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EPNS

A diagnostic approach to inborn errors of metabolism

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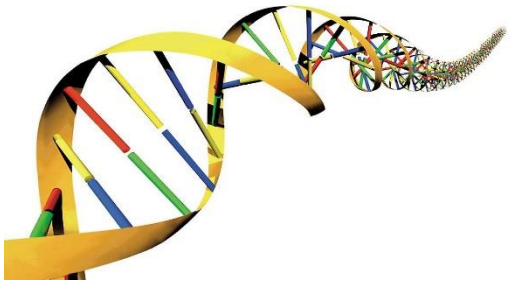
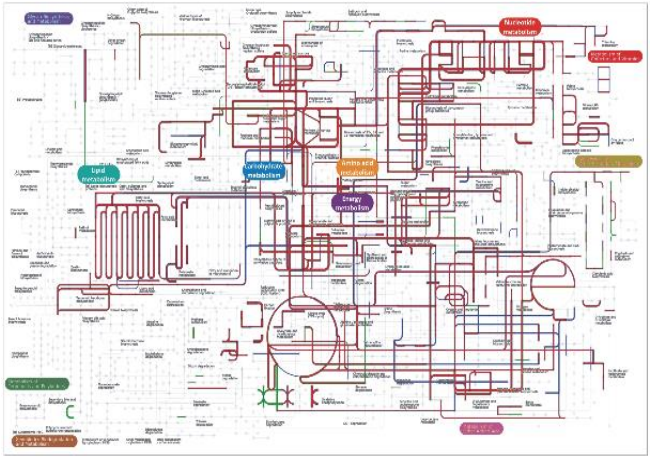
Genes and metabolic pathways



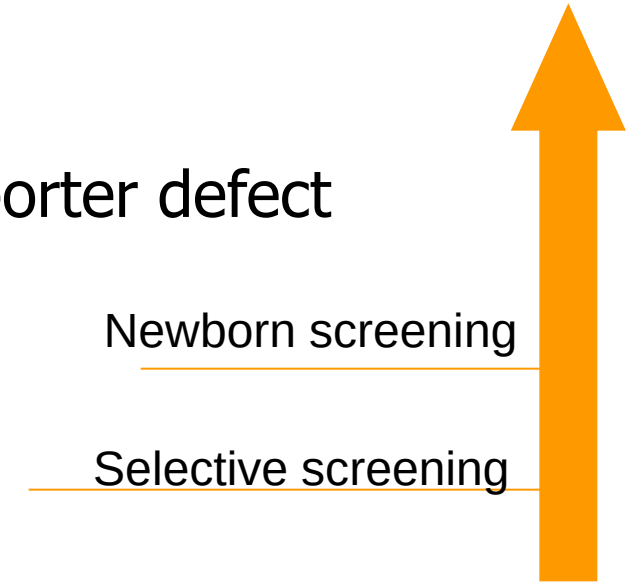


- About 22.000 genes encode all human proteins
- About 8000 genes encode metabolic pathways (estimate)
- Metabolic disorders have biomarkers
  (selective screening in plasma, urine, CSF)
- Some metabolic disorders are amenable to specific treatment
- Don´t be afraid of complex pathways- simplify

