Development and Application of Gold-lipidic Nanocomposites to Enhance Chemotherapeutic Delivery and Release

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Liposomal drug carriers are nano-scale, spherical particles with a phospholipid bilayer surrounding an aqueous core and are commonly used for chemotherapeutic delivery. Chemotherapy efficacy is limited by toxicity and tumor drug resistance; however, with increased circulation and improved tumor deposition due to the enhanced permeability and retention effect, liposomes increase treatment efficacy and reduce toxicity. However, the chemistry of many efficacious chemotherapeutics prevents their encapsulation within liposomes and poses a challenge for formulating treatments. To respond to this challenge, current drug research is aimed at the development of improved drug delivery technologies, particularly those carriers capable of multi-drug or component delivery because of their flexibility and high applicability.

I hypothesized that composite systems, gold nanoparticles within liposomes, may be used to improve drug delivery of both currently used therapeutics and ones traditionally incompatible with liposomal delivery. I formulated a novel gold-lipidic nanocomposite to capitalize on the drug delivery capabilities of liposomes and the facile conjugation of gold nanoparticles. I proposed new techniques for the formulation of nanocomposites comprised of 2 mm gold clusters capped with glutathione or mercaptosuccinic acid encapsulated within pegylated, long-circulating “stealth” liposomes.

Figure 1 displays the techniques used to formulate the gold-lipidic nanocomposites. Physical characterization was completed using atomic absorption spectroscopy (gold quantification), dynamic light scattering (size distribution), and cell metabolic assays (cytotoxicity). I also studied separation methods for the removal of unencapsulated gold. These nanocomposites can be produced by a simple, scalable method with narrow size distributions around 100 nm and consistent nanoparticle encapsulation. I tested the resulting encapsulation and proposed alternative separation methods to counteract the problems encountered with the dialysis method used in this study.

As part of this study, I compared intracellular uptake and in vivo biodistribution of the gold-lipidic nanocomposites to the standard liposomes. These data support my hypothesis that gold-lipidic nanocomposites can be prepared and they justify preclinical in vivo studies in murine models of human tumors to improve cancer treatment. While there were no differences in intracellular uptake between the standard liposomes and the nanocomposites, we did observe altered tumor deposition relative to tumor volume in nanocomposites compared to traditional liposomes. The initial results were ultimately very favorable and indicate much potential for future work in this area.

Future aims on the project include the co-encapsulation of gold nanoparticles and model chemotherapeutic in liposomes, investigation of the effect of gold nanoparticles on drug encapsulation and release, covalent linkage of paclitaxel to gold to enhance stability and tumor deposition, and exploration of multispectral opto-acoustic tomography to examine the ability of the targeted particles to identify metastasis and improve anti-tumor activity.

Statement of Research Advisor:

Christy’s research focused on the development of multifunctional nanomedicines to identify and treat primary cancers and metastatic disease using imaging probes and optimizing drug release. Her research will advance the development of composite nanomedicines that permit multi-modal imaging (e.g., optical, ultrasound and MRI) and can be tailored to improve concomitant delivery of multiple therapeutic agents simultaneously

—Robert “Rusty” Arnold, Drug Development and Delivery