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Purine salvage pathway enzymes as a target for therapy against pathogenic organisms lacking de novo purine synthesis – case study of *Helicobacter pylori.*

The scientific goal of the project is experimental verification of a potential new approaches to therapy against pathogenic organisms that lack the possibility of de novo synthesis of purine and purine nucleosides. Such organisms have to rely on the alternative metabolic pathway, so-called purine salvage pathway, to provide building blocks required for synthesis of genetic material - RNA and DNA. Thus, blocking this pathway should inhibit proliferation of such organisms.

Helicobacter pylori is a bacterial pathogen known for its ability to colonize and persist in the human stomach. It was discovered about 30 years ago. Nowadays H. pylori infection is present in over half of the world's population. According to the most recent data published in Poland and in Croatia the H. pylori infection rate among adults (ages 20 to 70 years) is estimated at 80%. Infection by H. pylori causes chronic inflammation (gastirtis), which if left untreated, may progress to gastric and duodenal ulceration and eventually to gastric cancer.
Although not all strains of H. pylori have the same virulence, about 10-20% of those infected develop a disease caused by this bacterium. Among those about 1% suffers from cancer. Therefore H. pylori is is regarded as the most successful and dangerous human pathogen.

The *H. pylori* eradication rates reached by the standard therapies dropped below 80%. In the absence of a licensed efficacious vaccine, continuous efforts have been made to improve the efficacy of the treatment aiming to overcome the antibiotic resistance and the frequent lack of the patient compliance. New approaches are needed to identify new drug targets and therapies. We have an idea for such a therapy, and this project will conduct basic research, which is necessary to verify on the molecular level whether the idea has a chance to subsequent practical implementation.

The project is intended to obtain two enzymes of purine salvage pathway from *H. pylori* , to examine their properties at the molecular level, and to design compounds that reduce activity of these enzymes (so-called inhibitors), and to check, in cell cultures whether the inhibition of each enzyme separately or inhibition of both of them simultaneously is sufficient to stop bacterial growth.

In this project experimental and computational interdisciplinary studies will be carried out, including genetic engineering and biochemical methods to obtain pure samples of both enzyme from H. pyloris, biophysical studies to determine properties of the enzymes, particularly their interactions with substrates and inhibitors, obtain three dimensional structure of both enzymes which enable to design specific inhibitors using molecular modelling methods. Finally, design inhibitors will be synthesized and it will be checked if they are able to stop growth of H. pylori cell cultures.
If the thesis of this project turned out to be correct, i.e. the inhibition of one of the tested enzymes or simultaneous inhibition of both enzymes would block the multiplication of the bacterium *Helicobacter pylori*, it would enable to develop new effective therapy against this pathogen, as well as against other microorganisms lacking the possibility of de novo synthesis of purines and purine nucleosides.