

Figure 1

Timeline

- 1948 Folate analogs shown to achieve dramatic remissions in acute lymphocytic leukemia¹³⁷
- 1954 Discovery of thymineless death illustrates lethal effect of specific limitation of DNA precursors¹
- 1958 Fluorinated pyrimidines shown to induce thymineless death by inhibiting thymidylate synthase²
- 1958 Dihydrofolate reductase and thymidylate synthase identified as primary and secondary targets for the action of folate analogs¹³⁸
- 1961 Discovery of ribonucleotide reductase, which catalyzes the first reaction committed to DNA synthesis, and a major cancer biomarker¹³⁹
- 1974 Elevation of spontaneous mutation rate proposed as critical element of carcinogenesis⁵³
- 1979 dNTP concentrations shown to be determinants of DNA replication fidelity¹⁴⁰
- 1981 Mutations affecting regulation of ribonucleotide reductase and dCMP deaminase shown to be mutagenic¹⁴¹
- 1992 Nucleotide pool “sanitation” shown to affect replication fidelity¹¹⁰
- 2006 Cancer cells shown to bear multiple mutations and mutational heterogeneity within a single tumor⁵⁴
- 2014 Inhibitors of nucleotide pool sanitation shown to have anticancer activities^{122,123}
- 2015 Cancer cells shown to have many mutations, but very few “driver” mutations, which direct the cell to a cancer phenotype⁵⁶
- 2015 Variation in cancer frequency among different tissues shown to arise not from environmental exposure or genetic predisposition but from random genetic change⁵⁸

