Modified glycosaminoglycans as nanocarriers of bioactive substances

Most compounds used as drugs have very low water solubility, which results in very low bioavailability in the human body, and therefore poor efficacy. The use of appropriate drug carriers significantly improves the drug bioavailability, reduces drug degradation and minimizes toxic side effects, which improves the therapeutic index. Pharmaceutical nanotechnology, also known as nanomedicine, is the development of nanoscale drug delivery systems (DDSs, nanoparticles).[1] In recent years, polymer nanoparticles are of great importance in the preparation of DDSs. Polymer-based DDSs are used to improve various pharmacological and therapeutic properties of conventional ("free") drugs (for example, their pharmacokinetics and biodistribution).[2] In addition, properly designed DDSs enable sustained and controlled release of drugs and can in a controlled manner deliver active substances to a designated place in a living organism. Glycosaminoglycans (GAGs) are extensively studied to develop nanoscale DDSs for therapeutic purposes in the treatment of various diseases, including cancer, glaucoma, wounds, and burns.[3,4] GAG polysaccharides are a group of biocompatible polymers found in the extracellular matrix (ECM) of living organisms. GAGs are natural linear polysaccharides commonly found in the human body; therefore, they have excellent good biocompatibility, biodegradability, and non-immunogenicity. This group includes compounds such as the well-known hyaluronic acid, heparin, or chondroitin sulfate.

This project aims to develop nanoparticles based on biopolymers and assess of their cytotoxicity and the possibility of application as carriers of bioactive substances. We plan to synthesize hydrophobically modified derivatives of glycosaminoglycans (HMGAGs) and explore methods for preparing polymer nanoparticles from these polymers. We believe that in aqueous media, above the critical aggregation concentration, these polymers self-assemble to form nanoparticles (such as polymer micelles) with an internal hydrophobic core and an external hydrophilic biocompatible coating. The hydrophobic core may solubilize poorly water-soluble drugs, while the hydrophilic crown isolates the encapsulated drug from the external environment, as shown schematically in Figure 1. The effect of pH, temperature, and the presence of serum proteins on the stability of nanoparticles will be determined. Our further efforts will focus on determining cytotoxicity of the HMGAG nanoparticles, as well as encapsulation efficiency of model bioactive substances in these structures. In our research, we plan to use various experimental methods as well as computer simulations. Therefore, our project should result in new polymer nanostructures that can effectively enclose and transport bioactive substances. In addition, based on computer simulations, we should gain insight into the organization and drug-loading capacity of the HMGAG nanoparticles at atomistic or molecular levels of detail.

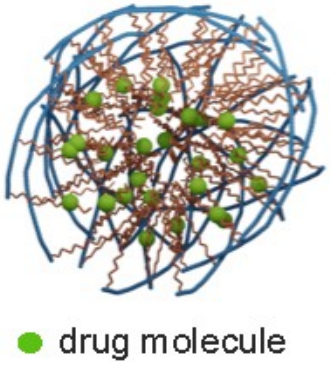

***Figure 1**. Illustration of nanoparticles made of hydrophobically modified glycosaminoglycans (GAGs) containing drug molecules.*

The results of this project are expected to contribute to better knowledge on the preparation of polymer nanostructures from hydrophobically modified polymers. The research will also help in a deeper understanding of the impact of the structure of these polymer (type and length of the hydrophobic moiety and degree of substitution) on interactions with biomembranes. Successful implementation of the project will also contribute to increase knowledge on the efficiency of accumulation of bioactive substances in polymer nanoparticles. This knowledge can be useful in developing new functional colloidal systems for biomedical, biotechnological and pharmacological applications (for example, controlled drug delivery systems).

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[3] S. Misra, V. C. Hascall, I. Atanelishvili, R. M. Rodriguez, R. R.Markwald, S. Ghatak, Int. J. Cell Biol. 2015, 537560.
[4] X. Yang, X. Shi, R. D'arcy, N. Tirelli, G. Zhai, J. Controlled Release 2018, 272, 114.