Abstract of Doctoral Dissertation

Degree requested Doctor of Soft Matter Science Applicant's name Mba Joshua Chidiebere

Title of Doctoral Dissertation

Development of thermo-responsive gold nanodiscs for a novel plasmonic photothermal cancer therapy
（プラズモンの光熱変換機能を利用した新奇ガン治療を可能にする温度応答性ディスク状金ナノ粒子の開発）

Cancer is one of the leading causes of death across the globe due to its diversity, heterogeneity, and complexity. To curb this menace, the need for effective cancer therapies has been at the forefront of scientific research for decades. Conventional methods of cancer therapy, such as surgery, chemotherapy, and radiotherapy are limited by the invasive nature, multidrug resistance, and selectivity issues, respectively. To solve these, gold nanoparticles` (AuNPs) biocompatibility, small size to penetrate tumors, and their ability to absorb and convert light to heat have been exploited for effective cancer therapy, known as plasmonic photothermal cancer therapy (PPTT). Here, cancer cells are killed by hyperthermia resulting from the heated AuNPs in the surrounding environment. Nevertheless, the activation of heat-shock response and inevitable damage to peripheral healthy tissues by higher temperatures above 50 ºC limit the use of this modality. There is need therefore for new cancer treatment strategy while exploiting the merits of the non-invasive and spatiotemporal selective photothermal cancer therapy.

Recent advances in the development of stimuli responsive nanoparticles have led to seamless design of functional materials with the ability to respond to the stimuli, often resulting in assembled and disassembled states. These self-assembled nanostructures with enhanced functions have emerged as efficient tools with countless list of uses. Particularly, thermo-responsive gold nanospheres, nanorods etc have been reported. Furthermore, anisotropic AuNPs like the nano rods, stars and triangles with sharp edges are useful for incorporation and intracellular delivery of AuNPs into cells for diverse bioapplications. However, another fascinating type of anisotropic gold nanoparticle is the gold nanodiscs (AuNDs). AuNDs is an attractive nanoparticle because of its large flat surfaces, dipolar plasmon modes and responsiveness to random incident light among others. Like other anisotropic AuNPs, AuNDs have the potentials for the fabrication of nanophotonic devices, new and smart optoelectronic nanodevices, metamaterials, and use in surface enhanced Raman spectroscopy (SERS) etc. Their atomically large flat surfaces promise better interaction ability for extracellular attachment to cells for diverse bioapplications. Additionally, the dipolar plasmon mode of AuNDs has the potential to offer unique plasmon coupling not seen in other shapes of AuNPs on assembly. The capability of

reversibly controlling nanoparticle assemblies with external stimuli have enabled dynamic tunable plasmon coupling for advanced applications. AuNDs` responsiveness to incident random light, and tunable ratio to light absorption and scattering make them strong candidate for preparation of plasmonic nanoassemblies for emerging functionalities when coated with stimuli-responsive ligands. In the light of the foregoing, controlled assembled functional architectures of AuNDs have the possibility to open endless range of applications in the fields of material science, chemistry, biology, and nanomedicine. Yet, up to the present, AuNDs are insufficiently represented in studies like other shapes of AuNPs despite their unique properties and inherent optical merits. There is therefore the need for fundamental and applied studies of AuNDs for use as active plasmonics for prospective aaplications. This study therefore is aimed to investigate the self-assemblies of circular plasmonic AuNDs to uncover the thermal behaviour of such circular plasmon-coupled systems for biomedical uses.

To mitigate the demerits of the current PPTT, a new nanoplatform with solutions is highly desirable. Previously, the thermo-responsive assembly of AuNPs based on hydrophobic interactions due to the dehydration of the ethylene glycol parts of a thermo-responsive ligand on heating was reported. Additionally, there is report on near infrared photoimmunotherapy where a photo induced ligand release from monoclonal antibodies resulted in a series of outcomes that led to the killing of cancer cells via membrane perturbation. Building on these, I proposed a novel PPTT strategy for cancer treatment using AuNDs functionalized with the thermo-responsive ligand as previously reported. This study was designed to exploit the hydrophobic interactions between the self-assembled AuNDs and cell membrane to cause membrane perturbation and consequent cancer cell death upon mild (LED) light irradiation. The postulation is that the perturbation of the cell membranes and the consequential disruption of the cell membrane by the resultant hydrophobic interactions between the assembled system and cancer cells will induce their death. This novel low temperature cancer therapy is poised to solve the problems of PPTT and offer new a way of cancer cell death via membrane perturbation due to hydrophobic interactions between the cell membrane`s biomolecules and the hydrophobic nanoplatform upon assembly.

Summarily, upon heating, the temperature stimulus caused a blue shift of the plasmon peak to form a face-to-face assembly of AuNDs due to the strong hydrophobic and van der Waals interactions between their large flat surfaces. The nanoplatform showed unique thermo-responsive and thermo-dynamic behaviours on heating. AuNDs exhibited rate-independent hysteresis from different thermo-dynamic processes, including strong van der Waals interactions, hydrogen bonding etc. The results of the photothermal conversion efficiency investigated with both gold nanorods and nanodiscs demonstrated an effective photothermal conversion efficacy suitable for the novel photothermal cancer therapy strategy. The nanoplatform demonstrated good therapeutic effects against cancer cells upon mild light irradiation and highlighted the potentials of this system as a new panacea for cancer.