Medical imaging is critical for cancer screening, diagnosis, preoperative planning, and monitoring progression or treatment. Computed tomography (CT) is the first-line imaging modality for diagnostic imaging due to its low cost, wide availability, and high spatiotemporal resolution for anatomic imaging. Image contrast in CT is derived from differences in the X-ray attenuation of tissues. The primary limitations of CT are relatively low soft tissue contrast and sensitivity (10⁻¹⁻¹⁰² M), but contrast agents, such as iodine, can improve the detection of soft tissues with similar attenuation by increasing the signal-to-noise ratio without increasing the radiation dose to the patient. Nanoparticle (NP) contrast agents can enable delivery of a greater mass concentration of the X-ray attenuating element per particle or molecule compared with molecular agents (i.e., iodine) and leverage absorption edges located near the mean photon energy of the photon energy spectrum in clinical CT systems. Therefore, the overall objective of this research was to investigate novel NP imaging probes for immunotargeting cancer cells and maximizing X-ray contrast in CT. Immunotargeted gold nanoparticles (Au@SiO₂-anti-HER2 NPs) exhibited specific binding to HER2+ cells and enabled contrast-enhanced detection of model HER2+ breast cancer tumors as small as 1·10⁵ cells (1 mm diameter). Moreover, photon-counting spectral CT enabled quantitative molecular imaging rather than only grayscale contrast in conventional CT. Hafnium oxide (HfO₂) NPs of controlled size were prepared by a sol-gel process to investigate the interaction of HfO₂ NPs with X-ray and mid-infrared radiation to assess potential as a multifunctional diagnostic probe for X-ray CT and mid-infrared biosensing, respectively. HfO₂ NPs exhibited superior or similar X-ray contrast compared to Au NPs, while both exhibited significantly greater X-ray contrast compared to iodine, due to the favorable location of the K-shell absorption edge for hafnium and gold. HfO₂ NPs also exhibited strong mid-infrared absorption and negative permittivity, which can support localized surface phonon polariton modes at several
frequencies and suggests potential as a mid-infrared biosensor. HfO$_2$ NPs were also prepared by hydrothermal syntheses to produce monodispersed, water-dispersible NPs at relatively low temperature and high yield. HfO$_2$ NPs, ~90 nm in diameter and colloidally stable in cell culture media for up to 10 days, were not cytotoxic to HeLa and THP-1 cells at up to 0.8 mg/mL concentration and were successfully taken up in endosomes as early as 4 hours. However, further improvements in the size and morphology of hydrothermally-derived HfO$_2$ NPs were desired for *in vivo* delivery. Therefore, the effects of adding a capping agent either before or after precursor hydrolysis and condensation, reactant concentration, reaction temperature, reaction time, capping agent, capping agent concentration, mineralizer concentration, and gadolinium dopant concentration were investigated on the size and morphology of as-prepared HfO$_2$ NPs. Spherical HfO$_2$ NPs, ~4-6 nm in diameter, were prepared using a gadolinium dopant and sodium oleate capping agent. In summary, immunotargeted Au@SiO$_2$-anti-HER2 NPs and HfO$_2$ NPs exhibited advantageous properties for potential use as novel X-ray contrast agents in diagnostic imaging.