

The Boston Society

Presents



**APPLIED
PHARMACEUTICAL
TOXICOLOGY**

2009 CONFERENCE

May 11 - 13, 2009

Conference Center at Harvard Medical

Boston, MA

Platinum



Silver



Pharmaceutical



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Welcome to the Applied Pharmaceutical Toxicology 2009 conference. The organizers of APT have gathered an outstanding group of speakers and have arranged the program to allow for extensive audience participation and discussion. We hope that all conference attendees will take the opportunity to engage in discussion to benefit fully from the APT experience. Thank you for your participation.

Organizers

*Jim Xu, Kevin Leach, Bruce Car, Drew Badger, Oliver Flint,
Laszlo Urban, Rick Robertson, Jim Green, Page Bouchard, Laura Andrews*

Speakers

*Bruce Car, Lois Lehman-McKeeman, John Donello, Don Robertson, Drew Badger, Vishal Vaidya, Bill Foster,
Doug Lauffenburger, Dmitri Mikhailov, Oliver Flint, Steven Whitebread, Scott Obach, Bob Chapin, Allison Easter,
Derek Leishman, Paul Levesque, Dale Morris, Ron Snyder, Jim Green, Luara Andrews, Pauline Martin,
Shawn Heidel, Rafael Ponce, Art Levin, Scott Henry, Akshay Vaishnav, Page Bouchard, Husam Younis*

Conference at a Glance

Monday:

**Integrative Systems Approaches to Discovery Toxicology
Application of in vitro Screening Technologies to Discovery Toxicology**

Tuesday:

**Leveraging Animal Models in Discovery
Predictivity of Non-clinical Safety Studies for Small Molecules**

Wednesday:

**Non-clinical Development of Oligonucleotide Therapeutics
Non-clinical Development of Biologics**

Conference Activity Locations

All APT events are at the Conference Center at Harvard Medical.

Workshop Presentations: Amphitheater (unless otherwise noted)

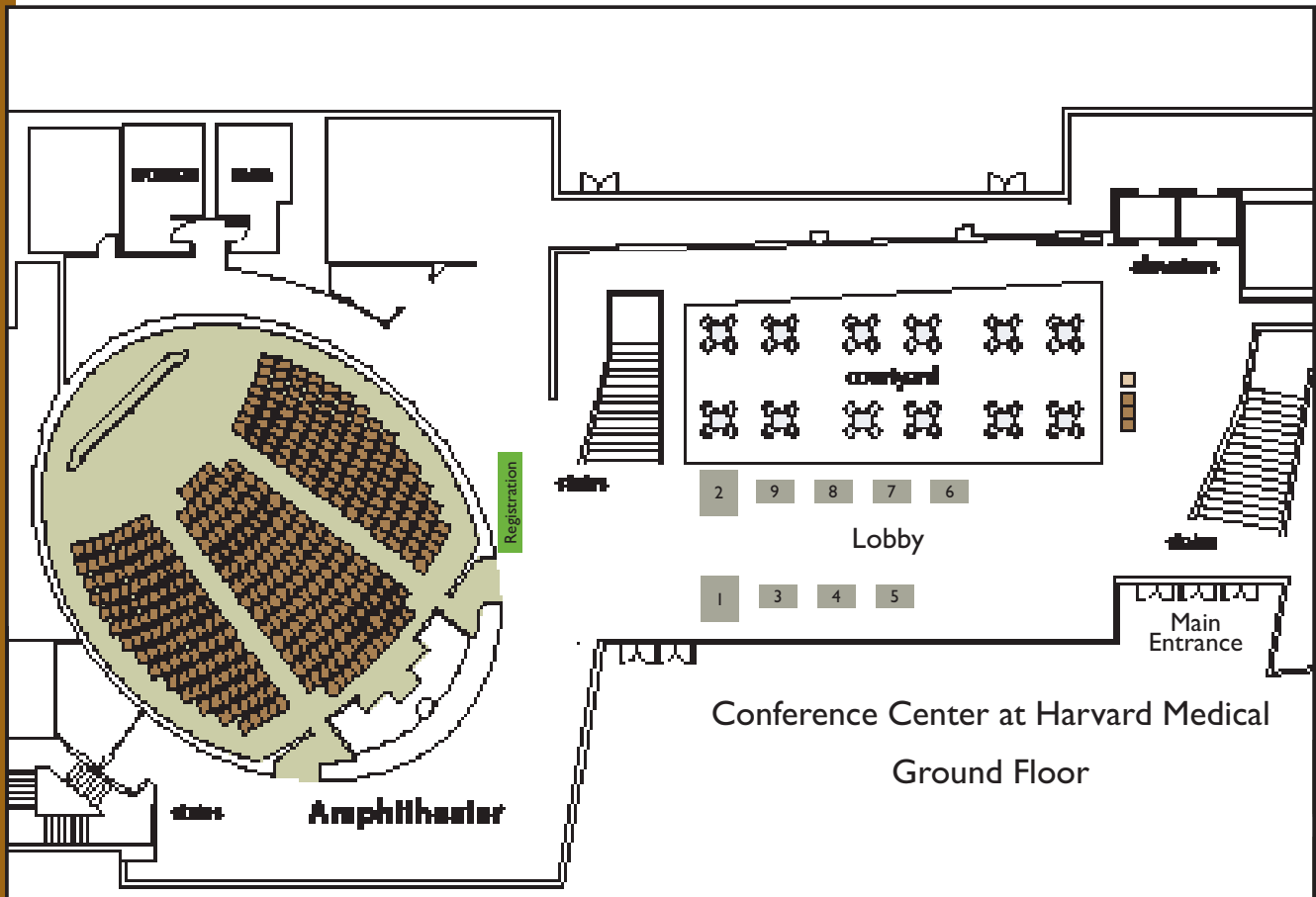
Exhibit Area: Lobby (Ground Floor)

