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Light Up Your Drug Discovery Path

Spring 2010 Brochure

MetabQuest
Research & Consulting

www.MetabQuest.com | Beijing | Chicago | Shanghai

MetID Contract Research | ADME-MedChem Outsourcing Consulting | Drug Discovery Methodology Research

About Us

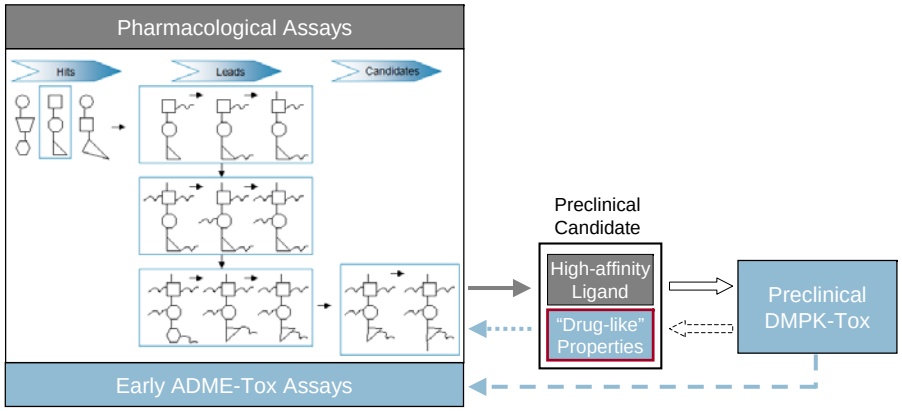
ADME-Tox (Absorption, Disposition, Metabolism, Excretion, and Toxicology) study has become an essential part of drug discovery research, aiming to build the necessary "drug-like" properties into drug candidates with higher successful probabilities in preclinical and clinical studies.

At MetabQuest, we are chemists with our focuses on chemical research of “ADME-Tox”.

We collaborate with R&D divisions of pharma companies, translational research institutes, and pharma R&D CRO's on:

- Metabolite identification (MetID) contract and sub-contract research
- ADME-MedChem outsourcing consulting
- Drug discovery methodology research: new drug design and optimization based on early ADME-Tox studies

Doing ADME-Tox In Drug Discovery: Build In the Desired Drug-like Properties



Full Panel of High Throughput ADME-Tox Assays
- is often misleading;
- lacks direct/fast impacts on MedChem programs.

1 Study ADME-Tox from the physiological viewpoint

- Customize/Design the Right Research Plan;
- Avoid Generating Misleading ADME-Tox Data;
- Refine ADME Data to Direct MedChem Efforts;
- Solving ADME-Tox Problems.

2 Study ADME-Tox from the chemical viewpoint

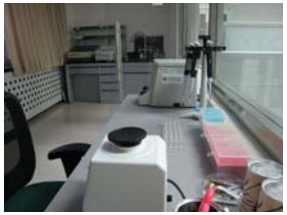
MetabQuest Specializes on Metabolite Identification (MetID) Contract Research

Instrumentation Limitation: triple quatrupole mass specs - best at quantitative analysis (high throughput assays); - only 1 degree of fragmentation (ms2, ms3 the most); - low resolution mass (e.g. [M+H$^+$]observed=473.17); - no complimentary structure ID techniques. **Expertise Limitation**: non-chemistry personnel - limited training on biotransformation and structural elucidation; - limited experience on regular and reactive metabolite ID; - often provide only mass spectra; structure ID relies on software.	**Instrumentation Advantages**: state-of-art ion trap mass specs - best at qualitative analysis (structural elucidation); - multiple degrees of fragmentation (ms2-ms10); - high resolution mass (e.g. [M+H$^+$]observed=473.1060, +2 ppm); - wide range of complimentary techniques. **Expertise Advantages**: organic/medicinal chemistry Ph.D.’s - extensive training on biotransformation and structural elucidation; - over 200 studies have been accomplished; - full structure ID and biotransformation mechanism elucidation.
Most ADME/PK Assay Data Providers	**MetabQuest**
Slow Turnaround: 2 weeks to 2 months; **High Cost;** Ambiguous Data/Reports; No Chemist-to-chemist Interaction.	**Fast Turnaround**: 2-5 days; **Low Cost**; Definitive Data/Detailed Reports; ADME-MedChem Consulting.

