THE HARTWELL FOUNDATION

2007 Individual Biomedical Research Award

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Targeted Delivery of Chemotherapeutic Controlled-Release Nanoparticles to Common Pediatric Brain Tumors Using Contrast Agent Microbubbles and Ultrasound

In children with brain tumors younger than 4 years old, radiation therapy is a consideration, adjuvant to chemotherapy. Unfortunately, the lack of precise control over the margin of error in delivering radiation through a course of treatment can create undesirable collateral damage due to the changing physiologic and anatomic environment of the rapidly developing young brain. Therefore, treatment is often delayed until they are about 5 years old, which is a strategy that significantly diminishes the chances of a positive prognosis. With technical advancements in the past decade making it possible to extend the basic principles of ultrasound for its use as a radically new method for ablating organ-confined tumors (e.g., prostate), non-invasive high-intensity focused ultrasound (HIFU) is an appealing alternative. Unfortunately, ultrasound beam aberrations and localized non-specific heating created by the skull limit the usefulness of this approach for brain tumors. By contrast, Dr. Price proposes the development of an innovative method for treating brain tumors at much lower power levels in comparison to HIFU. In principle, he has generated “ultrasound-activated” delivery agents comprised of chemotherapeutic drug bearing nanoparticles adhering to microbubbles (size of red blood cells), which after injection into the bloodstream receive pulsed, focused ultrasound treatment to release their contents. His proposal is to deposit therapeutic drug bearing controlled-release nanoparticles at the site of brain tumors by destruction of the microbubbles, resulting in mechanical damage to tissue and blood vessels, and occluding blood flow — ablating the tumor. Implementation is possible by virtue of his unique expertise in both controlled-release nanoparticle fabrication and microbubble-nanoparticle composite delivery agent fabrication, coupled together with the skill of his collaborators in Radiation Oncology and Cardiovascular Medicine. Price has demonstrated feasibility for targeted nanoparticle delivery and release into both skeletal muscle and rat glioma (cell culture). Using tumors implanted into the well-accepted mouse dorsal skin-fold window chamber, he will monitor nanoparticle delivery, blood flow changes, and tumor regression. If successful, the long-term plan is to take the methodology to a clinical trial and ultimately, derive treatment algorithms suitable for clinical intervention.