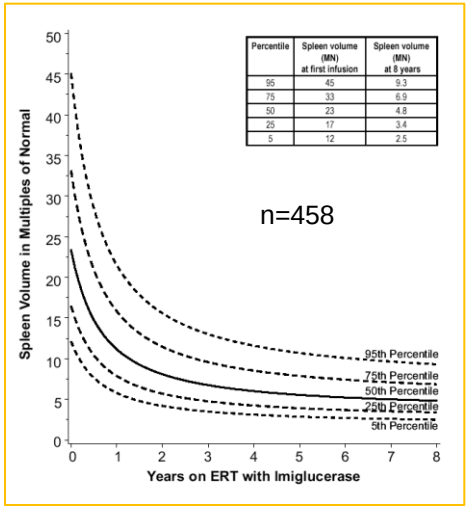
# Clinical Response to ERT in Gaucher Disease

## Liver Volume




| Percentile | Liver volume (MN) at first infusion | Liver volume (MN) at 8 years |
|---|---|---|
| 95 | 2.7 | 1.3 |
| 75 | 2.3 | 1.1 |
| 50 | 2.0 | 1.1 |
| 25 | 1.7 | 0.8 |
| 5 | 1.5 | 0.7 |

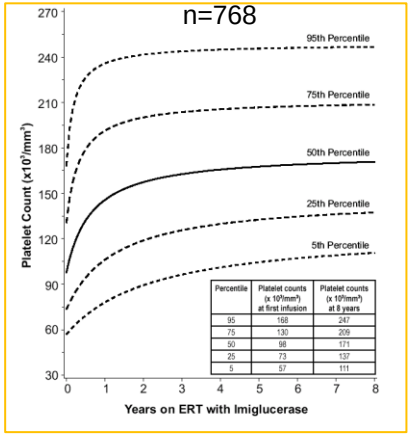
## Spleen Volume




| Percentile | Spleen volume (MN) at first infusion | Spleen volume (MN) at 8 years |
|---|---|---|
| 95 | 45 | 9.3 |
| 75 | 33 | 6.9 |
| 50 | 23 | 4.8 |
| 25 | 17 | 3.4 |
| 5 | 12 | 2.5 |

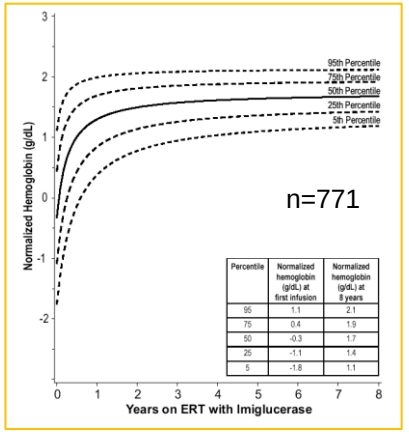
Visceral organ and hematologic responses to ERT treatment in children

## Platelet Count




| Percentile | Platelet counts (x 10³/mm³) at first infusion | Platelet counts (x 10³/mm³) at 8 years |
|---|---|---|
| 95 | 168 | 247 |
| 75 | 130 | 209 |
| 50 | 98 | 171 |
| 25 | 73 | 137 |
| 5 | 57 | 111 |

