OIL CORE- FUNCTIONALIZED GRAPHENE OXIDE SHELL AS MULTIFUNCTIONAL THERANOSTIC NANOTOOL FOR CANCER THERAPY

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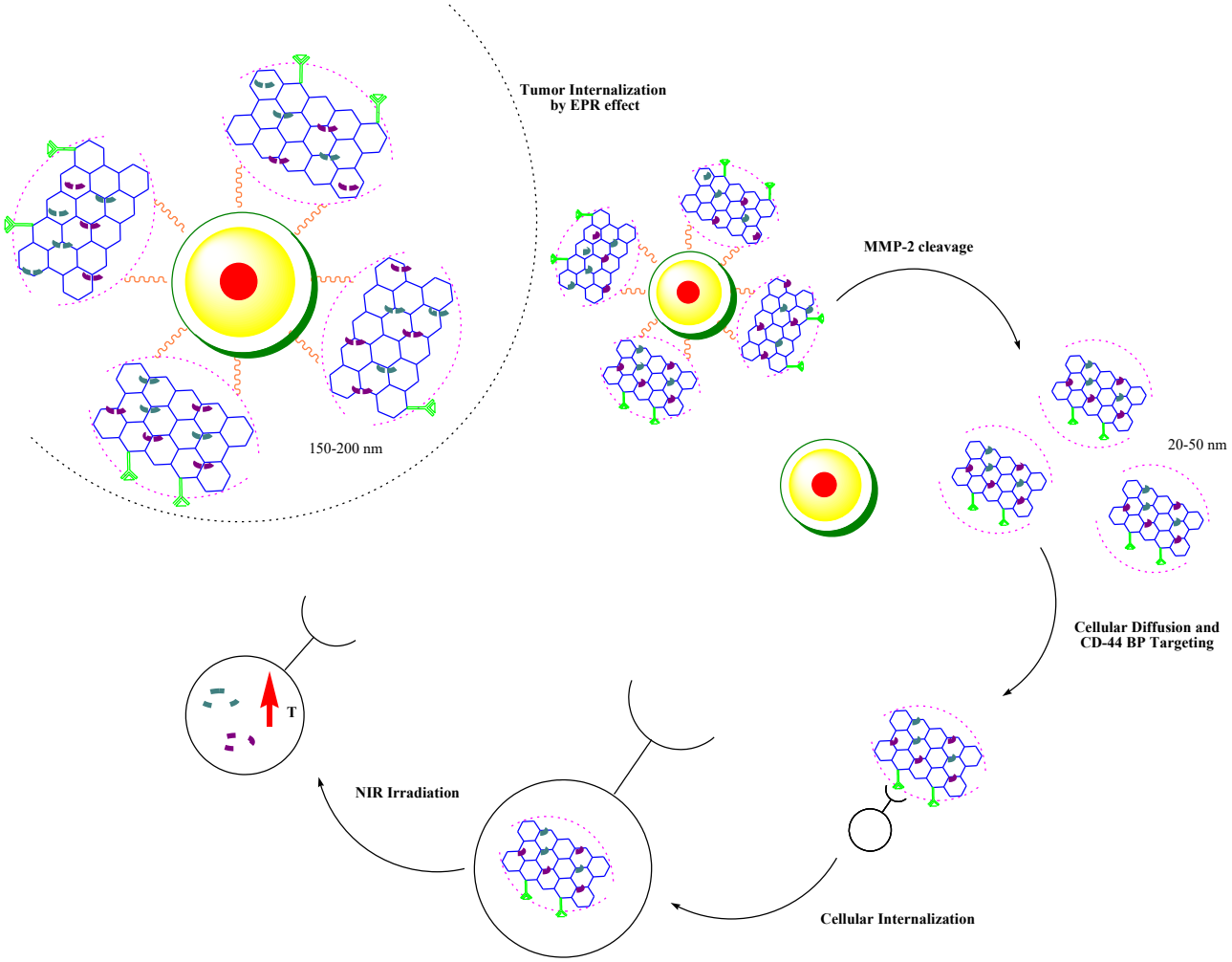
Despite considerable progress in the comprehension of the mechanisms involved in the origin and development of cancer, with improved diagnosis and treatment, this disease remains a major public health challenge with a considerable impact on the social and economic system, as well as on the individual. One way to improve effectiveness and reduce side effects is to consider responsive stimuli delivery systems that provide tailor-made release profiles with excellent spatial and temporal control. 2D nanomaterials possess special physicochemical properties (e.g. light, ultrasonic and magnetic responses) and biological behaviors such as endocytosis, biodistribution, biodegradation, and excretory pathways, which lead to their use in various biomedical applications. In particular, among 2D nanomaterials, graphene and its derivatives, have attracted enormous attention in cancer diagnosis and therapy because they combine, in a unique material, extremely small size, NIR absorption, delocalized electrons, extremely high surface area, and versatile surface functionality. Graphene is an allotropic form of carbon defined as a single layer (monolayer) of carbon atoms sp^2-bounded, which are densely packed in a hexagonal honeycomb lattice. In the original study of Novoselon et al., single or a few layers of pristine graphene were obtained with the "scotch tape" method of mechanical exfoliation of the graphite using adhesive tape. However, this method is not scalable, and therefore other approaches have been proposed, including chemical vapor deposition, arc discharge, and epitaxial growth on SiC. To date, the most widely used method when large scale graphene production is required, is the wet chemical exfoliation of graphite. To break the interactions that hold together the graphene layers in the graphite, intense oxidation of the aromatic system is necessary. The oxidation generates an intermediate, known as graphite oxide with a high density of oxygenated functional groups and which is then transformed into reduced graphene oxide by chemical or electrochemical reduction. Graphite oxide, obtained from the oxidation of graphite, can be exfoliated in solution to form graphene oxide (monolayer) (GO), or partially exfoliated to form few-layers graphene oxide. GO, initially considered as an intermediate of one of the graphene production processes, has become a material that can be considered both for fundamental research and for its potential applications. The simple, scalable, and economical production process, coupled with the peculiar chemical-physical characteristics, make GO one of the most promising nanomaterials in several fields and, notably, in the cross-section of nanotechnology and biotechnology. GO is a single or a few-layer material with a high oxygen content, typically characterized by atomic C / O ratios below 3.0 and generally closer to 2.0. Unlike the perfectly ordered crystalline structure of graphene, GO has a two-dimensional structure in which crystalline regions and regions with amorphous defects of sp^2/sp^3 hybridized carbons and functional groups containing oxygen, coexist. The different oxygenated functions located on one or both sides of the GO sheet, make this material soluble and dispersible in water and in many organic solvents and make the surface of GO very versatile for functionalization or chemical changes to finely modify its properties or to increase biocompatibility. The aromatic structure instead allows noncovalent interaction with π conjugated molecules and confers to the GO the ability to absorb light in the range of NIR (700-900 nm). This property is particularly interesting when considering cellular hyperthermia in the treatment of tumors as a minimally invasive alternative to surgery. Furthermore, functionalized graphene oxide and nanocomposites based on GO have interesting optical and magnetic properties and can be employed as contrast agents for various biological imaging modalities including fluorescence imaging, photoacoustic imaging, and magnetic resonance imaging.

