Research Proposal

"Cancer therapy using active delivery of gold nanoparticles"

Cancer is the second leading cause of human death with more than 10 million new cases every year. Generally, any malignant growth or tumor from an abnormal and uncontrolled division of body cells is named cancer. Cancers are traditionally treated with surgery, radiation, and chemotherapy. Each of these approaches bears the risk of killing normal cells or fatally damaging healthy tissue. Hence, treatment options are limited, and accurate diagnosis and prognosis is difficult in many cases. Moreover, because of the very painful nature of these treatments patients at times decline to go for such therapies.

In cancer treatment, the goal is to stop cancer cells from proliferating. Currently, most of anti-cancer drugs work at least partly in this way. Unfortunately, they also affect some normal cells causing severe side effects. Cytotoxic medicines are toxic to normal cells. They all tend to work by interfering with some aspect of how the cells divide and multiply. For example, some work by affecting the genetic material of the cell directly; others work by blocking cells from using nutrients needed to divide and multiply. There are many different cytotoxic medicines used in the treatment of cancer. In each case the one (or ones) chosen will depend on the type and stage of cancer.

Cytotoxic medicines work effectively in cases where the cancer cells are rapidly dividing and multiplying. Most normal cells in the body, such as muscle cells, heart cells, brain cells, and bone cells, do not divide and multiply very often. They are not usually much affected by cytotoxic medicines. However, some normal cells in the body divide and multiply quite rapidly. For example, hair cells, bone marrow cells, and cells lining the mouth and gut. These may be affected by cytotoxic medicines and lead to side effects.

Nowadays all challenges are toward finding some ways to kill cancer cells specifically. Therefore it is interesting to produce some systems for killing cancer cells without using any drug or chemical agents causing some side effects in normal cells. Nanotechnology, an emerging interdisciplinary research field, has great potential to offer new methods to avoid making the side effects. Potential benefits of nanomaterials are well recognized in the literature and some commentators argue. In medicine, most interest is in the use of nanoparticles to enhance drug delivery with interest also in in-vitro diagnostics, novel biomaterial design, bioimaging, therapies and active implants. With their unique optical, thermal, and electromagnetic properties, nanoparticles-biomaterial composites have tremendous potential in novel methods for detection, characterization, and therapy of cancer. Carbon nanotubes, gold nanoparticles (GNPs) and cadmium selenide quantum dots have been studied more in this area. Nanoparticles have emerged as novel therapeutic modalities for cancer treatment while minimizing effects on safe tissues, avoiding the traditional ravishing effects of cancer drugs, higher payload capacity, prolonged blood circulation times, reduced cytotoxicity to healthy tissues, improved antitumor efficiency, and entry into cells.

The aim of this project is to explore a strategy that does not use cytotoxic agents to stop cancer cells from proliferation. The project will develop a strategy for the directed association of nano-particles to mechanically activate processes that will cause the cancer cells to be isolated from their apoptotic signals and therefore rendered incapable of reproduction.

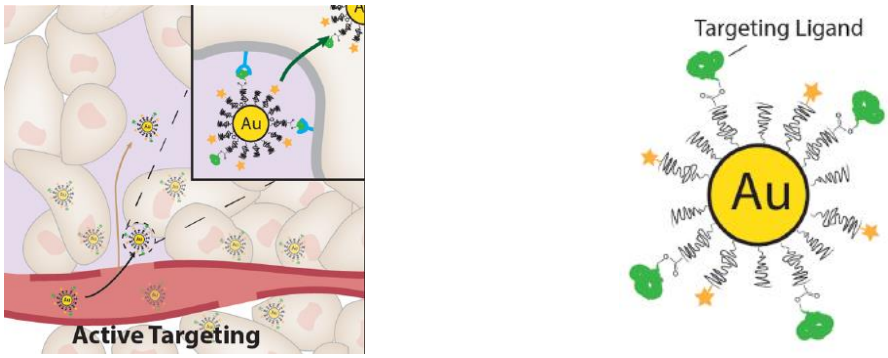
Actively delivering nanoparticles to cancer cells (in particular, orthotopic melanoma tumors) would be studied. Active targeting exploits the overexpression of surface receptors on cancer cells by providing targeting ligands that can engage these receptors. Ligand incorporation facilitates the entry of nanoparticles to cancer cells via receptor-mediated endocytosis, after which they can release their drug payloads to provide a therapeutic action. Previous research on active targeting has used an assortment of ligands ranging from proteins (antibodies and their molecular fragments), small molecules (vitamins, peptides, or carbohydrates), and nucleic acids (aptamers). The size of nanoparticles must be efficiently suitable in diameter to move away from the vasculature and throughout the tumor. This condition is necessary for engaging cancer cell surface receptors and attacking molecular targets within cancer cells.

GNPs would be chosen in this study for their broad use in nano-medical research. GNPs can be easily and stably surface-modified via thiol-metal chemistry. They are also biologically inert, and non-toxic and can be

accurately synthesized with different shapes and sizes ranging from 3 to 200 nm. GNPs are not susceptible to photo-bleaching and they appear biocompatible and non-cytotoxic, as supported by recent experiments on human cells. Gold has a low level of in vivo toxicity, and scalable synthesis of GNPs with tunable dimensions is straightforward. With the "silver enhancement" method, GNPs catalyze the selective surface deposition of metallic silver, enabling their visualization as size-enhanced entities in tissue sections under light microscopy. Additionally, the high electron density of GNPs permits the direct visualization of their cellular localization with transmission electron microscopy. The combination of these imaging methods, when used together with inductively coupled plasmonic mass spectrometry (ICP-MS) that can be employed to measure organ-level gold content, renders GNPs a versatile imaging platform for the top-down elucidation of the nanoparticle biodistribution on organ, tissue, and sub/cellular levels.

GNPs with different core diameters would be prepared for active targeting by surface modification with either PEG or PEG in conjunction with OPSS-modified transferrin. The addition of surface ligands increases GNP hydrodynamic diameters.

Figure 1 shows the mechanism of targeting orthotopic melanoma tumors using active GNP which would be employed in this project. Systemically circulating nanoparticles enter the tumor space through leaky blood vessels and may sequester in cancer cells (beige) or vascular pools (purple) of the interstitial matrix. Inset demonstrates that active particles are capable of endocytosis through surface-bound targeting ligands (green).



(a) (b)

Figure 1. Illustration of the proposed mechanism for a) active gold nanoparticle tumor targeting would be exploited in this study, and b) Model nanoparticle designs would be used in this study.

This project will focus on GNPs as promising novel agents for cancer therapy. The use of non-toxic and biocompatible nanoparticle-capping materials is nevertheless crucial for medical applications. The therapeutic agents will be tested *in vitro* on a range of cancer cells incubated under standard conditions.