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A Baseline Investigation for the Use of Copper Isotope Ratios as Biomarkers of Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality in the world. HCC is particularly dangerous due to the absence of a reliable biomarker for early detection, limiting treatment options for patients who have advanced stages of the disease. Isotope metallomics, blending the fields of biomedicine and geochemistry, allows the study of bio-metal dyshomeostasis, and is a promising strategy to improve early detection of many public health concerns. Here, we explore the use of stable Cu isotope ratios (65Cu/63Cu) as a biomarker of oxidative stress in the liver with a baseline study that compares Cu isotope ratios of healthy wildtype mice and Nrf2-knockout mice.

Nrf2 is a transcription factor that regulates cellular antioxidant responses. It helps combat hepatocarcinogenesis by conjugating carcinogens with glutathione (an amino acid produced in the liver) and, therefore, decreases DNA adducts. Nrf2-knockout mice, mice lacking Nrf2, cannot respond normally to hepatocellular oxidative stress. It is likely that Nrf2 regulates Cu transport in the liver by controlling levels of various proteins (e.g., Atp7b) that bind to Cu. We therefore examine the sensitivity of Cu isotope measurements in livers and serum of both wildtype (Nrf2 replete) and knockout (Nrf2 deficient) mice to gain a better understanding of the mechanistic controls on the isotope system and its relationship to oxidative stress in the liver.

In our baseline Nrf2 study, we assess the influence of physiological (age, sex) and lifestyle (food, water) factors on copper isotope fractionation in wildtype and knockout mice. Cu isotope ratios are measured on the Neptune Plus MC-ICP-MS at Texas A&M University using a standard-sample bracketing technique with Ga doping for internal normalization. Our measurements of an internal Caltech copper standard (ESPI) yield a δ65Cu (‰) relative to NIST 976 of +0.100±0.007‰ (2SE). Preliminary results on wildtype mice livers suggest significant offsets in δ65Cu between pups and their mothers (~0.4-0.7‰), no significant differences between male and female pups of a single brood, but slight differences between different broods (~0.3‰). Measurements on wildtype and knockout mice are ongoing, and potential relevance to HCC will be explored at the conference.