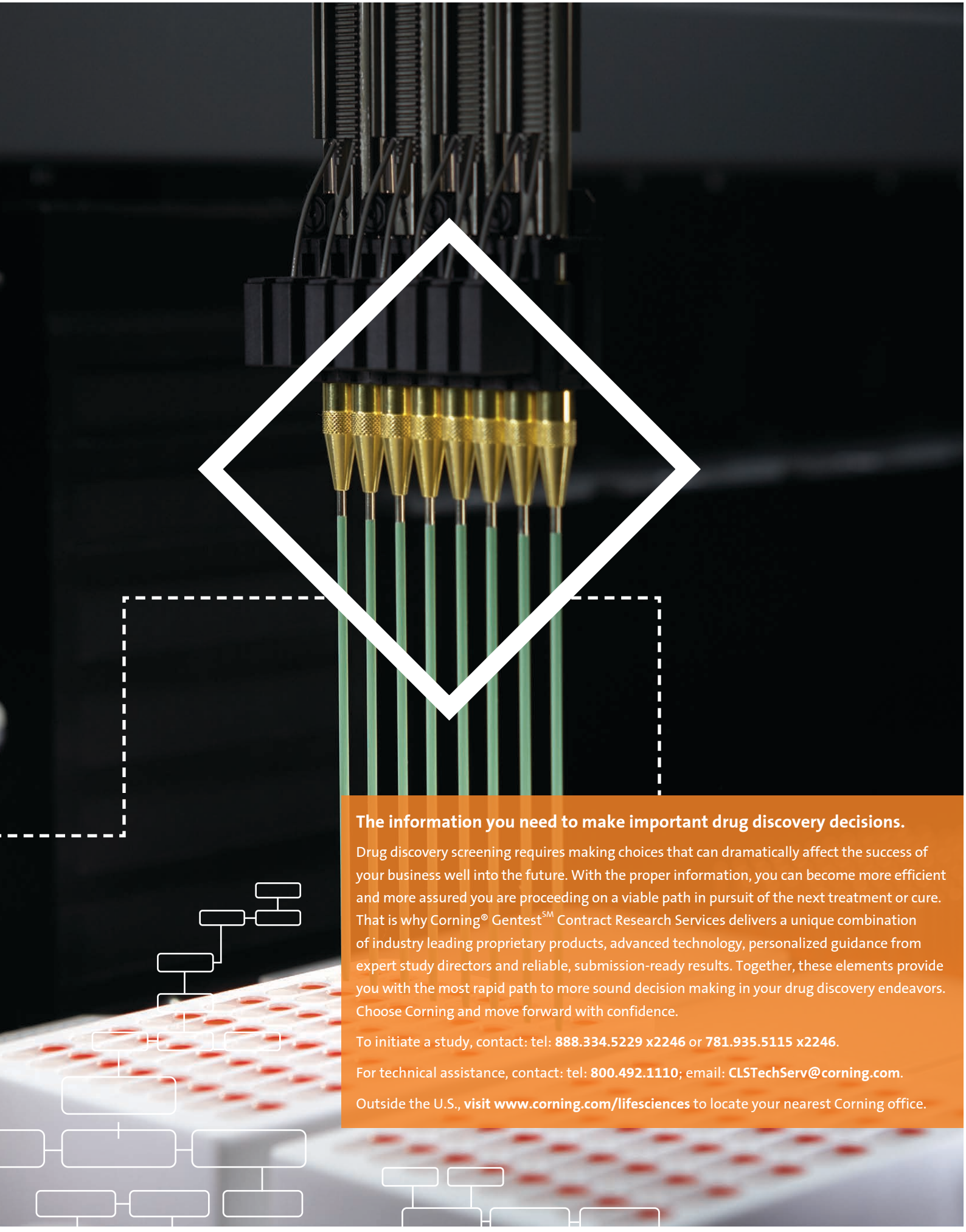
In Vitro ADME Discovery Screening Research Services

The most rapid path to more sound decision making

CORNING



The information you need to make important drug discovery decisions.

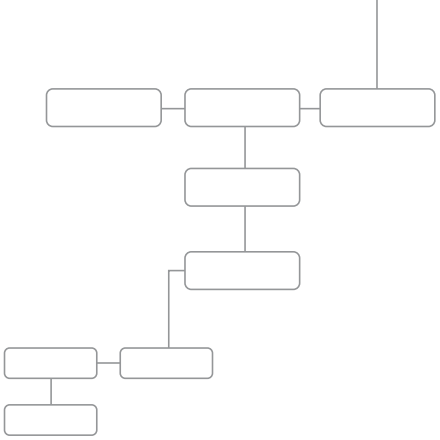
Drug discovery screening requires making choices that can dramatically affect the success of your business well into the future. With the proper information, you can become more efficient and more assured you are proceeding on a viable path in pursuit of the next treatment or cure. That is why Corning® Gentest℠ Contract Research Services delivers a unique combination of industry leading proprietary products, advanced technology, personalized guidance from expert study directors and reliable, submission-ready results. Together, these elements provide you with the most rapid path to more sound decision making in your drug discovery endeavors. Choose Corning and move forward with confidence.

To initiate a study, contact: tel: **888.334.5229 x2246** or **781.935.5115 x2246**.

For technical assistance, contact: tel: **800.492.1110**; email: **CLSTechServ@corning.com**.

Outside the U.S., **visit www.corning.com/lifesciences** to locate your nearest Corning office.

THE MOST rapid path to more sound decision making



Tested Science. Reliable Results.

Drug developers now require faster and more predictive compound screens to reduce time-to-market and potential drug-drug interactions. Corning Life Science's ADME Contract Research Services group works as an extension of a client's team to provide reliable data and faster results. Utilizing state-of-the art techniques, products, and equipment, Corning is able to assist clients in screening for viable drug candidates during drug discovery or by preparing regulatory agency submission-quality reports for your drug development compounds.

Only Corning Contract Research Services delivers a combination of industry leading proprietary products, advanced technology, expert guidance from renowned study directors and reliable, submission ready results. Together, these elements provide you with the most rapid path to more sound decision making in your drug discovery endeavors.