This thesis aims to develop a multifunctional nanocomposite based on nano-graphene oxide (nGO) sheets and oil/water nanoemulsions (O/W NEs) coated with a shell of biodegradable polymers, for tumor theranostics, integrating selective targeting with combined chemo/photothermal therapy (PTT) and photoacoustic (PA)/magnetic (MRI) imaging. In this complex theranostic platform, nGO acts as a drug delivery system, photothermal agent, and contrast agent for photoacoustic imaging, while the O/E nanoemulsion has the dual role of improving the bioavailability of nGO and transporting the magnetic contrast agent as well as a possible anti-oxidant agent to protect healthy tissues from the anti-cancer treatment. The approach we aim to explore is a multistage approach whereby the complete platform should have the potential to remain relatively stable during blood circulation after intravenous injection and then accumulate in tumor tissues through a passive targeting mechanism based on the enhanced permeability and retention effect (EPR).

Accumulation in the tumor tissue should be verified by the magnetic signal of the contrast agent loaded in the nanoemulsion. The cleavage of the metalloproteinase-sensitive linker will result in the release of the smaller nanocarrier of graphene oxide, which, upon increasing diffusion thus, tissue penetration, will accumulate to the target tumor cells thanks to the implementation of an active targeting logic promoted by the functionalization with an active targeting peptide. After internalization into the tumor cells, verified by the photoacoustic signal of the graphene oxide, irradiation with 808 nm laser should trigger the release of the drug and local heat eventually leading to highly efficient cell death via the combination of chemotherapy and PTT therapy.



During the first year of the thesis, the activity was mainly focused on the study of literature to obtain information on synthesis and characterization of GO, and the main chemical-physical properties. In the second year, the synthesis of graphene oxide was optimized and a lot of effort was devoted to the research of an effective method in the reduction of lateral dimensions. For applications in nanomedicine it is essential to obtain GO sheets with narrow lateral distribution and lateral dimensions below 50 nm. At the same time, a new, biodegradable and oil-soluble contrast agent, Iron (III) oleate was synthesized and loading and stability in O/W emulsions coated with biodegradable polymers have been evaluated. In the third year, the ongoing activities regard the coating of nGO with an antifouling polysaccharide, namely hyaluronic acid, and its deposition around oil in water nanoemulsions as well as the implementations of the functional peptides and the physico-chemical and biological characterization of the nGO and oil core-nGO shell complete nanocarrier.

References:

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