Biochemistry

Metabolism

22.11.2018 – 11.12.2017

Nucleotide Metabolism

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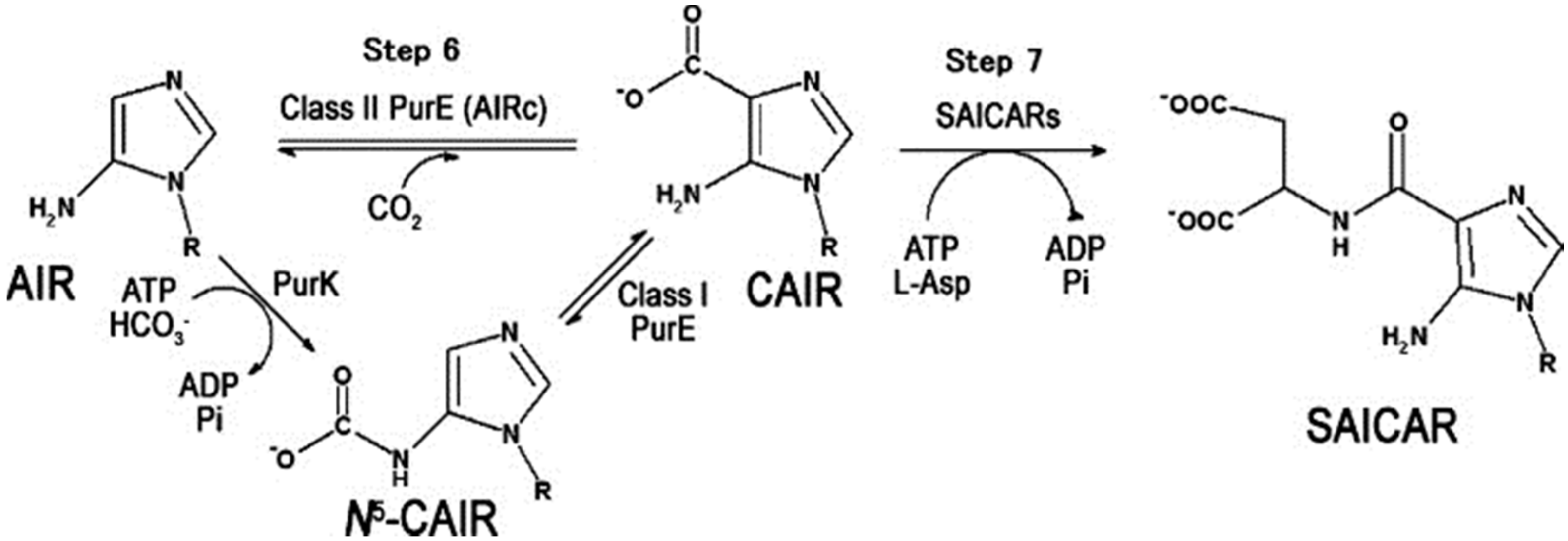
Annex to purine biosynthesis:
Acquisition of CO_2

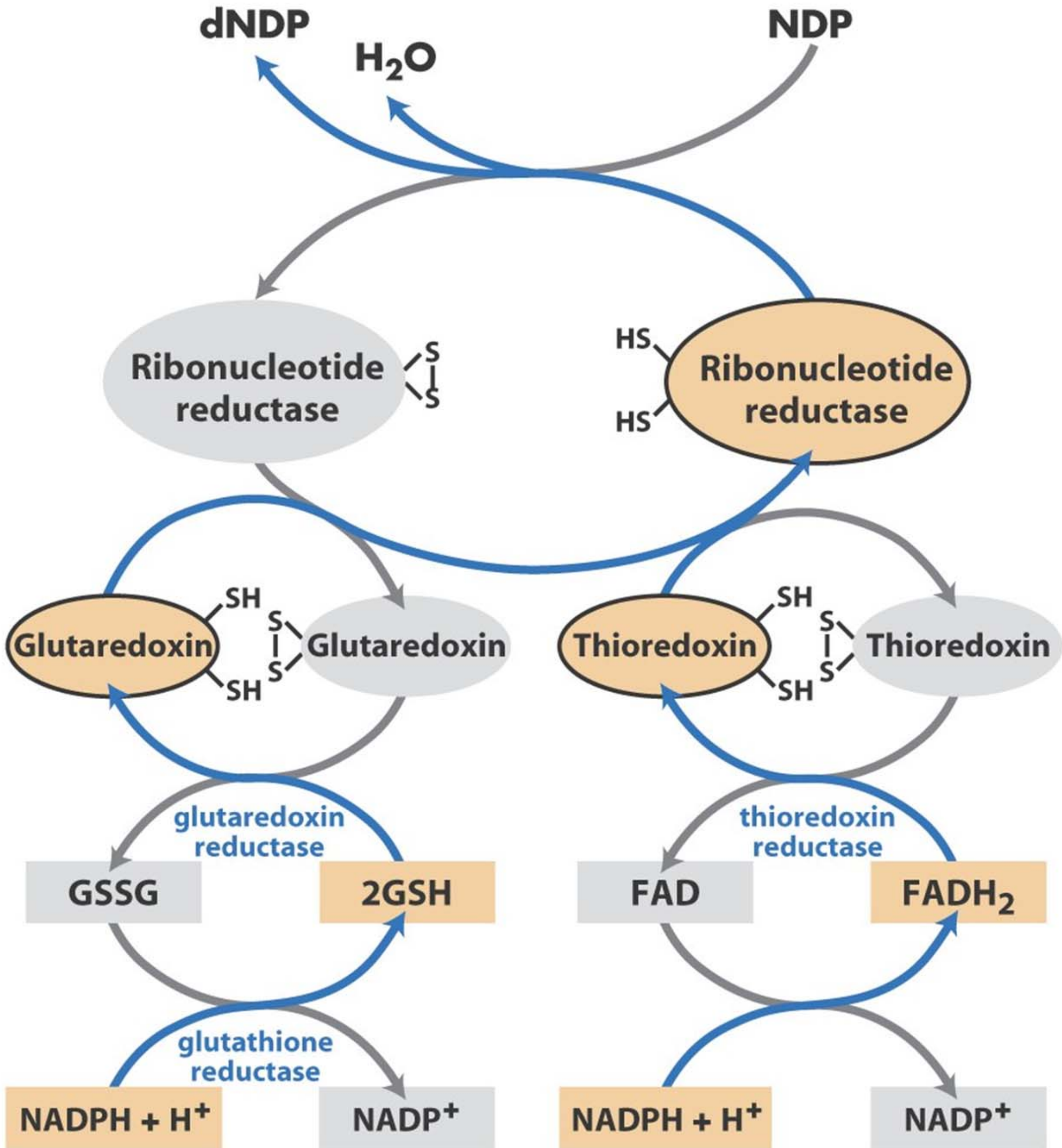


AIRc: AIR carboxylase (active in higher EK in an ATP-dependent manner)