Inborn errors of metabolism

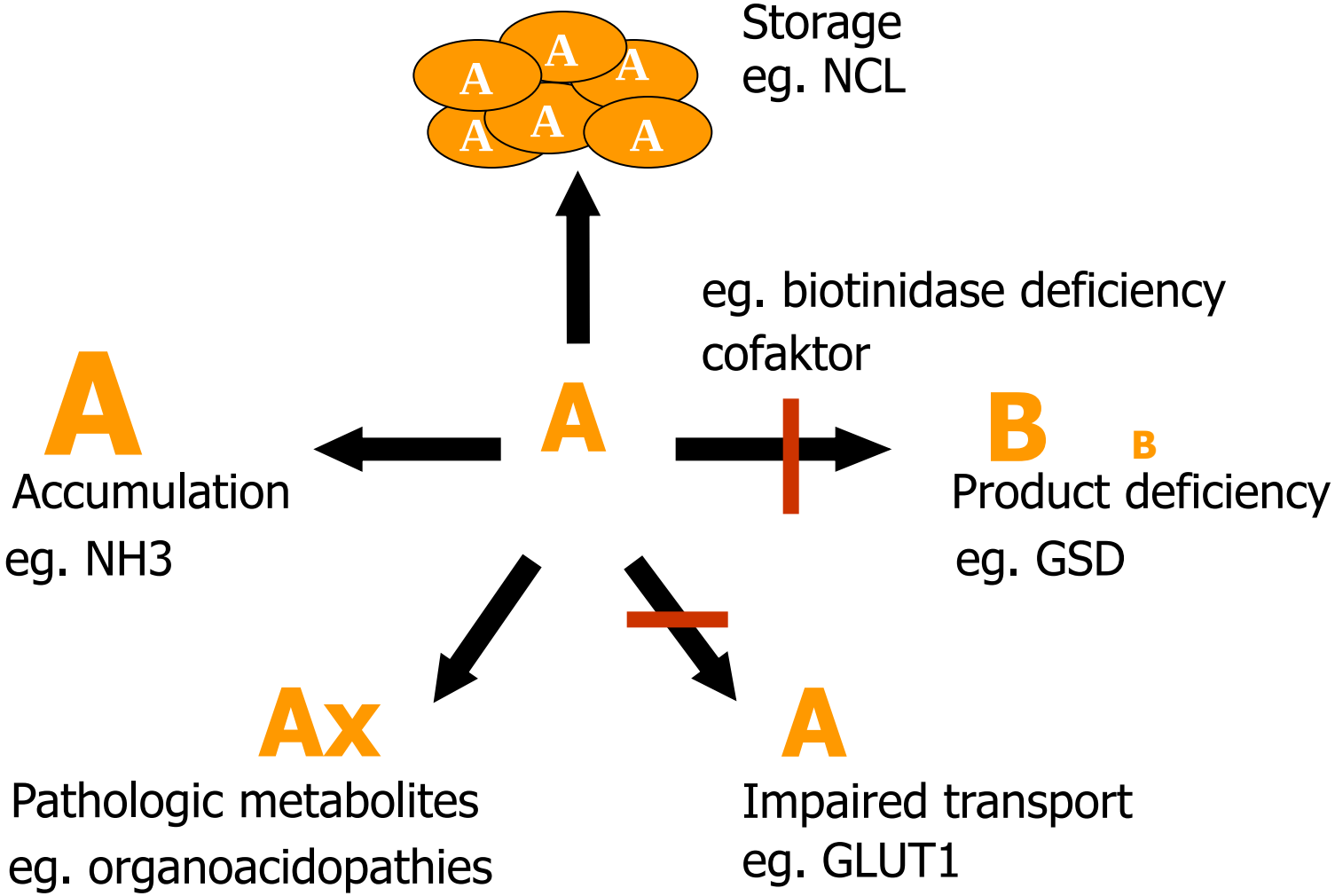
Causality

- Genmutation
- Enzyme defect / Transporter defect
- Metabolite pattern
- Phenotype