## Hemoglobin Level



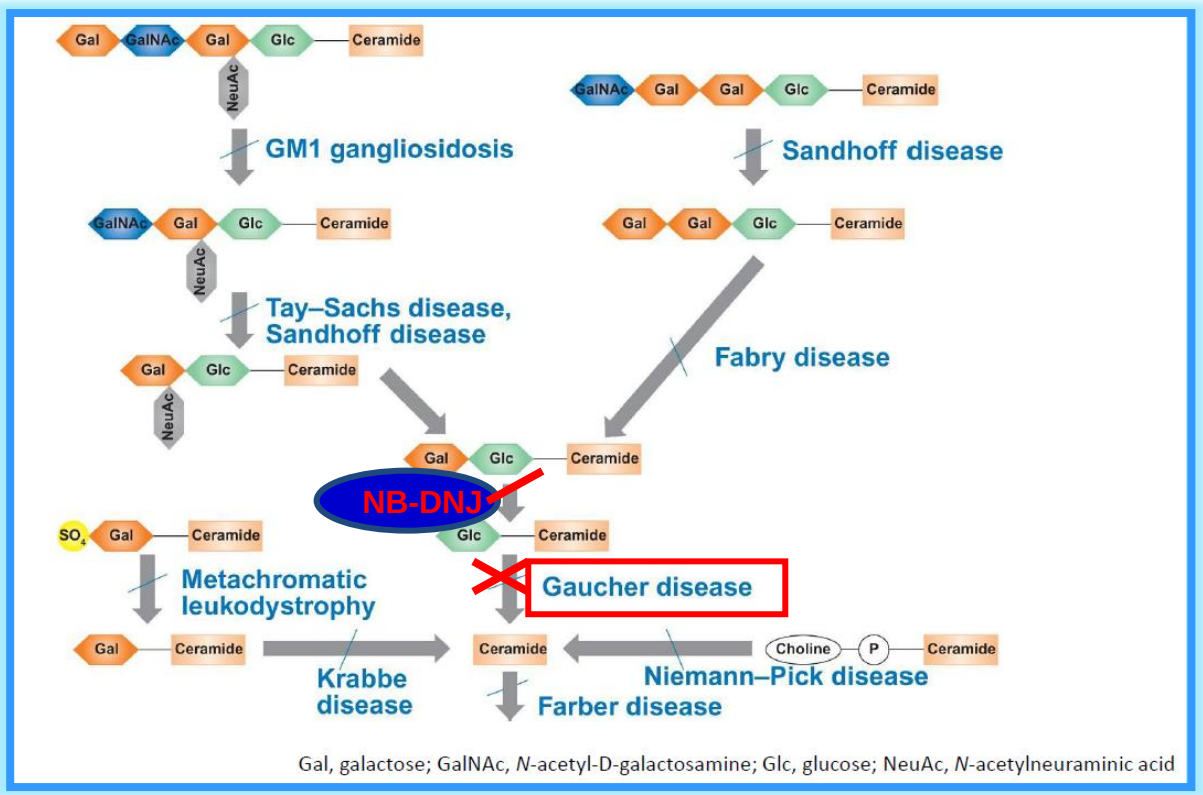

| Percentile | Normalized hemoglobin (g/dL) at first infusion | Normalized hemoglobin (g/dL) at 8 years |
|---|---|---|
| 95 | 1.1 | 2.1 |
| 75 | 0.4 | 1.9 |
| 50 | -0.3 | 1.7 |
| 25 | -1.1 | 1.4 |
| 5 | -1.8 | 1.1 |

*Andersson et al, Pediatrics 2008;122(6):1182-1190S*

# Limitations of ERT

- Immune response
- No brain access - tried in Gaucher type II (neurologic form)
- Limited results on bone
- Intravenous infusion therapy

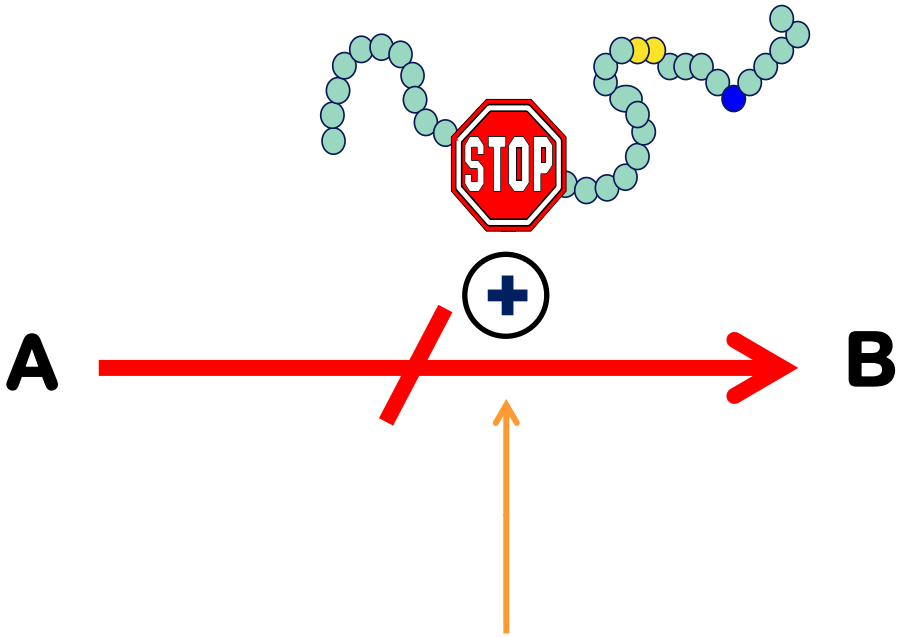
# Substrate Reduction Therapy (SRT) in Gaucher Disease




