

Cancer (neoplasm) is a collection of related diseases, which can be characterized by an uncontrolled growth of the cells in the human body and the ability of these cells to migrate from the original site and spread to distant sites (metastasize). Cancer is one of the biggest challenges in public health care and global economy, causing 8.2 million deaths (14 million new cases) and economic losses of around 1.16 trillion US dollars every year. Success in cancer control depends on effective diagnostics and efficiency of tumor treatment. Therefore, it is evident that special attention should be paid on approaches that allow simultaneously to detect and cure the tumor.

Such an opportunity can be found out within the realm of nanomedicine. Nanoparticles (NPs), as entities with the size of 1–100 nm, are attractive as imaging and therapeutic agents in oncology due to their unique physical and/or chemical properties. NPs, or in more general term, nanomaterials (NMs) play potentially the role of theranostic agents which could radically improve cancer diagnostics and serve as customizable therapeutic devices. Metal-based nanomaterials (MNMs) have gained significant attention in this group. Thanks to their unique material- and size-dependent physicochemical properties they can be applied for imaging, and more effective thermo- or radiotherapy of malignant tissues. MNMs have been proposed to improve drug (or gene) delivery during cancer treatment or to act as drugs themselves. Among MNMs, gold nanoparticles (GNPs) and nanorods (GNRs), as well as semiconductor quantum dots (QDs), hold a prominent place in enhancing the flexibility of theranostic action. Despite the fact, that theranostic MNMs are successively applied in in-vivo tests, till now their intracellular speciation is not known and metal species involved are not identified. Also, the role of the main low- and high-molecular-mass components of cancer cytosol in the speciation changes is not clarified. A better understanding of the mode of action of MNMs inside cancer cells could be a significant step to promote their approval for clinical trials. Furthermore, there is also an acute need to explain the effect of size, shape and surface modification of MNMs on their uptake, distribution pattern, and speciation inside the cell. Given such a knowledge attained, more effective theranostic MNMs can be designed.

The main goal of the proposed project is the development of advanced analytical methodology, with use of mass spectrometric techniques serving as detectors for capillary electrophoresis separation technique ? for preclinical characterization of theranostic metal-based nanomaterials with regard to cellular speciation. The obtained results will extend knowledge on vital biological processes in which these promising diagnostic and cancer treatment materials participate inside the cell. Due to premature status of combined mass-spectrometry-based techniques in the field of nanomedicine and, in particular, a lack of methodologically developed approaches to unambiguous screening of nanoparticle? biomolecule systems, the proposed project will be essentially original. The developed methodology and acquired information will not be commercially oriented and used. The elaborated methods and procedures will be applied to characterize the chemical processes and relevant metal forms, responsible for uptake, cancer cell distribution, and possibly targeting of the selected MNMs, depending on their size, shape, surface modification, as well as actual chemical form entering the cell. An insight into the mechanism of action of MNMs to be thus gained would facilitate and accelerate their preclinical development and help to discover more potent diagnostic and therapeutic MNMs.

Planned within the scope of the present project are five scientific tasks, which will be realized using mainly three analytical techniques: standalone ICP-MS (inductively coupled plasma mass spectrometry; following sample ultracentrifugation or target species isolation) – to quantify metal content in cells, cell compartments, and DNA conjugates; CE-ICP-MS (capillary electrophoresis hyphenated to ICP-MS) – to characterize the intracellular speciation of MNMs and to monitor its time-dependent changes; CE-ESI-MS/MS (CE coupled to electrospray tandem mass spectrometry) – to identify MNM species bound to cellular proteins using a shotgun metalloproteomic procedure. It should be emphasized that in all these studies, MNMs will be used in their original form but also as the protein-bound form dominating in blood serum.

Situation of the project on the intersection of chemistry, biology, and medicine makes it interesting from scientific as well as from practical points of view. CE-based hyphenated methods have never been applied to investigate such intricate and practically important subject as cellular processing of MNMs. To the best of our knowledge, CE-ESI-MS also will be for the first time used to analyze MNMs. Some of MNMs under scrutiny - differently surface-modified GNRs, also have never been tested at the level of cellular speciation. The results of the project fulfilment will significantly contribute to a better understanding of the mechanisms by which the selected MNMs express their theranostic functions.