Abstract

Cancers are a group of diseases which have diverse etiology, course and prognosis. They are one of the leading causes of death in developed countries. In addition cancer progression is the source of burdensome symptoms for oncologic patients resulting in significant decrease of quality of their life. Considering the plethora of molecular mechanisms leading to cancer development the course of the disease is often difficult to predict and outcomes of treatment are disappointing. Moreover, a dozen of available forms of cancer treatment are associated with significant adverse effects on patients health and general condition. Another important aspect is the limitation of therapy efficacy caused by the side effects. To overcome the crucial limitations of cancer treatment a novel methods of therapy are developed. The main concept of modern forms of treatment is the personalization of therapeutic strategies. The point of such solution is to match the drug of specific mechanism of action to the adequate phenotype of cancer. Mentioned personalization could be acquired by utilizing drugs selectively affecting the molecular pathways crucial for cancer development, drug conjugation with antibodies specific to cancer antigens or by nanoparticle based drug delivery (drug delivery systems – DDS). DDS could be further modified by addition of ligands for specific receptors or transporters overexpressed by cancer cells to obtain enhanced drug activity with simultaneous higher selectivity. Another tested solution to achieve mentioned properties is utilization of pH cleavable bonds for drugs conjugation to DDS.

The aim of articles from the presented series of publications was to utilize modified PAMAM (polyamidoamine) dendrimers as the carriers for anticancer one – drug or multi – drug combinations consisted of drugs of different mechanisms of action. Dendrimers were modified by functionalization of terminal amide groups with polyhydroxyl alcohols and/or biotin. The rationale of such modifications was to increase water solubility of dendrimer – drug conjugates and also to obtain higher selectivity of conjugates uptake by cancer cells. Drugs were covalently attached to dendrimers as a result of different pathways of syntheses which are described in the main part of the text. In one of the articles the novel path of conjugation by pH cleavable phosphoroamide bond was presented. Obtained conjugates were tested on cellular models (in vitro) to determine their biological activity. The results of biological tests indicate that dendrimers functionalized by polyhydroxyl substituents and/or biotin (as DDS) contributed to enhancement of anticancer effect of the conjugated drugs and drugs combinations. It was also proved that conjugation of two drugs of different mechanisms of action to such modified PAMAM lead to addition in their anticancer activity. Moreover, it was shown that the mixture

of one drug conjugates (each with different drug) at specific stoichiometry provided selectivity in inhibition of cancer cells proliferation (metabolic activity). Finally the novel strategy of conjugation using phosphoroamide bond was proved as a tool for obtainment of conjugates which composition is stable in neutral pH while drug release (from conjugates) is induced by acidic environment.

The results obtained in the series of presented articles could provide novel useful solutions for development of efficient and selective therapeutics for cancer treatment.