Calss I PurE is homologous to AIRc, $K_{M[HCO_3^-]}$ = 110mM
PurK: $K_{M[HCO_3^-]}$ = 0.1mM
} active in plants, yeast and PK (*E. coli*)

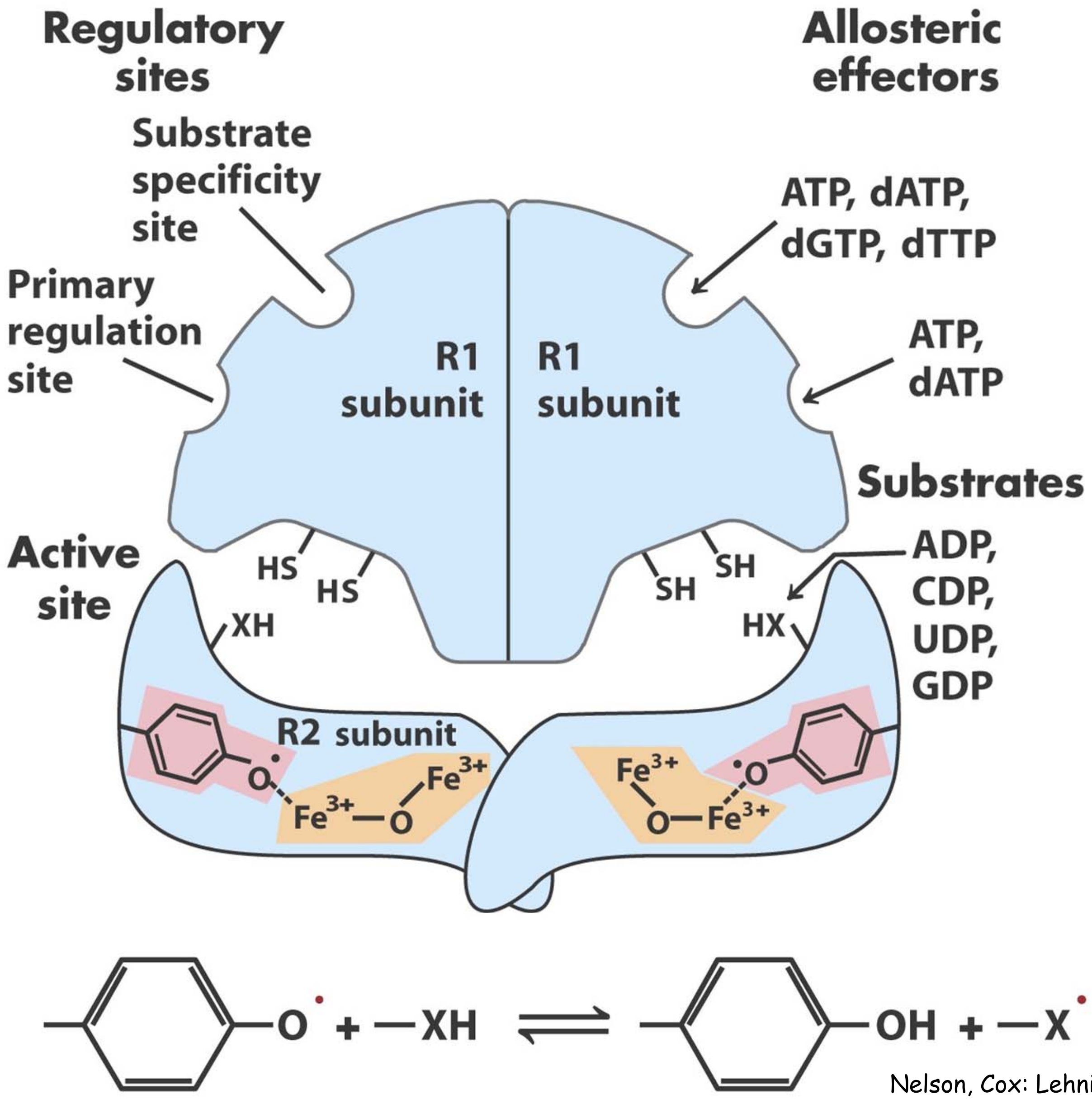
N^5-CAIR is rather unstable (half-life 15 s at pH 7.5 and 25°C) ⇒ in yeast and plants N-terminus of Class I PurE is fused to C-terminus of PurK thus enabling a rapid transfer of the $-COO^-$ from N^5-CAIR to CAIR

