Clinical symptoms of Defects in pyrimidine metabolism

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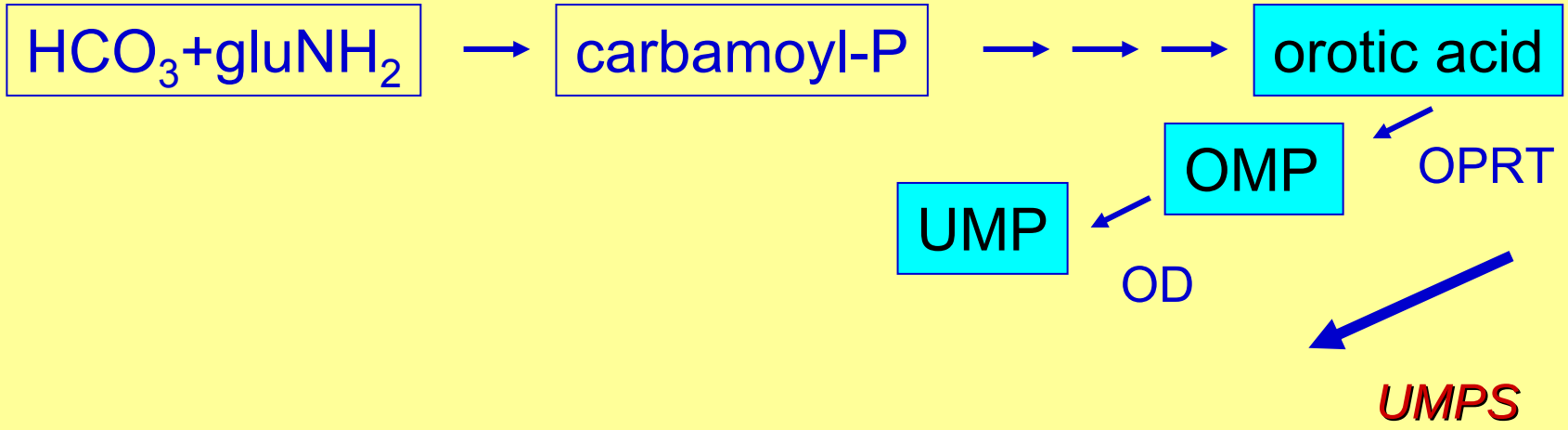
Overview

- Biosynthesis: UMP Synthase

- Degradation:
  - **Pyrimidine 5‘-Nucleotidase(UMP-Hydrolase)**
  - [Thymidine-Phosphorylase, mitochondrial]
  - **Dihydropyrimidine Dehydrogenase**
  - **Dihydropyrimidinase**
  - **Ureidopropionase**



UMPS = uridinemonophosphate synthase

Bifunctional enzyme (one gene):

a) Orotate phosphoribosyl transferase (OPRT)

b) Orotidine decarboxylase (OD)

UMPS deficiency

- = Hereditary orotic aciduria

  Hallmarks:

