

Development of cancer cells involves a few various pathways. One of them is infinite proliferative capacity being an effect of the enzyme telomerase and dysfunction of chromosome ends - telomeres. Human telomeres are composed of guanine rich and cytosine rich duplex with a characteristic single-stranded overhang of the guanine rich strand. The guanine rich strand can form a four-stranded G-quadruplex structure, and its complementary cytosine rich strand may adopt the so-called intercalated i-motif structures. Formation of i-motif within cytosine rich strand of telomere has been observed at reduced pH. In vitro studies suggest that formation of i-motif can indirectly facilitate formation of G-quadruplex and this leads to inhibition of telomerase activity. This, in turn, stops the infinite proliferation of cancer cells. Therefore, compounds which are able to inhibit telomerase activity are extensively studied as new anticancer drugs.

Carboxylated single-walled carbon nanotubes (that is carbon nanotubes with carboxyl groups attached to its surface) have been found as a unique moiety which can selectively stabilize human telomeric i-motif structure. Carbon nanotubes are unique structures revealing pipe-like shape with a hollow internal space. Due to interesting physicochemical properties they are studied, among the others, as drug delivery systems. Drug delivery systems are very useful as they allow to deliver active compounds directly to disease sites or to precisely release the drugs at those sites. Therefore, application of drug delivery system allows reduction of severe side effects and administration of smaller amounts of drugs but with the same or even enhanced effect.

It was demonstrated that stabilization of i-motif DNA by carboxylated carbon nanotubes can inhibit telomerase activity both in vitro and in vivo, and induced telomere uncapping and production of DNA-damage response and subsequent cell growth cessation. It is anticipated that carboxylated carbon nanotubes induce local pH reduction and this facilitates DNA duplex disassociation and i-motif formation. Because tumor microenvironment reveals a reduced pH due to hypoxia, it is supposed that other functionalized carbon nanotubes like aminated, hydroxylated, PEGylated or carrying nitrogenous bases can stabilize i-motifs formed spontaneously due to lowered pH. Furthermore, carbon nanotubes reveal empty internal space which can act as a carrier of small molecule drugs. Highly specific interaction with i-motif can be utilized as a trigger for drug release from the carbon nanotube interior precisely in cancer cells nuclei.

The studies will be based on application of molecular dynamics simulations. The method is based on construction of a model of a system of interest and analysis of its behavior using supercomputers. Such an approach can provide information about the nature of the nanotube-i-motif interaction and will lead to recognition of specific forces, responsible for its stability, acting in the nanotube-i-motif complex. Proper analysis of these forces and associated changes in the structure of the functionalized nanotubes can be utilized for triggering drugs release directly in cancer cells nuclei. Technical details of the assumed methodology include: application of the large scale massively parallel lammmps code, application of empirical force fields for description of the nanotube (ai-Rebo) and constituents of i-motif and drug molecules (Amber).

Outcomes of this project will provide molecular level understanding of the structure, mechanism of formation and thermodynamic stability of the nanotube-i-motif complex. Available literature data, concerning this important biological structure, suggest that the nanotube-i-motif is highly specific target to cancer cells. Therefore, its understanding and analysis, in reference to production of signals for drugs release, can be utilized in designing of highly selective multimodal drugs carriers to tumor sites.