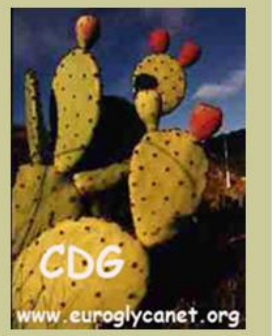


KU LEUVEN

congenital disorders of glycosylation (CDG)

advances in treatment

Jaak Jaeken

Center for Metabolic Diseases

KU Leuven

Antwerpen, 18-05-2018

disorders of glycosylation

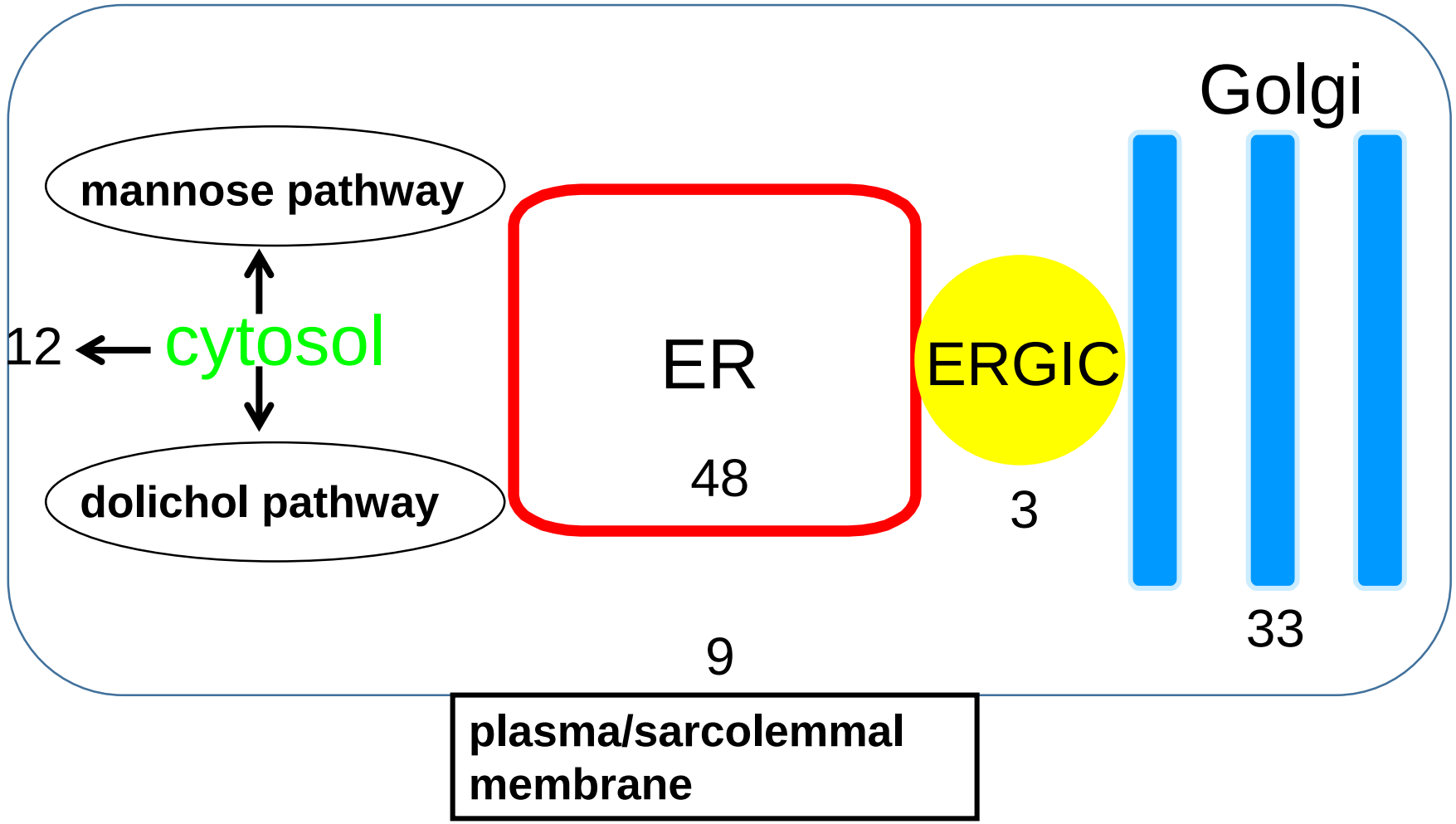
- ***hypoglycosylation***
  - genetic: **CDG**
  - non-genetic: e.g. alcoholism/infection
- ***hyperglycosylation***

