The discovery of antibiotics and their introduction into common practice was one of the most important medical achievements of the previous century. However, euphoria was brief. Rapid emergence of multiple-drug resistant bacteria has increasingly occurred in many parts of the world and constitutes a serious threat to public health and patient safety. The problem of resistance involves many pathogens that cause infections in the hospital and in the community. Success at fighting infectious disease will depend upon development of new, effective and safe antimicrobial compounds.

The formation of disulfide bridges, a post-translational modification of extra-cytoplasmic proteins leads to the stabilization of their tertiary and quaternary structures and often influences their activity. The oxidation reaction between two cysteine thiol groups leads to the formation of a disulfide bond and the concomitant release of two electrons. While disulfide bonds can form spontaneously in the presence of atmosphere, the reaction is slow. Instead, *in vivo* disulfide bond formation is catalyzed by a range of proteins, the thiol oxidoreductases of the Dsb (*disulfide bond*) system. A process which plays an essential role in the assembly of many virulence factors takes place in oxidative environments; in the periplasm (the space between cytoplasmic and outer membrane) in gram-negative bacteria cells. Thus proteins of the Dsb system, which play a key role in the virulence of many pathogenic microorganisms, represent possible new drug targets. Inhibition of their interactions with substrates or their redox partners could constitute a means of blocking the formation of virulence factors.

Our studies, presented in this project, will focus on the mechanism of action of *H. pylori* and *H. hepaticus* Dsb proteins and their roles in the virulence process. Both species persistently infect their hosts, leading to chronic inflammation; in both cases, this inflammation can progress to carcinoma. *H. pylori* infections induce both acute and chronic gastritis and peptic ulcers. *H. pylori* is also considered to be a high risk factor for the development of mucosa-associated lymphoid tissue lymphoma and adenocarcinoma of the stomach. *H. hepaticus* persistently colonizes the colon, inducing inflammation, and it invades the liver of susceptible mice, causing hepatobiliary disorders such as hepatitis and hepatocellular carcinoma. There is increasing evidence that *H. hepaticus* may also be a human pathogen, since infection by *H. hepaticus* can be associated with cholecystitis and gallbladder cancer.
With regards to *H. pylori*, we have characterized the Dsb system of this pathogen and its influence on the development of gastric cancer. **Our recent work** led to the characterization of the first dimeric oxidoreductase **(HP0231**) that functions in an oxidizing pathway of *H. pylori* and has an impact on multiple essential virulence factors. **So, the first goal of the project is to further expand our knowledge about HP0231.** Based on previously gained knowledge and knowledge about HP0231 function and structure resulting from the presented project, we intend to **develop inhibitor/s against this *H. pylori*-specific protein.** The lack of *H. pylori* HP0231 impairs translocation of CagA, main *H. pylori* oncoprotein, into gastric epithelial cells. The proposed research concerning *H. hepaticus*, a member of the enterohepatic microorganisms, is innovative. Although, there is evidence that suggests an association between infections of mice or humans by this bacterium and development of hepatobiliary cancers, the knowledge about molecular aspects of its virulence are insignificant. The *H. hepaticus* Dsb oxidizing system is probably different from that of *H. pylori* (*in silico* analysis). Thus, **the second goal of this proposal is to gain an understanding of the *H. hepaticus* Dsb system and its influence on virulence factors.**
This proposal relies on the cooperation of complementary interdisciplinary research groups of different expertise in various field of molecular biology. We believe that the project will provide a significant contribution to the knowledge of basic research in such fields as biochemistry and microbiology. The lessons gained from basic research, should help combat infectious diseases.