NADPH-dependent reduction of ribonucleotides to deoxyribonucleotides



Nelson, Cox: Lehninger Biochemistry

Ribonucleotide reductase: the key to the DNA-world



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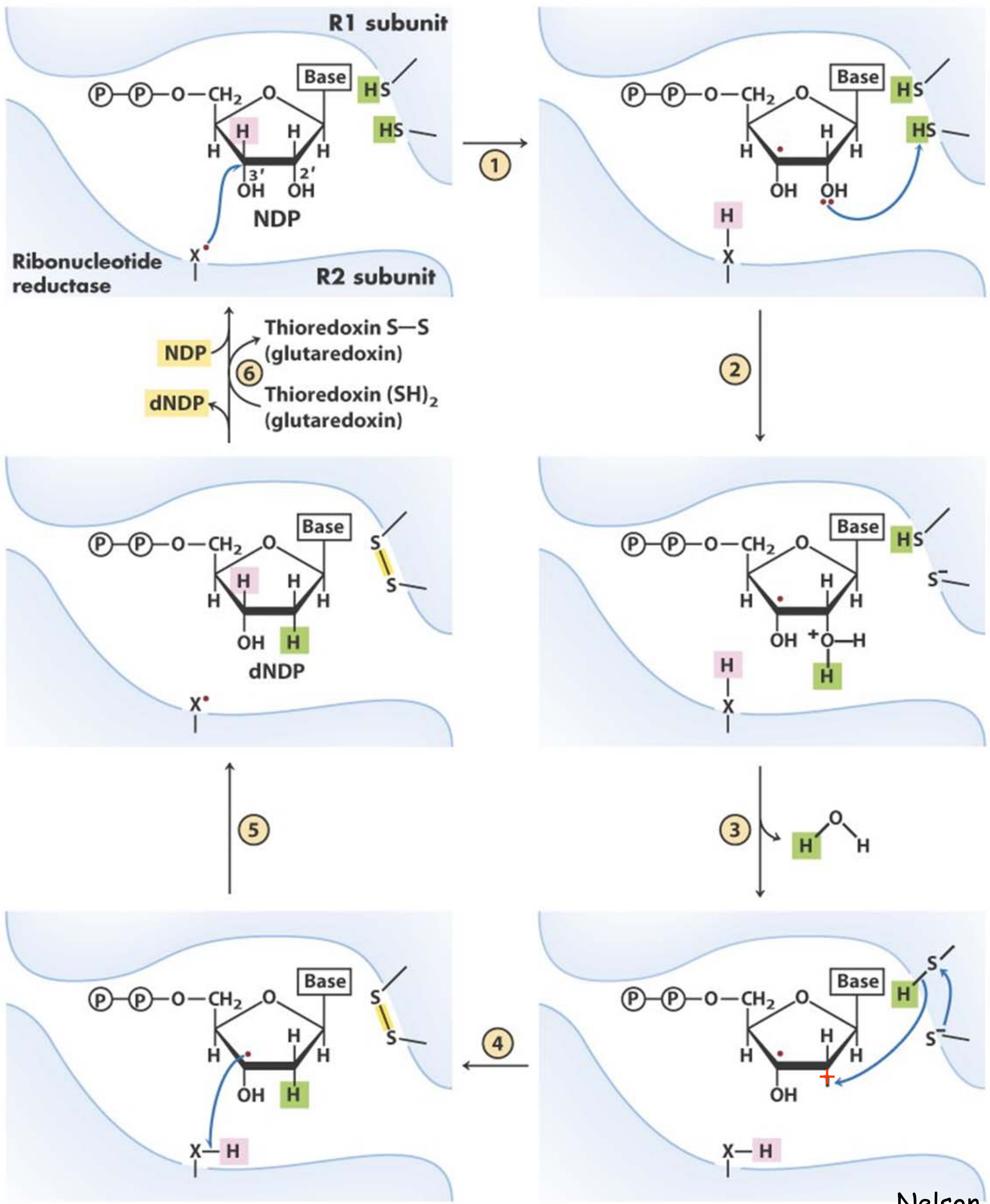
Catalytic mechanism of ribonucleotide reductase



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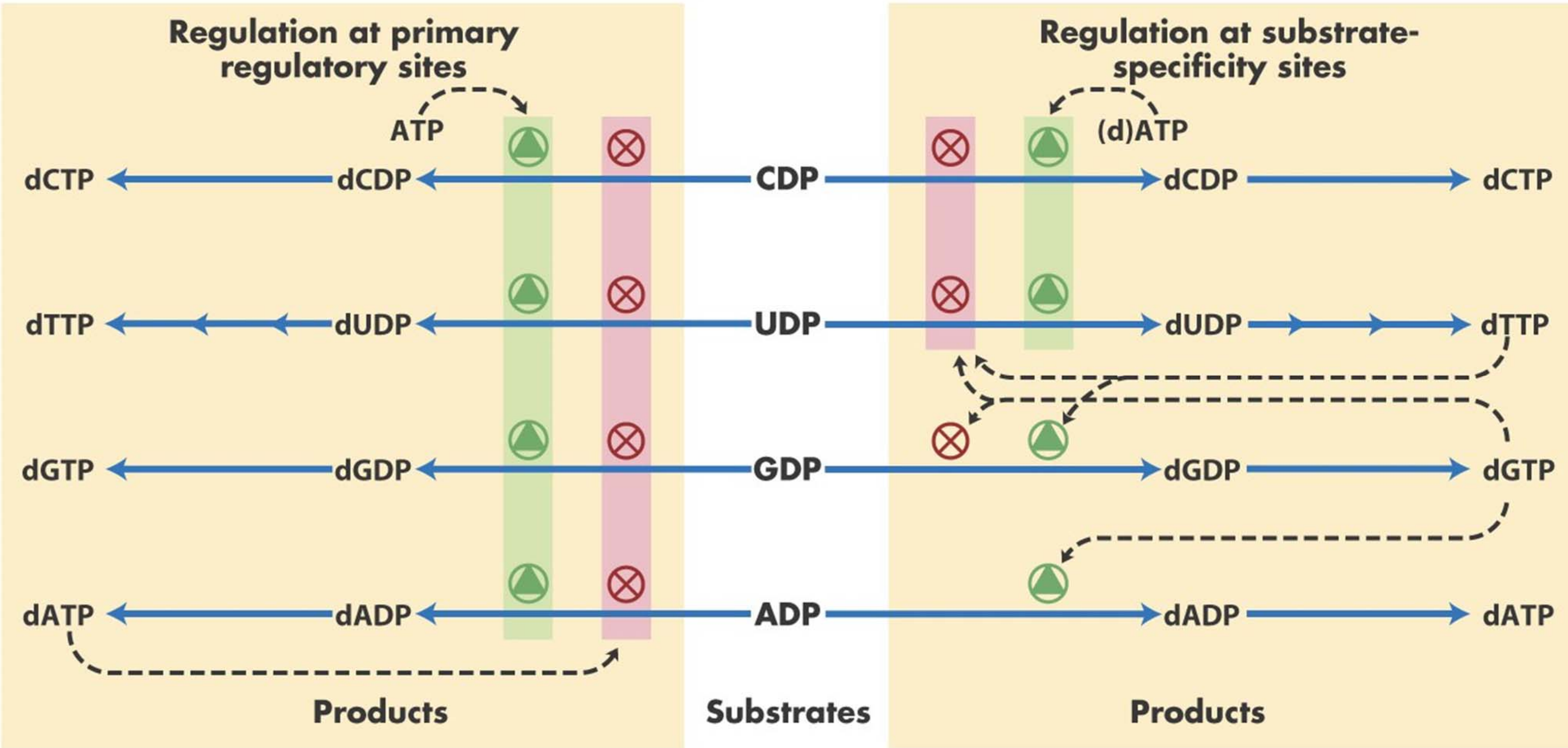
Complex regulation of ribonucleotide reductase by (d)NTPs



