Melanoma is the deadliest form of skin cancer. Unlike most skin cancers, it does not stay restricted to the skin but spreads throughout the body to vital organs such as the liver and brain. Its incidence is rising, and there are currently no drugs that are effective. The survival rate for late-stage disease is only sixteen percent. The greatest challenges in treatment are delivering drugs everywhere in the body where melanoma cells are found, as well as destroying every cell. Gold nanoparticles have several desirable properties for the creation of new methods of targeting and destroying melanoma. Their bright reflectance (and in some cases fluorescence) allows individual particles to be tracked for long periods using light microscopy; they may also be tracked using ultrasound and CT. They travel through the bloodstream to tumors much more rapidly than individual drug molecules, and the concentration of these molecules on the particle surface is more toxic than when the drug is dispersed throughout the cell. Most importantly, they are able to overcome the resistance of cancer cells to doxorubicin, which is removed from resistant cells via efflux pumps. We are developing new types of gold-cytotoxic drug conjugates that are able to destroy resistant melanoma cells more effectively than drugs alone both in vitro and in two mouse models (B16 and SK-MEL-28). At the same time, these conjugates are less damaging to normal cells than the anti-cancer drugs alone, which helps prevent the side effects associated with cancer treatment. Gold and other heavy elements can also amplify the dose of delivered radiation by enhancement of the photoelectric effect. The greatest barrier to such therapy is the large amount of the heavy element that must be delivered to the tumor to obtain a significantly improved response. We present targeted nanoparticle formulations designed to amplify radiation therapy both directly and via energy transfer to traditional photosensitizing drugs. This work will help in the development of safe, effective treatments for this devastating form of cancer. The same approach is also being tested for glioblastoma, an aggressive form of brain cancer for which there is currently no effective therapy.