  e.g. deficient deglycosylation: lysosomal diseases

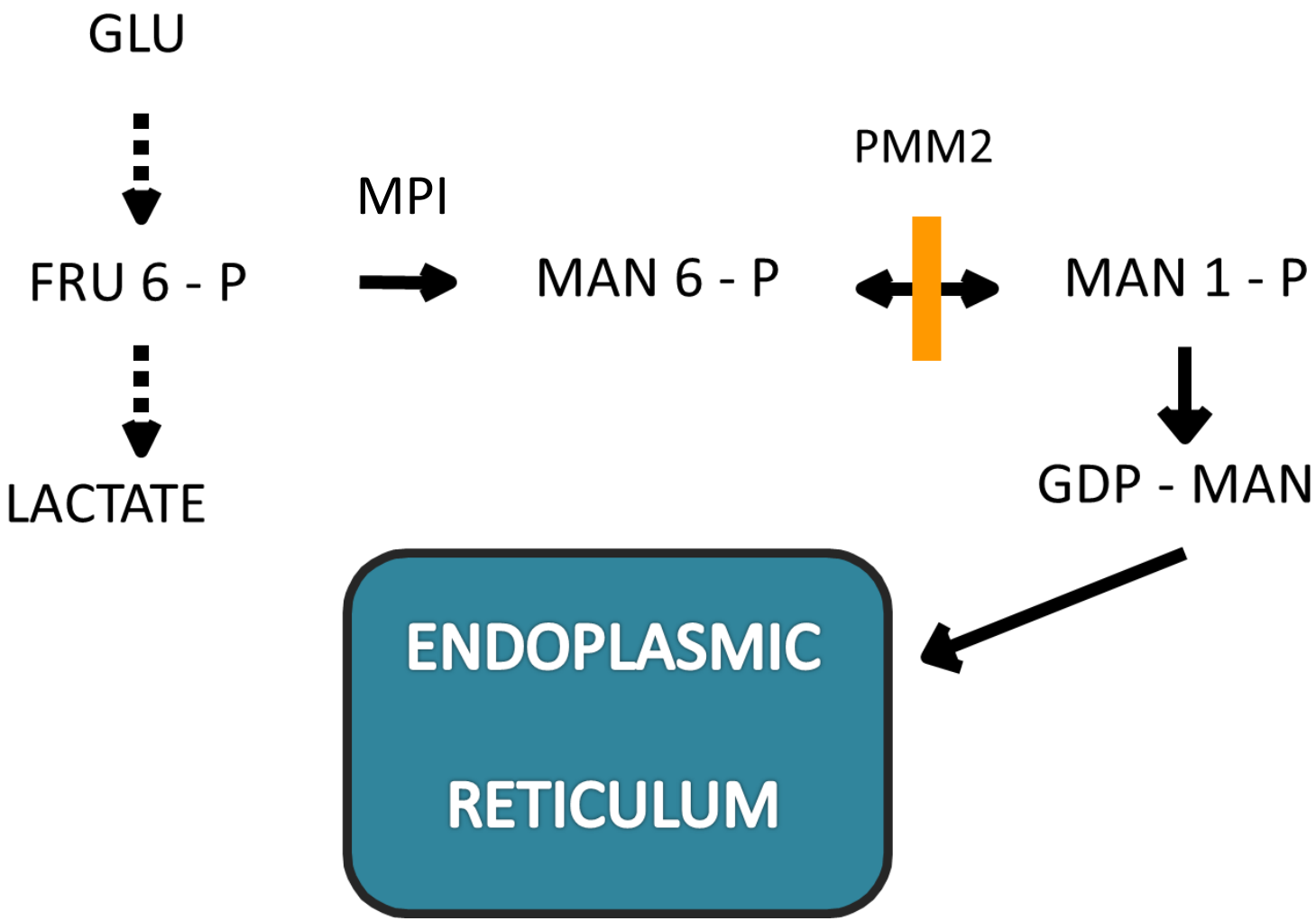
CDG classification (105)

- defects in protein N-glycosylation (28)
- defects in protein O-glycosylation (21)
- combined N- and O-glycosylation defects (39)
- defects in lipid glycosylation (2)
- GPI anchor synthesis defects (15)

