

Platinum nanoparticles and anticancer drugs – analysis of interactions and biological activity

mgr Marcin Zakrzewski

Cancer is one of the most dangerous diseases of the 21st century. In 2022 alone, almost 20 million new cases were diagnosed worldwide, while approximately 10 million cancer-related deaths were recorded. Moreover, the global cancer burden is projected to further increase, reaching nearly 35 million yearly diagnoses by 2050, irrespective of the country's human development index (HDI). Although therapeutic approaches have significantly advanced over the years, chemotherapy still remains one of the most widely applied treatment regimens. In spite of its efficacy, it is not indifferent to normal cells, resulting in damage to healthy tissues and adverse effects, some of which as severe as gastrointestinal toxicity, myelosuppression, or cardiotoxicity. In addition to that, prolonged treatment frequently leads to the development of drug resistance, reducing therapeutic effectiveness. Therefore, the search for modulatory agents that would improve the efficacy and/or selectivity of anticancer agents is of considerable importance. Among the proposed modulatory candidates are nanoparticles, which, by definition, are small particles sized between 1 and 100 nm. Due to their physicochemical properties, including a variety of sizes, shapes, compositions, and possible surface functionalisation, nanoparticles have been studied in numerous scientific fields. Besides their intrinsic cytotoxicity towards cancer cells, they have demonstrated a significant potential as modulators of anticancer drug activity, as well as components of drug delivery systems, the design of which is to improve treatment selectivity and efficacy.

The primary aim of this doctoral dissertation was to evaluate if platinum nanoparticles (PtNPs) of distinct diameters, namely 5, 30, 50, and 70 nm, interact with three anticancer agents: daunorubicin (DAU) and idarubicin (IDA), both belonging to the anthracycline antibiotics group, and mitomycin C (MMC), an alkylating antibiotic. The additional aim of these studies was to determine whether such interactions influence the biological activity of the investigated active pharmaceutical ingredients (API). To address these objectives, a combination of physicochemical and biological methods was employed. The physicochemical characterisation methods included fluorescence, Fourier-Transform Infrared (FTIR), and Near-Infrared (NIR) spectroscopies, as well as isothermal titration calorimetry (ITC) and differential scanning calorimetry (DSC). Furthermore, particle size and aggregation patterns were assessed using dynamic light scattering (DLS), nanoparticle tracking analysis (NTA), and atomic force microscopy (AFM). The biological activity was evaluated using the Ames mutagenicity assay with *Salmonella enterica* serovar Typhimurium strains TA98 or TA102 to assess the influence of PtNPs on the mutagenic potential of DAU, IDA, and MMC, as well as cytotoxicity studies. The latter consisted of in vitro analyses using two models: comparison between cancerous MelJuSo and non-cancerous HaCaT cells for the PtNPs-DAU study, and comparison between two breast cancer cell lines, namely SK-BR-3 and MCF-7, for PtNPs-IDA and PtNPs-MMC studies.

The results of all these studies demonstrated that PtNPs interact with all three investigated antineoplastic agents, although the extent and nature of these interactions differed between the compounds. Thermodynamic analyses indicated predominantly endothermic interactions that were most likely driven by favourable entropy changes. Spectroscopic analyses further confirmed changes in the chemical environment of the investigated compounds following combination with PtNPs, while fluorescence quenching indicated close-proximity interactions for the PtNPs-anthracyclines combinations. Importantly, the registered interactions influenced the biological activity of the compounds, generally resulting in a reduced mutagenic potential of the combined APIs, and, in several experimental systems, enhanced cytotoxic effects towards cancer cells. However, the magnitude and direction of these effects varied depending on the drug, nanoparticle sizes, and the concentration of both.

Overall, the findings presented in this dissertation demonstrate that platinum nanoparticles constitute an interesting and promising platform for the modulation of anticancer drug activity and may serve as a basis for the development of nanoparticle-assisted therapeutic strategies.