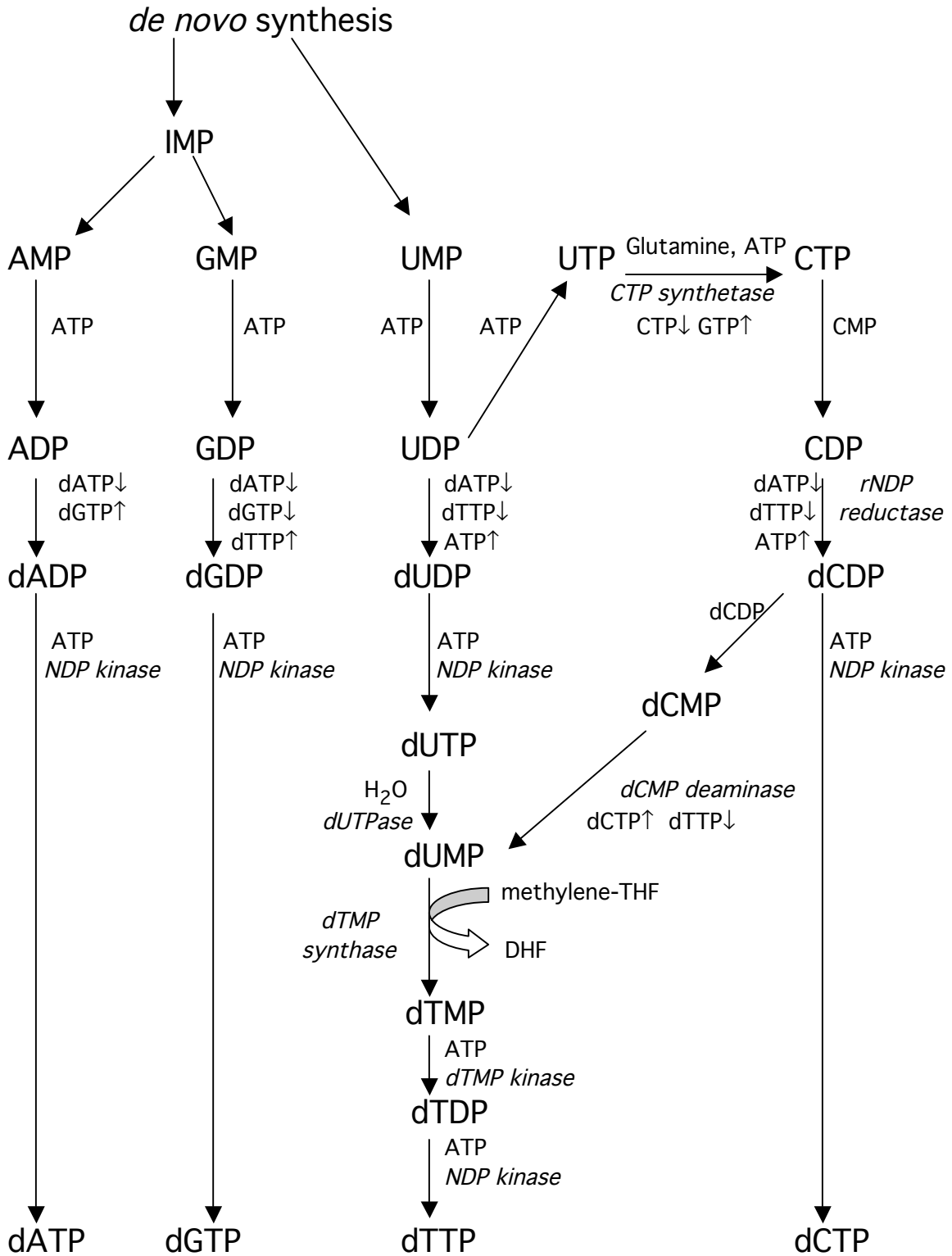


Figure 2

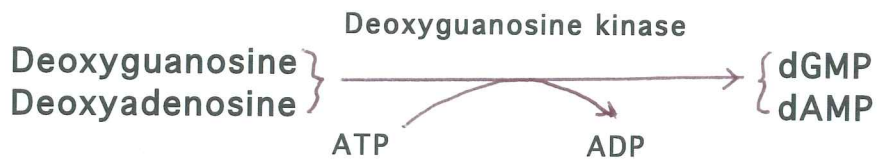
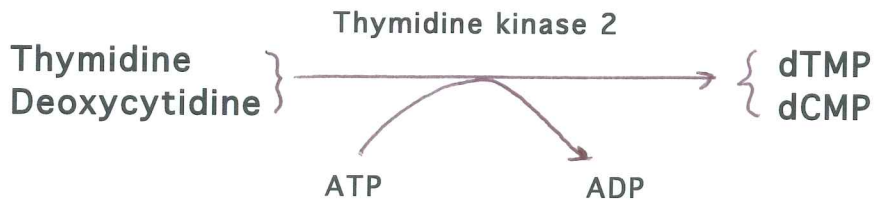
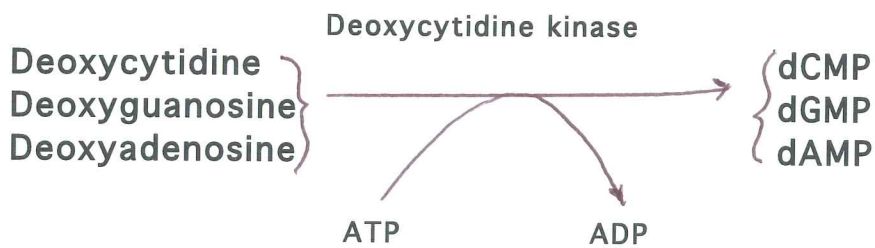
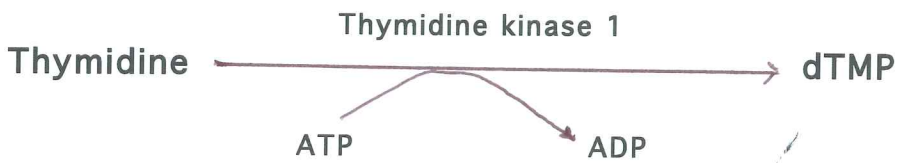
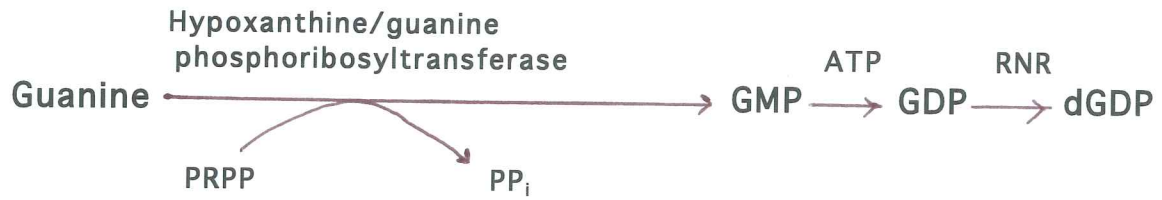


