# Development of an assay to predict chemoresistance

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Most patients with cancer will not benefit from chemotherapy because their cancer is resistant to chemotherapy. Platinum-based drugs, such as cisplatin, carboplatin and oxaliplatin, are frequently used to treat solid cancerous tumors. However, response rates are as low as 25-30% for non small cell lung cancer, and 50% for bladder cancer. Even though response rates for these and other cancers are low, platinum-based chemotherapy is still routinely used as part of first-line therapy because of the possibility that the patient will have a substantial response or even a cure compared to other treatment alternatives. Unfortunately, this means that many patients will suffer the toxic effects of the therapy for no benefit while incurring substantial costs. There exists an unmet medical need to identify platinum-based chemoresistance prior to initiation of chemotherapy, which will enable more personalized treatment. We have developed a new technology called PlatinDx that can potentially identify chemoresistance in cancer patients before they receive carboplatin, a widely used chemotherapeutic drug. PlatinDx utilizes tracing of chemotherapeutic drug microdoses with accelerator mass spectrometry (AMS), the most sensitive method available for measuring the biodistribution of microdoses. Our hypothesis is that cellular drug concentrations and the resulting DNA damage caused by a single subtoxic microdose (~1/100$^{th}$ the therapeutic dose) of carboplatin will correlate to patient outcomes such as tumor shrinkage and mortality. The microdose concept is particularly relevant to chemotherapy, since the substantial toxicity risks associated with the therapeutic dose will be mitigated during the diagnostic procedure. In preclinical studies, we have found that microdoses of [$^{14}$C]carboplatin induce DNA damage that is linearly proportional to the damage caused by therapeutic carboplatin, and that chemoresistant cell lines always have relatively low concentrations of carboplatin-DNA damage. Our in progress Phase I study will define the optimal amount of [$^{14}$C]carboplatin to use in microdoses for patients with non small cell lung cancer (NSCLC) and Transitional Cell Carcinoma (TCC), a type of bladder cancer. For Phase II, we will apply this methodology to a large clinical study with enough patients to attain sufficient statistical power to correlate the AMS data to patient outcomes. The ultimate aim of this work is to develop and commercialize a robust analytical platform to predict cancer response to chemotherapy.

PlatinDx is being developed by a collaboration between UC Davis, Lawrence Livermore National Laboratory, Response Genetics, Inc. and Accelerated Medical Diagnostics, LLC, our recently formed startup company. Our goal is to recruit STEM students and entrepreneurs to our team in order to improve the planning and execution of our research and business development efforts. UC Davis physicians that are participating in this project include Drs. Chong-xian Pan (co-PI), Ralph de Vere White, David Gandara and Lucky Lara.