Mercaptopurine (6-mercaptopurine) together with azathioprine and 6-thioguanine belong to a group of widely used chemotherapeutics and immunosuppressants. However, insufficient therapy outcome or severe adverse effects such as myelosuppression are still being reported. Technological progress in DNA and RNA sequencing facilitates effective identification of causative genes responsible for the therapy failure, i.e., description of genetic variants for enzymes involved in metabolism of physiological purines as well as thiopurine drugs. Variants of these enzymes may substantially alter concentrations of cytotoxic forms of thiopurines, which affect therapy success rates.

Currently, a number of mutations in genes that play role in thiopurine metabolism have been annotated. Nevertheless, molecular mechanisms underlying the effect of these mutations are not fully elucidated. Knowledge of 3D structure for these enzymes may shed light on the effect of the genetic variants to protein function and mechanisms modulating therapeutic efficacy of thiopurines.

This thesis focuses mainly on biochemical and structural characterization of thiopurine-S-methyltransferase, fosfatase NUDT15 and cytosolic 5′-nucleotidase II. It summarizes current state of knowledge and emphasizes the importance of structural biology methods for explaining the role of mutant variants in thiopurine metabolism.