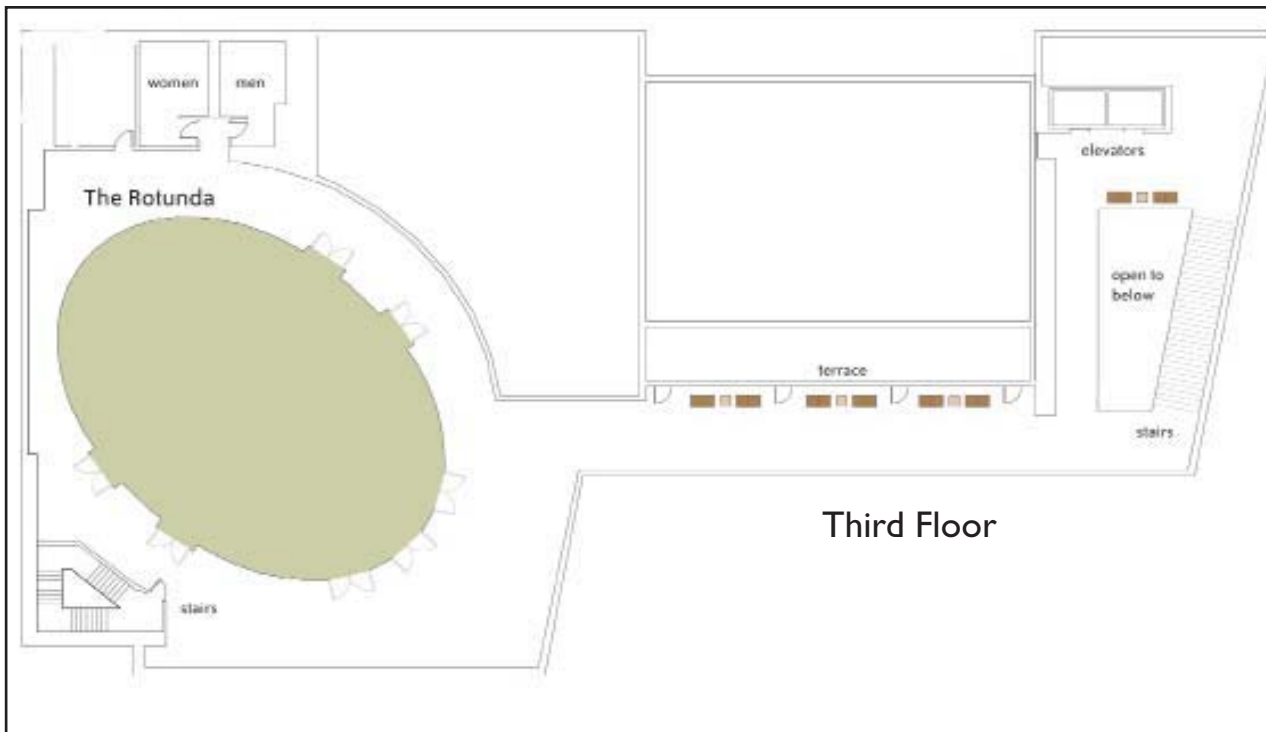
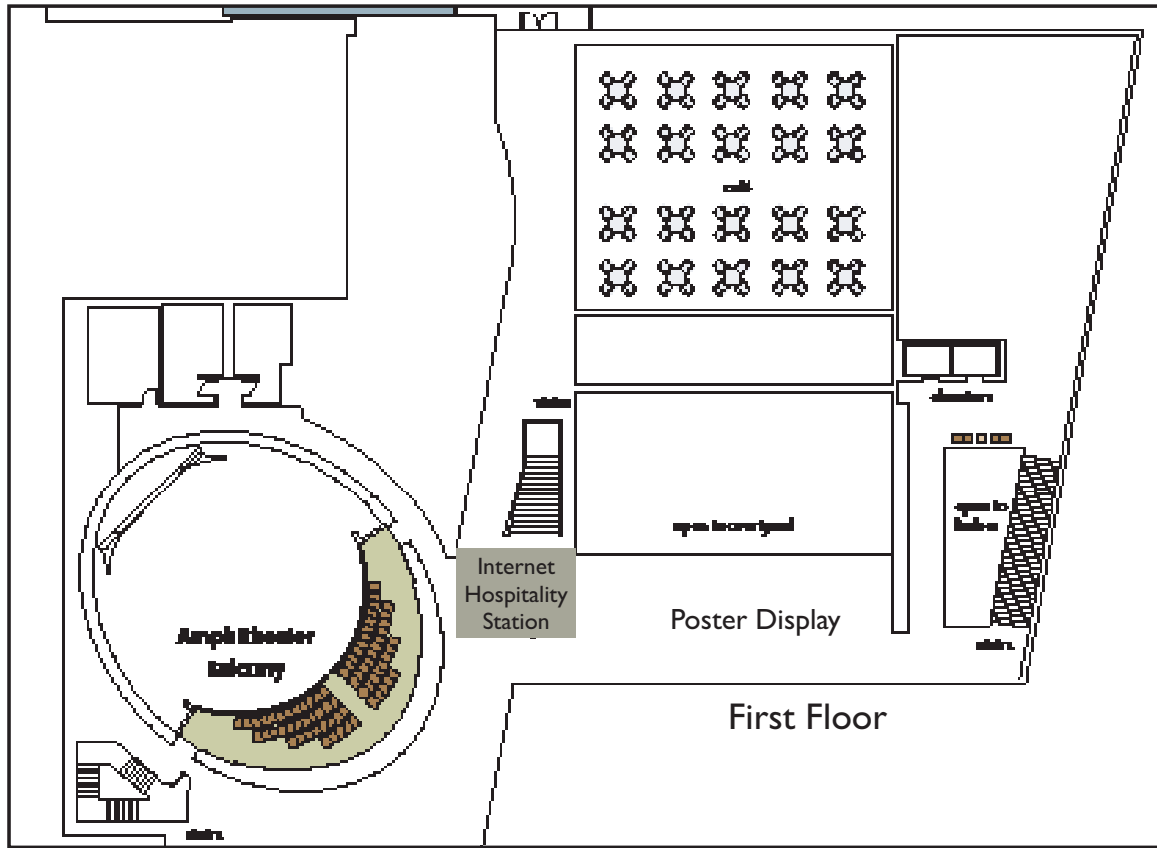
Luncheon Workshop: Rotunda (Third Floor)

Evening Receptions : Lobby (Ground Floor)

Poster Display: Lobby (First Floor)

Internet Hospitality Station: Lobby (First Floor)





Monday May 11, 2009

DISCOVERY TOXICOLOGY

- 08:30 AM - 9:15 AM **Plenary Speaker:** *Bruce Car, BMS: The mindset of discovery toxicology*
- Session I - Kevin Leach:**
Integrative Systems Approaches to Discovery Toxicology
- 09:30 AM - 10:00 AM Kim-1: a qualified biomarker for kidney toxicity, **Vishal Vaidya, Harvard**
- 10:20 AM - 10:50 AM Whole genome transcriptomics as a non-clinical pharm/tox endpoint, **Bill Foster, BMS**
- 11:00 AM - 11:30 AM **Break**
- 11:30 AM - 12:00 PM Quantitative systems analysis of hepatocellular responses to inflammatory cytokines and pharmacological agents, **Doug Lauffenburger, MIT**
- 12:10 PM - 01:10 PM **Lunch**
- Session II - Oliver Flint:**
Application of in vitro Screening Technologies to Discovery Toxicology
- 01:10 PM - 01:40 PM Adrenocortical toxicity following CYP11A1 metabolism of a kinase inhibitor, **Oliver Flint, BMS**
- 01:50 PM - 02:20 PM Applying informatics to enhance quality of integrated safety assessment, **Dmitri Mikhailov**
- 02:30 PM - 03:00 PM Developing drugs with a good safety profile: The impact of in vitro safety pharmacology profiling, **Steven Whitebread, Novartis**
- 03:10 PM - 03:20 PM **Break**
- 03:20 PM - 03:50 PM In vitro bioactivation and covalent binding assays: Do they help? **Scott Obach, Pfizer**
- 04:00 PM - 04:30 PM Mouse embryonic stem cells in vitro as predictors of developmental toxicity in vivo, **Bob Chapin, Pfizer**
- 04:40 PM - 05:10 PM The use of the in vitro techniques in the assessment of seizure liability, **Allison Easter, AZ**