Expert Study Directors that facilitate informed decisions

Corning ADME Contract Research Study Directors have been helping customers test their drug compounds for over 17 years. Our Study Directors are highly skilled scientists with in-depth knowledge of absorption, transport and metabolism. This expertise gives Corning Study Directors the ability to partner with clients to develop and deliver a broad range of *in vitro* ADME studies to meet their discovery and development project needs. Corning ensures the highest level of quality standards and adheres to current regulatory requirements and applicable FDA-sponsored guidance documents.

Advanced technology and leading processes

Corning uses leading-edge technology, like RapidFire™ high-throughput mass spectroscopy for CYP Inhibition. Our industry leading brand of products including Corning® Supersomes™, Corning Gentest™ hepatocytes, human liver microsomes, transporter proteins, Corning BioCoat™ assay systems, and Falcon® permeable supports, make Corning the company clients have come to rely on and trust.
The combination of advanced technology, processes and latest product offering, including use of the Corning UltraPool™ HLM 150 donor pool, combine to deliver high quality, accurate and rapid results. Through every step of the drug discovery process, sponsors will work directly with our highly specialized Study Directors who will respond efficiently to the rapidly changing technology.

Corning ADME Discovery Services

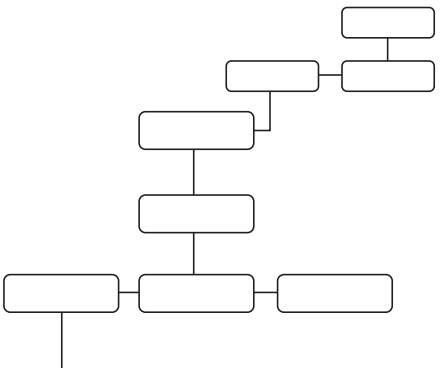
CYP INDUCTION expertise

Enzyme Induction Studies with Cytochrome P450 and UGT Induction

Induction of cytochrome P450 and UGT enzyme catalytic activity is a leading mechanism of metabolism-based drug-drug interactions. *In vitro* induction studies are valuable predictors of *in vivo* drug-drug interactions and the magnitude of that interaction.

Features

- Testing for enzyme activity, mRNA or western blotting for a comprehensive portfolio of inducible enzymes, including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, UGTs and transporters
- Fully validated LC/MS/MS analytical methods for the major inducible CYPs in enzyme activity assays
- Flexibility to adapt to clients' needs to customize testing conditions for comparison with in-house data
- Use of highly characterized Corning Gentest Inducible-qualified cryopreserved hepatocyte cells for predictable results
- Use of customer-reserved lots of cryopreserved hepatocytes for consistent comparisons over extended periods
- High quality submission-ready data analysis
- Expert Study Directors who deliver assays aligned with FDA and EMA recommendations
- Induction of Cytochrome P450 and UGT in animal livers *ex vivo*
- Strict tissue traceability and sourcing from US-based Organ Procurement Organizations that meet high ethical standards



Extensive Suite of Assays

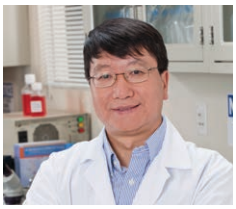
For more than ten years, Corning has been providing regulatory agency submission-quality enzyme induction services in human hepatocytes. Corning induction assays go beyond the standard CYP1A2, 2B6 and 3A4 tests. Additional enzymes that may be requested by regulatory agencies are available with enzyme activity, mRNA or western blot endpoints, including CYP2C8, CYP2C9, CYP2C19, UGTs and transporters.

Assay Flexibility and Customization

Corning provides induction assays using both cryopreserved and fresh hepatocytes to meet EMA and FDA draft guidance recommendations for regulatory filings. Using pre-qualified Corning Gentest inducible hepatocytes ensures a predictable response and accelerated data availability. Corning has expertise in adapting clients' protocols to facilitate comparison with in-house databases. Customizations can include the choice of extracellular matrix, treatment media, seeding density, positive control-inducing chemical concentration and delivery solvent, as well as many other client-specified adaptations.

High Quality Reagents, Extensive Selection and Supply

Corning has an extensive portfolio of high viability hepatocytes that are pre-qualified to meet any researcher's hepatocyte criteria, including CYP3A4, CYP2B6 and CYP1A2 fold induction, and basal and induced activity. The large lot sizes provide researchers the benefit of using the same lot for long-term, multi-site projects including the client's in-house studies, where reproducible and comparative data is desirable.



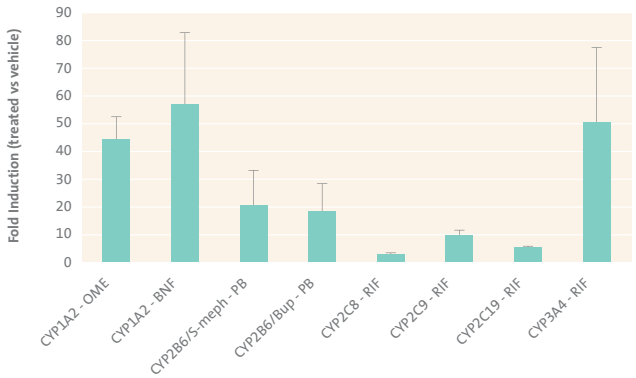
George Zhang

STUDY DIRECTOR

With over 15 years of research experience, Dr. George Zhang's expertise spans the areas of drug metabolism, enzyme induction and toxicity using *in vitro* models such as human hepatocytes. Prior to joining Corning, George investigated oxidative stress-induced hepatocyte toxicity and cytoprotection as an Assistant Research Professor in the Department of Pharmaceutical Sciences at Washington State University. He received his Ph.D. in Pharmacology and Toxicology from the University of Liverpool, UK where he studied nephrotoxicity and its antidotes. George also completed additional post-doctoral training on oxidative stress in myocardial ischemia and reperfusion at the University of Leicester, UK, Department of Surgery. He has authored and co-authored over 35 peer-reviewed papers in the areas of cytochrome P450 induction, oxidative stress and cytoprotection.

