Design and development of novel nanoformulation-based delivery systems for the prevention and the treatment of challenging pathological conditions

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In the last decades, nanoformulation-based tools started to draw attention as novel entities in diagnostic and therapeutic fields. Nanomedicine has become an important key to overcome and solve intricate medical limitations (1). The challenge to design and develop new nanodelivery systems was faced in this doctoral project. In particular, two main topics were investigated: tissue hypoxia and drug resistance. The aim of the first topic was to develop nanoformulations suitable for the delivery of oxygen in a controlled manner. Notably, hypoxic tumors are more resistant to chemotherapy and radiation. In particular, the pancreatic tumor is an aggressive type of cancer in which the microenviroment is extremely hypoxic and the cells become easily resistant to drugs. For this purpose, core-shell nanobubbles were designed for the supply of oxygen, drugs and adjuvant agents to the tumor site. Novel nanobubble formulations were developed to combine oxygen, Gemcitabine as chemotherapy and Curcumin as a modulator of overexpressed efflux pump proteins (P-glycoprotein) in resistant cancer cells. The synergistic effect of Oxygen-loaded nanobubbles carrying Gemcitabine and Curcumin may represent an interesting platform to overcome current drawbacks with the present treatment of pancreatic cancer (2). In addition, for preventing metastatic spreading in prostate cancer cells, Curcuminoid-loaded in dextran-shelled nanobubbles were prepared as adjuvant theranostic tools. Indeed, Curcuminoids were released with a prolonged in vitro kinetics and the nanobubbles prevented their degradation. Additionally, nanobubble echogenic properties can be visualized by ultrasound imaging **(3).** On the other hand, resistance to chemotherapy is a major problem that limits the effectiveness of successful treatment of cancer. Albumin-based Doxorubicin-loaded nanoparticles were prepared to provide controlled release of the drug, to reduce the toxicity due to side effects and to overcome the resistance. They showed a significant viability and proliferation inhibition on cancer cell lines resistant for Doxorubicin, representing a promising platform for increasing the efficacy of chemotherapy (4). Finally, hypoxia-sensitive liposomes were studied for co-delivery of siRNA and Paclitaxel specifically targeting hypoxic areas. The synergic effect of the silencing of P-glycoprotein with the siRNA and chemotherapy could potentially offer a novel and effective treatment for patients who have established multidrug resistance (5). In conclusion, the study of several nanoplatforms was conducted with the aim to overcome therapeutic limitations and enhancing the successful of the treatment of different pathological conditions.

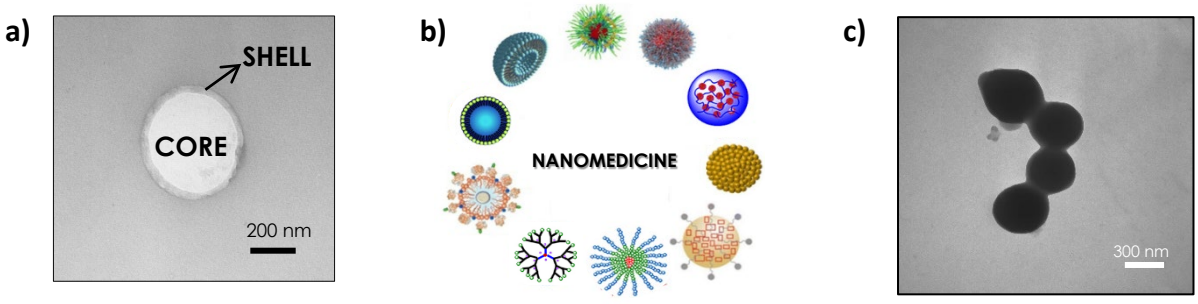

FIGURE. A) TEM IMAGE OF OXYGEN-LOADED NANOBUBBLES; B) REPRESENTATION OF DIFFERENT NANODELIVERY SYSTEMS; C) TEM IMAGE OF Albumin-based Doxorubicin-loaded nanoparticles.

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