Drug Metabolism and Pharmacokinetic Services

The drug metabolism and pharmacokinetic (DMPK) platform at CDI provides a full range of bioanalytical services and expertise in support of drug discovery screens, preclinical development and clinical trials. The mass spectrometry (MS) core of 3 industry leading triple-quadrupole (MS/MS) AB Sciex mass spectrometers facilitates low level detection and quantification of small molecules in complex matrices such as plasma, tissue homogenates and other biological fluids, enabling the comprehensive assessment of absorption, distribution, metabolism and excretion (ADME) properties of each drug. These quantitation methods are validated according to the FDA Guidance for Industry on Bioanalytical Method Validation. In addition to the quantitative applications of the MS core, the Thermo Q-Exactive high resolution mass spectrometer (HRMS) provides accurate mass detection of unknown compounds, which is necessary for the elucidation of metabolites in biological fluids, S9 fractions and cell-based assays. These mass spectrometry resources, in concert with years of technical and scientific knowledge of our DMPK staff, currently supports an array of drug discovery programs at CDI, and at collaborating pharmaceutical companies and research institutes.

Pharmacokinetic Studies/Applications:

- Pre-clinical and Clinical *in vivo* PK
- Bioanalysis
    - LC-MS/MS assay development in biological matrices (plasma, serum, csf)
    - LC-MS/MS quantitation in biological matrices (plasma, serum, csf)
- Biodistribution
    - LC-MS/MS quantitation in target organs
    - Laser capture microdissection and LC-MS/MS quantitation from regions of interest in target organ sections (See LCM section)
- Drug formulation profiling and development
- PK analysis performed with Phoenix® WinNonlin®

Drug Metabolism Applications:

- High Resolution Mass Spectrometry (HRMS) using Thermo Q-Exactive Orbitrap based MS
- Microsomal and S9 fraction stability assays
- Thermo Fisher Compound Discoverer™ enabled Metabolite identification for soft spot targeting
- Cellular drug metabolism assays

In-Vitro Applications:

- Cellular drug uptake assays
- Cellular drug stability assays
- Plasma protein binding

Laser Capture Microdissection LC-MS:

Laser Capture Microdissection (LCM) using the Leica LMD 6500 enables the fine dissection of micron level regions of interest from tissue sections that cannot be isolated by traditional techniques. The industry

leading sensitivity of the MS/MS systems in our MS core permits the quantification of analytes in the extracts of these microscopic LCM sections. This technique is referred to as LCM-LC-MS. The quantitative spatial distribution data provided by LCM-LC-MS in concert with efficacy data enables high fidelity PK-PD modeling at the site of disease.

Advanced Workflows routinely combine traditional PK with mass spectrometry imaging and laser capture microdissection coupled to LC-MS/MS quantitation to enable region- and cell-specific drug localization and quantitation.