"MetID" Is An In-depth Chemistry Research, Not An Assay with Generic and "Validated" Protocol.

MetabQuest Lab Dedicated for MetID Research

View from Outside



Sample Preparation Room

Two LC-ITMS's

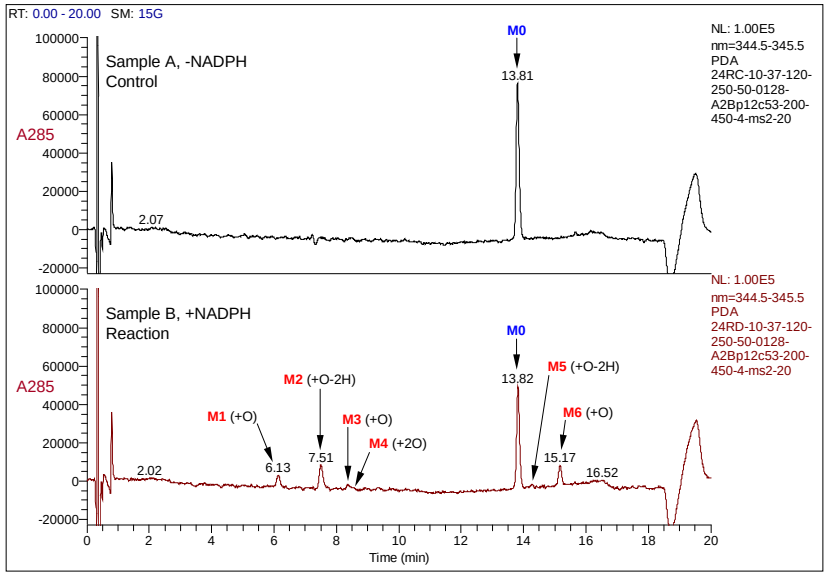
LC-FTMS

We Specialize on Metabolite Identification (MetID) Contract Research

Available species: human, rat, dog, monkey, mouse	Type A In Vitro Systems	Type B In Vitro Systems	In Vivo Systems
	Sub-cellular fractions from liver or intestine; blood/plasma, etc.	Fresh or cryopreserved hepatocytes	Worked up samples of plasma, urine, bile, feces, etc.
MetID-I (LR profiling)	1. Chromatograms of "control sample" and "reaction sample"; 2. Extracted ion chromatograms (XIC's) of parent compound and each metabolite; 3. MS and MS2 of parent compound and each metabolite.		
MetID-II (HR profiling)	(In addition to MetID-I) 4. High resolution mass spectra (XIC's and MS spectra) of parent compound and each metabolite.		
MetID-III (LRMS identification)	(In addition to MetID-I) 4. Fragmentation analysis and structural elucidation of each metabolite; 5. Metabolism pathway and biotransformation mechanism elucidation.		
MetID-IV (HRMS identification)	(In addition to MetID-III) 6. High resolution mass spectra (XIC's and MS spectra) of parent compound and each metabolite.		
*r*MetID-I (Reactive/toxic metabolite screening)	1. Chromatograms of "control sample" and "reaction sample"; 2. Extracted ion chromatograms (XIC's) of parent compound and "reactive metabolite-trapping agent" adducts; 3. MS and MS2 of parent compound and "reactive metabolite-trapping agent" adducts.		
*r*MetID-II (Reactive/toxic metabolite identification)	(In addition to rMetID-I) 4. Fragmentation analysis and structural elucidation of "reactive metabolite-trapping agent" adducts; 5. Bioactivation mechanism elucidation.		