  - **Megaloblastic anemia in infants**

  >> If untreated: Failure to thrive

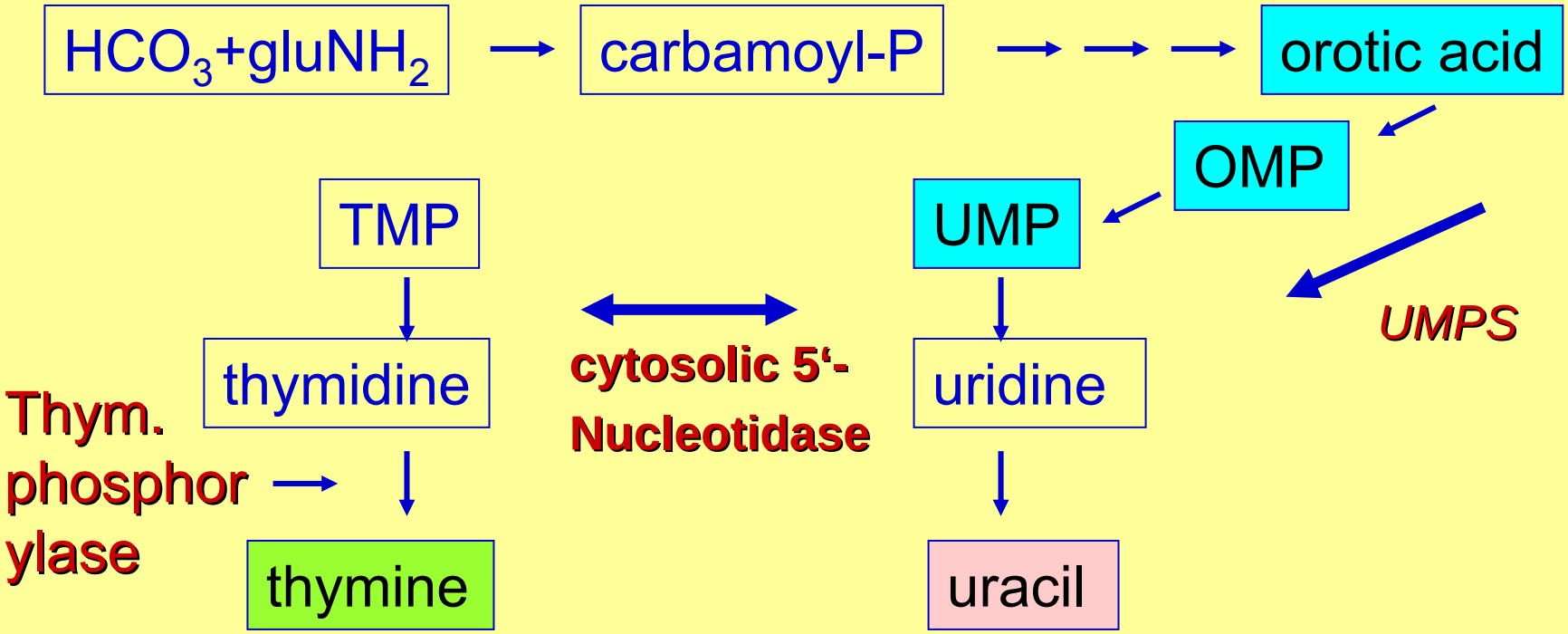
  Psychomotor retardation

- Therapy: uridine (≥100-150 mg/kg/d)