Figure 3

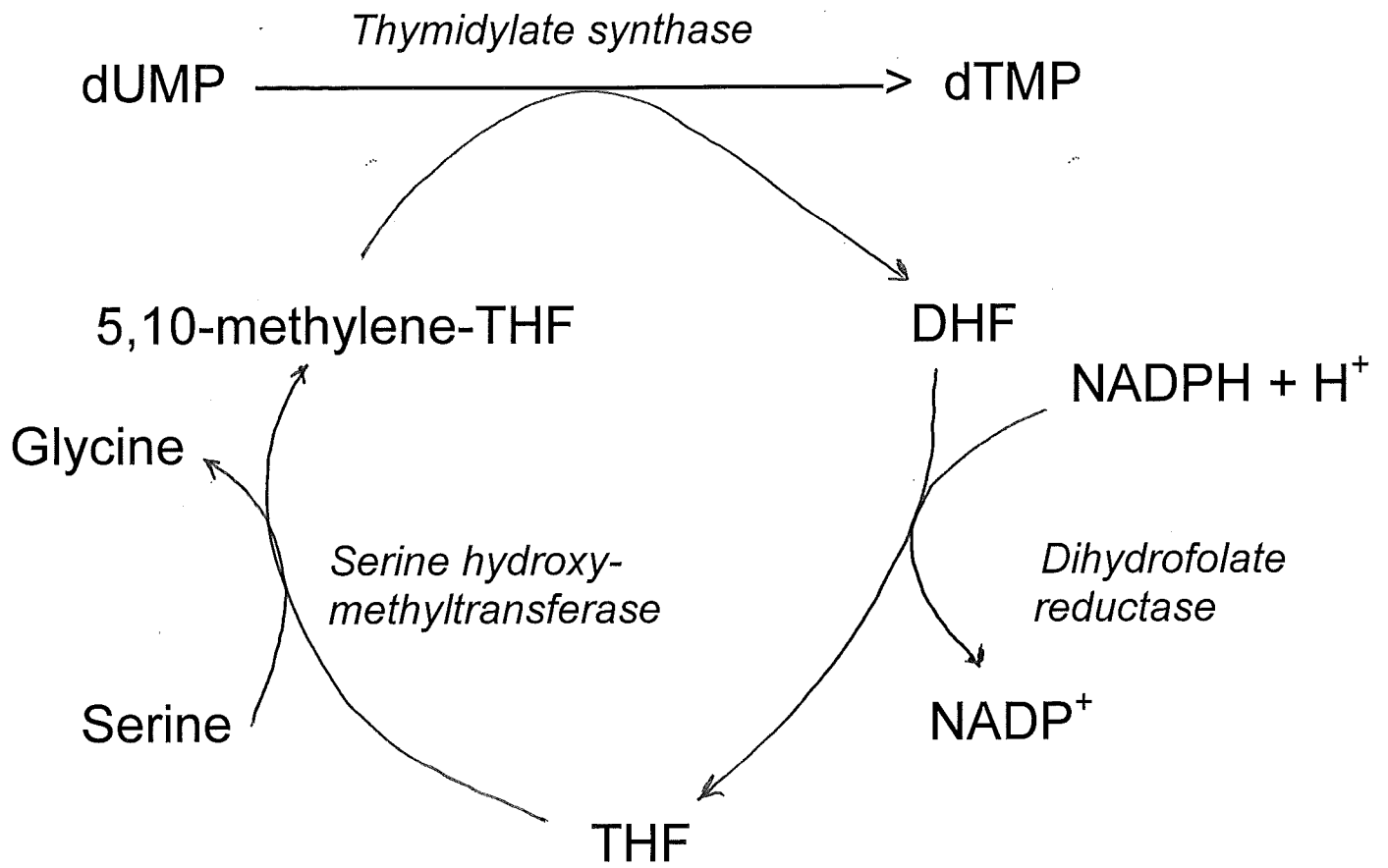