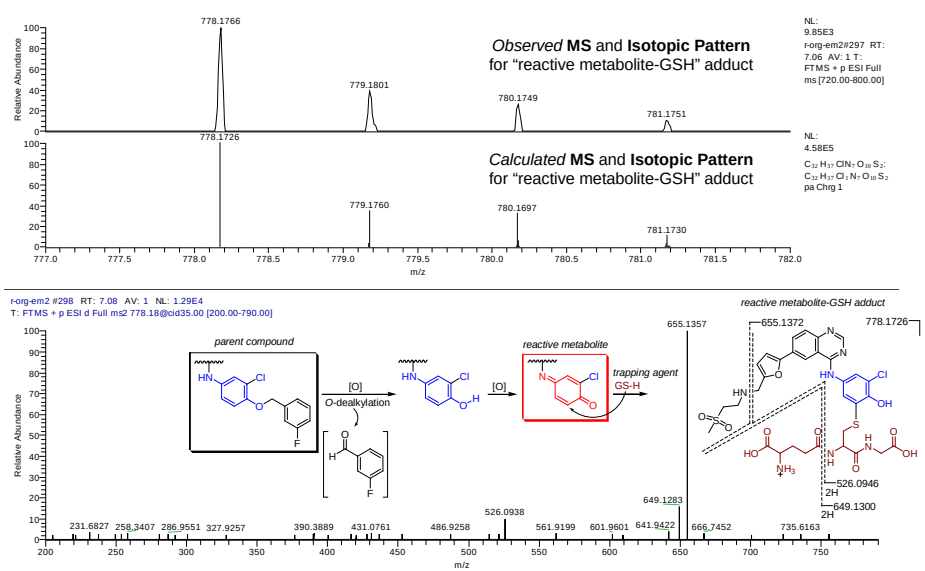
Additional structural identification research:
1. purification of major metabolite followed by NMR analysis;
2. chemical synthesis of metabolite standard for structural confirmation;
3. on-line H-D exchange experiment;
4. pre-column or post-column chemical derivatization tandem MS/MS analysis; etc.

Metabolite Identification (MetID) Sample Report



Sample report with detailed fragmentation analysis, structural elucidation, and other info are available at metabquest.com (link)

Reactive/toxic Metabolite Identification (*r*MetID) Sample Report

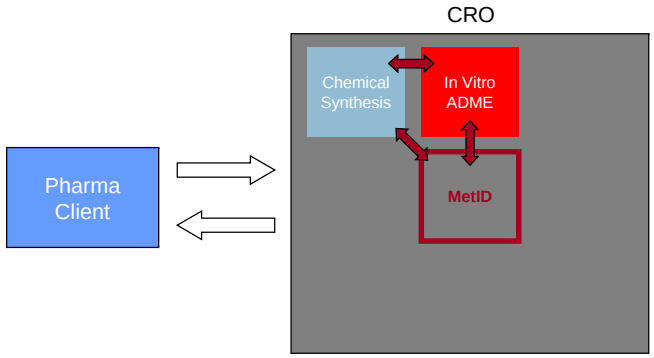


Sample report with chromatograms, detailed fragmentation analysis,, and other info are available at metabquest.com (link)

We Work Closely with Integrated Drug Discovery and Development CRO's – Case Study # 1

Case Study 1:

- Client asks CRO to synthesize 20 compounds of a lead series and then test their "human and rat liver microsomal stability";
- Most of the 20 compounds show very poor metabolic stability in both species;
- Client wants to do MetID study on a couple representative compounds to identify the "soft spot" for structural modification;
- CRO sub-contracts the MetID study to MetabQuest; MetabQuest delivers detailed MetID reports in 2 days;
- Client designs more compounds and outsources them to CRO for chemical synthesis and in vitro ADME studies.

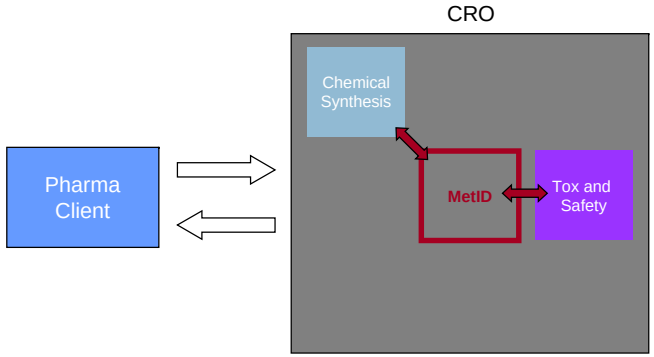


❑ Quick diagnosis of soft spot (responsible for poor in vitro ADME properties) for new drug design in lead optimization;

We Work Closely with Integrated Drug Discovery and Development CRO's – Case Study # 2

Case Study 2:

- Client wants CRO to do tox studies for the pre-clinical drug candidate but asks the CRO first to do "cross-species hepatocyte MetID" to identify the animal species that are close to human;
- CRO will not be able to take this tox project without the MetID research capability;
- CRO sub-contracts the MetID study to MetabQuest; MetabQuest delivers detailed cross-species MetID reports in 5 days;
- Based on the MetID results, client chooses rat and monkey as tox species;
- CRO takes over the pre-clinical tox study projects from client.