CDG locations



PMM2-CDG

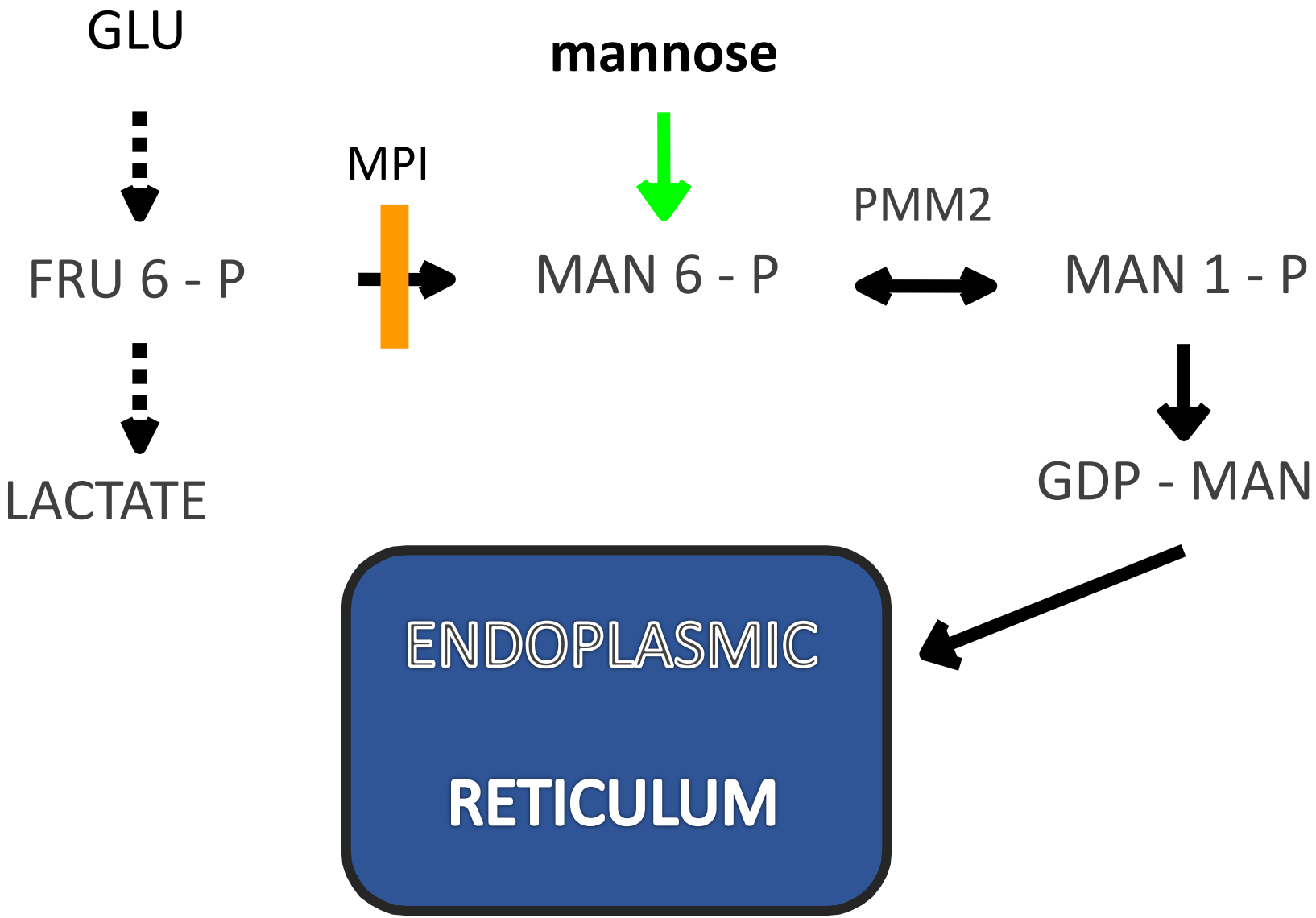

GLU
FRU 6 - P
LACTATE
MPI
MAN 6 - P
PMM2
MAN 1 - P
GDP - MAN
ENDOPLASMIC
RETICULUM

Mannose Corrects Altered N-Glycosylation in Carbohydrate-deficient Glycoprotein Syndrome Fibroblasts

K. Panneerselvam and H. H. Freeze

J Clin Invest 1996

MPI-CDG


GLU
mannose
MPI
PMM2
FRU 6 - P
MAN 6 - P
MAN 1 - P
LACTATE
GDP - MAN
ENDOPLASMIC
RETICULUM

Phosphomannose Isomerase Deficiency: A Carbohydrate-Deficient Glycoprotein Syndrome with Hepatic-Intestinal Presentation

J. Jaeken, G. Matthijs, J-M Saudubray et al.

Am J Hum Genet 1998

"basic" treatments (14 CDG)

- nutrient supplementation
- pharmacological treatment
- transplantation

"basic" treatments

- **nutrient supplementation**
- **pharmacological treatment**
- **transplantation**

nutrient supplementation

- monosaccharides
- vitamin
- oligoelement
- nucleotide

monosaccharide supplementation

- **mannose**: MPI-CDG (mannose phosphate isomerase deficiency)
- **fucose**: SLC35C1-CDG (GDP-fucose transporter deficiency)
- **galactose**: ° SLC35A2-CDG (UDP-galactose transporter deficiency)
  - ° SLC39A8-CDG (Golgi Mn/Zn transporter deficiency)
  - ° TMEM165-CDG (Golgi Mn transporter deficiency)
  - ° PGM1-CDG (phosphoglucomutase 1 deficiency)

supplementation of other nutrients

- **vitamin B6**: PIGO-CDG (GPI anchor defect)
- **manganese**: SLC39A8-CDG (Mn/Zn transporter defect)
- **uridine**: ° PGM1-CDG (phosphoglucomutase 1 deficiency)
  ° CAD-CDG (pyrimidine biosynthesis)