Tuesday May 12, 2009

Session III - Drew Badger: Leveraging Animal Models in Discovery

- 08:45 AM - 09:15 AM Applying efficacy models to hazard identification: Valuable tools or red herrings?
Lois Lehman-McKeeman, BMS
- 09:25 AM - 09:55 AM Don't kill my compound too quickly: Memoirs of a pharmacologist,
John Donello, Allergan
- 09:55 AM - 10:25 AM **Break**
- 10:35 AM - 11:05 AM Metabonomics and the muddle of models, **Don Robertson, BMS**
- 11:15 AM - 11:45 AM Bridging the gap between discovery and regulatory toxicology, **Drew Badger, Amira**
- 11:55 AM - 12:55 PM **Lunch**

DEVELOPMENT TOXICOLOGY

Session I - Rick Robertson: Predictivity of Non-clinical Safety Studies for Small Molecules

- 12:55 PM - 01:20 PM How well do non clinical studies predict clinical cardiac safety? **Derek Leishman, Lilly**
- 01:30 PM - 01:55 PM Customizing CV safety strategy for early risk perspective, **Paul Levesque, BMS**
- 02:05 PM - 02:35 PM **Break**
- 02:35 PM - 03:00 PM Species comparison of the adverse effects of p38 MAP kinase inhibitors.
Dale Morris, Pfizer
- 03:10 PM - 03:35 PM The use of in silico and direct genotoxicity testing to evaluate potential genotoxic impurities in drug product, **Ronald Snyder, Schering**

Wednesday May 13, 2009

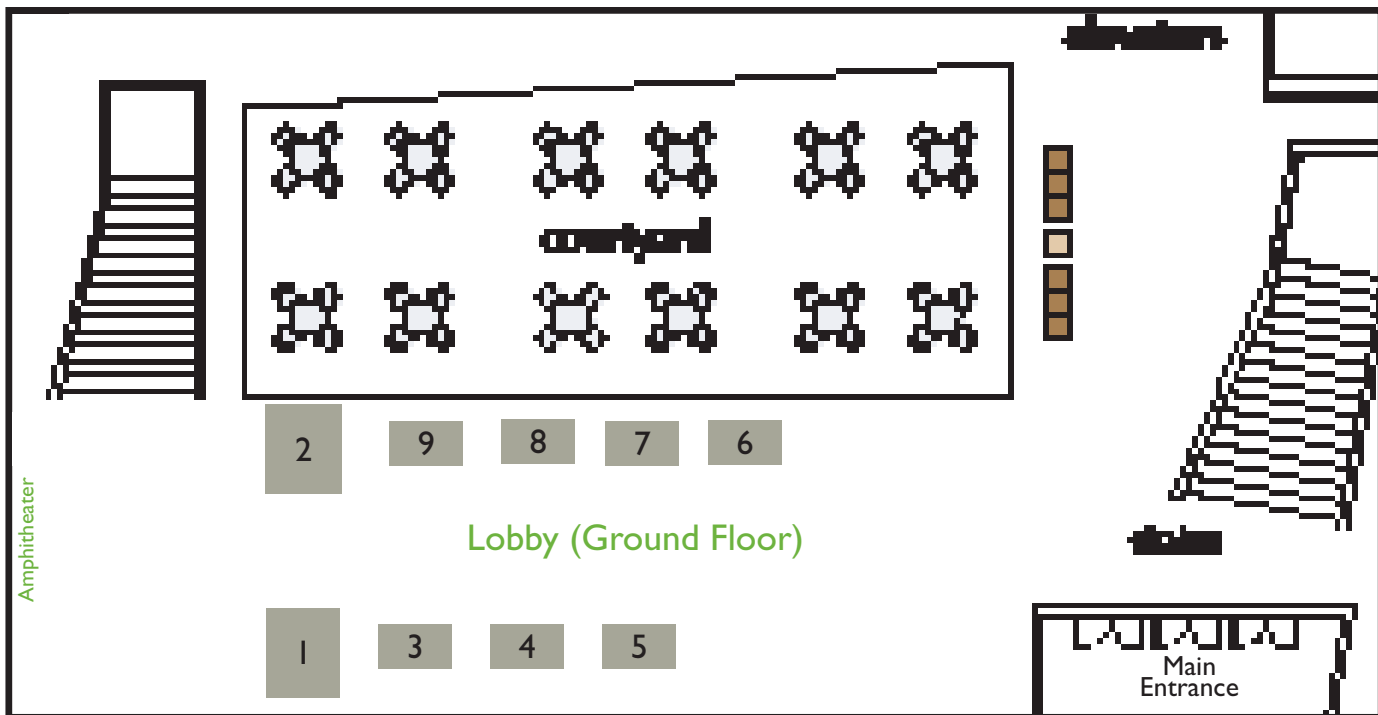
DEVELOPMENT TOXICOLOGY

Session II - Laura Andrews: Non-clinical Development of Biologics

- 08:00 AM - 08:20 AM Unique aspects of safety assessment programs for biologics, **Jim Green**, *Biogen Idec*
- 08:30 AM - 09:05 AM Program designs and the selection of species utilized for safety assessment studies, **Laura Andrews**, *Genzyme*
- 09:15 AM - 09:50 AM Developmental and reproductive toxicity testing for biopharmaceuticals, **Pauline Martin**, *Centocor*
- 10:00 AM - 10:30 AM **Break**
- 10:30 AM - 11:05 AM Carcinogenicity assessment of biotherapeutics, **Shawn Heidel**, *Lilly*
- 11:15 AM - 11:50 AM Immunogenicity and safety assessment of biologics: Recommendations from BioSafe, **Rafael Ponce**, *Amgen*
- 12:00 PM - 01:00 PM **Lunch**

Session III - Page Bouchard: Non-clinical Development of Oligonucleotide Therapeutics

- 01:00 PM - 01:25 PM A retrospective on oligonucleotide therapeutics: understanding the class effects, **Art Levin**, *Consultant*
- 01:35 PM - 02:00 PM Antisense Oligonucleotide: Progress in the Development of a Novel Therapeutic Platform, **Scott Henry**, *ISIS*
- 02:10 PM - 02:40 PM **Break**
- 02:40 PM - 03:05 PM siRNA toxicology, specific considerations in program and study design, and general overview of key findings and risk assessment perspectives, **Akshay Vaishnav**, *Alnylam*
- 03:15 PM - 03:40 PM Toxicology testing of aptamer therapeutics; specific considerations in program and study design, overview of key findings, and risk assessment perspectives, **Page Bouchard**, *Archemix*
- 03:50 PM - 04:15 PM Differential immunostimulatory properties of CpG and non-CpG oligonucleotides, **Husam Younis**, *Pfizer*



Sponsor Listing by Booth Number

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Monday Discovery Toxicology Workshop

The Evolution of the Mindset, Science and Business Model of Pharmaceuticals Discovery Toxicology, **Bruce Car**

