Personalized Chemotherapy through the Combination of Microdosing and Accelerator Mass Spectrometry

Maike Zimmermann[1,2], Sisi Wang[1], Tzu-yin Lin[1], Hongyong Zhang[1], Michael Malfatti[3], David R. Gandara[1], Marc Dall'Era[5], George Cimino[2], James Keck[4], Ralph de Vere White[5], Kenneth W. Turteltaub[3], Chong-xian Pan[1,6] and Paul T. Henderson[1,2]

[1]Department of Internal Medicine, Division of Hematology and Oncology, University of California Davis Medical Center, UC Davis Comprehensive Cancer Center, 4501 X Street, Suite 3016, Sacramento, California 95817
[2]Accelerated Medical Diagnostics, Inc, 3347 Monaghan Street, Dublin, California 94568
[3]Biosciences and Biotechnology Division, Physical and Life Sciences Directorate, Lawrence Livermore National Laboratory, 7000 East Ave., Livermore, California 94551
[4]The Jackson Laboratory, 600 Main Street, Bar Harbor, Maine 04609
5Department of Urology, University of California Davis Medical Center, 4501 X Street, Suite 3003B, Sacramento, California 95817
[6]VA Northern California Healthcare System, Mather, CA 95655

Platinum-based chemotherapy is the primary therapeutic intervention for over 300,000 cancer patients per year in the US. These compounds, including cisplatin, carboplatin, and oxaliplatin, are DNA alkylating agents that kill cancer cells through formation of DNA adducts and are routinely used in combination with other cancer drugs. Although some patients are cured by this type of chemotherapy, as many as 70% of lung cancer patients and 50% of bladder cancer patients show no benefit and could be more appropriately treated with alternative therapies. Currently, there is no diagnostic test that predicts therapy response towards these agents before the start of treatment. There is a critical need for a rapid, accurate test to identify cancer patients who are likely to benefit from platinum-based chemotherapy and those who will only have to endure the toxic side effects. We are developing an assay platform as a predictive test for response to chemotherapy drugs. The technology consists of two components: (1) the biomarker generation through microdosing and (2) the measurement of the drug-DNA adduct frequency

ratio via accelerator mass spectrometer (AMS). This technology enables detection of drug uptake, drug-DNA damage and other phenotypic markers prior to initiation of chemotherapy. In our clinical studies, we are giving cancer patients a subtherapeutic microdose (1% of the usual therapeutic dose) of ^{14}C-labeled carboplatin to form the transient biomarker and then quantitate the number of drug-DNA adducts using the high sensitivity and precision of AMS. The level of drug-DNA adducts in white blood cells and tumor biopsy tissue will be correlated to the therapeutic response. We hypothesize that a threshold level of platinum-DNA damage is required for cell death to occur, and that a non-toxic microdose is predictive of the clinical pharmacodynamics of a therapeutic dose. Indeed, preclinical results in a variety of cancer cell lines and mouse PDX models show that microdose-induced carboplatin-DNA adducts correlate to therapy-induced adduct level and drug sensitivity. In our on going clinical study, the extent of DNA damage was seen to correlate with responsiveness to treatment for ten patients. Patients with the highest DNA monoadduct levels responded best to carboplatin-based chemotherapy according to a standard set of clinical criteria. However, more data is needed to achieve statistical significance. This novel microdosing approach is a feasible strategy for characterizing the capacity for cells in vivo to form and repair carboplatin-DNA adducts prior to the initiation of cytotoxic chemotherapy, and may enable more personalized treatments to reduce the economic and human cost of cancer.