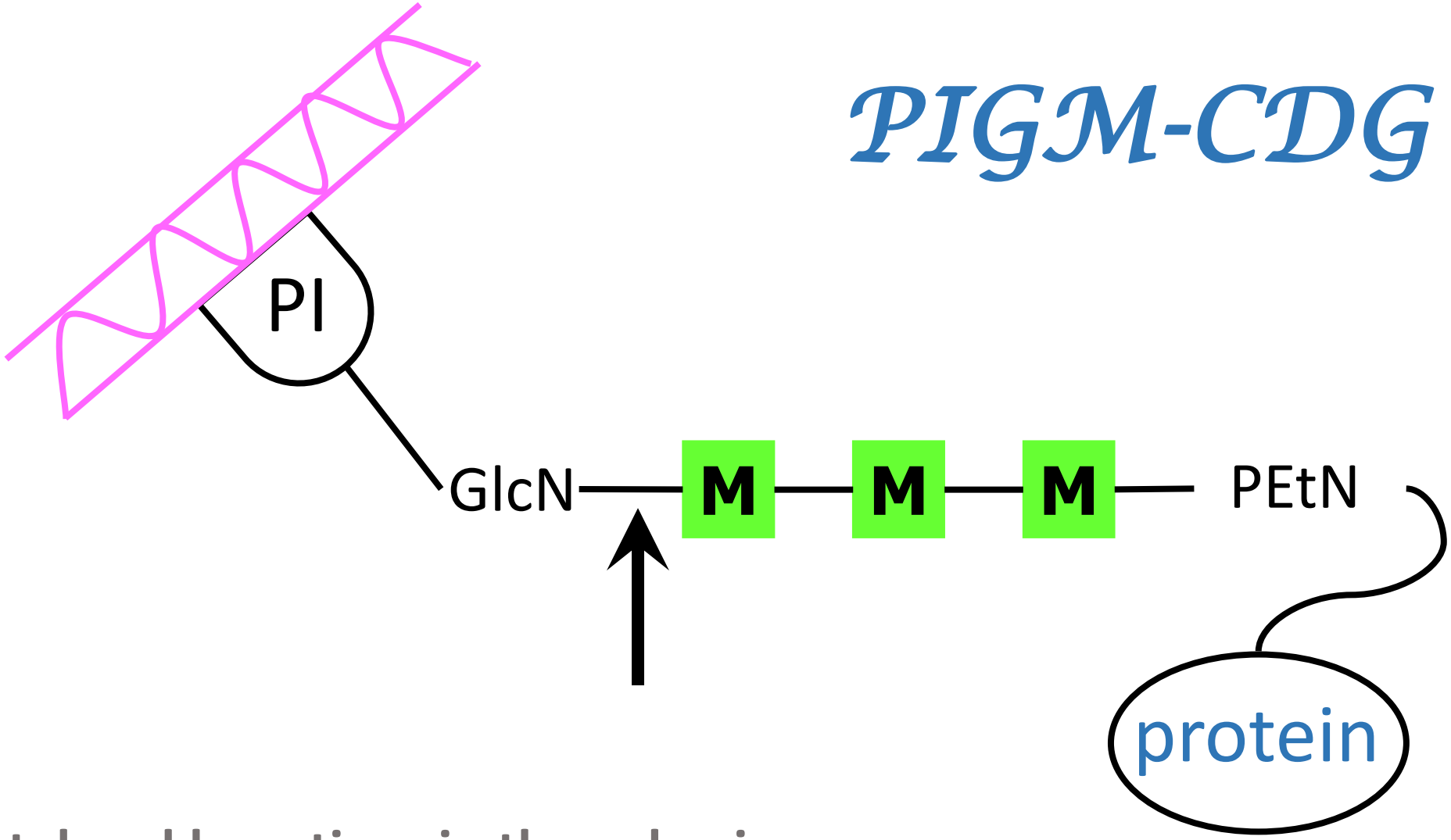
"basic" treatments

- nutrient supplementation
- **pharmacological treatment**
- transplantation

pharmacological treatment

sodium butyrate: PIGM-CDG (GPI anchor promotor defect)

PIGM-CDG



- portal and hepatic vein thrombosis
- absence seizures

PGM-CDG: treatment

- **histone deacetylation at the *PIGM* promotor**
- **BUTYRATE: inhibition of histone deacetylation**