P450 Enzyme	Positive Control Inducer
CYP1A2	Omeprazole, ß-naphthoflavone
CYP2B6	Phenobarbital
CYP2C8	Rifampin
CYP2C9	Rifampin
CYP2C19	Rifampin
CYP3A4	Rifampin

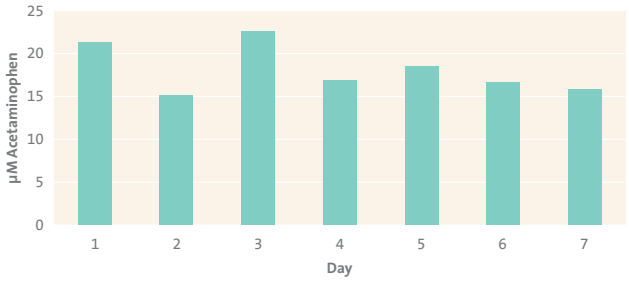
Robust Dynamic Range to Assess Induction Response



Flexibility to use multiple inducers or assays for the same enzyme with robust analytical sensitivity. Mean and standard deviation of fold induction of enzyme activity in 3 donors after treatment of 50 µM omeprazole (OME), 20 µM ß-naphthoflavone (BNF), 1 mM phenobarbital (PB) or 10 µM rifampin (RIF). Enzyme activities measured were phenacetin O-deethylase, S-mephenytoin N-demethylase, bupropion hydroxylase, amodiaquine N-deethylase, diclofenac 4'-hydroxylase, S-mephenytoin 4'-hydroxylase and testosterone 6ß-hydroxylase.

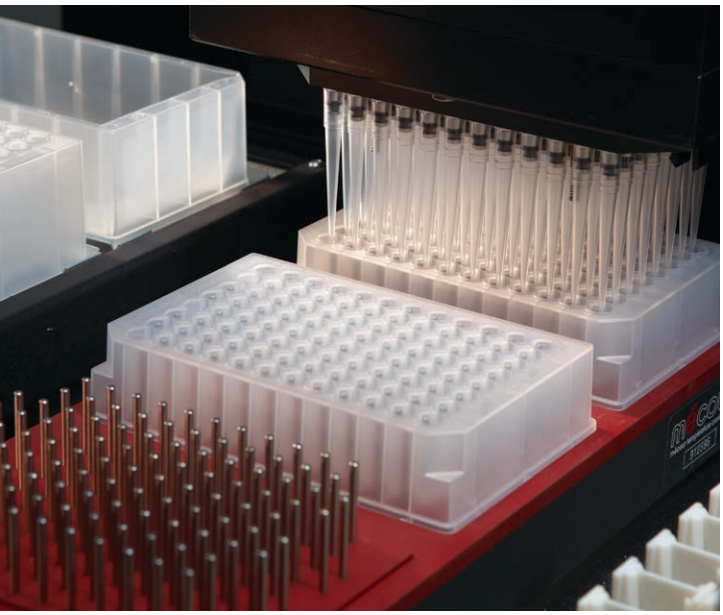
Reproducible Induction Response in Corning® Gentest™ Inducible-qualified Human CryoHepatocytes

Omeprazole-induced CYP1A2 catalytic activity in Corning Gentest Inducible-qualified Human CryoHepatocytes on 7 independent days



Highly reproducible, robust data. Phenacetin O-deethylase activity in a single donor (lot 246) of Corning Gentest Inducible-qualified Human cryopreserved hepatocytes in 7 independent experiments conducted over the span of 18 weeks. Cells were treated with 50 µM omeprazole (OME) for 2 days prior to determination of enzyme activity. The amount of acetaminophen metabolite formation was determined by incubating cells with 100 µM phenacetin for 30 minutes.

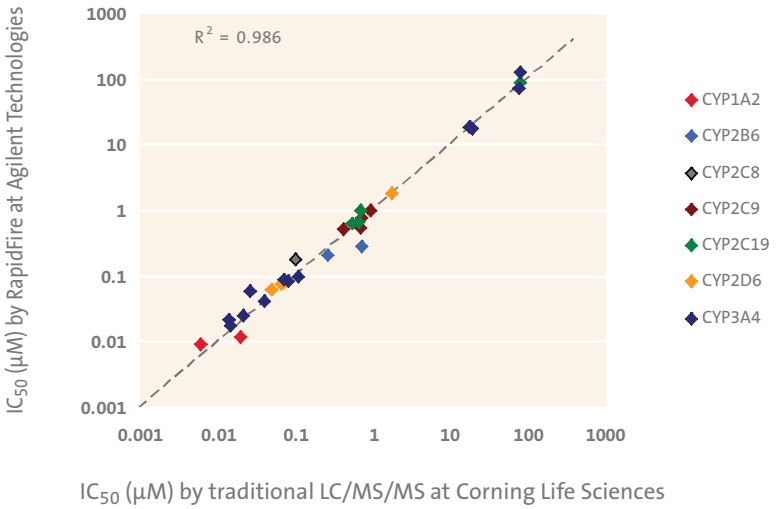
CYP INHIBITION expertise



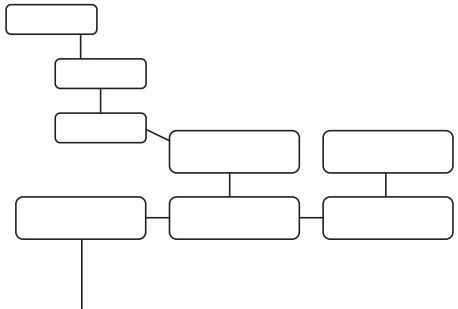
High-throughput CYP Inhibition service with FDA-recommended probe substrates

Inhibition of cytochrome P450 enzyme catalytic activity is a leading mechanism of metabolism-based drug-drug interactions. *In vitro* inhibition studies are valuable predictors of *in vivo* drug-drug interactions and the magnitude of that interaction. In many cases, this information can eliminate the need for further *in vivo* studies. The *in vitro* ADME market leader in P450 products and services, Corning, and the technology leader in high-throughput mass spectrometry, Agilent Technologies, are combining expertise to provide a novel mass spectrometry-based, high-throughput complete service package for cytochrome P450 inhibition. Corning CYP Inhibition Services deliver high-quality data analysis with use of Corning® UltraPool™ HLM 150 liver microsomes. Complete package of sample preparation and rapid turnaround of data analysis is provided at the conclusion of this service.

