Novel core-shell micro-sized systems for macrophage-targeted drug delivery via phagocytosis

One of the main challenges of contemporary medicine and pharmaceutical sciences is therapy safety. Because of lack of selectivity in many cases systemic treatment leads to unpleasant and often serious side effects. In order to minimize risk of their occurrence, proper amount of active pharmaceutical ingredient should be delivered selectively to target cells and tissues. Latest discoveries in field of cytology and related pathophysiological processes allow identification of new potential drug delivery target cells and particular target macromolecules. Unquestionable progress was achieved in field of pathophysiology of diseases linked to macrophages – multifunctional subgroup of immune system cells. In the last decade various research groups identified macrophage phenotypes lined to obesity, fibrotic lung and renal diseases, electrical impulse conduction in heart and HIV infections. These discoveries are reflected in interest in drug delivery systems aiming macrophage subgroups, however proposed until now solutions are targeting wider macrophage populations. Project proposed by us aims to design micro-sized drug delivery systems capable to target narrow phenotypic subpopulations linked to particular diseases. Project idea is based on innate ability of macrophages to phagocyte foreign bodies such as bacteria or particles. Properly designed microspheres with active substance incorporated to polymer matrix will be enriched with ligand attractive to target cells. Proposed system is flexible; modification of parameters such as: size, drug type, coating composition, surface charge and ligand will allow designing carriers addressing different macrophage subsets. As a model system serving as proof of concept, we propose microspheres loaded with drugs exhibiting toxicity against macrophages – bisphosphonates. Such polymeric cores will be coated with polyelectrolyte multilayers and enriched with targeting ligands – ubiquitin, fractalkine and CD47 protein. Proposed drug delivery system is meant to aim alveolar macrophages subgroup linked to development of lung fibrosis in various diseases. This cell phenotype was identified by prof. Shizuo Akira group and independently by different research teams. Meticulous analysis of macrophage population inhabiting fibrotic lungs allowed identifying cells which elimination inhibits development of fibrotic changes. Thorough analysis of this phenotype surface protein expression allowed selecting potential targeting macromolecules – CXCR4, CX3CR1 and SIRP-α. Ligands immobilized on particle surface, due to high affinity to these receptors, will promote phagocytosis by cells exhibiting high surface expression. It will allow selective elimination of cells related to pathological process. Proposed system would be composed of four types of macromolecules organized in layered spherical structure (Fig. 1), carriers exhibiting promising parameters will be tested in vitro on model macrophage cell lines.

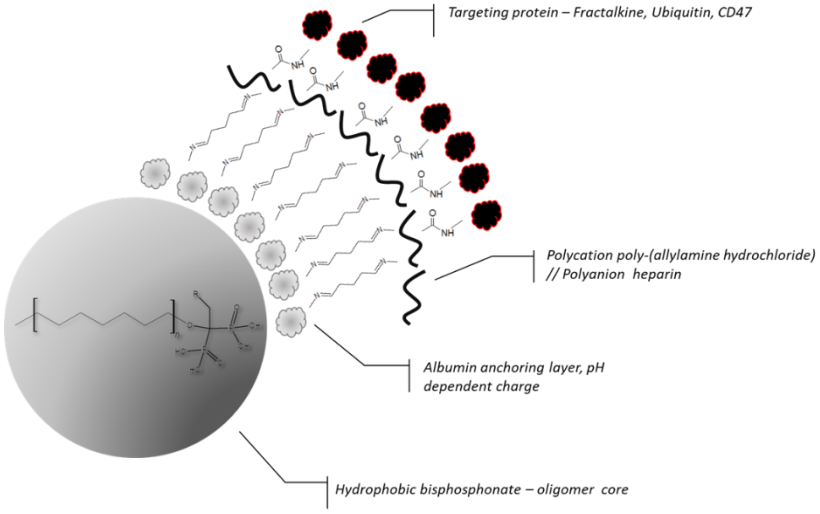

Figure 1 *Schematic representation of proposed microparticle drug delivery system*