↓

increased *PIGM* transcription

↓

cessation of convulsions

Almeida et al 2007

"basic" treatments

- nutrient supplementation
- pharmacological treatment
- **transplantation**

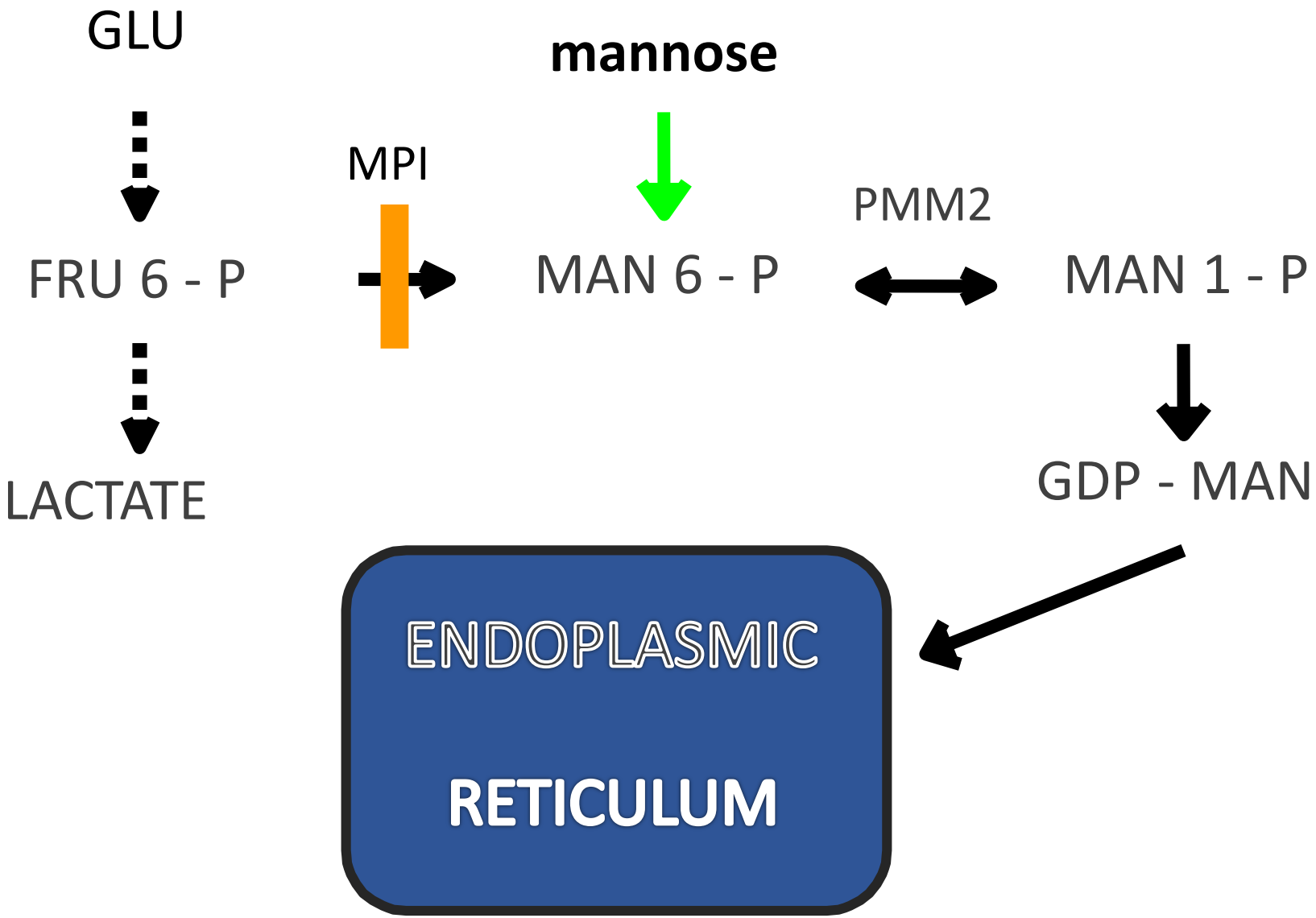
transplantation

- **liver**: °MPI-CDG
  °CCDC115-CDG
- **heart**: DOLK-CDG limited to the heart
- **hematopoietic stem cells**: PGM3-CDG

zooming in on a few treatable CDG

- MPI-CDG
- SLC39A8-CDG
- CAD-CDG

MPI-CDG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MPI-CDG: presentation

- liver dysfunction
- recurrent diarrhoea
- recurrent vomiting
- hypoglycemia
- hyperinsulinism

MPI-CDG: treatment

oral mannose

1 g/kg per day (in 4 to 6 doses)

***but* ……**

liver transplantation in MPI-CDG

- **2 y**: congenital hepatic fibrosis
  protein-losing enteropathy
- **15 y**: diagnosis of MPI-CDG
  oral mannose: problematic!
- **25 y**: progressive edema and ascites
  progressive hemolytic jaundice
- **28 y**: recurrent hepatic encephalopathy/dyspnea
  R/ LTx

Janssen et al 2014

SLC39A8-CDG

solute carrier family 39, member 8 (Mn and Zn membrane transporter) deficiency

combined N- and O-glycosylation disorder

SLC39A8-CDG: phenotype

8 patients

- ***neurological presentation***
  - severe intellectual disability
  - hypotonia
  - strabismus
  - cerebellar atrophy
- ***variable features***

  epilepsy, dwarfism, bone abnormalities, ……..