Correlation Data between Conventional LC/MS at Corning and RapidFire® at Agilent Technologies



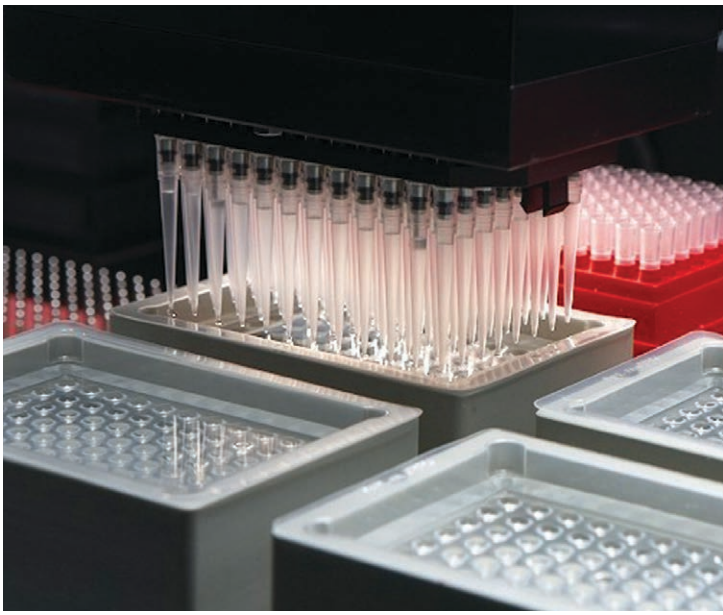
Data from 8 different enzyme/substrate pairs and 1 to 3 inhibitors for each pair was generated using traditional LC/MS/MS at Corning and RapidFire technology at Agilent Technologies. Inhibitors include ketoconazole, alpha-naphthoflavone, montelukast, S-benzylnirvanol, sulfaphenazole, azamulin, paroxetine, ticlopidine, S-fluoxetine, tienilic acid, verapamil, and diltiazem.



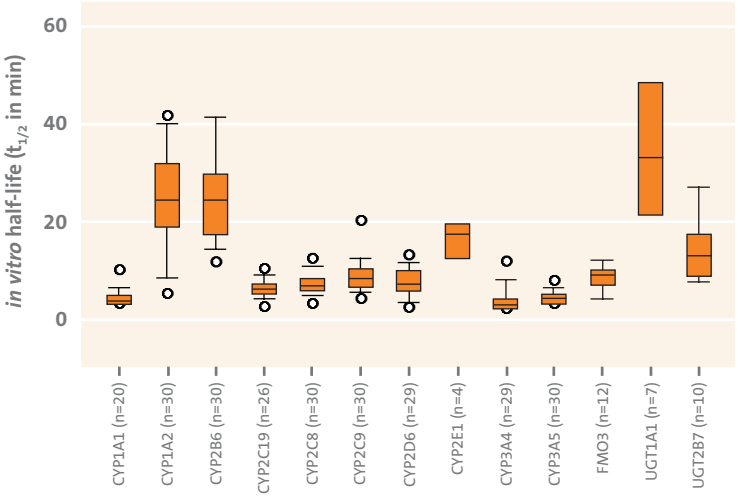
REACTION PHENOTYPING expertise

Enzyme identification by substrate loss analysis using Corning® Supersomes™ enzymes

Reaction phenotyping studies help identify the number and identity of P450, UGT or other enzyme-mediated pathways of elimination—important information that affects population variability in metabolism and the risk of becoming a victim drug in a drug-drug interaction event. Using Corning Supersomes, the gold standard for recombinant metabolizing enzymes, is a key element to delivering reproducible results. Enzyme concentrations for specific enzymes are fixed or scaled to provide activity proportionate to the average content in human liver microsomes. Enzyme content can be optimized for higher turnover—important for low-clearance drug candidates.



Historical Assay Performance for High-Throughput Reaction Phenotyping using Corning Supersomes Enzymes



Enzyme	Substrate	Enzyme conc.	Substrate conc.
CYP1A1	Amodiaquine	100 pmol/mL	10 µM
CYP1A2	Phenacetin	100 pmol/mL	10 µM
CYP2B6	Bupropion	50 pmol/mL	1.0 µM
CYP2C19	Omeprazole	100 pmol/mL	10 µM
CYP2C8	Amodiaquine	25 pmol/mL	10 µM
CYP2C9	Diclofenac	25 pmol/mL	10 µM
CYP2D6	Dextromethorphan	50 pmol/mL	10 µM
CYP2E1	P-nitrophenol	100 pmol/mL	1.0 µM
CYP3A4	Midazolam	25 pmol/mL	5.0 µM
CYP3A5	Midazolam	25 pmol/mL	5.0 µM
FMO3	Benzydamine	0.5 mg/mL	0.1 µM
UGT1A1	Estradiol	0.5 mg/mL	2.5 µM
UGT2B7	7-hfc	0.5 mg/mL	5.0 µM

In vitro half-life results obtained for positive controls under the conditions listed in the table. Boxes represent the 25th-75th percentile, the line indicates the median, error bars indicate the 90th and 10th percentiles, and circles represent outliers outside the 5th/95th percentiles. Data was obtained using multiple lots of Corning Supersomes enzymes on independent days.

PERMEABILITY AND DRUG TRANSPORT expertise

P-gp Interaction Assessment with Caco-2 or MDR1-LLC-Pk$_1$ Cell Monolayers

Bidirectional transport assays across Caco-2 and MDR1-LLC-PK$_1$ monolayers comply with the FDA recommended approach to determine apparent permeability of a test article and assess P-glycoprotein (P-gp) mediated transport and inhibition.

