Roswell Park Comprehensive Cancer Center

Bioanalytics, Metabolomics & Pharmacokinetics (BMPK) Shared Resource

Example Collaborations with Roswell Park and Other Investigators

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The mission of the BMPK Shared Resource is to support pre-clinical and clinical drug development, clinical research, and translational pharmacology by providing state-of-the-art bioanalytical data and PK/PD modeling of results. An important example of BMPK's contributions is our endogenous androgen assay, a high pressure liquid chromatographic analytical method with tandem mass spectral detection (LC-MS/MS) that measures five (5) androgens at picogram concentrations (Wilton JH, Titus MA, Efstathiou E, Fetterly GJ, Mohler JL. Androgenic biomarker profiling in human matrices and cell culture samples using high throughput, electrospray tandem mass spectrometry. Prostate. 2014 May;74(7):722-31. PMID:24847527). The method has been applied to cell culture, xenografts, biodistribution studies and clinical trial specimens, and has been expanded to include the simultaneous detection of various enzyme inhibitors (e.g., finasteride and dutasteride) in the same assay to allow direct correlation of androgen levels with androgen enzyme metabolic inhibitor concentrations. BMPK is expanding this methodology to a broad scale targeted metabolomics platform for the semi-quantitative profiling of ~20 additional steroidal compounds (e.g., progesterone, hydroxyprogesterone, pregnenolone, corticosterone, cortisone, cortisol, aldosterone, etc.) to monitor the effects of various drugs, treatment regimens, and phenotypes on hormone levels in samples from cell culture, animal studies, and clinical trials. Continued development of this methodology provides initiative to develop an assay to monitor the entire human steroidal metabolome in a single sample analysis and serves as a platform to develop other targeted (e.g. methionine, fatty acid synthesis, and polyamine pathways) and non-targeted metabolic profiling strategies that can be applied across RPCI.

BMPK collaborated with CureFAKtor Pharmaceuticals, LLC, an RPCI spin-off company, to develop and validate a highly sensitive and selective LC-MS/MS assay to quantitate C4 in dog plasma samples after IV or oral administration. (Wilton J, Kurenova E, Pitzonka L, Gaudy A, Curtin L, Sexton S, Cance W, Fetterly G. Pharmacokinetic analysis of the FAK scaffold inhibitor C4 in dogs. Eur J Drug Metab Pharmacokinet (2016) 41:55–67. DOI 10.1007/s13318-014-0233-6.) C4 is a focal adhesion kinase (FAK) inhibitor, which had been shown to reduce tumor growth either alone or synergistically with other chemotherapeutic agents in animal tumor models. The analytical method had a lower limit of quantitation of 2.5 pg/mL for C4 (S/N=55; n=8; CV%=10.2) and contained three predicted mass spectral transitions for the detection and measurement of three of its metabolites (desmethyl-C4, didesmethyl-C4, and hydroxy-C4). The high sensitivity of this assay detected C4 out to 168 hours post-dose, which provided data for refined PK assessments. The study revealed that C4 has linear pharmacokinetics and does not accumulate following multiple-dose administration. The mean plasma concentration–time profiles revealed a tri-exponential decline following either IV or oral administration, independent of dose. Oral bioavailability for the different formulations were TPGS (45 %), Maalox (42 %), Pepcid (37 %), and PBS (30 %).

BMPK collaborated with Dr. Kathleen Tornatore, University at Buffalo, to develop an assay for quantitation of mycophenolic acid (MPA) and mycophenolic acid glucuronide (MPAG) in 67 medically stable African American (AA) and Caucasian American (CA) renal transplant patients who received enteric-coated mycophenolate sodium (ECMPS) and tacrolimus for immunosuppression (Tornatore KM, Meaney CJ, Wilding GE, Chang SS, Gundroo A, Cooper LM, Gray V, Shin K, Fetterly GJ, Prey J, Clark K, Venuto RC. Influence of sex and race on mycophenolic acid pharmacokinetics in stable African American and Caucasian renal transplant recipients. Clinical Pharmacokinetics. 2015 Apr;54(4):423-34. doi: 10.1007/s40262-014-0213-7. PMID: 25511793). BMPK developed a high throughput LC-MS/MS assay using solid phase extraction (SPE) in a 96-well plate format on a TOMTEC Quadra 4 robotic liquid handler for sample extraction and cleanup. The study analyzed 720 human plasma samples from four groups (13 female AA, 22 male AA, 16 female CA, and 16 male CA). Data generated by BMPK was part of the first published report investigating gender and racial differences in MPA and MPAG pharmacokinetics. The study concluded that females have a slower MPA clearance, a higher MPAG AUC_{0-12}, and greater severity of gastrointestinal adverse effects. These findings have important clinical implications for ECMPS dose adjustments based on sex and race, and the potential need for therapeutic drug monitoring.

BMPK provided bioanalytical and pharmacokinetic support for FL118, the lead compound of RPCI spin-off company Canget BioTekpharma, LLC, in collaboration with its Chief Scientific Officer, Dr. Fengzhi Li. The camptothecin analog, FL118, is able to overcome inherent and/or acquired tumor resistance typically observed with other camptothecin analogs such as irinotecan and topotecan (Ling X, Liu X, Zhong K, Smith N, Prey J, Li F. FL118, a novel camptothecin analogue, overcomes irinotecan and topotecan resistance in human tumor xenograft models. Am J Transl Res. 2015 Oct; 7(10):1765-1781. PMCID: PMC4656756). SCID mice bearing human colon (SW620) and head and neck (FaDu) tumors were treated with irinotecan or topotecan until drug resistance was observed. The mice were treated with FL118 administered IV or IP [5% DMSO and 0.05-0.125% (w/v) hydroxypropyl-β-cyclodextrin in saline]. Tumor and plasma samples were collected at serial time points over 48 hours for pharmacokinetic analysis. An ultra-performance liquid chromatographic (UPLC) assay with fluorescence detection (370/510 nm) was developed at BMPK and used for the bioanalytical measurement of FL118 concentrations. Pharmacokinetic analysis of the concentration results showed that FL118 has a significantly longer half-life in tumors (6.85 hr in FaDu, and 12.8 hr in SW620) versus plasma (1.79 hr) with measureable levels of FL118 detected in SW620 tumors up to 48 hours after drug administration. FL118 appears to effectively overcome irinotecan and topotecan resistance in human tumor xenografts without inducing its own drug resistance. These observations and pharmacokinetic results will be used by Dr. Li and his company to further the clinical development of this drug for cancer treatment.