Diagnostics

Consequences of enzyme defects



Diseases of cell organells

Human Cell

Golgi –glycosylation of proteins

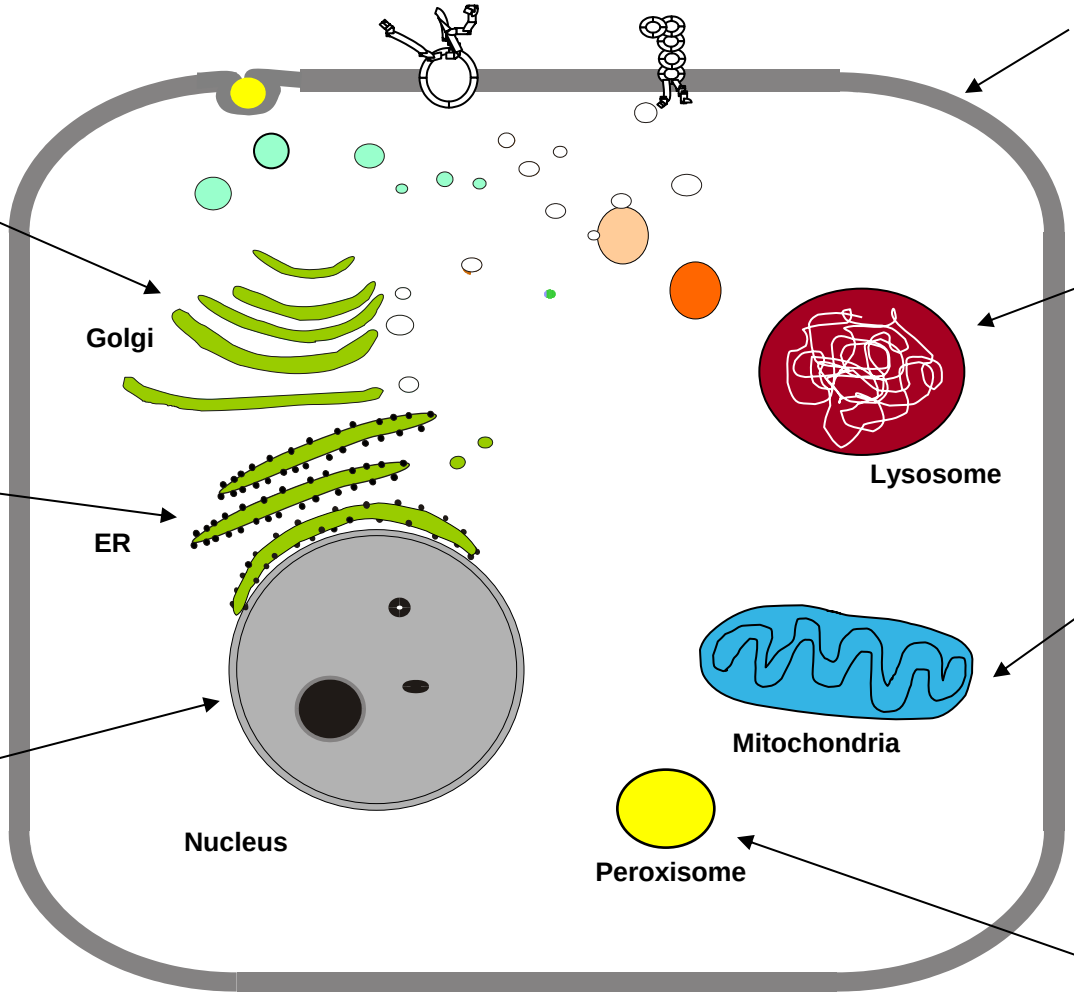
CDG Syndromes (N and O)

Endoplasmatic reticulum-synthesis of proteins, lipids etc.

CDG Syndromes

Screening: Transferrin electrophoresis-**N**

Nucleaus-DNA replication



Lysosomes-intracellular degradation and recycling

Pompe, MPS*, Gaucher, gangliosidoses*, Fabry*

Screening*: MPS/urine, oligosaccharides/urine sialic acid, GB_3/urine

Mitochondria – ATP production **mitochondriopathies,** mitochondrial syndromes **(Leigh, MERRF, MELAS etc)**