Figure 4

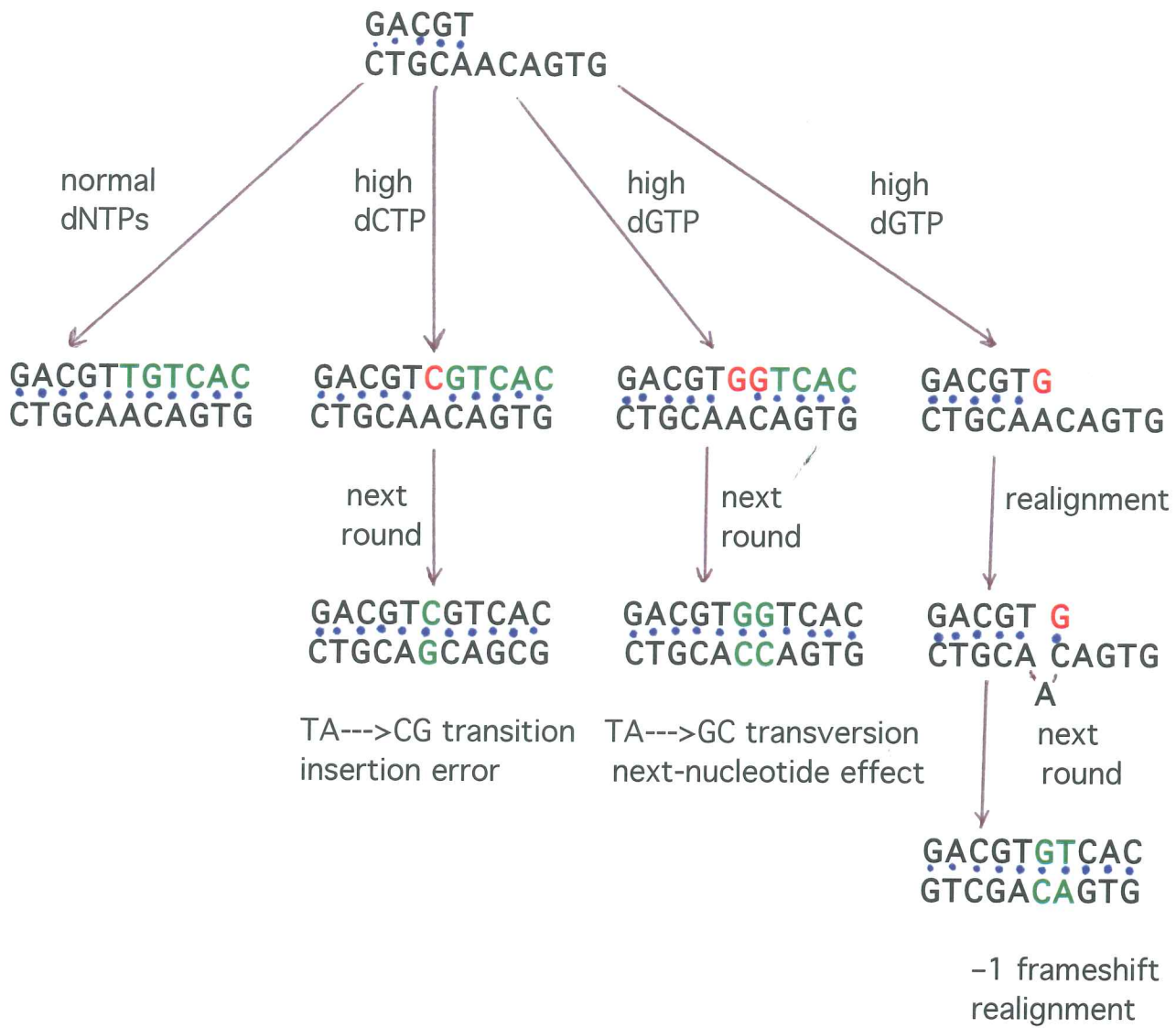


Figure 5