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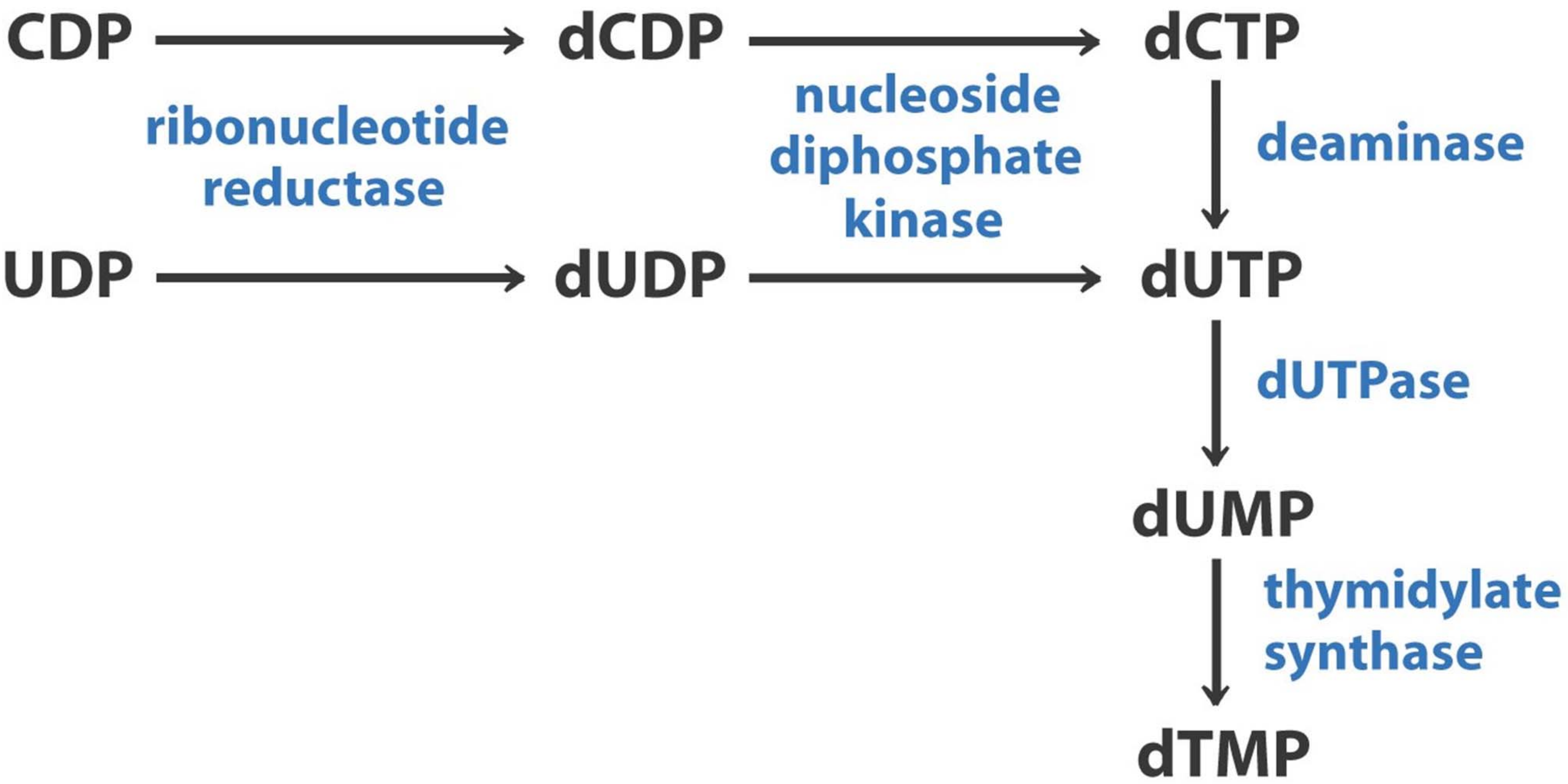
Biosynthesis of thymidylate (dTMP) via dUTP