Boycott et al 2015
Park et al 2015

SLC39A8-CDG: serum biochemistry

- **Mn and Zn: absent to low-normal**
- **transferrin IEF: type 2**
- **transferrin glycans ESI-TOF MS**

  mainly hypogalactosylation

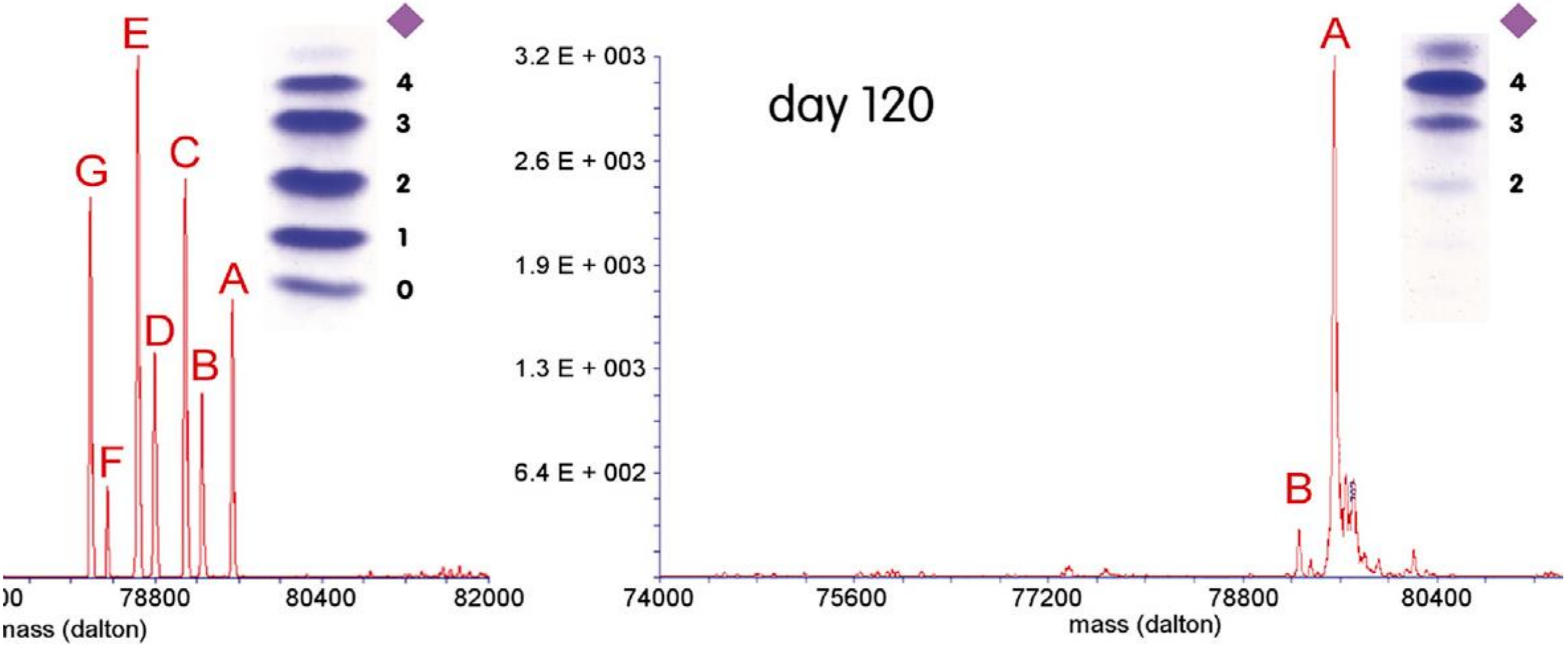
Boycott et al 2015
Park et al 2015

SLC39A8-CDG: treatment

- β-1,4-galactosyltransferase is Mn-dependent
- deficient galactosylation
- galactose therapy: 1 - 3.7 g/kg per day
- rapid normalisation of glycosylation!

