Peptides are widespread in nature, and they are crucial for maintaining various physiological functions. Among them are hormones, neurotransmitters, etc. Their participation in biological processes, high selectivity and degradation to nontoxic amino acids brought much interest in their application as drugs. Some peptides have currently therapeutic application, e.g. oxytocin, insulin, somatostatin. Unfortunately, there are certain obstacles limiting the use of peptides as drugs. The main problem is their hydrophilic nature, which leads to decreased cell membrane penetration, effecting in poor intestinal permeability and consequently insufficient oral bioavailability. Oral bioavailability is defined as the amount of a drug that is detected in systemic circulation, in unchanged form, after oral administration. Nevertheless, despite some serious limitations, research on peptide drugs is one of the fastest developing sections in pharmaceutical industry.

In this project, we are showing a new approach to improve permeability of hydrophilic, biologically active peptides and thus, increasing their oral bioavailability. This strategy is named *Lipophilic Prodrug Charge Masking (LPCM)*. It assumes, that charges of active peptides would be transiently masked by appropriate hydrophobic groups attached by cleavable ester bonds. This will make peptide much more lipophilic, and will facilitate the penetration through intestinal enterocytes. Once, such a prodrug gets into the blood circulation, the charge masking group would be cleaved by enzymes, responsible for cleaving ester bonds- esterases, that are ubiquitous in body fluids. Thus, the free, unmodified, biologically active peptide will be released (Figure 1). Our recently published research, confirms feasibility of LPCM method, showing that the strategy improved peptides bioavailability over 70 fold. We introduced LPCM strategy also to oxytocin, obtaining similarly satisfactory results (data not published). Even though, outcome of our research is very promising, LPCM is a novel approach and needs further evaluation and optimization. We believe, that in the future it may become general solution enhancing bioavailability of various peptides with proved therapeutic activity.

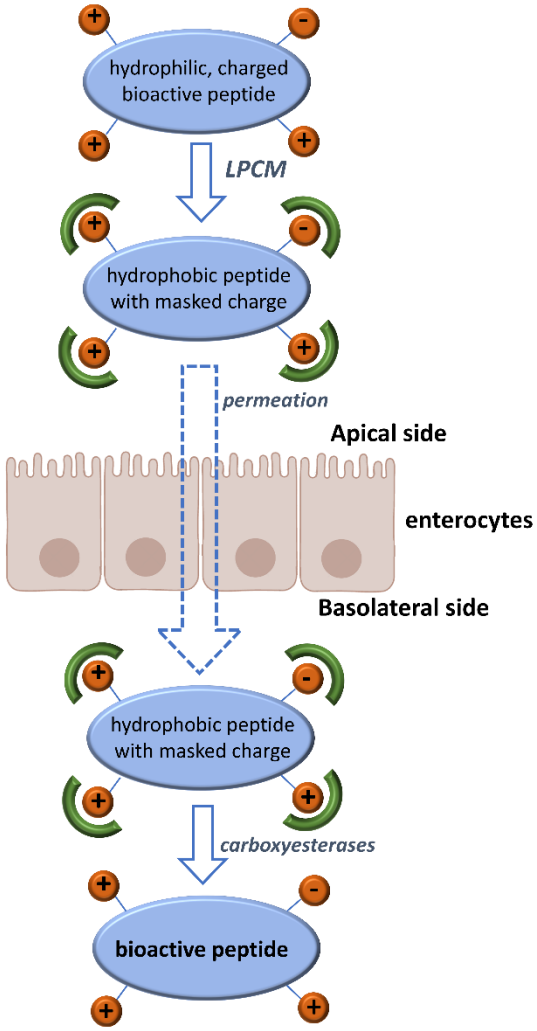

Figure 1. Scheme of LPCM strategy.

During our research, we will study LPCM method applying it to various peptides with known and proved biological activity e.g. oxytocin, octreotide etc. We are planning to synthesize peptides and their prodrugs, that would differ in the type and the number of charge masking groups. It is important to find a balance between improved lipophilicity and solubility of a prodrug. In next step, permeability assay will be performed for peptides and their analogs with masked charges (using Caco-2 cell model), and then serum stability will be studied. Structures of peptides characterized by high proteolytic susceptibility would be modified to improve their stability. Synthetic part will be in scope of Polish group responsibilities, while the permeability assay will be performed by coworkers from Israel (with active participation of Polish team members).

Results of our preliminary research clearly showed that LPCM strategy can be applicable and potentially successful for biologically relevant peptides and gives strong foundation for further interest in this method. It is worth noting, however, that although it seems to be very promising and auspicious, LPCM is the new approach and further development and optimization are needed. In our opinion, this strategy has potential to be applicable for various peptides, and our results would have significant contribution to the progress in attractive, but demanding field of utilization of peptides as drugs.