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Caco-2 is the *in vitro* gold standard method to evaluate test article permeability (P_{app})

An important factor in oral bioavailability is the ability of a compound to be well absorbed in the small intestine. Polarized cell monolayers have become the gold standard in *in vitro* test systems to quickly and cost effectively assess the permeability of a test article. Caco-2 cells resemble small intestinal epithelial cells in morphology and expression of certain enzymes and transporters. It is the most frequently used cell line for permeability testing and the recommended approach to rank order compounds according to the FDA's Biopharmaceutics Classification System (BCS) as low, medium, or high permeability compounds [1].

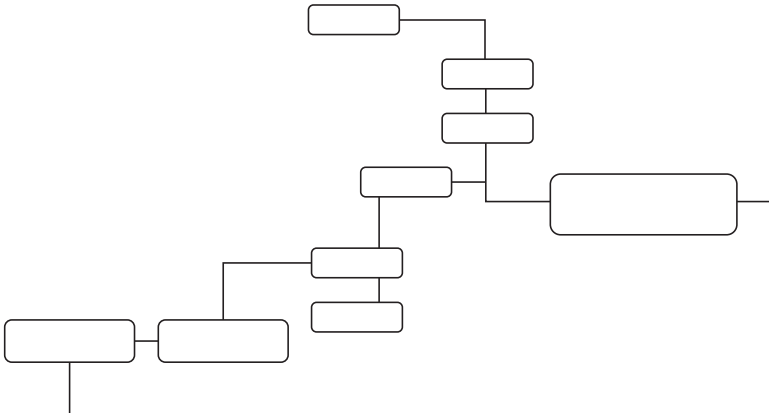
Caco-2 and MDR1-LLC-PK$_1$ cell lines are well characterized for efflux transporter activity

Efflux transporters other than P-gp, such as breast cancer resistance protein (BCRP) and multidrug resistance-associated protein (MRP2) can be expressed in commonly used cell lines such as MDCK.

Corning's Caco-2 and MDR1-LLC-PK$_1$ cells are characterized for P-gp, BCRP, and MRP2 activity facilitating interpretation of efflux results.

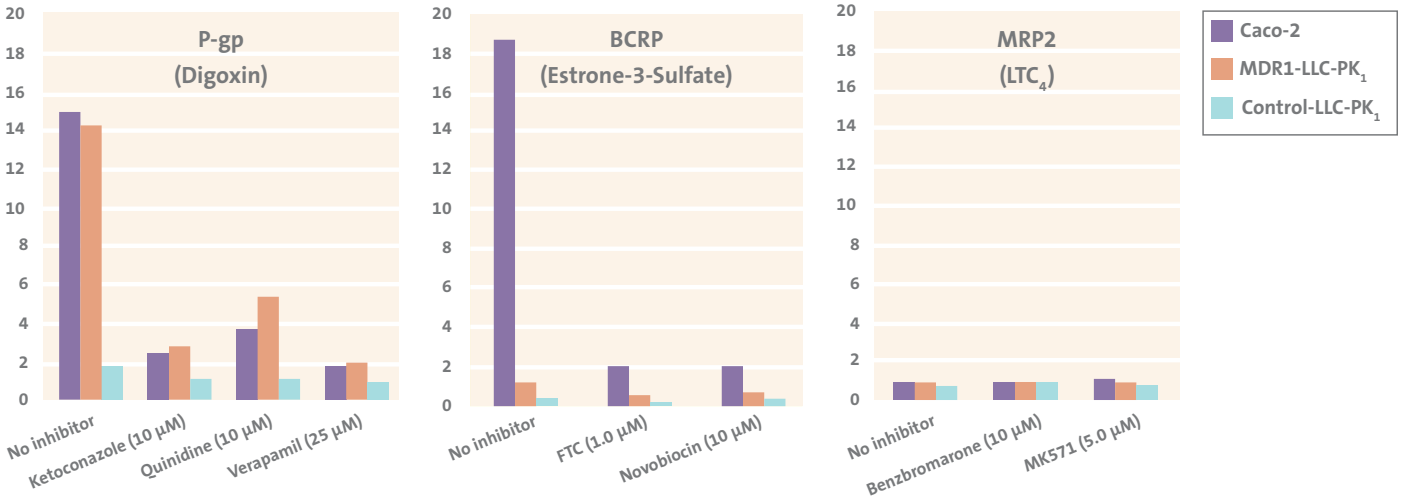
FDA recommends bidirectional transport assays in polarized cell models to identify substrates and inhibitors of P-glycoprotein

Transporter proteins expressed in various tissues including intestinal epithelium, kidney, liver, and blood-brain barrier are recognized for their effects on drug disposition. Current-FDA guidance [2] recommends the testing of investigational drugs for interactions with P-glycoprotein (P-gp) using bidirectional transport assays in polarized cell models. Caco-2 and MDR1-LLC-PK$_1$ cells both show high levels of P-gp activity making them excellent models for P-gp-mediated drug transport studies.



[1] U.S. FDA/CDER, Biopharmaceutics Classification System (BCS), August 2000.
[2] U.S. FDA/CDER, Drug Interaction Studies - Study Design, Data Analysis, and Implications for Dosing and Labeling, DRAFT GUIDANCE, September 2006.

Efflux Transporter Activity in Caco-2 and LLC-Pk$_1$ Cell Monolayers



P-gp, BCRP, and MRP2 transporter activity assessment in Caco-2 and LLC-PK$_1$ cell monolayers

Data represents efflux ratios of each probe substrate and the effects of prototypical inhibitors on the activity of each transporter. Efflux ratios were generated from mean A-B and B-A P_{app} values of duplicate monolayers.

Efflux of the P-gp probe substrate digoxin was observed in both Caco-2 and MDR1-LLC-PK$_1$ cells, and can be inhibited by the known P-gp inhibitors ketoconazole, quinidine, and verapamil. Efflux of the BCRP probe substrate estrone-3-sulfate (E3S) was observed in Caco-2 cells only, with an efflux ratio similar to that of digoxin. E3S efflux is significantly inhibited by the BCRP inhibitors novobiocin and fumitremorgin C (FTC). No efflux was observed for the MRP2 substrate LTC_4 in either Caco-2 or MDR1-LLC-PK$_1$ cells. LLC-PK$_1$ control cells showed no efflux activity for any of the probe substrates.