Defects of pyrimidine degradation

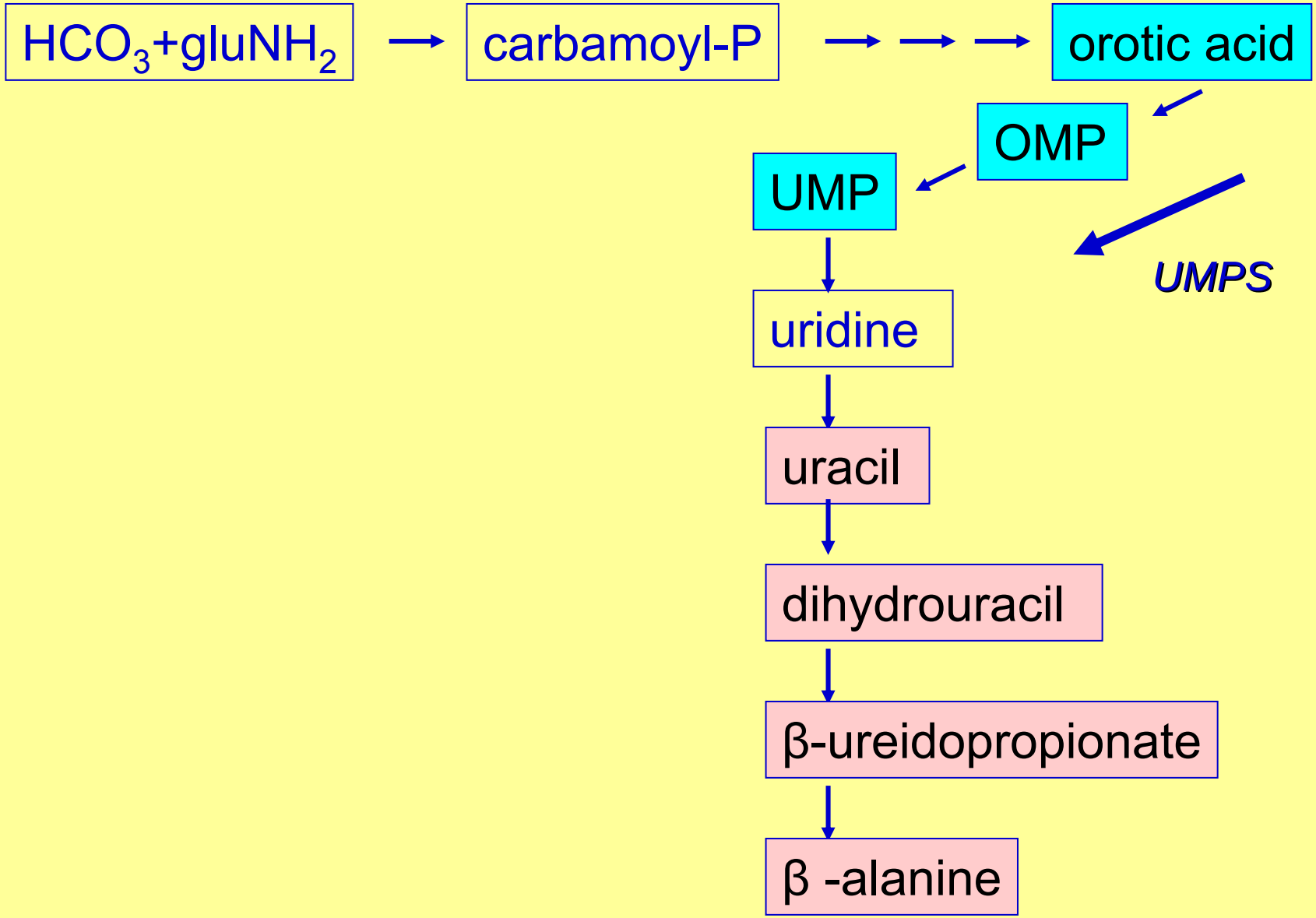
- Pyrimidine 5‘-Nucleotidase deficiency
  - chronic hemolytic anemia + basophilic stippling of erythrocytes

- Thymidine phosphorylase deficiency
  = MNGIE=Mitoch. NeuroGastroIntestinal Encephalomyopathy
  Mitochondrial disorder with **elevated urinary thymidine excretion**


HCO_3+gluNH$_2$
carbamoyl-P
orotic acid
OMP
UMP
UMPS
TMP
thymidine
thymine
cytosolic 5'-Nucleotidase
uridine
uracil
Thym. phosphor ylase