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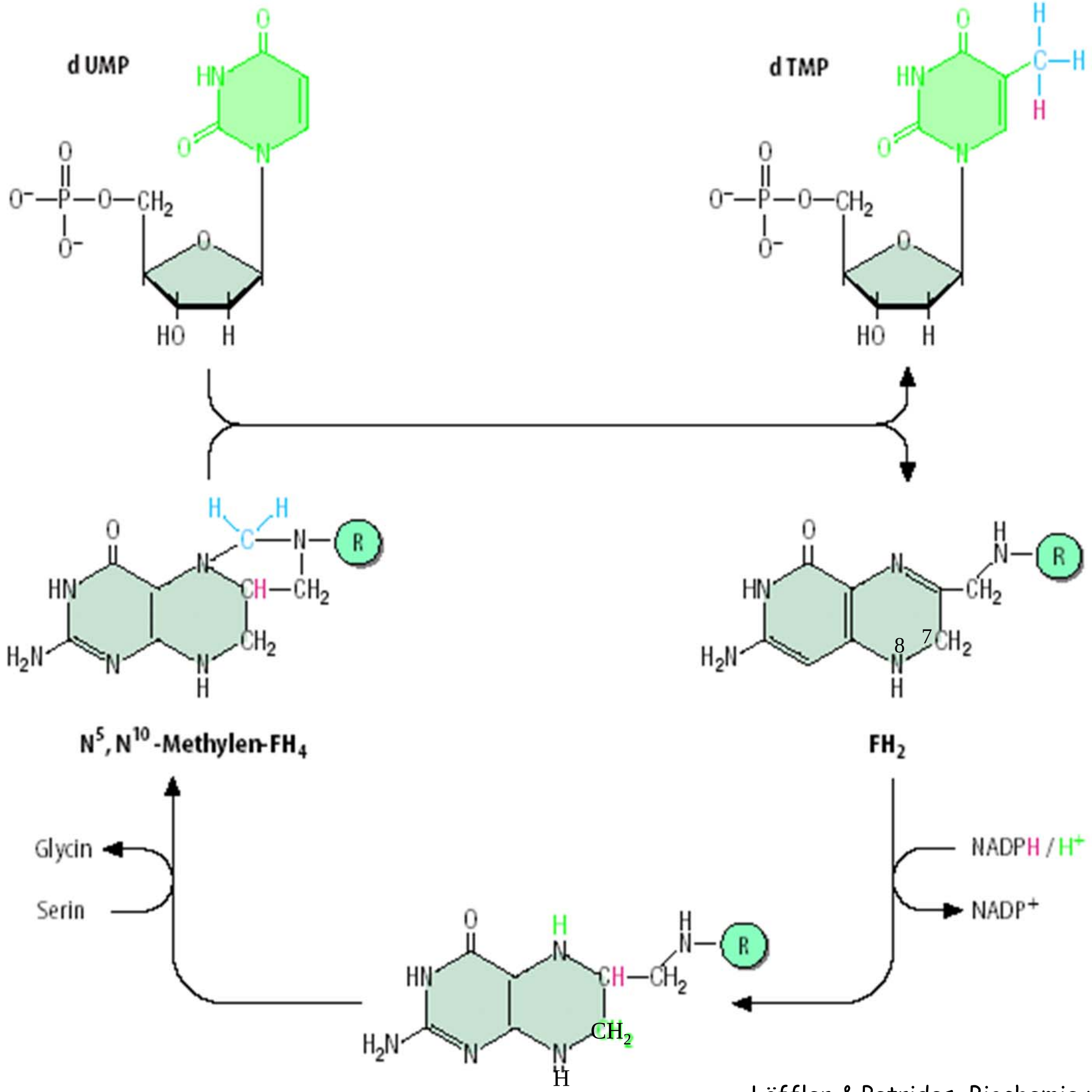
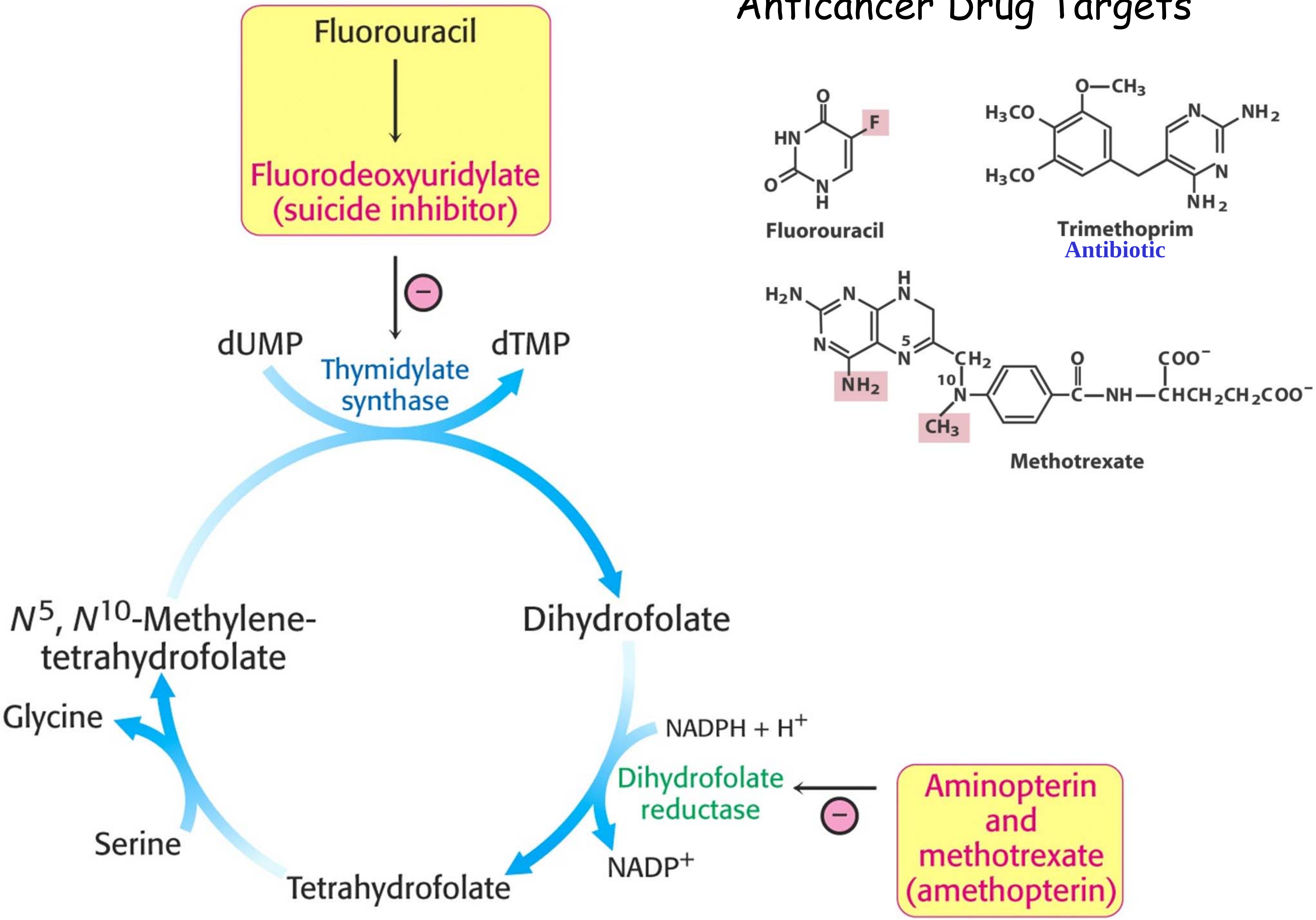
Thymidylate synthase catalyses conversion of dUMP to dTMP