Expression of Human MDR1 cDNA Cell Lines

MDR1-LLC-PK$_1$ and Caco-2 cell monolayers are widely used for permeability and transporter interaction studies for assessment of P-glycoprotein (P-gp)-mediated drug transporter interactions as recommended by the USFDA.

MDR1-LLC-PK$_1$ cells predominantly express human P-gp against a low background of porcine P-gp and other transporters making MDR1-LLC-PK$_1$ an excellent model to study human P-gp specifically. This is unlike Caco-2 cells that exhibit both human P-gp and BCRP (Kapadnis et al, 2009 Drug Met Rev. Abstr. no 359).

Corning provides a cell line expressing human MDR1 cDNA for use by researchers' research products and contract research services

Lisa Fox

STUDY DIRECTOR

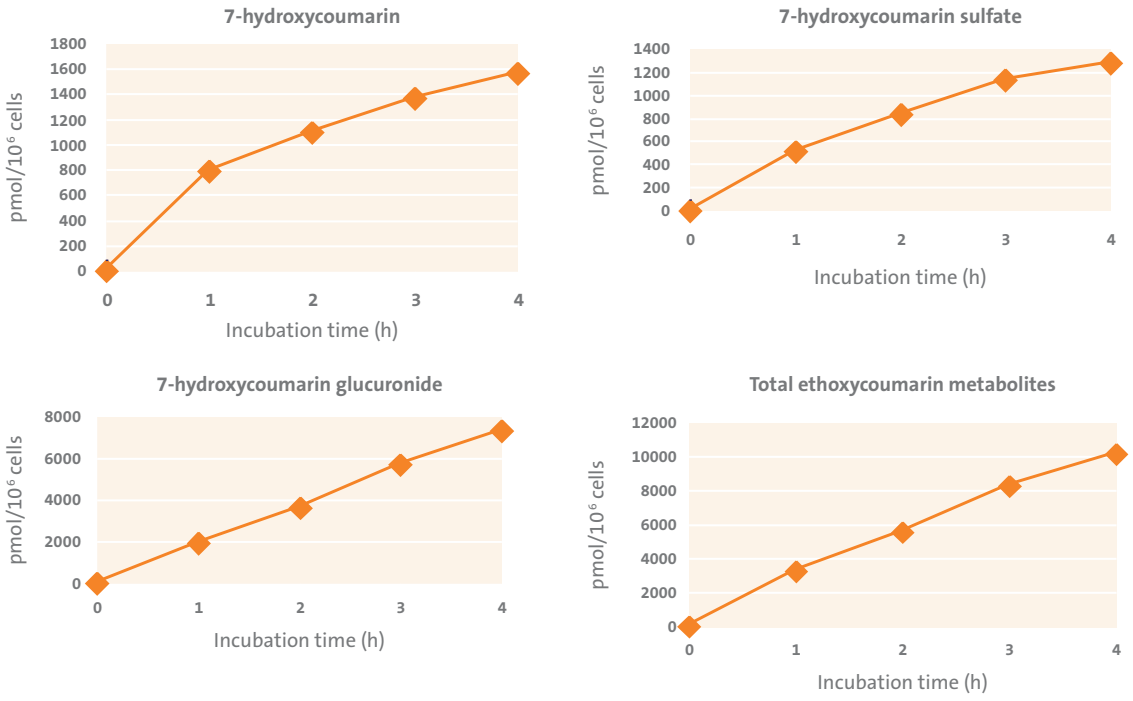
Lisa is a Senior Research Scientist and Study Director working in the area of ADME cell-based products and services. In her eleven years at Corning, Lisa's main R&D focus has been in the development of transporter models and services (hepatocytes, Caco-2 and transporter cDNA-expressing cell lines, membranes vesicles, oocytes, and cell culture permeable support systems). In her role as a Study Director within the ADME Contract Research Services group, Lisa directs drug-transporter interaction, permeability, and plasma protein binding studies in both Discovery and Development platforms. Before joining Corning, Lisa worked in the Clinical Pharmacokinetics and Disposition department of a large pharmaceutical company, and in a Harvard/BIDMC research group studying the roles and functions of mast cells.

METABOLIC STABILITY expertise

Metabolic stability assays measure the stability of a test compound by incubating the test compound with liver microsomes, hepatocytes, or S9 enzyme sources from human and animal species. Evaluating primary metabolism and pharmacokinetics in the liver helps identify whether a compound is chemically stable and metabolized at an acceptable rate within the body.

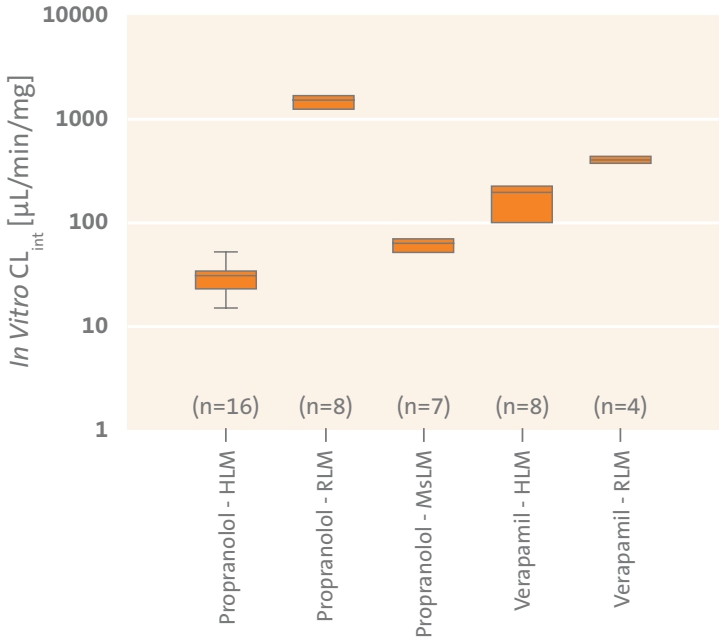
Corning provides rapid *in vitro* metabolic stability testing using several different enzyme sources. Most often, this test utilizes hepatocytes or liver microsomes. Corning's metabolic stability testing using hepatocytes features a carefully selected, single freeze, mixed gender 10-human donor pool and results provided for human and preclinical species. Our metabolic stability testing using microsomes maintains data consistency from assay-to-assay with mixed gender human liver microsomes donor pool consisting of 150 donors. Results are highly reproducible over extended periods of time using various lots of microsomes.