Pyrimidine 5‘-Nucleotidase-Superactivity

- Existence now doubted
- Psychomotor retardation, seizures, extreme hyperactivity, slurred speech
- Responded well to high dose uridine
- Only metabolic marker >> reduced excretion of uric acid to approx. 50%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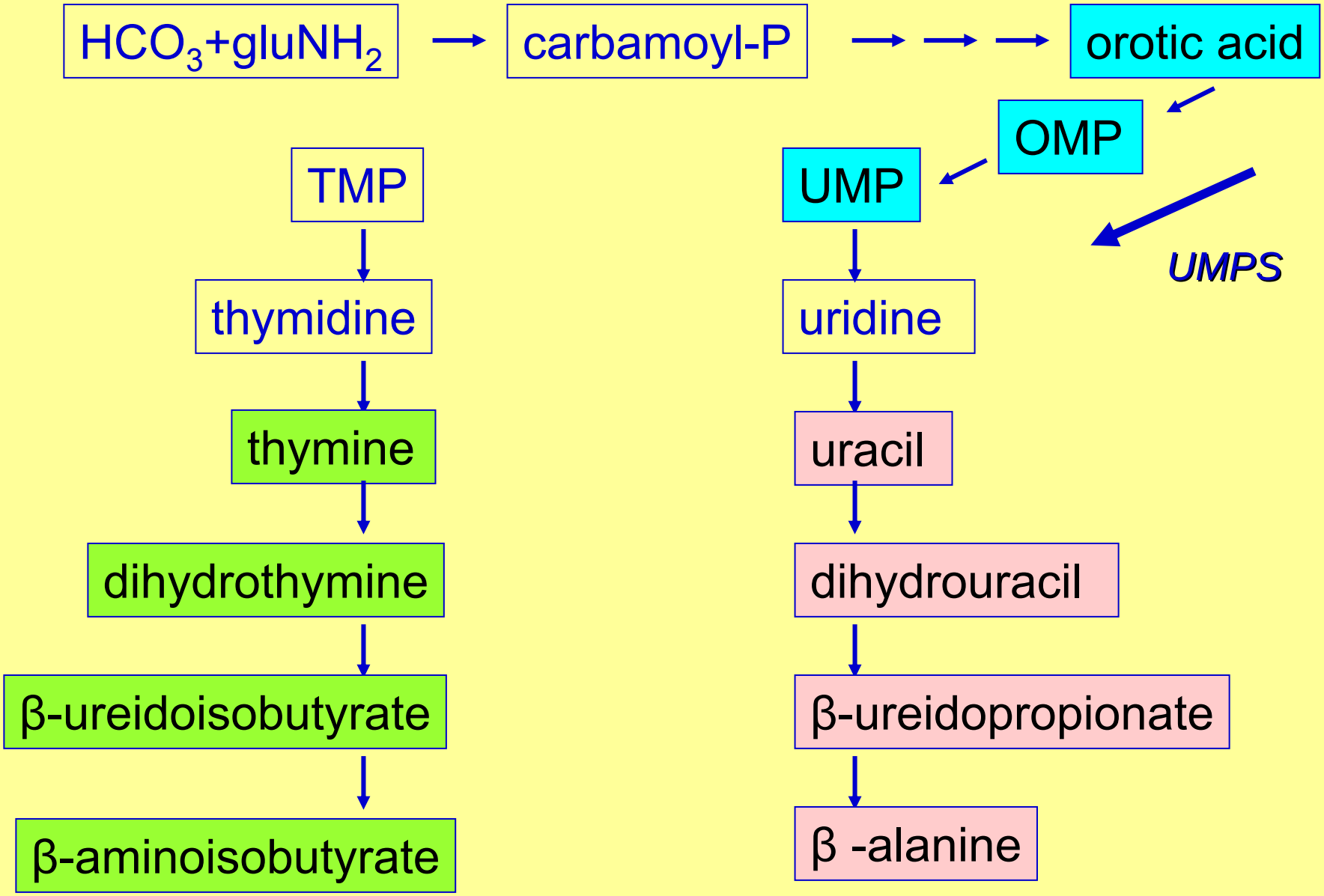