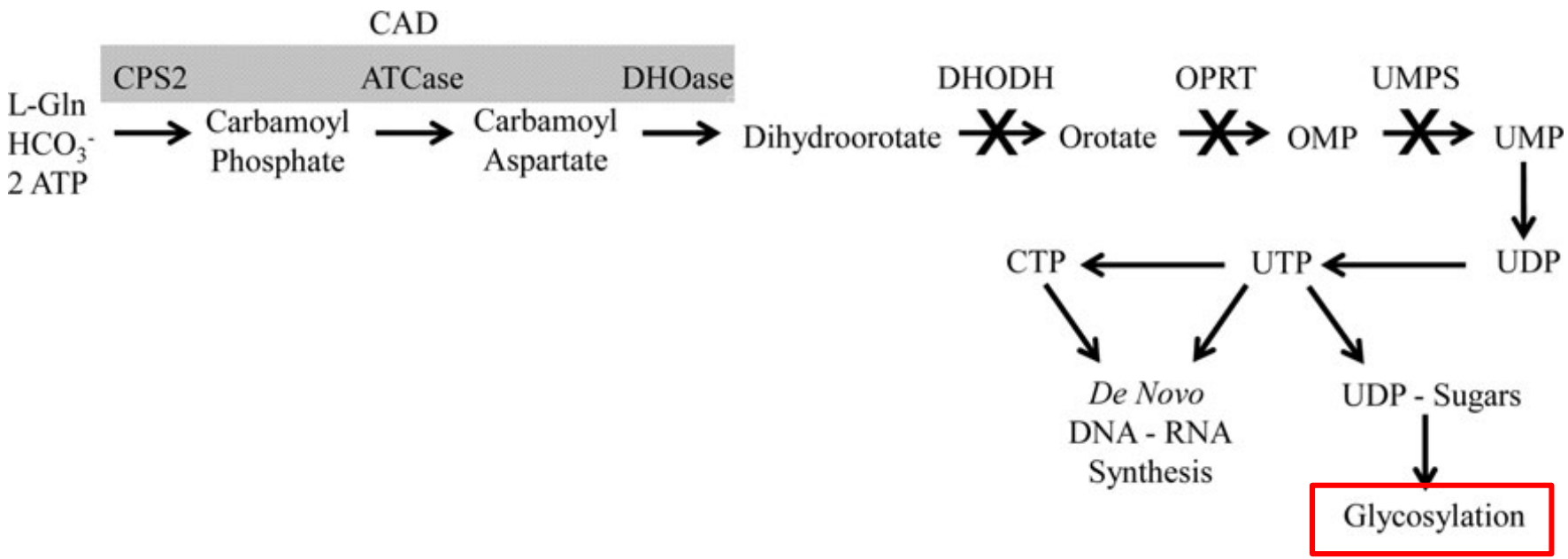
Park et al 2015

SLC38A8-CDG: galactose treatment



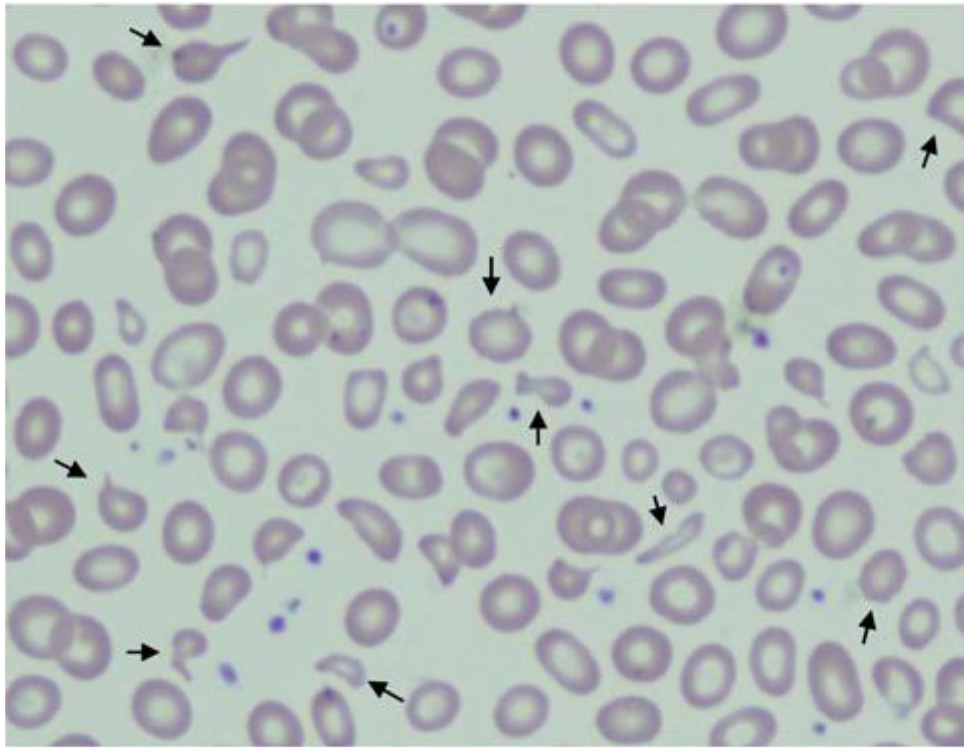
CAD-CDG

defect in de novo pyrimidine biosynthesis



CAD-CDG: phenotype

- developmental disability with regression
- therapy-resistent epilepsy
- anemia with anisopoikilocytosis
- decreased UDP-sugars in fibroblasts



Koch et al 2017

CAD-CDG: treatment

oral uridine 100 mg/kg per day in 4 daily doses

- **epilepsy abolished**
- **psychomotor development greatly improved**
- **anemia disappeared**
- **UDP sugars normalized in fibroblasts**