Time Course of Ethoxycoumarin Metabolism in Human Cryopreserved Hepatocytes



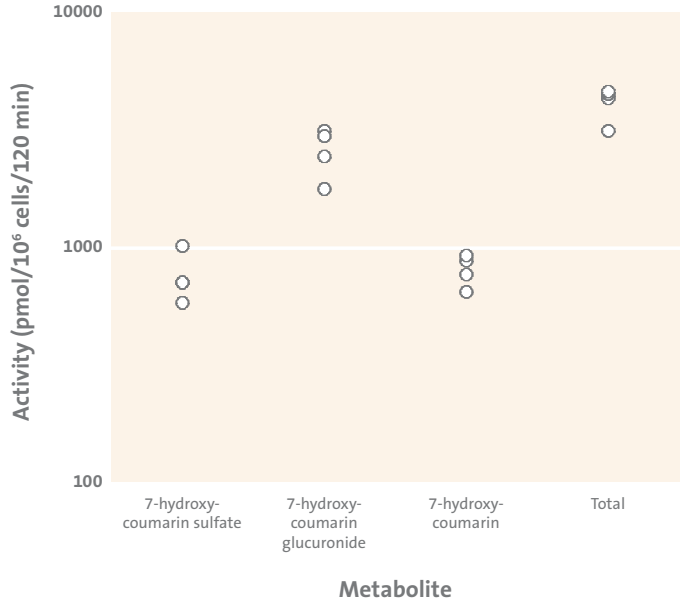
Time course of ethoxycoumarin metabolism in a 10-donor pool of single freeze, cryopreserved hepatocytes showing the expected linearity in formation of metabolites.

Historical Assay Performance for Metabolic Stability in Human, Rat, and Mouse Liver Microsomes



In vitro intrinsic clearance results obtained for positive control compounds in human (HLM), rat (RLM), and mouse (MsLM) liver microsomes. Boxes represent the 25th-75th percentile, the line marks the median, error bars indicate the 90th and 10th percentiles. Data was obtained using multiple lots of microsomes.

Interday Reproducibility of Ethoxycoumarin Metabolism



Metabolism of 50 µM ethoxycoumarin by a 10-donor pool of human cryopreserved hepatocytes. Values represent means of duplicate determinations on 4 independent days.

Product Highlights

Corning Study Directors have immediate access to high-quality Corning products for conducting studies, including Corning® Gentest™ HLMs, hepatocytes, chemicals and Corning Supersomes™, the industry gold standard for recombinant enzymes and the full portfolio of Corning cell culture products—enabling trusted science and reliable results.

Corning Gentest CryoHepatocytes

Corning Gentest metabolism-qualified human cryohepatocytes are suitable for in vivo *like metabolic stability and drug clearance studies. Every lot is extensively tested for phase I and II metabolic activities.*

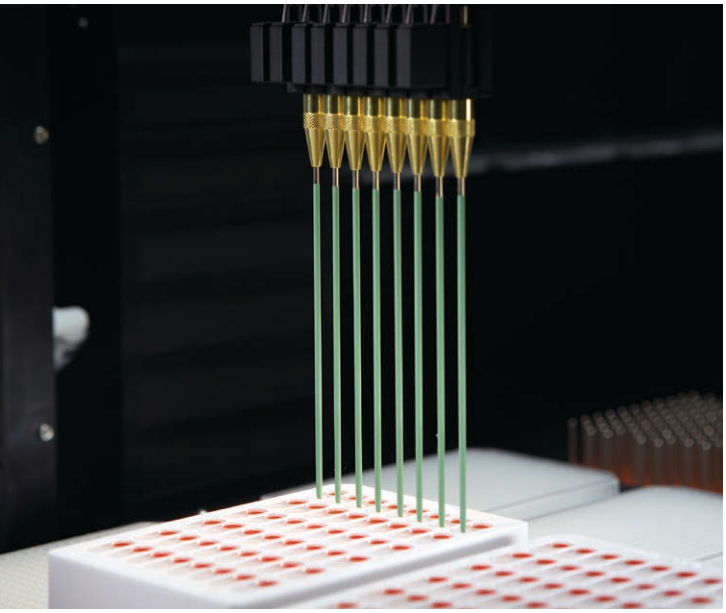
Corning UltraPool™ HLM 150

Corning launched Corning UltraPool HLM 150, the first commercially available large donor pool. This donor pool of 150 donors is statistically modeled to provide researchers with a high degree of lot-to-lot consistency for CYP and UGT enzyme activity and naturally represents the "average patient" and known CYP polymorphisms.

Corning Supersomes

Corning Supersomes enzymes have been validated by multiple laboratories for well over a decade, providing consistent batch-to-batch performance and the widest selection of enzymes. Assays are qualified for 35 human and rat Corning Supersomes enzymes. Human cytochrome P450 Corning Supersomes enzymes are formulated with P450 enzyme, human cytochrome P450 oxidoreductase, and human cytochrome b5 to deliver optimal performance.