β-ureidopropionate
β -alanine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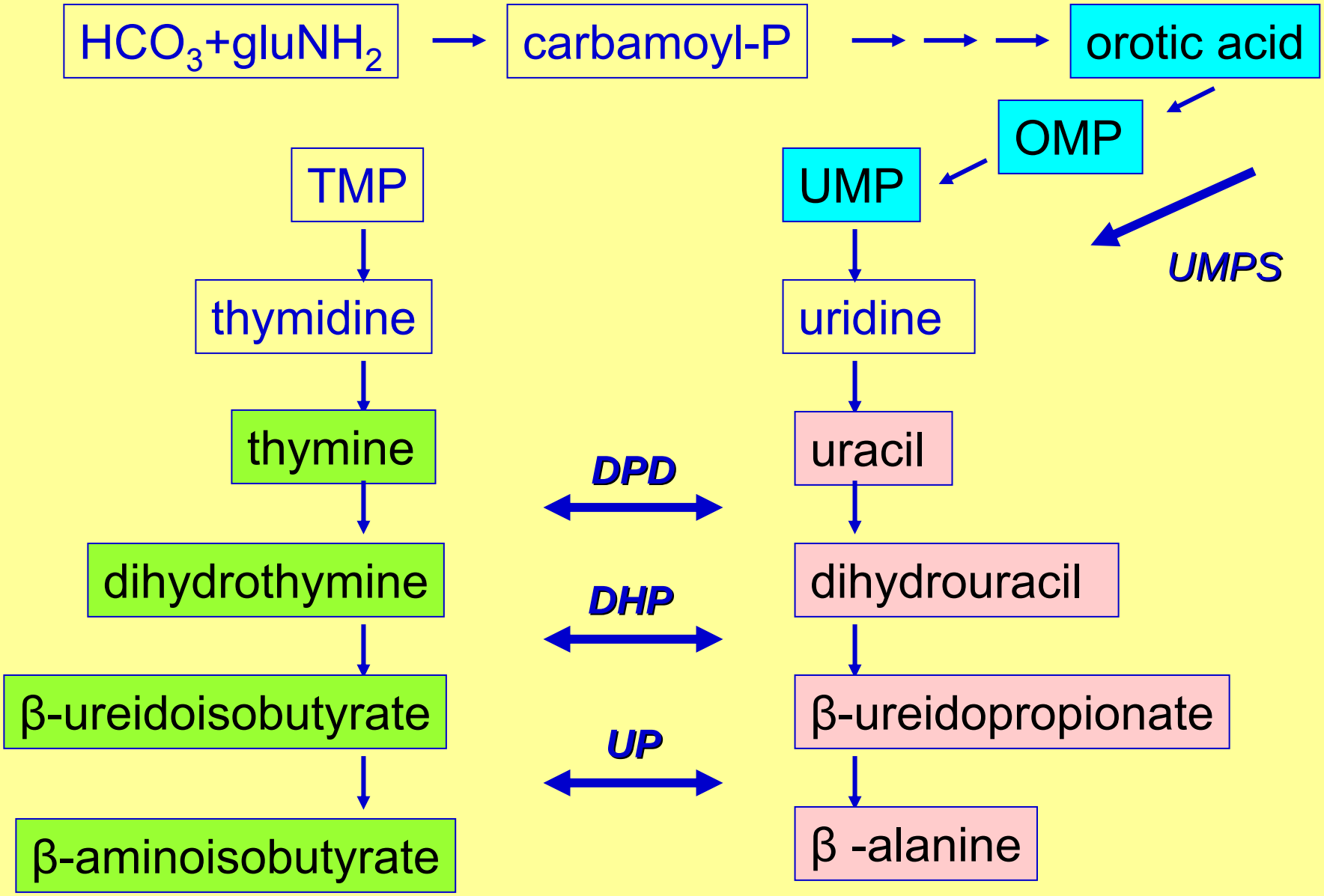
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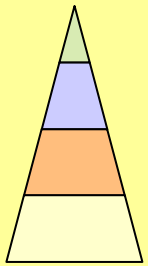
DPD
DHP
UP
uridine
uracil
dihydrouracil
β-ureidopropionate
β -alanine

