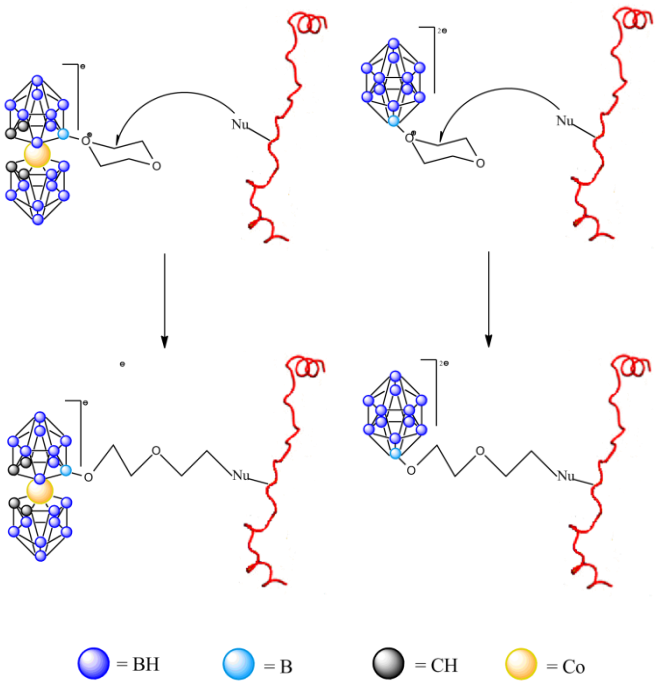
The objective of this project is to evaluate the influence of attachment of boron clusters to peptide, thymosin β4 (Tβ4) on its physicochemical properties and biological activity. Boron clusters are compounds consisted of boron, hydrogen and optionally carbon atoms and have cage-like structure. Boron clusters can be used to modify the pharmacokinetic profile of therapeutic peptides, as they can form aggreagtes, interact with cyclodextrins and blood plasma proteins. Pharmacokinetics describes how the body affects a specific drug after administration. In this project, conjugates of two boron clusters with distinct physicochemical porperties will be synthesized. Studies will also include evaluation of physicochemical properties of obtained conjugates, their biological activity and interaction with serum albumin.

Tβ4 is a peptide with a broad biological activity leading to enhanced regeneration of various tissues after injury. However, Tβ4 has a short half-life in plasma, which decreases its effect. Binding of Tβ4 with boron clusters will give the peptide the ability to form complexes of several peptides and interact with serum proteins. Boron clusters can form strong complexes with cyclodextrins. Cyclodextrins are compounds made up of sugar molecules bound together in a ring. Interior of cyclodextrins is hydrophobic and can be utilized to complex many compounds. Cyclodextrins attached to a carrier can be used as platforms to form complexes with Tβ4-dodecaborate conjugates. Tβ4 in such complexes would be characterized by longer plasma half-life and enhanced effect on target tissues. Boron clusters can also self-assemble forming aggregates and binds to serum albumin, main protein in human blood plasma, which serves as a transport protein e.g. for fatty acids, hormones and pharmaceuticals. This interactions can also increase the half-life of Tβ4 in blood plasma and enhance its biological activity.

In this project conjugates of Tβ4 and selected boron clusters will be synthesized. In obtained conjugates, Tβ4 will be modified in different regions of its sequence, allowing evaluation of the dependence between site of the modification and biological activity. We will select the conjugates with the best properties. The physicochemical properties, such as structure of the peptide and tendency to aggregation will be examined. The influence of obtained conjugates on the survival of cardiomyocytes and myocytes cultivated at conditions with low oxygen concentration, will be evaluated. In the final part of the project, we will study the interactions of conjugates with human and bovine serum albumins.

Many peptides, which show promising pharmacological activities suffer from short plasma half-life and therefore, lower activity in clinical trials. Half-life of Tβ4 administered intravenously to humans was 1 – 2h, depending on dose. That means that Tβ4 is cleared from the body shortly after administration. A situation were administered dose produces high initial concentration of the drug and then the concentration rapidly decreases impairs efficacy of a treatment. Frequent re-dosing is also necessary, which causes high fluctuations of the concentration of a drug that can be harmful for the patient. For these reasons, it is important to develop strategies which will allow to increase the half-life of Tβ4 and other therapeutic peptides.



Scheme of mechanism of conjugation reaction of boron clusters with thymosin β4.