Developing a New Accelerator Mass Spectrometry Assay for Quantitation of Platinum DNA Adducts for Response to Platinum-Based Chemotherapy

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Auspices Statement

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Project Overview
Platinum-based drugs are the most successful class of compounds for the treatment of cancer. These drugs kill cancer cells through toxic DNA damage. However, many patients are unresponsive to treatment or acquire drug resistance. We will address this problem using 14C-labeled carboplatin and 14C-labeled oxaliplatin, both platinum-based anticancer drugs, and accelerator mass spectrometry (AMS), the most sensitive method for studying long-lived isotopes. We will measure platinum-DNA adducts in cultured cancer cells and mice exposed to the compounds. This study aims to develop an assay for determining which patients will benefit from carboplatin treatment and which will be resistant. This project is being conducted in collaboration with researchers from the UC Davis Cancer Center.

Project Goals
This project will develop robust assays for quantitation studies on platinum-DNA adduct formation and repair using AMS detection of radiolabeled tracers for ultimate use in human studies. The unique analytical method developed is expected to provide the scientific proof-of-principle framework for the application of AMS to drug metabolism and personalized medicine for platinum-based drugs. We expect AMS data from cells and mice dosed with carboplatin to clearly differentiate resistant from sensitive tumors. Such differences may include rates of accumulation in cells and DNA of the radiolabeled drug and different rates of DNA repair. Applications of the resulting methodology to chemotherapy in humans will be proposed if we are successful.

Relevance to LLNL Mission
The ability to track pharmokinetics at exceedingly low isotopic doses will directly contribute to Livermore's mission in biosciences to improve human health and has potential applications in bioterror detection for LLNL's missions in national security and homeland security.

Accomplishments and Results
Several human cancer cells lines were exposed to 14C-labeled platinum drugs. The cells and DNA became radiolabeled. The drug bound to the DNA in two phases: monoadducts to a single strand of DNA preceded diadducts that formed from crosslinking of the drug between two sites in the DNA. The sensitive cells always accumulated more radioactivity than the resistant cells, indicating a strategy for predicting which tumors will respond to therapy in humans. This data resulted in two peer-reviewed papers, a US patent and several talks and conference presentations. We accomplished of the first two specific aims in the proposal which were to develop the method using purified DNA and extend the assay to cultured cancer cells. The final goal of a human clinical study with AMS was not attained, but is funded by the American Cancer Society.

Patents

Publications

Peer-reviewed journal articles

Invited Speaker (presented by Paul Henderson)

1. “Recent advances in molecular toxicology.” 232nd National Meeting of the American Chemical Society, Division of Chemical Toxicology, San Francisco, September 10, 2006.
2. “Kinetics of carboplatin-DNA binding in genomic DNA and bladder cancer cells.” UC Davis Cancer Center Annual Symposium, October 2006.

Conference Proceedings:

