Abstract of the PhD thesis by mgr inż. Magdalena Alenowicz titled "Design and synthesis of conjugates consisting of cell penetrating peptides and biologically active compounds for improved pharmacological properties"

One of the problems that modern medicine and pharmacology face is the insufficient effectiveness of therapy caused i.a. by low level of distribution of drug to the source of disease. In effect the doses used are significantly higher, which results in development of drug resistance among pathogens as well as in patient's drug poisoning. Invention of new compounds with better antimicrobial properties, improvement of drugs' selectivity, activity, bioaccessibility, together with reduction of their toxicity and susceptibility to enzymatic degradation as well as limitation of development of microbe drug resistance – all seem to be vital issues in modern medicine and pharmacology.

One of the methods that allow to overcome the aforementioned difficulties is conjugation of drugs with cell penetrating peptides (CPP). The research presented in this PhD thesis encompasses the effort to improve the therapeutic properties of two well-known drugs – cisplatin (cPt) and vancomycin (VAN). A strategy was developed to improve bioaccesibility and therapeutic effect of the drugs by means of conjugation with CPP.

During design of peptides and conjugates two methods of conjugation were taken into account –non-covalent complexes with cPt as well as covalent bond between CPP and VAN. Vancomycin and peptides were suitably modified during synthesis in order to enable covalent bond formation. Conjugation was performed with use of Huisgen 1,3-dipolar cycloaddition („click" reac tion). Moreover, all peptides were fluorescently labeled in order to enable analysis of their cell penetration and tracing of their distribution by means of fluorescent microscopy. Anti-cancer activity of cisplatin conjugated with CPP as well as the ability of vancomycin conjugated with CPP to penetrate into central nervous system were tested. Cisplatin dosed in mixture with TP10 had stronger toxic effect on cancer cells than cPt by itself, and at the same time presented relative harmlessness towards healthy cells. Conjugates of VAN with TP10 presented higher antimicrobial activity towards *S. aureus* and *Enterococci* than VAN by itself. Moreover, tests performed on mouse model showed that conjugate of VAN and CPP penetrated the blood-brain barrier and were spotted in brain.

The presented research may inspire further broadened tests in search for new strategies of application of those two well-known drugs.