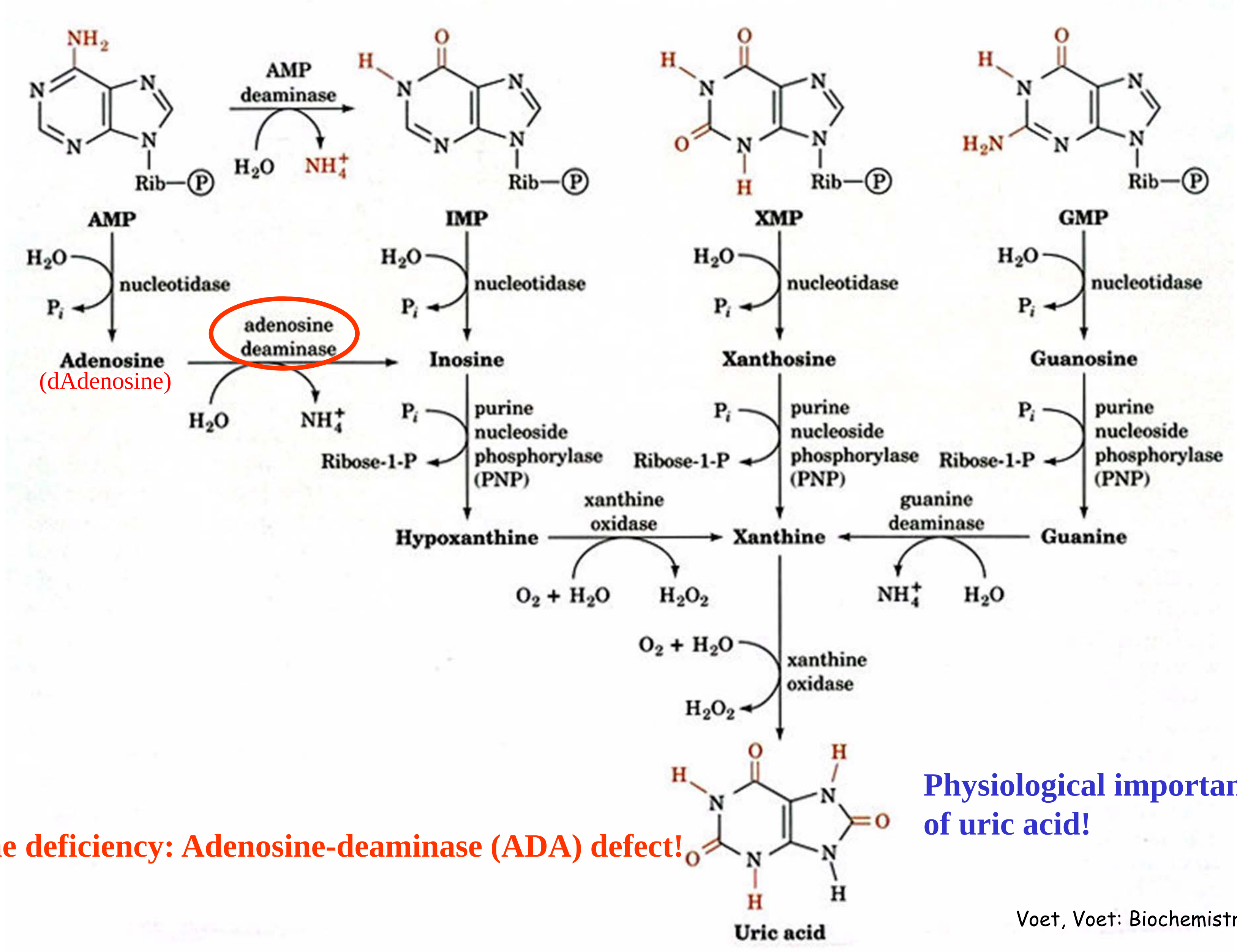
Löffler & Petrides, Biochemie und Pathobiochemie

Anticancer Drug Targets



Berg, Tymoczko, Stryer: Biochemistry

Catabolism of purine nucleotides



Immune deficiency: Adenosine-deaminase (ADA) defect!

Physiological importance of uric acid!

Voet, Voet: Biochemistry

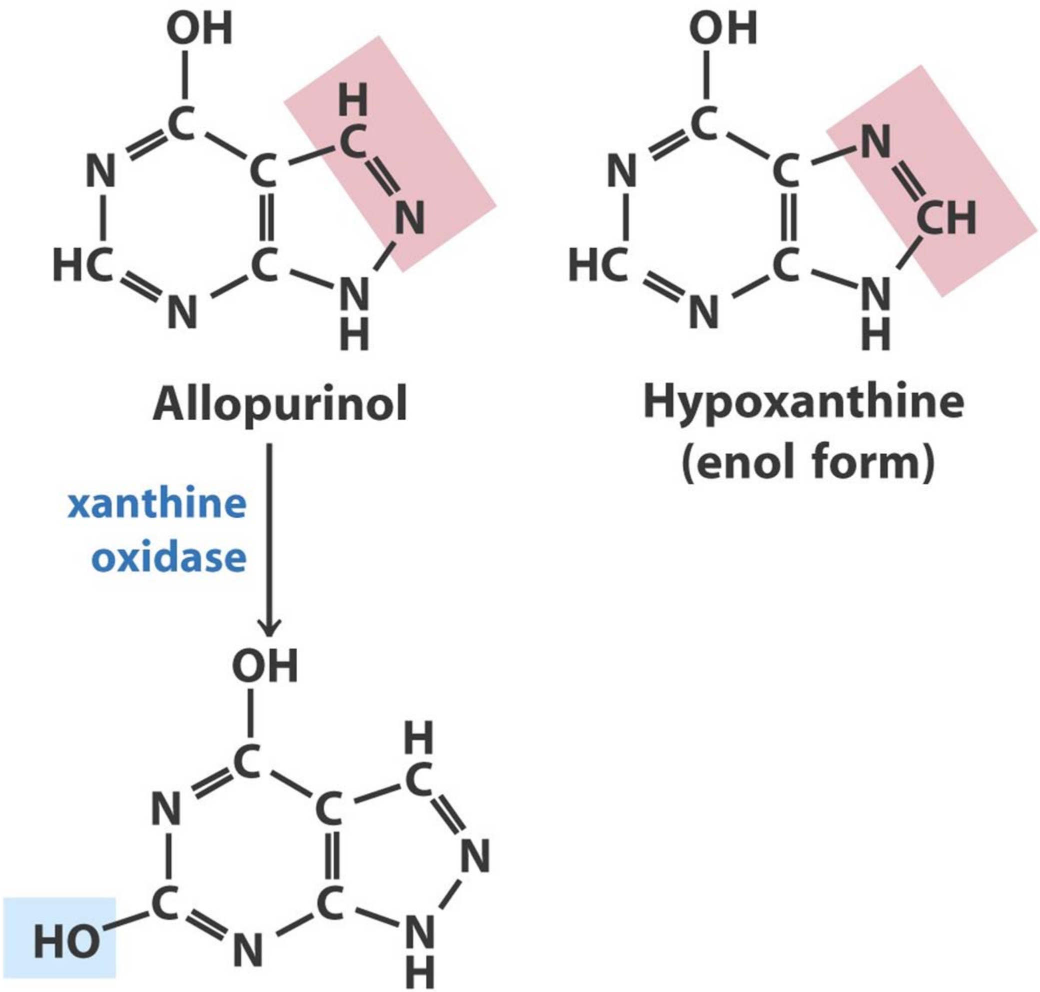
Uric Acid: The Oxidant-Anitoxidant Paradox

Early 1980s hypothesis:
Silencing of the uricase gene with an increased blood level of uric acid provided an evolutionary advantage. *In vitro* experiments: uric acid is a powerful scavenger of singlet oxygen, peroxyl radicals and hydroxyl radicals. Thus it protects as a major antioxidant of plasma from ox. damage thus increasing life span and decreasing the risk for cancer.