The concept that focused toxicology expertise embedded in the Discovery environment will reduce compound loss is no longer new, though the gestalt of this entity has evolved from many efforts across multiple functions to a single group now in several companies. In general, the charge of these groups has been to vet molecules and molecular targets for liabilities likely to lead to a drug's attrition or safety issues in the clinic. How this charge has been executed has changed considerably over time. Drugs exposed to cell lines representing the spectrum of target organs and tissues with subsequent cytotoxicity assessments were early shown to be of little predictive usefulness. Focused primary and some cell line assays, however, when used reactively could be quite useful. These cell lines were resurrected and subsequently reentered as new cytotoxicity endpoints, high content morphologic endpoints, transcriptomic and metabolomic indices were applied, reconfirming their general lack of predictive robustness. In silico predictions for complex toxicity came and went and exist now largely as literature collation tools with mixed impact. Through all this experimentation, a few staples - predictive hepatocellular toxicity assays, predictive genotoxicity assays, electrophysiology of stably transfected cell lines, rat embryo culture and others provided quite valuable supplements to information obtained from knockouts, in vivo safety pharmacology, toxicology, pharmacology studies, and the often overlooked historic scientific literature. The value of predictions, weak or strong, depends entirely on the thoughtful integration of pharmacology, biotransformation, pharmacokinetics and pharmaceuticals data sets with those of toxicology. Having identified a broad range of assays able to detect multiple causes of compound failure, attrition was substantially reduced from historic highs, however, assay creep led Discovery groups away from hypothesis testing to checkbox screens in a risk-averse process that delayed passage of compounds from Discovery to Development at considerable cost. The current cycle recognizes and attempts to reign in our testing fetish when appropriate, accepting slightly increased risk for significant savings in cycle time and money, and thereby allowing a greater scientific focus of limited Discovery resources.

Integrative Systems Approaches to Discovery Toxicology, **Vishal Vaidya**

Drug-induced nephrotoxicity plays a major role in the high incidence and prevalence of kidney injury in both hospitalized and non-hospitalized patients, which in many circumstances can be prevented or at least minimized by effective predictive toxicity screening in preclinical drug development studies. The absence of sensitive, specific, reliable and reproducible renal injury biomarkers affects the evaluation of response to therapy and individual patient safety, especially dose monitoring decisions for important life saving drugs with potential inherent kidney toxicity risk. For the last 100 years there have been no accepted kidney injury biomarkers. The standard metrics such as serum creatinine and blood urea nitrogen are very insensitive and non-specific functional biomarkers. The urine has yielded the most promising markers for the early detection of acute kidney injury (AKI) and further characterization is anticipated, which will qualify these markers as useful tools for the earlier diagnosis, identification of mechanism of injury, and assessment of site and severity of injury. Hopefully, one or more of these biomarkers, either alone or in combination, will prove to be useful in facilitating early diagnosis, guiding targeted intervention and monitoring disease progression and resolution. Translational biomarkers have the potential to not only transform the way we do predictive nephrotoxicity assessment but also the way we diagnose and treat patients with AKI.

KIMI biomarker discovery of kidney tox, **Bill Foster**

Transcriptional profiling of tissues from non-clinical studies can provide helpful additional and timely perspective on the pharmacology and toxicity of early drug candidates. Developing these helpful perspectives, however, is contingent on assessing the omic study data in relationship to: the traditional study data, historical collections of omic data, and relative to established omic phenotypes and pharm/tox mechanisms of action. This talk provides examples from early non-clinical drug safety studies where data integration and systems biology viewpoints played an essential role in developing transcriptomic contributions to safety assessment. The additional perspectives provided by non-clinical transcriptomics, though often helpful, are generally of lower resolution and involve greater interpretive cost and tox/path expertise than was originally envisioned as the promised landscape at the inception of omics/toxicogenomics a decade ago.

Monday Discovery Toxicology Workshop

Quantitative Systems Analysis of Hepatocellular Responses to Inflammatory Cytokines and Pharmacological Agents, **Doug Lauffenburger**

We are pursuing a systematic approach to quantitatively assess relationships between multiple combinations of inflammatory cytokines and pharmacological agents in inducing hepatotoxicity in a set of in vitro systems including primary rat hepatocytes, primary human hepatocytes, and a transformed hepatic cell line (HepG2). Our goal is to gain insights concerning how physiologically-relevant cytokines might facilitate development of lethal (apoptotic and necrotic cell death) and/or sub-lethal (loss of differentiated function) hepatotoxicities by idiosyncratic hepatotoxic drugs. In the work we report here, combinatorial data sets of cytokine- and drug-induced lethal hepatotoxicity phenotypes in each cellular system were subjected to factorial analysis and principal component analysis to identify multivariate relationships between underlying drug and cytokine treatment variables and to compare these relationships between cellular systems. A subset of cytokine treatment conditions were used to explore the differential lethal and sub-lethal hepatotoxicity sensitivities of each cellular system (or, more likely, primary rat hepatocytes only) to multiple sets of non-idiosyncratic and idiosyncratic drug pairs, showing that cytokine-drug hepatotoxicity synergies exist at physiologically relevant drug concentrations and are informative in distinguishing idiosyncratic

Adrenocortical Toxicity Following CYP11A1 Metabolism of a Kinase Inhibitor, **Oliver Flint**

Kinase inhibitors have been found to induce a wide range of unexpected toxicities. In this study we describe an adrenal-specific toxicity of a Met-kinase inhibitor, mediated by local metabolism of the drug to a toxic reactive metabolite. The specific metabolizing enzyme involved was identified by mRNA silencing. Comparison of treated human and rat adrenal cell lines indicated a possible species-specific toxicity for the rodent.

Applying informatics to enhance quality of integrated safety assessment, **Dmitri Mikhailov**

Novartis has established informatics approaches to enable integrated safety assessment in discovery phase. These include decision support applications for prospective evaluation of early cardiosafety risks and broad in vitro safety pharmacology panel. In addition we have developed predictive chemogenomics models to generate off-target mechanistic hypotheses for compounds that have shown in vivo toxicity in preclinical studies and to suggest possible follow up studies. The talk will include several case studies.

Developing drugs with a good safety profile: The impact of In vitro Safety Pharmacology Profiling, **Steven Whitebread**

One of the main reasons for the failure of drugs during development and in the clinic is safety, or an insufficient safety margin at the efficacious dose. In vitro Safety Pharmacology Profiling is the routine testing of new chemical entities in panels of in vitro assays, each of which have been linked to specific adverse drug reactions in humans. Novel experimental approaches and integrated use of in vitro Safety Pharmacology Profiling data increasingly aid medicinal chemists in the selection of lead candidates with the best safety profile and to reduce the risk of failure during development. We will provide specific examples of the more refined use and impact of in vitro Safety Pharmacology Profiling data on drug discovery programs.

Monday Discovery Toxicology Workshop

In vitro bioactivation and covalent binding assays: Do they help?, **Scott Obach**

The use of in vitro assays to assess the potential for bioactivation of new compounds in early drug research has become common. Such assays include nucleophile trapping assays and covalent binding assessments in which new compounds are incubated in human-derived in vitro systems containing active cytochrome P450 enzymes. While these assays have been advocated as useful for decision making in drug discovery screening strategies, there is growing evidence that their fidelity is not great enough to be able to distinguish from those compounds that will have unacceptable levels of toxicity in humans from those that will be generally regarded as safe. In a quantitative assessment of metabolism-dependent covalent binding, we assessed the performance of three different human-derived in vitro systems of varying complexity with eighteen radio-labelled drugs, nine of which are considered human hepatotoxins and nine that are not. Covalent binding data alone do not distinguish the two groups of drugs but inclusion of cofactors involved in detoxication of reactive intermediates, consideration of the contribution of the bioactivation pathway relative to total metabolism, and the consideration of total daily dose helped separate the toxins from the non-toxins. In an attempt to explain the covalent binding results additional biotransformation investigations on individual case examples were conducted and will be described. The placement of in vitro bioactivation screening in drug discovery will be proposed.