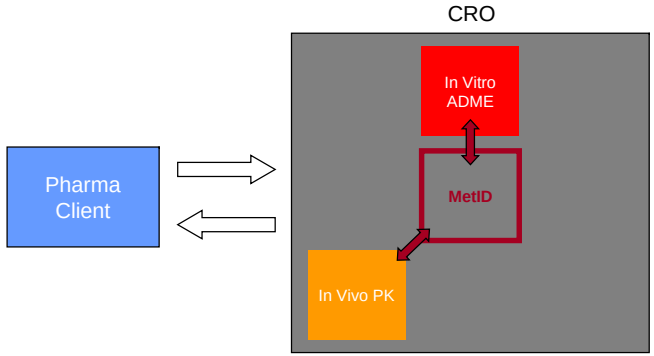
❑ Identify animal species for tox studies for preclinical development;

❑ Detect reactive/toxic metabolite and provide chemical strategy to minimize tox risk;

We Work Closely with Integrated Drug Discovery and Development CRO's – Case Study # 3

Case Study 3:

- Client outsources rat PK studies of the lead compounds to CRO; the 3 compounds show poor bioavailability;
- Client wants to know how to improve bioavailability and sends PK data to MetabQuest;
- MetabQuest asks the client to go back to CRO for "rat liver microsomal stability" and "Caco-2 experiment";
- The data confirms that low metabolic stability and strong P-gp regulation are the reasons for low bioavailability;
- MetabQuest does MetID study and designs new lead compounds;
- Client synthesizes the new compounds and sends them to CRO for more in vitro ADME and PK studies.



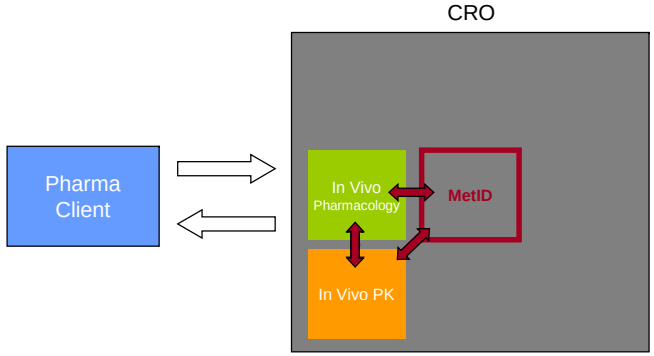
❑ Diagnose out the chemical fragment that are responsible for poor PK;

❑ Identify the correct in vitro system that predicts in vivo;

We Work Closely with Integrated Drug Discovery and Development CRO's – Case Study # 4

Case Study 4:

- Client outsources in vivo pharmacology and PK (both in rat) to CRO;
- The CNS drug candidate shows good efficacy in rat after oral dosing but is not detected in rat brain tissue;
- Client wants the CRO to check if active metabolite is playing the role;
- CRO sub-contracts the rat hepatocyte MetID study to MetabQuest; MetabQuest identifies a major circulating metabolite that might have better permeability across blood-brain barrier and may be also active;
- Client and CRO continue in vivo pharmacology and PK studies on this metabolite.



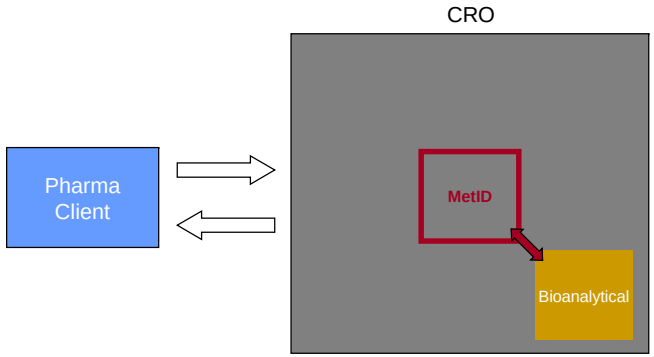
❑ Address PK-PD discrepancy in animal studies;

❑ Design and evaluate prodrug approaches;

We Work Closely with Integrated Drug Discovery and Development CRO's – Case Study # 5

Case Study 5:

- Client wants to study the tissue distribution of the pre-clinical drug candidate and its metabolites;
- Two CRO's send close quotes to the client; client asks if the CRO's have the MetID capability as it is the first experiment to do;
- One CRO quickly reaches collaboration agreement with MetabQuest and wins the project;
- MetabQuest does MetID studies first; the reliable results and fast turnaround allow the CRO to continue with the bioanalytical project smoothly.