Epidemiologic studies beginning of 21st century:
Cardiovascular disease, hypertension, metabolic syndrome are strongly associated with high blood levels of uric acid and in many cases predict development of hypertension, visceral obesity, insulin resistance, diabetes typeII, kidney disease, cardiovascular events.

Nucleosides, Nucleotides, Nucleic Acids (2008) 27:608-19

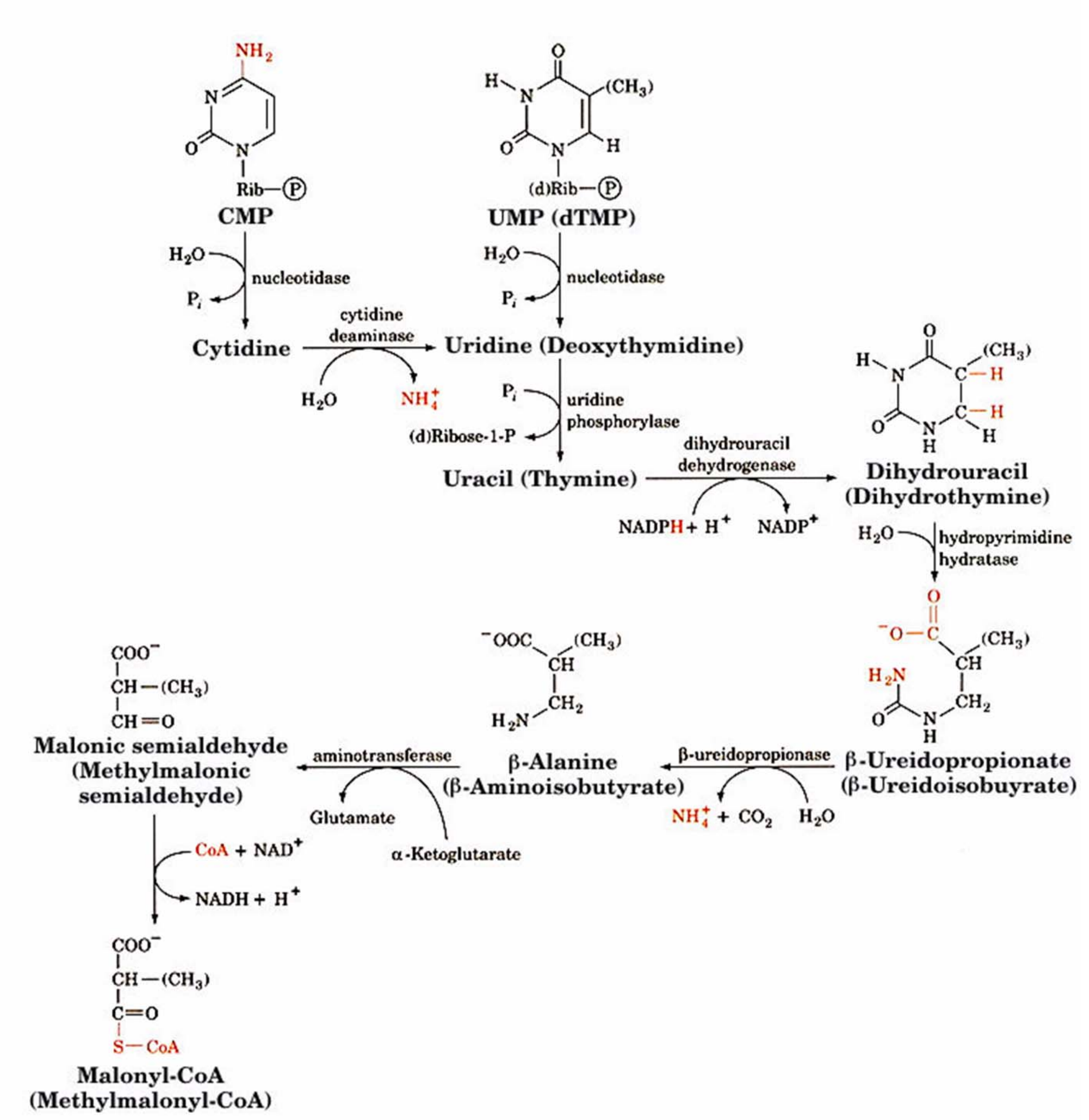
Allopurinol, an inhibitor of xanthine oxidase
prevents crystalline deposits of uric acid (gout)