Mouse embryonic stem cells in vitro as predictors of developmental toxicity in vivo, **Bob Chapin**

The promise of stem cells is being met first in applications which assess drug safety. For 7 years now, our lab has been using and working to improve the stem cell-based assay which predicts effects on embryofetal development. This assay was developed, evaluated and "validated" by the European Commission for the Validation of Alternative Methods (ECVAM). No alternative test is ever perfect, particularly in the early years of use, so we focused our efforts on further understanding the limits of the test, exploring possible improvements, and folding in those changes which produced greater predictivity. This presentation describes that journey towards a more predictive assay, which now includes several measures of gene expression in addition to the original concentrations that inhibit cell growth or differentiation by 50%, as well as the slope of that line at those points, and a different statistical predictive model

The use of the in vitro techniques in the assessment of seizure liability, **Alison Easter**

The evaluation of a compound for seizure potential typically occurs late in drug discovery, with convulsion in animals as the first indication of risk. We have developed a preclinical screening strategy to better assess seizure liability in which assays are placed in step-wise cascade according to throughput and predictivity. At the early phases of discovery, in vitro techniques are the most suitable due to relatively high throughput and low resource requirements. This presentation will focus on two aspects of our strategy, pharmacological profiling and in vitro brain slice electrophysiology, and how these tools can be used in the early assessment of seizure liability and their predictive value when compared to more traditional in vivo approaches.

Tuesday Discovery Toxicology Workshop

Applying efficacy models to hazard identification: Valuable tools or red herrings? **Lois Lehman-McKeeman**

Discovery programs typically include animal models for evaluating efficacy, and as studies in these models often precede in vivo assessments of toxicity, they can provide the first evidence for potential target-related or chemotype-mediated toxicities. Such early evidence for drug-related toxicities at pharmacologically-effective dosages can have major impact on program directions and viability. However, although the efficacy models may replicate important aspects of the intended disease and yield meaningful data on pharmacodynamic effects, they may or may not provide accurate information on toxic outcome. In order to leverage efficacy models for early toxicology evaluations, it is important to understand whether the nature of the disease state alters drug disposition or alters the dose-response relationship for potential adverse effects. For example, recent data indicates that constitutive expression of numerous hepatic cytochrome P450 enzymes and xenobiotic transporters is altered in ob/ob mice, suggesting that biotransformation and pharmacokinetics may differ in this model relative to normal

Tuesday Discovery Toxicology Workshop

mice. Furthermore, high fat diets that are widely used in rat or mouse models of diabetes or obesity markedly alter hepatic gene expression as determined by transcriptional or metabonomic profiling, with significant alterations in cell cycle regulation, xenobiotic metabolism and inflammatory cytokines and chemokines. Consequently, it is possible that drug candidates may show altered metabolic clearance and potential for toxicity in an obese model relative to the lean and otherwise healthy animal used in standard toxicology studies. In general, the use of disease models can facilitate early toxicology assessments, but it is important to have some information on the overall phenotype of the model in relation to assessing compound liabilities and interpreting the outcome of these studies.

Don't kill my compound too quickly: Memoirs of a pharmacologist, John Donello

Within the drug discovery and development organization, compound development requires individuals of disparate scientific cultures and disciplines to develop a common understanding of stage specific strategic goals. One strategic approach to increase the productivity and cost efficiency of drug discovery/development is to “Kill Compounds Early”. In other words, accelerate the attrition of compounds early in the discovery/development cycle. However, the “kill compounds early” strategy is fraught with peril that may actually slow the acquirement of key learnings within a discovery program. To be successful, execution of this strategy 1) requires the immediate, short and long term goals of a discovery team be clearly defined and understood by all team members 2) incorporate prior knowledge about the drug target, the chemical class, and pharmacology to identify key criteria and 3) generate valuable and pertinent data at the appropriate time so that it will accelerate the iterative speed of the discovery team. This presentation will highlight the benefits, challenges, and potential pitfalls of this strategy within the discovery organization (from the pharmacologist's viewpoint) and provide examples why a more seamless strategic and scientific integration of toxicology with discovery pharmacology may enhance the overall value of a product.

Metabonomics and the Muddle of Models, Don Robertson

Despite advances in cellular and molecular approaches, animal models remain the primary tools by which the pharmaceutical industry demonstrates the efficacy and safety of candidate therapeutic agents. Despite this reliance, much remains unknown about the models we use and the factors that affect how they perform. This ignorance can lead to inappropriate assumptions, questionable procedures and incorrect conclusions from data generated in these models. Like other “omic” technologies, metabonomics has a shocking disregard for the results you want to see, but forces you to look at what actually happens which sometimes includes all kinds of findings you might wish you had never generated. Examples of model influences that are frequently overlooked in toxicology circles include animal sourcing, diet and fasting status and routine veterinary procedures. While most studies are properly controlled and conducted, increasing economic and ethical pressure dictate that we at least consider our models and how we use them to ensure we get optimal results from them. Metabonomics has proven to be a powerful tool in meeting this objective. Understanding the strengths and weaknesses of our models will have the beneficial effect of reducing the number of animals we need to use within a study as well as reducing the incidence of studies that aren't reproducible and findings which we can't explain.

Bridging the gap between discovery and regulatory toxicology, Drew Badger

Drug Development is a continuum of activities designed to maximize the chance for successful registration of safe therapeutics and accelerate the attrition of non-druggable molecules. At the early stages, it is critically important for a drug discovery program to know if toxicities are inherent to a novel target or are due to a specific compound or chemotype. At later phases, the goal is to support clinical development and satisfy accompanying regulatory requirements with longer term general and specialty toxicity studies. Invariably, information is learned throughout all phases of development and only by using the entire composite of early screening and longer term study data can the potential target liabilities as well as compound-specific effects be most fully vetted. Involving participants from a broad base of clinical and non-clinical disciplines, while challenging, can provide a critical link among interdependent disciplines and this is rarely encountered other than in small companies. This presentation will present examples of approaches to characterize target vs. off-target toxicity and the merits of novel approaches. This presentation will also discuss the importance of understanding how customers (i.e., regulatory toxicology and regulatory authorities) value discovery and investigative toxicology data to ensure the best screening and characterization paradigms are developed

Tuesday Development Toxicology Workshop

How Well Do Non Clinical Studies Predict Clinical Cardiac Safety?, **Derek Leishman**

Cardiovascular safety, alongside hepatotoxicity, is a key reason for safety-based drug candidate attrition. A large component of this is the propensity to prolong the QT interval of the cardiac electrogram. This is generally as a result of off-target pharmacology, blockade of the hERG channel. As such this is a key issue in selecting the right candidate for clinical evaluation. A very small QTc prolongation in man can result in significant delay in drug approval, restricted use, failure to approve or withdrawal of drugs from the market. This has spurred a great deal of interest in predicting QT prolongation in man. Data will be shared demonstrating the good predictivity of nonclinical assays for the detection of the clinical endpoint. Cardiac repolarization as measured by the QT interval can be prolonged by other mechanisms and as such these are on-target effects which need to be managed rather than selected against – key examples of such effects on the QTc interval which will be illustrated. The experience in QTc prediction has encouraged a greater rigour around the translation for other cardiovascular endpoints. Thus there is a growing appreciation of other cardiovascular safety issues and how these impact candidate selection and data will be shared to illustrate how off- and on-target effects can be manifest on blood pressure and cardiac contractility. These will serve to illustrate the utility of early cardiovascular screening in the candidate selection paradigm.