PROTEIN BINDING expertise

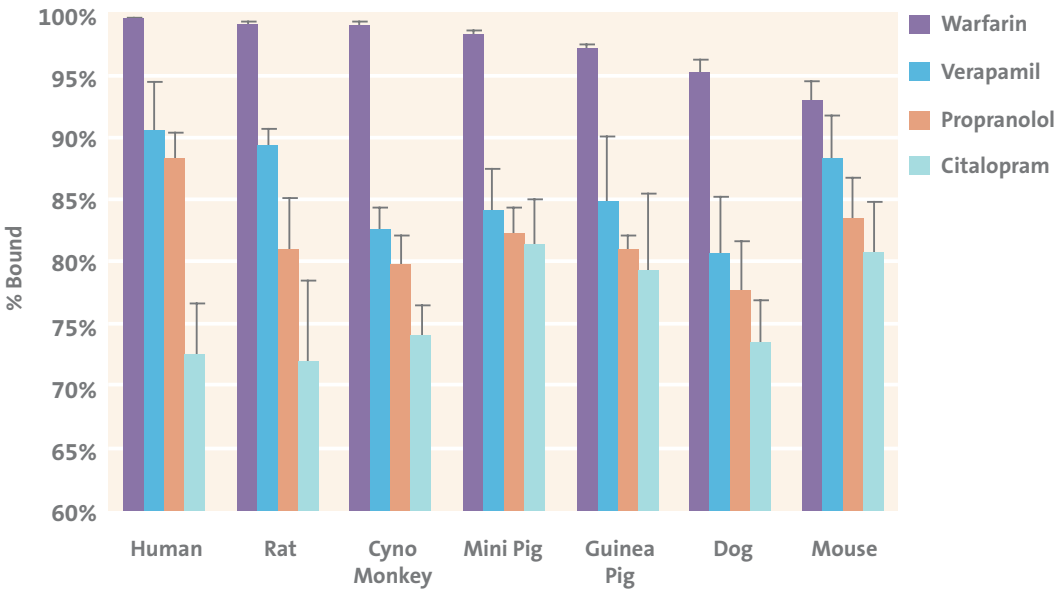


Plasma Protein Binding using Rapid Equilibrium Dialysis

Assessment of plasma protein binding by rapid equilibrium dialysis applies the gold standard equilibrium dialysis technique to a high throughput discovery setting to accurately determine the bound and unbound fractions of a test article in human or animal plasma. Corning Life Sciences conducts PPB assays by rapid equilibrium dialysis with LC/MS/MS quantitation which provides a cost-effective screening of large numbers of compounds and fast turnaround times.

Results obtained at Corning using rapid equilibrium dialysis in human plasma are consistent with data reported in the literature. Results are highly reproducible over extended periods of time using various lots of plasma.

Comparison of Protein Binding of Comparator Compounds in Human and Animal Plasma



Comparison of mean % bound values across seven species at 10 µM final concentrations. Data represent the means of replicates (N ≥ 5) with standard deviations as error bars.

David Stresser

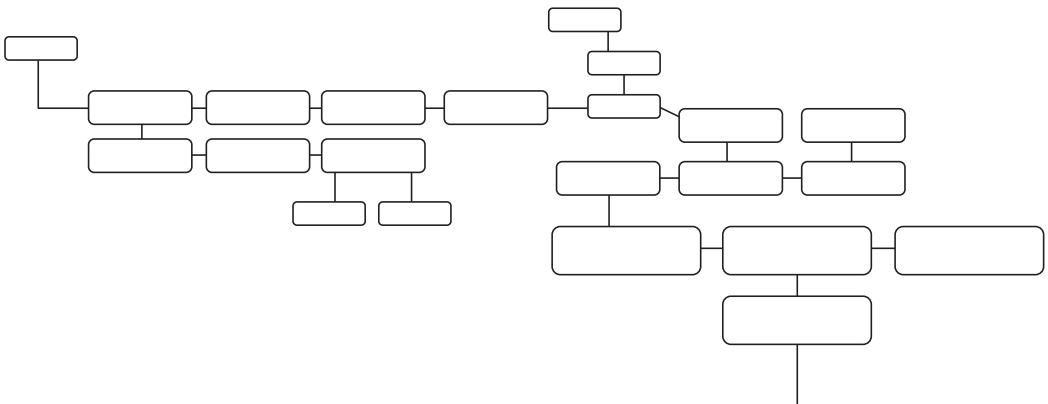
PROGRAM MANAGER

Dr. David Stresser has over 13 years experience in his current role, including services as a Study Director in the areas of CYP inhibition, induction and metabolism. Previously, David was a post-doctoral associate at the University of Massachusetts Medical School in Worcester, MA, in the Department of Pharmacology and Molecular Toxicology. David received a Ph.D. in Toxicology from Oregon State University. He has been an invited speaker at various international meetings and universities and is a regular instructor at the High-Throughput Drug Metabolism/Disposition course co-sponsored by EUFEPS. Most recently, he organized a short course covering *in vitro* ADME methods sponsored by the Society for Biomolecular Screening (Lille, France 2009). Dr. David Stresser holds a patent entitled "Use of fluorescein aryl ethers in high throughput cytochrome P450 inhibition assays" and has authored and co-authored 31 articles in the field of drug metabolism.

Protein Binding in Human Plasma Compared with Literature Values

	PERCENT BOUND		
Compound	**Literature**	**Experimental**	
Amitriptyline	95%	95.4%	(0.48%)
Atenolol	6-16%	4.0%	(16.40%)
Bumetanide	93%	98.9%	(0.19%)
Carbamazepine	76%	83.9%	(3.85%)
Erythromycin	84%	79.1%	(4.96%)
Haloperidol	92%	90.8%	(1.20%)
Imipramine	89-92%	91.9%	(0.89%)
Ketoprofen	>99%	99.6%	(0.17%)
Metoprolol	12%	3.5%	(32.00%)
Naproxen	99%	95.3%	(1.73%)
Propranolol	81-93%	83.2%	(3.95%)
Terfenadine	97%	99.5%	(0.30%)
Warfarin	99%	99.5%	(0.08%)
Furosemide	91-99%	89.8%	(1.23%)
Tolbutamide	96%	98.9%	(0.36%)
Verapamil	90%	92.9%	(1.83%)
Thioridazine	>95%	99.9%	(0.04%)
Tacrine	75%	63.3%	(6.21%)
Nadolol	30%	25.3%	(8.11%)
Linezolid	31%	49.0%	(15.60%)
Citalopram	80%	63.0%	(2.58%)

Comparison of % bound values obtained at Corning using rapid equilibrium dialysis in human plasma with literature data. Experimental values are means of replicates (N ≥ 4) with standard deviations in parentheses. Majority of literature values were collected from www.RXlist.com.



To initiate a study, contact:
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