Koch et al 2017

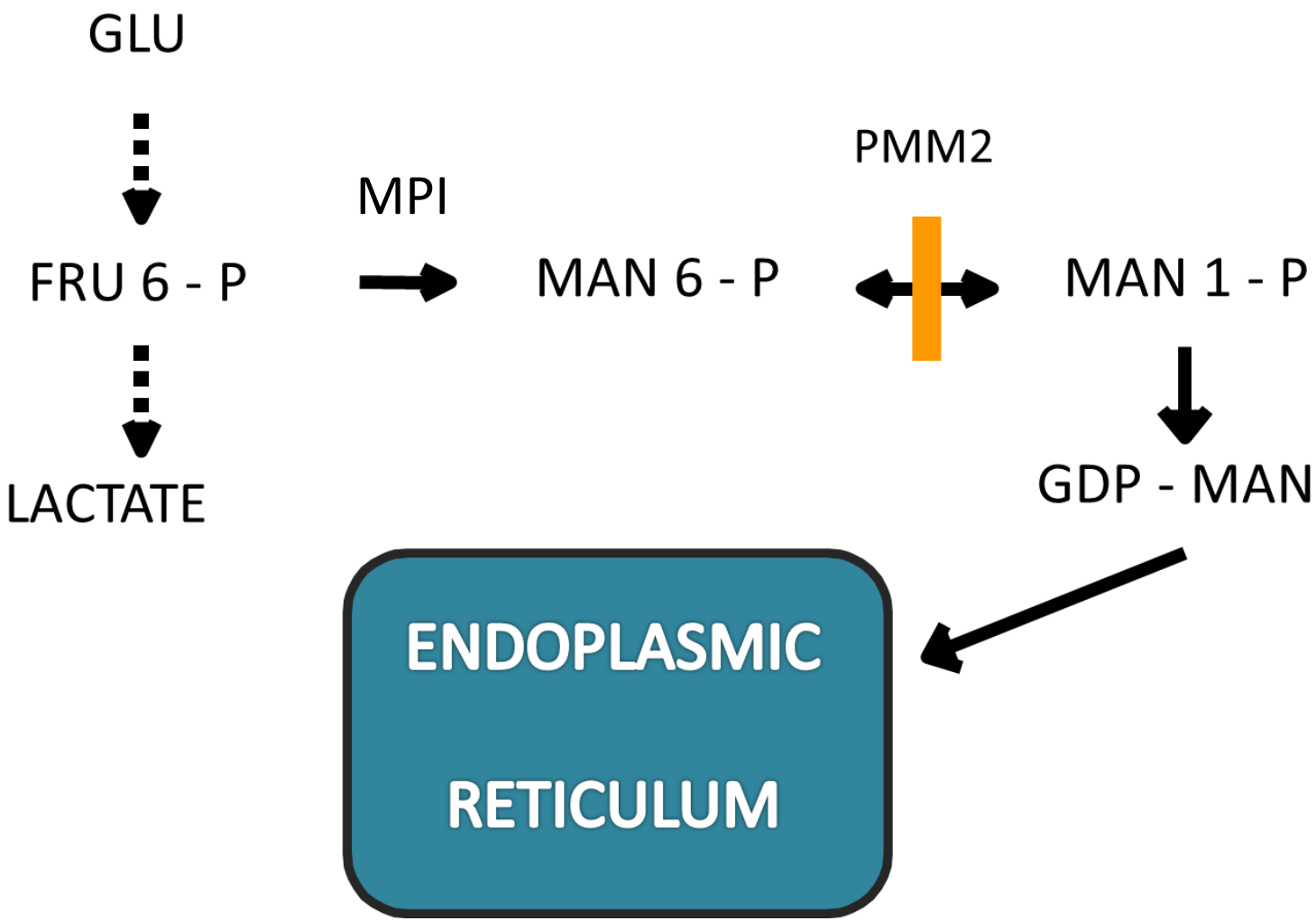
what about PMM2-CDG?

mystery why mannose ‘works’ in vitro but not in vivo!

PMM2-CDG: prospects for treatment

- **Man-1-P pharmacological formulation under development**
  liposomes as delivery system
- **pharmacological chaperones (Yuste-Checa et al. 2017)**
- **antisense therapy using morpholino oligonucleotides**
  (Yuste –Checa et al. 2015)

PMM2-CDG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  (Yuste –Checa et al. 2015)

conclusions

- **The best treatable CDG are MPI-CDG and CAD-CDG;**

  do not miss these diagnoses!

- **Efficient treatment of PMM2-CDG: still a long way to go.**
- **Provide patients with the best possible symptomatic treatment.**

collaborating teams

- Leuven Center for Human Genetics
  - **G. Matthijs**
  - **R. Péanne**
  - **E. Blommaert**
  - **V. Race**
  - **L. Keldermans**
  - **E. Souche**
- Université Catholique de Louvain, Brussels
  - **E. Van Schaftingen**
- Université de Lille, Unité de Glycobiologie
  - **F. Foulquier**
- Institute for Polymers and Biomaterials, Catania
  - **D. Garozzo**
  - **L. Sturiale**