Customizing CV Safety Strategy for Early Risk Perspective, **Paul Levesque**

The cost impact of late-stage attrition of drug candidates or withdrawal of marketed drugs due to cardiovascular toxicity has motivated the pharmaceutical industry to implement a more proactive approach to cardiovascular risk assessment, particularly with respect to drug-induced proarrhythmia associated with delayed ventricular repolarization. Effective cardiovascular risk assessment should go beyond check box characterization in late discovery of a clinical candidates' hERG potency or effect on QT interval, and provide earlier evaluation of this and other of potential cardiovascular toxicities through the implementation of predictive in vitro and in vivo assays. The overarching goal is to identify target- or structure-based liabilities earlier so that optimized drug candidates less prone to failure can be identified and progressed into clinical development. Centralizing cardiovascular expertise in the discovery toxicology environment facilitates involvement in discovery programs from the early stages of target selection, throughout lead optimization and into late discovery including GLP safety pharmacology and toxicology. An important role of early risk assessment is to provide risk perspective through integration of relevant pharmacodynamic and pharmacokinetic data, human dose projections and consideration of target and indication, in order to make informed decisions and avoid unnecessary attrition of otherwise acceptable compounds. For in vitro or in vivo cardiovascular liability assays to influence early discovery effectively, they should require low quantities of compounds, provide rapid results to drive decision-making and medicinal chemistry efforts; and offer flexibility based on program needs that may differ based on the liability, drug class, and target/indication. The cardiovascular liability testing algorithm should be customized appropriately for each program, ranging from a minimal effort to tiered in vitro and in vivo assays designed to optimize against a known liability and triage lead compounds. While early cardiovascular risk assessment requires significant additional upstream resources, if implemented based on sound scientific rationale, it can lead to significant downstream cost savings through earlier toxicity identification and resolution. Case studies will be presented to illustrate the utility of early proactive cardiovascular testing for identifying and resolving issues, providing risk perspective, and selecting improved drug candidates while avoiding excessive risk aversion.

Species comparison of the adverse effects of p38 MAP kinase inhibitors, **Dale Morris**

P38 kinase (p38K) is a member of the mitogen-activated protein kinase (MAPK) family and is a pivotal member of a signal transduction cascade leading to the regulation of cytokines and growth factors in a variety of cell types. Selective inhibitors of the p38alpha kinase isozyme are currently being evaluated as a potential disease modifying treatment for rheumatoid arthritis and other chronic inflammatory diseases. In preclinical toxicology testing of a series of p38 kinase (p38K) inhibitors in the rat, dog and monkey, a number of general and organ toxicities were identified, ranging from adverse clinical signs and hematological changes to tissue necrosis. Early generation inhibitors were found to induce a number of toxicities in the rat, including CNS, renal, gastrointestinal, liver, pancreas and adrenal toxicity. In the dog, an acute lymphoid and gastrointestinal toxicity was observed which was not identified in either the rat or the monkey. To investigate the mechanism and role of p38 kinase inhibition in these observed toxicities, kinase selectivity screening and in vitro and in vivo models were used to further characterize the effects of various inhibitors. Results of these studies demonstrated that most organ toxicities with the various compounds in the rat or monkey, when corrected for free fraction plasma exposures, were not correlated with p38 kinase inhibition. In contrast, the acute lymphoid and gastrointestinal toxicity in the dog was found to be directly correlated with inhibition of p38alpha MAP kinase. A description of the experimental approaches and models used in evaluating the safety of p38K inhibitors, and implications for kinase inhibitor safety assessment in general, will be discussed. The Pfizer Institutional Animal Care and Use Committee reviewed and approved the animal use in these studies. The Pfizer animal care and use program is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International

Tuesday Development Toxicology Workshop

The use of in silico and direct genotoxicity testing to evaluate potential genotoxic impurities in drug product, **Ronald Snyder**

Genetic Toxicology screening in Discovery has been effectively used for determining genotoxic liability of a compound (s) for lead identification and optimization. This screening has also been mandated by OSHA to alert workers of possible genotoxicity of process intermediates. In drug development, the identification and genotoxicity of all impurities present in drug product has been a matter of due diligence but in the absence of risk assessment, no formal guidance was available to address acceptable limits of genotoxicity. This has recently changed with the new regulatory guidelines relating to the identification of potential genotoxic impurities (PGI) in synthetic process, drug product and marketed drugs. The overall process of assessment of genotoxic potential will be discussed in the context of: 1) the major features of these new guidelines; 2) the strengths and limitations and proper use of in silico predictions and existing databases in internal decision making; 3) approaches to understanding when and how direct testing should be conducted; and 4) the theories of regulatory threshold of toxicological concern (TTC) and biologically-based threshold phenomena. A perspective on the importance and biological relevance of assessment for PGIs is provided.

Wednesday Development Toxicology Workshop

Unique Aspects of Safety Assessment Programs for Biologics, **Jim Green**

An overview talk on ICH S6, the differences in terms of non-clinical safety assessment of small molecules and biologics, and challenges each faces, and areas of ICH S6 that are subject to current changes as part of the ICH maintenance process. This presentation will serve to introduce the topic areas, which will be discussed in detail by subsequent speakers.

Program Designs and the Selection of Species Utilized for Safety Assessment Studies, **Laura Andrews**

As the development of biotherapeutics becomes a more advanced science based challenge, the selection of relevant animal models, utility of traditional species and alternatives to traditional safety approaches are becoming more accepted and in fact, necessary. The last ten years has seen a significant advancement of our knowledge and development of biotechnology-derived products for the treatment of debilitating, life threatening diseases. As the therapies being developed are more sophisticated and generally more specific the need to establish safety in relevant models has become more and more of a challenge. Alternatives to the traditional safety approach include the use of homologous proteins, transgenic animals, animal models of disease as well as state of the art non-invasive, non-terminal technologies such as high resolution imaging and scanning methods. In addition, a science based approach to rationale study design has allowed for a better use of animals through the development process. Study design considerations must be addressed in order to most effectively utilize animals and wherever possible reduce the need for large numbers and multiple studies. The opportunities and challenges for these approaches as well as the approach to implementing these areas to help reduce animal use and advance the science of biotechnology drugs will be discussed.

Developmental and Reproductive Toxicity Testing for Biopharmaceuticals, **Pauline Martin**

Biopharmaceuticals are large molecular weight proteins or peptides that are produced by modern biotechnology techniques incorporating genetic engineering and hybridoma technologies. The principles of DART testing for biopharmaceuticals are similar to those for small molecule pharmaceuticals and in general follow the guidance outlined in ICHS5(R2). However, because many biopharmaceuticals are species-specific, alternate approaches may be needed to evaluate DART potential as outlined in ICH S6. For molecules that show species specific cross-reactivity that is restricted to non-human primates (NHP), some aspects of DART may be needed in the NHP. For biopharmaceuticals that are uniquely specific and only active on intended human targets or humans and chimpanzee targets, surrogate molecules that cross-react with the more traditional rodent species may need to be developed and used for DART testing. Alternatively genetically-modified transgenic animals may also need to be considered. Surrogate molecules and transgenic animals may even be considered for DART testing even if the biopharmaceutical is active in NHPs in order to reduce the use of NHPs. Because of the unique properties of biopharmaceuticals, a case-by-case approach is needed for DART and general toxicity evaluation that requires consideration of specific product attributes including biochemical and biophysical characteristics, pharmacological activity and intended clinical indication.

