META-IODOBENZYLGUANIDINE AS AN EXOGENOUS BIOMARKER OF CARDIAC OCT3 FUNCTION

Mike Boeckman[1], Zahra Talebi[1], Yan Jin[1], Erin K. Hertlein,[2] Sharyn D. Baker[1], Daniel Addison[3] and Alex Sparreboom[1]

[1]Division of Pharmaceutics and Pharmacology, College of Pharmacy, The Ohio State University, Columbus, OH, USA; [2]College of Medicine, University of Cincinnati, Cincinnati, OH, USA; [3]Division of Cardiovascular Medicine, Department of Medicine, The Ohio State University, Columbus, OH, USA.

Background: Doxorubicin (DOX) is an anthracycline used in the treatment of various malignancies, including breast cancer and certain leukemias, but its use is limited by a debilitating cardiotoxicity. We previously reported that the uptake of DOX into cardiomyocytes is mediated by the organic cation transporter OCT3, and that inhibition of this mechanism ameliorates cardiotoxicity without affecting antitumor activity (Huang et al, 2021). Since OCT3 inhibition is not associated with altered plasma levels of DOX, alternative cardiac biomarkers of OCT3 are needed to optimize dosing strategies of OCT3 inhibitors used with DOX. We hypothesize that meta-iodobenzylguanidine (mIBG), an analog of norepinephrine used to image neuroendocrine tumors, can serve this purpose as it is a known substrate of OCT3 that accumulates in cardiac tissue.

Methods: Pharmacokinetic studies were performed in wild-type mice and age- and sex-matched mice with a genetic deficiency of OCT3 or the related transporters OCT1 and OCT2 (OCT1/2), MATE1, or OCT1/2 and MATE1 (OCT1/2/MATE1). Non-radiolabeled mIBG was injected i.v. as a bolus dose at 15 mg/kg. Plasma and heart samples were collected at various time points (up to 4 hours), and pharmacokinetic parameters were calculated using Phoenix WinNonlin. In separate experiments, mice received 0.5 mCi of iodine-123 labeled mIBG for single-photon emission computerized tomography (SPECT-CT) scanning. Images from the axial, coronal, and sagittal perspectives were gathered 30 min after injection, and signals were quantified in cardiac tissue of wild-type and OCT3-deficient mice.

Results: While the observed AUC of unlabeled mIBG in plasma was similar between wild-type mice and transporter-deficient animals, the levels of mIBG in hearts of OCT3-deficient mice were statistically significantly reduced compared to wild-type mice with mean heart-to-plasma ratios of 3.5 ± 0.598 and 38 ± 8.05, respectively ($P<0.001$). Levels of mIBG in the hearts of mice deficient in OCT1, OCT2, and/or MATE1 were either unchanged or slightly increased compared to results obtained in wild-type mice. In the SPECT-CT images, wild-type mice showed a higher average cardiac accumulation of 23.3E+05 Bq/mL of mIBG compared to OCT3-deficient mice with an

average of 6.13E+05 Bq/mL ($P<0.0001$). Interestingly, there was not a significant difference in the uptake in the liver of these animals.

Discussion: These findings confirm that radiolabeled mIBG can be utilized in conjunction with SPECT-CT scans as a non-invasive cardiac biomarker of OCT3 function, and that deficiency in OCT3 results in a stark decrease in signal. We are currently planning a high-throughput screen to identify novel small-molecule inhibitors of OCT3 that can be tested for OCT3-modulatory properties in vivo using a newly developed transgenic mouse model with cardiomyocyte-specific expression of human OCT3. By repeating these experiments with and without OCT3 inhibitors, we hope to observe a similar drastic decrease in mIBG signal in cardiac tissue upon OCT3 inhibition. It is expected that the proposed strategy can ultimately be translated to patients with cancer requiring treatment with DOX-based regimens to ameliorate cardiotoxicity.

Huang KM, Zavorka Thomas M, Magdy T, Eisenmann ED, Uddin ME, DiGiacomo DF, Pan A, Keiser M, Otter M, Xia SH, Li Y, Jin Y, Fu Q, Gibson AA, Bonilla IM, Carnes CA, Corps KN, Coppola V, Smith SA, Addison D, Nies AT, Bundschuh R, Chen T, Lustberg MB, Wang J, Oswald S, Campbell MJ, Yan PS, Baker SD, Hu S, Burridge PW, Sparreboom A. Targeting OCT3 attenuates doxorubicin-induced cardiac injury. Proc Natl Acad Sci U S A. 2021 Feb 2;118(5):e2020168118. doi: 10.1073/pnas.2020168118. PMID: 33495337; PMCID: PMC7865186.