Abstract

This work investigates new frontiers in Nanomedicine to overcome tumor heterogeneity by developing traceable theranostic platforms that can distribute site-specifically in areas of interest. This study was made possible due to the close collaboration between Politecnico di Torino, Turin, Italy, and the Department of Nanomedicine at the Houston Methodist Research Institute, Houston, Texas.

To date, heterogeneous distribution of drugs or treatment modalities within the tumor mass has been a crucial limiting factor for a vast range of theranostic applications. Understanding the interactions between a nanomaterial and the tumor microenvironment would help to overcome the challenges associated with poor distribution due to tumor heterogeneity as well as the clinical translation of nanotheranostic materials. The delivery of small molecules and anticancer agents to specific regions within solid tumors is limited by penetration depth and poor spatial drug distribution, hindering efficacy. Another major issue is biofouling, the unwanted adsorption of cells, proteins, or intracellular and extracellular bio-molecules that can spontaneously occur on metal nano-complexes. This phenomenon leads to a protein corona and destabilizes a colloidal solution, resulting in undesired macrophage-driven clearance, and consequently causing failed delivery of a targeted drug cargo.

In this thesis, surface passivation of metal nanomaterials, such as Gold Nanoparticles (GNPs), with various chemical functionalities results in observed behavioral differences in cellular uptake and intratumoral distribution. We show that when the nanoparticle surface chemistry is altered, dramatic changes occur in their penetration and localization in heterogenous solid tumors. Gold nanoparticles were synthesized, passivated with different molecules, and administered in vitro and in in vivo models of Non-Small Cells Lung Cancer. The main result and contribution of this work is that GNP surface passivation affects nanoparticle transport behavior within the cellular and tumor microenvironment. Controlled delivery of GNPs passivated with different surface chemistries resulted in differences in intratumoral distribution as well as zonal delivery within the tumor. These results are useful for directing anticancer therapies to regions of biomarker overexpression.

We found changes in the surface functionalization of gold nanomaterials can alter their cytotoxicity or improve their biocompatibility. For instance, gold nanorods (GNRs), nanoparticles with tunable light absorption properties, have a controversial safety profile, limiting their clinical translation due to surfactant stabilization during synthesis. We explored changing the charge of the surfactant used to stabilize the GNRs, and the resulting effects on lung and cervical cancer cell viability. Altering the GNR surface charge using an anionic surfactant improved cell survival and reduced cytotoxicity when compared to cationic surfactants. Changing the surfactant net charge resulted in significant dose-dependent as well as time-dependent effects of nanorod treatment on cell viability.

Finally, plasmonic silica-gold core-shell nanoparticles, known as gold nanoshells (GNS) were investigated for their photothermal properties. We tested the ability of GNS to generate heat and create ablation lesions due to light excitation. GNS can be synthesized to exhibit strong optical resonances across the electromagnetic spectrum depending on their core-to-shell ratio. This optical absorption can be tuned to longer wavelengths, such as the near infrared. Importantly, as the particles are gold-coated, they are resistant to oxidation and remain biocompatible, allowing for their use clinically. Here, we show that light exposure of near-infrared sensitive (NIRS) gold nanoshells to their resonant wavelength (808 nm) reveals local heating to temperatures greater than 50 ºC, inducing cell death. Further, we show that under continuous exposure to light for over 1000 seconds, temperatures between 50-60 ºC can be maintained without continued rise. These results indicate the possibility to create photothermal ablation lesions via nanoparticle-induced heating in deep regions of target tissue.

Overall, the work presented in this thesis demonstrates that modifying the GNP surface chemistry changes their physicochemical properties, which can be exploited to enhance nanoparticle biodistribution in heterogeneous tissues, thereby making GNPs versatile and valuable tools for biomedical applications.