Wednesday Development Toxicology Workshop

Carcinogenicity Assessment of Biotherapeutics, Shawn Heidel

Carcinogenicity assessments of Biotherapeutics present many challenges. Since they are generally not metabolized to potentially genotoxic metabolites, Biotherapeutics are not direct acting carcinogens. Rather, the concern is the potential for epigenetic carcinogenesis. There are multiple hypothetical ways that Biotherapeutics can influence epigenetic carcinogenesis. Those with the most credibility include tumor promotion and evasion of immune surveillance. This presentation will focus on current ICH regulatory guidance for carcinogenicity assessments of Biotherapeutics, what's been done historically, and potential alternatives to the 2-year rodent bioassay for assessing epigenetic carcinogenicity.

Immunogenicity and safety assessment of biologics: Recommendations from BioSafe, Rafael Ponce

Administration of biotechnology-derived therapeutics may be associated with formation of anti-drug antibodies (ADA) that can alter exposure and/or pharmacological activity, and may induce toxicity. This presentation will review recommendations from an industry panel on incorporation of ADA data when interpreting nonclinical safety studies, and discuss FDA feedback on these recommendations.

A retrospective on oligonucleotide therapeutics: understanding the class effects, Art Levin

It has been 15 years since the introduction of oligonucleotide therapeutics into clinical trials. Those years have been filled with hopes, a few successes and some disappointments. At the end of that 15 years we now have a body of information on how to develop oligonucleotides as therapeutic agents. That body of information is facilitating the development of the current generation of oligonucleotide therapeutics, perhaps with a greater success rate than was achieved by the first generation of oligonucleotide drugs. Some of the most important advances were in the fields of pharmacokinetics and toxicology and these advances have served to accelerate the development of subsequent classes of oligonucleotide therapeutics. The field of oligonucleotide therapeutics has benefited from a general understanding of the properties of oligonucleotide therapeutic agents as most share common properties like their polyanionic nature, their propensity to bind to plasma proteins, and similar molecular weights. For unmodified oligonucleotides, these similarities allowed us to generalize among many sequences, but with the advent of more advanced chemistries with unique modifications, the predictability from sequence to sequence is reduced. A recap of the lessons learned should allow us to profit from our experiences and apply that understanding to the latest generations of oligonucleotide drugs.

Antisense Oligonucleotide: Progress in the Development of a Novel Therapeutic Platform, Scott Henry

Dedicated research and development of antisense inhibitors for therapeutic use has been in progress for almost 20 years. The application of antisense inhibitors of gene expression while simple in concept and potentially broadly enabling, still faces the same challenges as any pharmacologic agent. In context of therapeutic discovery these challenges include selection of potent inhibitors, pharmacologic specificity in early in vitro/in vivo pharmacology models, relevance of gene target, tissue distribution and cell uptake, target organ toxicity and therapeutic index for specific indications. Knowing the properties of compounds in a given platform such as antisense inhibitors should allow for some of these challenges to be addressed with relative high efficiency. This presentation will highlight the nonclinical development and safety assessment of antisense oligonucleotides. The toxicity studies performed cover the full spectrum of regulatory safety studies including chronic administration, reproductive toxicity and genetic toxicity studies. The study design aspects unique to antisense oligonucleotides will be discussed in the context of general preclinical development strategy. This will include the use of species active surrogate inhibitors. The toxicities common to this class of compound will be described in the context of toxicokinetic and toxicodynamic relationships. The impact of these changes of safety assessment depends greatly on the intended indication, route of administration, and duration of treatment. A prospective look at potential for near-term and long-term applications, along with future directions, will be provided.

Wednesday Development Toxicology Workshop

siRNA toxicology, specific considerations in program and study design, and general overview of key findings and risk assessment perspectives, Akshay Vaishnav

Toxicology Testing of Aptamer Therapeutics; Specific Considerations in Program and Study Design, Overview of Key Findings, and Risk Assessment Perspectives, Page Bouchard

Aptamers are non-naturally occurring single stranded structured oligonucleotides that bind to their targets with high affinity and specificity. Most aptamer therapeutics target extracellular or cell surface proteins and block protein:protein interactions as their pharmacological mechanism of action. Aptamers are discovered through an in vitro selection process known as Systematic Evolution of Ligands by Exponential Enrichment (SELEX). Once “hits” are identified from the SELEX process, those hits are minimized to the smallest binding entity with the desired binding properties, and then optimized by systematic incorporation of chemical modifications to increase the affinity and potency against the target as well as to stabilize against nuclease mediated metabolism. That optimized “core” aptamer is typically then conjugated with polyethylene glycol (PEG) to increase its molecular weight, thereby slowing renal clearance and exit from the plasma compartment to achieve sustained circulating plasma concentrations. The resulting aptamers are macromolecules with an oligo-weight of ~5-15 kDa, and a final MW of ~30-60 kDa when PEGylated. Because aptamers are oligonucleotides, they share many class based properties and development considerations with other oligonucleotide therapeutics. However, aptamers also differ considerably from the other oligonucleotide therapeutics in their mechanism and site of action, complex and diverse chemical compositions, variable structures and length, and PEG conjugation. In the discovery and development of aptamer therapeutics, one must be knowledgeable and considerate of scientific and regulatory practices for oligonucleotide therapeutics, biotherapeutics and small molecules, and apply those practices in novel and appropriate ways for this new class of agents. Our approach to the discovery and development of aptamer therapeutics and an overview of our nonclinical findings to date will be described.

Differential immunostimulatory properties of CpG and non-CpG oligonucleotides, Husam Younis

Immunostimulatory oligodeoxynucleotides (ODN) are being considered for a number of clinical applications that include as adjuvants for vaccines and in cancer therapy. The mechanism(s) of pro-inflammatory ODN involve activation of toll-like receptors. This presentation will overview the current properties and mechanisms of ODN induced immune stimulation and described the differential effects of CpG and non-CpG ODN. General considerations for the nonclinical safety of immunostimulatory ODN will also be discussed.

Shawn Heidel

Dr Heidel earned his BS degree and worked as a technician in cancer research before completing DVM and PhD degrees from the University of Wisconsin. Dr. Heidel joined the Toxicology division of Eli Lilly and Company and was a toxicology project leader and group leader prior to his current role as Head of Nonclinical Safety Assessment. He has been a member of Lilly development teams for a wide variety of neuroscience and biotechnology drugs that have included small molecules, recombinant proteins, peptides, and antisense oligonucleotides. His current role includes leading a group that is responsible for the design, implementation, and regulatory representation of nonclinical safety assessment plans that support drug development and registration. In addition, he chairs the committee that approves the design of toxicology studies for Eli Lilly and Company. External to Lilly, Dr Heidel is the chair of BioSafe, which has over 30 member companies and has sponsored many meetings with industry and regulators, and is authoring numerous manuscripts on preclinical safety evaluation of biopharmaceutical products. Dr Heidel has been a representative of the BIO, EuropaBIO, and Japan Health Sciences organizations for International Conference on Harmonization (ICH) discussions of safety issues pertaining to biopharmaceuticals.