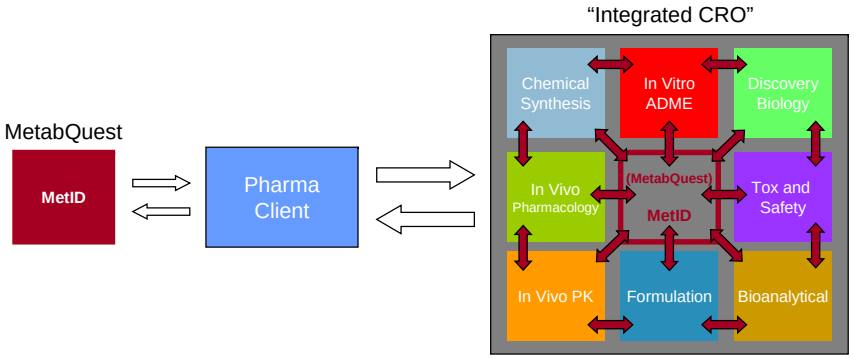


- Understand the metabolism fate of the drug candidate before tissue distribution studies of the drug candidate and its metabolites;

Have MetabQuest in the Collaboration to Accelerate Drug Discovery Research

MetabQuest collaborates with R&D divisions of pharma companies and pharma R&D CRO's on:

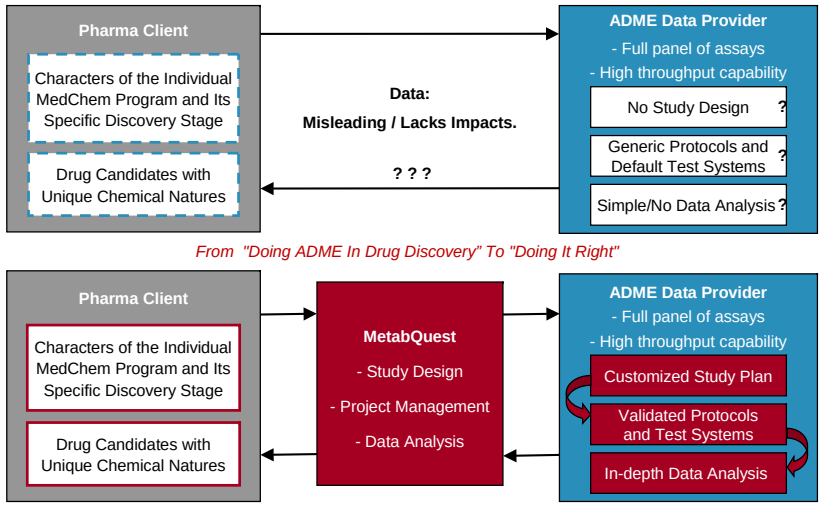
Metabolite Identification (MetID) Contract Research



Have MetabQuest in the Collaboration to Outsource ADME-MedChem In A Better Way

MetabQuest collaborates with R&D divisions of pharma companies and pharma R&D CRO's on:

ADME-MedChem Outsourcing Consulting



Fast, Reliable, and Low-cost MetID Contract Research

- Browse/download "MetID and BARA Sample Reports" (pdf) for more information;
- To initiate a MetID or BARA contract research, please download the "Research Request Form" (doc), fill it, and send back to us:

[Email] info@metabquest.com or [Fax] +86 (10) 6275 2632.

ADME-MedChem Outsourcing Consulting and Drug Discovery Methodology Research

- Browse/Download the "Sample Seminar Abstract" (pdf) of the seminars we have given to MedChem and ADME/PK scientists at major pharma companies in the US and in China;
- For ADME-MedChem outsourcing consulting and presentation requesting, please download the "Consulting Brochure and Request Form" (doc), fill it, and send back to us:

[Email] info@metabquest.com or [Fax] +86 (10) 6275 2632.

Career and Other Inquiries

[Email] info@metabquest.com or call/visit our Beijing/Chicago/Shanghai offices.

The above info is available at www.MetabQuest.com