Oxypurinol = Alloxanthine: Sticks in the active site of XO => suicide inhibitor

Nelson, Cox: Lehninger Biochemistry

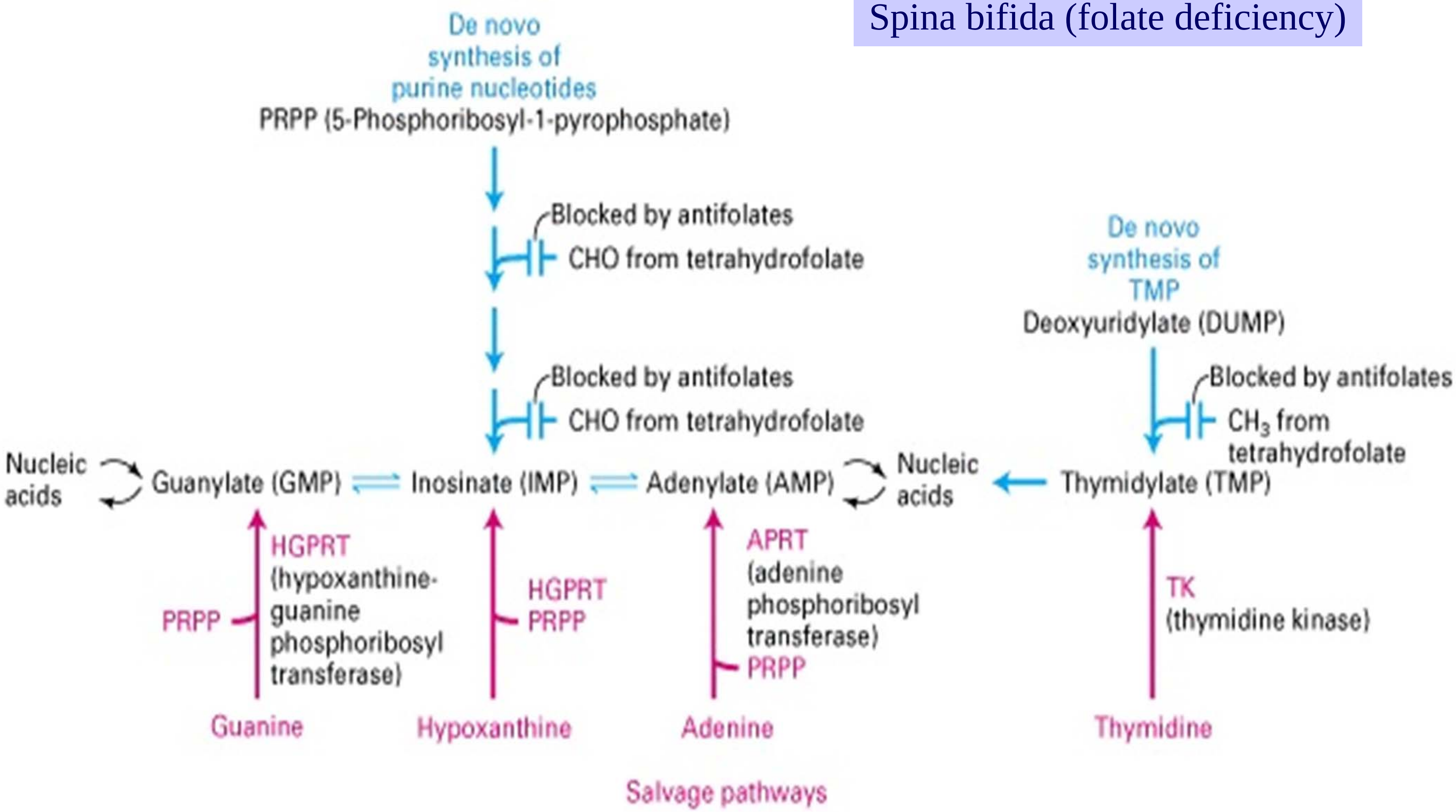
Catabolism of pyrimidine nucleotides



Voet, Voet: Biochemistry

De novo and salvage pathways for nucleotide synthesis

Spina bifida (folate deficiency)

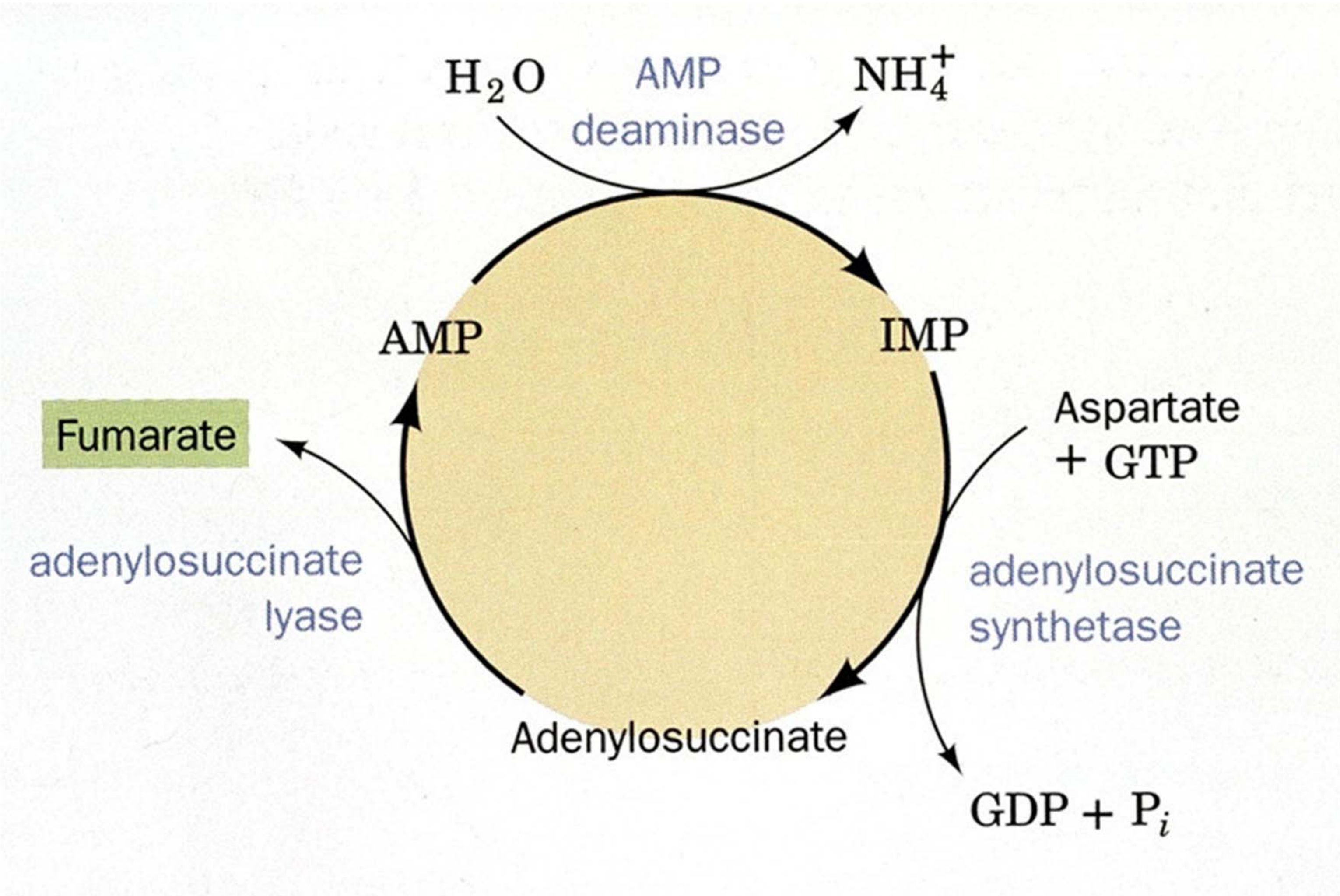


Lesch-Nyhan syndrome: hereditary disease (HGPRT-deficiency)

Lodish et al. Molecular Biology of the Cell

The purine nucleotide cycle: anaplerotic function in skeletal muscle

Pathology: Myoadenylatedeaminase



Net: Asp + GTP + H_2O ⟶ Fumarate + GDP + P_i

Voet, Voet: Biochemistry