**MIGLUSTAT,** an Imminosucre N- butyldesoxynojirimycine (NB-DNJ) (= analogue of glucose) inhibits the glucocerebroside synthase, the first committed step in glycolipid biosynthesis

- Oral therapy
- Indicated in mild to moderate GD type I in case ERT is not an option
- Advantage : **Cross the blood-brain barrier**
- Intended to treat neuronopathic GD type III, but no effectiveness in clinical trials.
- Frequent side effects (gastrointestinal, neurologic)

# Therapeutic strategies in LSD

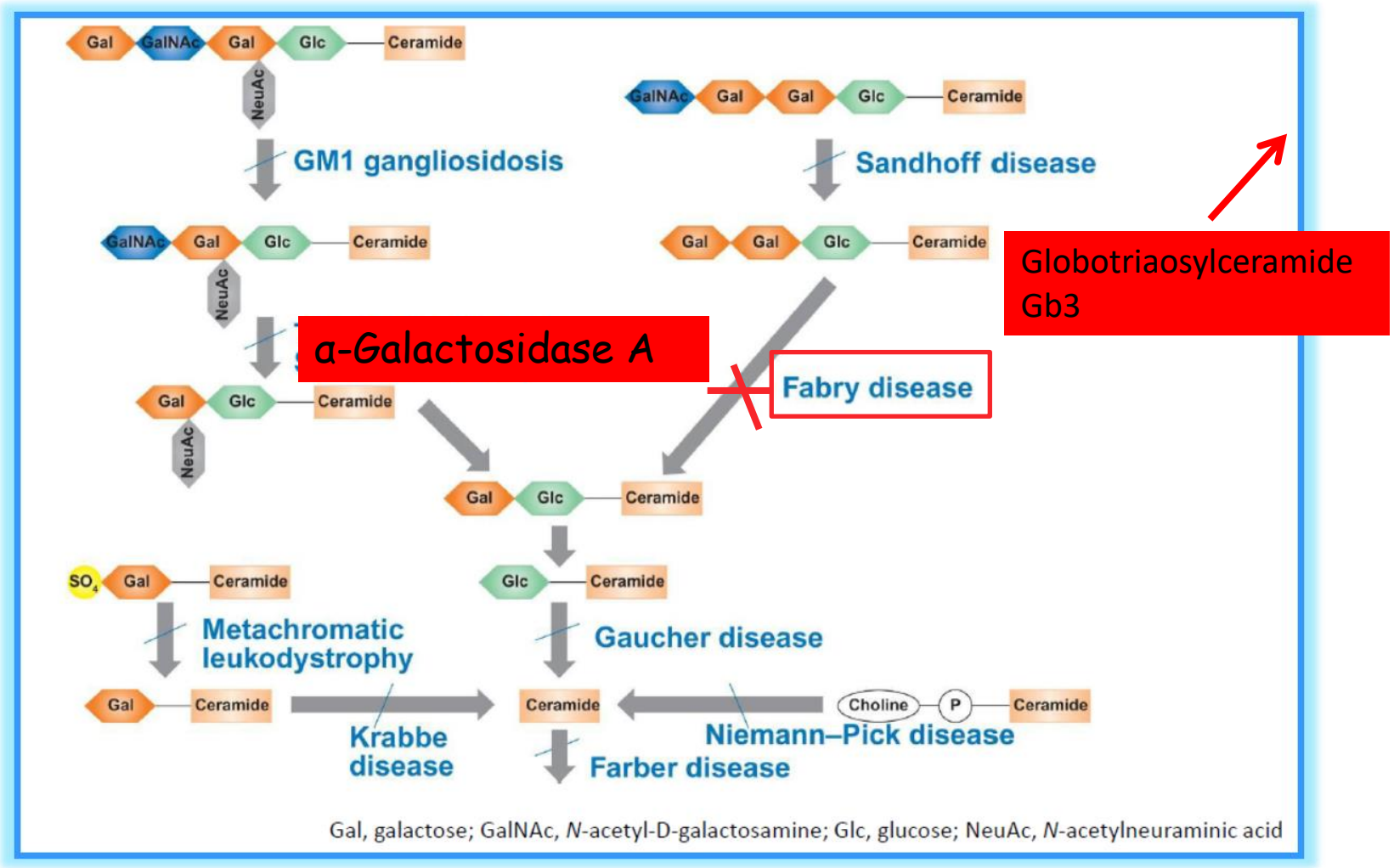



Stimulation residual enzyme