Pyr.bases‘ degradation disorders

- DPD = Dihydropyrimidine Dehydrogenase deficiency (? Hundreds of cases?)
- DHP = Dihydropyrimidinase Deficiency (1 dozen cases)
- UP = Ureidopropionase deficiency (4 cases)

- **Clinical pictures not distinguishable**

Symptomatology



Asymptomatic (cave 5‘-Fluoro-Uracil!)

>> severe neurological disorder

- No degenerative course (exceptional)

Hallmarks:

- Seizures

- Mental retardation

- Motor retardation

Pathophysioloy

- Deficit of β-alanine ??
- β-alanine binds to
  - **glycine receptor**
  - **glycine binding site of NMDA-glut. receptor**
  - **GABA transporter**
  - **$GABA_A$ receptor**
- Inhibitory neuromodulator, neurotransmitter for nocireception

BUT

Study Van Kuilenburg et al.

- CSF concentration of β-alanine not reduced in DPD patients

Instead:

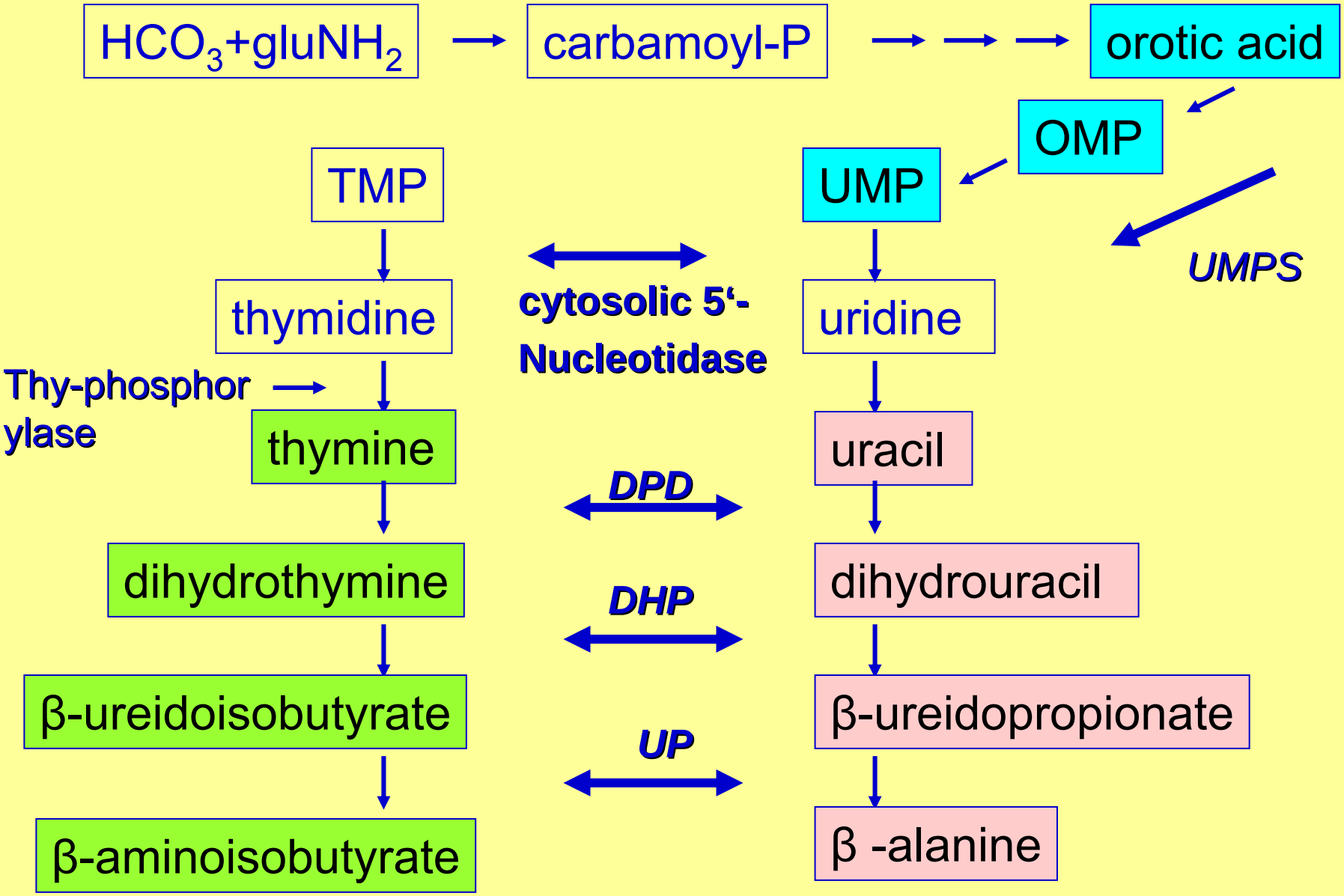
- CSF concentrations of β-aminoisobutyrate (β-AIB) reduced

➢ pathomechanism and therapy unresolved

Take-home messages

- Hereditary orotic aciduria should not be missed because it is treatable

- Pyrimidine bases‘ degradation defects show unspecific clinical syndromes,
  - screening useful because of 5‘-FU toxicity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