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LLNL-TR-401377

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

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February 14, 2008

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Auspices Statement

This work performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract DE-AC52-07NA27344. This work was funded by the Laboratory Directed Research and Development Program at LLNL under project tracking code 06-LW-023.

FY07 LDRD Final Report

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

LDRD Project Tracking Code: 06-LW-023
Paul T. Henderson, Principal Investigator

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 biothreat 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

Henderson P.T. Hah S.S. and Turteltaub K.W. Use of accelerator mass spectrometry for individualized drug therapies. US Patent Pending.

Publications

Peer-reviewed journal articles

1. Hah, S.S.; Stivers, K.M.; de Vere White, R.; Henderson, P.T. Kinetics of Carboplatin-DNA Binding in Genomic DNA and Bladder Cancer Cells As Determined by Accelerator Mass Spectrometry, *Chemical Research in Toxicology*, **2006**, *19,* 622-626.
2. Hah, S.S.; Sumbad, R.A.; de Vere White, R.; Turteltaub, K.W.; Henderson, P.T. Characterization of Oxaliplatin-DNA Adduct Formation in DNA and Differentiation of Cancer Cell Drug Sensitivity at Microdose Concentrations, *Chemical Research in Toxicology* **2007,** 20(12), 1745-1751.

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.
3. "Metabolism of 8-oxoguanine in MCF-7 cells and personalized platinum therapeutics" Mayo Clinic, Rochester MN, December 8, 2006.
4. "Applications of accelerator mass spectrometry to cancer research." Washington University Department of Chemistry, St. Louis, MO, April, 2007.

Conference Proceedings:

1. (Poster) Hah, S. S.**;** Henderson, P. T. "*In vitro* kinetics of carboplatin-DNA binding in genomic DNA and bladder cancer cells as determined by accelerator mass spectrometry," the *2006 Pathobiology of Cancer Workshop of the American Association for Cancer Research*, Snowmass Village, CO, July 16-23, 2006 (presenter: Sang Soo Hah).
2. (Poster) Hah, S. S.**;** Mundt, J. M.; Henderson, P. T. "Mechanistic considerations of 8-oxoguanine incorporation into DNA and RNA from the nucleotide pool in human breast cancer cells," the *232th National Meeting of the American Chemical Society*, San Francisco, CA, September 10-14, 2006 (presenter: Sang Soo Hah).
3. (Poster and Oral) Hah, S. S.; Henderson, P. T. "Kinetics of carboplatin-DNA binding in genomic DNA and bladder cancer cells as determined by accelerator mass spectrometry," the *232th National Meeting of the American Chemical Society*, San Francisco, CA, September 10-14, 2006 (presenter: Sang Soo Hah).
4. (Poster) Hah, S. S.**;** Henderson, P. T. "Biomedical applications of accelerator mass spectrometry: Kinetics of carboplatin-DNA binding in genomic DNA and bladder cancer cells," the *37th Annual Meeting of the Environmental Mutagen Society*, Vancouver, British Columbia, Canada, September 16-20, 2006 (presenter: Sang Soo Hah).
5. Chong-Xian Pan Sang Soo Hah, Rhoda A. Sumbad, Ralph W. de Vere White, Kenneth W. Turteltaub, and Paul T. Henderson "Characterization of Oxaliplatin-DNA Adduct Formation in Naked DNA and Cancer Cells Using Accelerator Mass Spectrometry" UC

Davis Cancer Center's 13th Annual Cancer Research Symposium on September 28, 2007 (Oral presentation by Chong-Xian Pan and Poster Presentation by Paul Henderson).

6. Hah, S.S., Sumbad, R.A. Biomedical Applications of Accelerator Mass Spectrometry: Kinetics of Oxaliplatin-DNA Binding in Genomic DNA and Human Cancer Cells American Association for Cancer Research Annual Meeting, April 18, 2007
7. Hah, S.S., Sumbad, R.A., Turteltaub, K.W., Henderson, P.T. Quanitiation of oxaliplatin-DNA binding in genomic DNA and human cancer cells using accelerator mass spectrometry 2007 American Association of Pharmaceutical Sciences National Biotechnology Conference, June 27, 2007.