- Enzyme Enhancement Therapy with pharmacologic « chaperone »

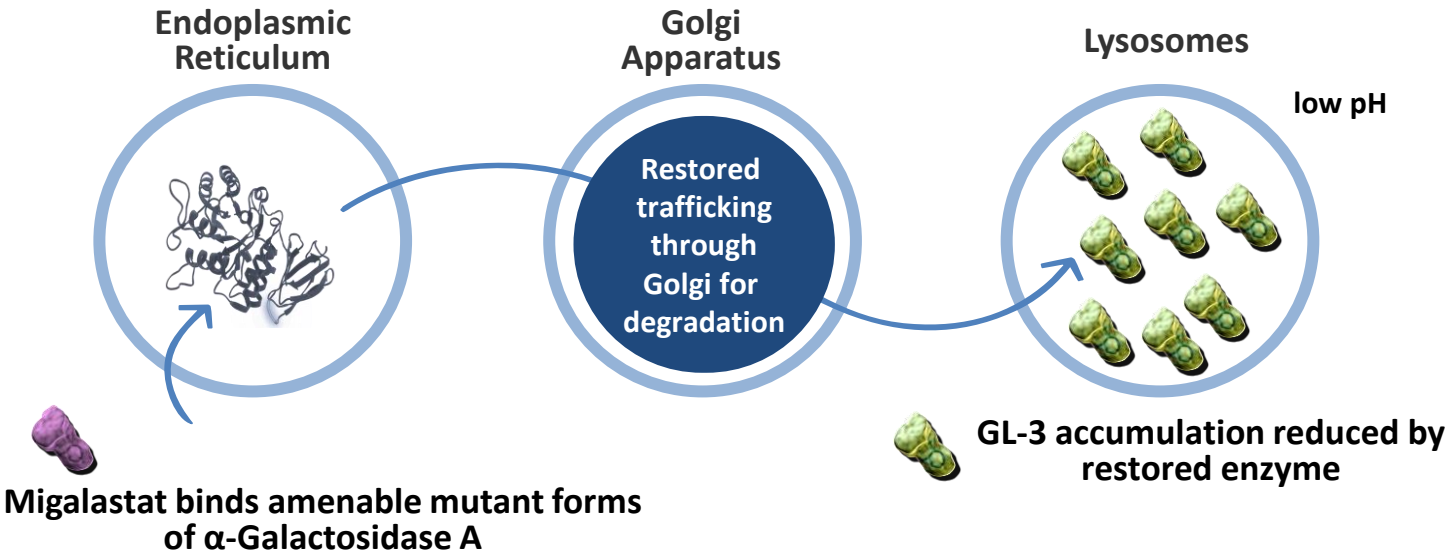
# Pharmacologic chaperone restore the residual mutant enzyme activity

## Fabry Disease



# Pharmacologic chaperone restore the residual mutant enzyme activity in amenable mutant form

**Mechanism**




**Migalastat**

- Iminosugar
- High volume distribution
- Cross the Blood brain barrier
- No immunologic reaction

*Warnock DG et al. PLoS One 2015;10:e0134341; Fan J-Q et al. Nat Med 1999;5:112–115;*

*Yam GH-F et al. FASEB J 2005;19:12–18; Ishii S et al. Biochem J 2007;406:285–295*