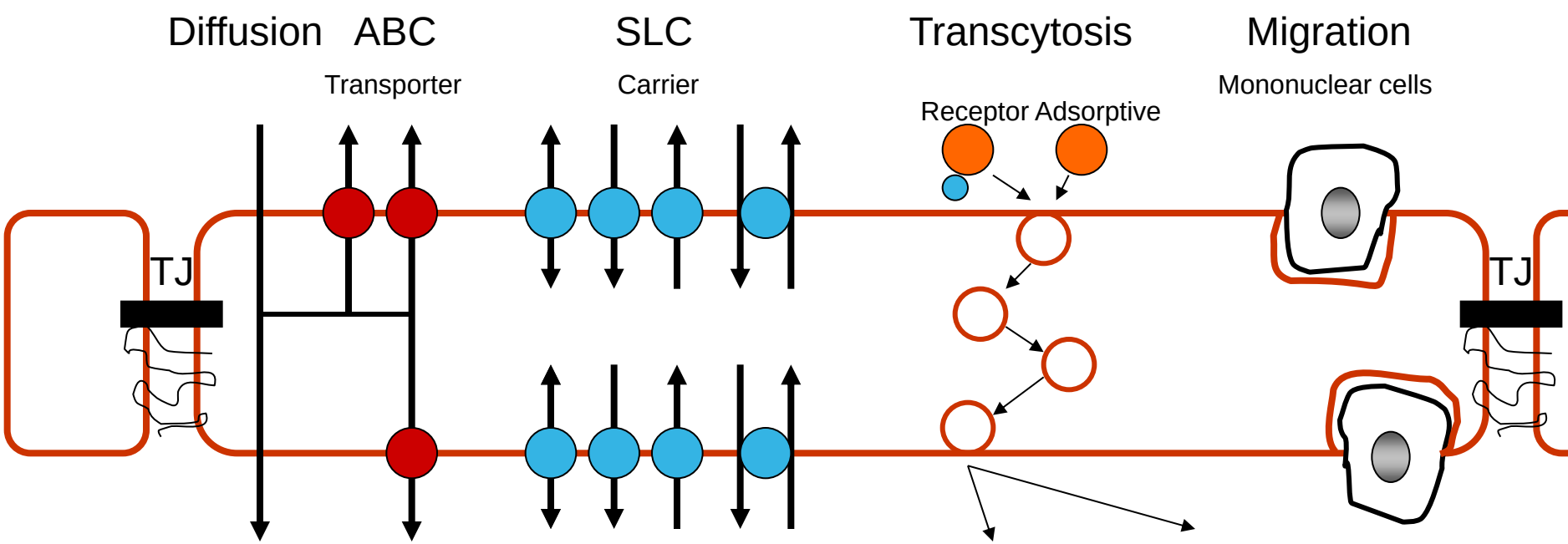
Screening: Lactate

Peroxisomes- Lipid metabolism

Zellweger syndrome, X-ALD, Mb. Refsum etc

Screening: VLCFA, phytanic, pristanic acid

Transport mechanisms via the blood brain barrier



Diffusion	ABC Transporter	SLC Carrier	Transcytosis ReMT	Transcytosis AdMT
Lipidsol. non-polare molecules	Lipidsol. non-polare molecules and conjugates	Glucose, aminoacids, creatin, folate, peptides, FFA, org. anions, org. kations, dicarbon acids	transferrine lipoproteins, IgG, insulin, leptin, TNFα, etc.	kati. albumin, histone, TAT, $SynB_1$

Modified from Maurizio Scarpa

Therapeutic strategies in inborn errors of metabolism

Substrate-level	Substratreduction Supplemenation Substrate-inhibition	eg PKU, Organacidopathies eg. Cofactors, Creatin, eg. Niemann Pick C
Enzyme-level	Enzyme-replacement therapy Chaperons	(Mb. Gaucher, Fabry, Pompe, MPS I, II, VI…) PKU
Gen-level	Gen-/ Organ-replacement	MPS I, UCD, OA c-ALD, MLD, Mb. Krabbe,