Jim Green

Dr. Green is Senior Vice President of Preclinical and Clinical Development Sciences at Biogen Idec, Inc., in the USA. Formerly, he was Senior Director, Product Development and Safety Evaluation at Genentech, Inc., and before that Director of Toxicological Research in the Pharmaceutical Division of the Ciba-Geigy Corporation. Dr. Green is a diplomat of the American Board of Toxicology and is a former member and past Chairman of the U.S. Pharmaceutical Research and Manufacturers Association's Drug Safety Subsection Steering Committee. He is currently a member and past Chairman of Biotechnology Industry Association's nonclinical safety evaluation expert committee, BioSafe. He is also a member of a number of professional societies, including the American Chemical Society, American College of Toxicology, American Society of Toxicology and the American Society of Toxicologic Pathologists. Dr. Green received his BA in biology from the University of Rochester and MS and Ph.D. in toxicology from New York University. He has presented and published extensively in the area of safety evaluation of biotechnology products

Pauline Martin

Pauline Martin obtained her Ph.D. from the University of London in 1989 and has worked in Preclinical Research and Development within the pharmaceutical industry for 20+ years. After her Ph.D. she moved to the United States and worked at small pharmaceutical companies in California and Virginia where she was focused on the nonclinical development of small molecular weight drugs in the Cardiovascular and CNS therapeutic areas. In 1999 Pauline moved from small molecule development to biologics development and joined the preclinical development department at Biogen in Cambridge, Massachusetts where she was Associate Director/Director of Toxicopharmacology. In 2002 Pauline moved from Boston to Pennsylvania and is currently Director of Toxicology at Centocor where she is focused on the nonclinical development of biotherapeutics primarily in the therapeutic areas of immunology and oncology.

Scott Obach

Scott Obach is a Senior Research Fellow in the Pharmacokinetics, Dynamics, and Drug Metabolism Department at Pfizer in Groton, CT. He received his Ph.D. in biochemistry from Brandeis University in 1990, followed by a post-doctoral fellowship in 1990-1992 at the New York State Department of Health Research Laboratories. In 1992, Scott joined the Drug Metabolism Department at Pfizer Inc. as a Research Scientist. He currently serves on the editorial boards of Drug Metabolism and Disposition, Chemico-Biological Interactions, Drug Metabolism and Pharmacokinetics, and Xenobiotica and is a member of the Drug Metabolism Technical Group of PhRMA. His research interests include application of enzyme kinetics to drug metabolism, in vitro-in vivo correlations for prediction of human pharmacokinetics and drug interactions, and mechanism of cytochrome P450 catalysis and other biotransformation reactions. He is an author or coauthor on over ninety research publications and has given invited oral presentations at over thirty scientific conferences.

Ronald Snyder

Education: BS from Moravian College, Bethlehem, PA (1970), MS. (1972) and Ph.D. (1979) in Genetics from Emory University, Atlanta, GA both working in the Drosophila laboratory of Dr. P. Dennis Smith (isolation of mutagen-sensitive mutants). Post-doctoral training at Oak Ridge National Laboratories under the supervision of Dr. James Regan (DNA repair in mammalian cells) and at Johns Hopkins School of Public Health in the laboratory of Dr. Larry Grossman (molecular genetic techniques in DNA repair).

Work Experience: Genetic Toxicologist at Stauffer Chemical Co. Farmington, CT (1982-1986); Senior Scientist in Cancer Drug Discovery at Marion Merrell Dow Pharmaceuticals, Cincinnati, OH (1986-1993); Staff Scientist at Wood Hudson Cancer Research Laboratory, Newport, KY (1993-1995); Head of Genetic Toxicology at Abbott Laboratories, Chicago, IL (1995-1999); Director of Genetic Toxicology for DuPont Pharmaceuticals, Newark, DE (1999-2002); Head of Genetic Toxicology and Senior Research Fellow at Schering-Plough Research Institute, Summit, NJ (2002 to present).

Achievements: Establishment and scientific oversight of Discovery/Genetic Toxicology interface for Abbott, DuPont Pharma, Schering-Plough; Establishment of toxicogenomics investigational toxicology group at Schering-Plough; author or co-author of over 100 peer-reviewed publications and 4 patents in the area of DNA/Chemical interactions; Publications have been cited over 2050 times in over 520 different scientific journals; Editorial board member of Mutation Research Reviews, Environmental and Molecular Mutagenesis, Mutagenesis, and Drug and Chemical Toxicology; active reviewer for other toxicological journals; chair/co-chair assignments at EMS and SOT meetings; Member of EMS Executive Board and various committees. Recipient of Scientific Excellence awards from EMS and GTA; Co-Founder of Drug Discovery Toxicology SIG in SOT.

Current Research: The mechanisms and genotoxic consequences of non-covalent DNA/drug interactions in mammalian cells; establishment of cell-based systems for detection of DNA intercalation and DNA topoisomerase interactions

Don Robertson

Dr. Robertson received a BA in biology from The King's College (NY) as well as a Master's degree in Environmental Health Sciences and a Ph.D. in Toxicology from the University of Michigan where he subsequently was appointed as a post-doctoral fellow. He is a diplomate of the American Board of Toxicology and past-president of the Michigan Society of Toxicology. He serves on several editorial boards and is an ad hoc reviewer for numerous toxicology-oriented journals. He joined Pfizer (then Parke-Davis) in 1986 eventually reaching the level of Director and Research Fellow in Drug Safety R&D (DSRD). His growing involvement in metabonomic sciences led to his full-time appointment as the Pfizer Safety Sciences Leader of the Metabonomic Evaluation Group in 2003. With the closure of Pfizer's Ann Arbor facility, he took the opportunity to relocate to Bristol-Myers Squibb in September of 2007 where he is a Research Fellow in Discovery Toxicology and co-leader of the Applied and Investigative Metabonomics Group. His expertise in metabonomic technology has led to various appointments to both industrial and regulatory groups interested in utilizing and understanding this emerging technology. He is a charter-member of the COMET metabonomics consortia and served as the chair of the biology committee within the Metabolomics Standardization Initiative. He has published and presented extensively on the topics of metabonomics and drug-induced toxicity and was senior editor of the volume entitled "Metabonomics in Toxicity Assessment".

Drew Badger

Drew Badger is currently Senior Director of Toxicology and Regulatory Affairs at Amira Pharmaceuticals. He is a board certified toxicologist (DABT) with 10 years experience in drug safety evaluation and product stewardship. He earned his PhD in Pharmacology & Toxicology from The University of Arizona in 1998, and a BS in Environmental Biology & Chemistry from Humboldt State University in 1993. Within the Society of Toxicology (SOT), he is a founding member of the Communications Committee, Founder and President of the Drug Discovery Toxicology Specialty Section, and a former President of the Southern California SOT Regional Chapter. Drew was elected Councilor and participated twice on program committee for the American College of Toxicology (ACT). He chaired/presented in sessions at both ACT and SOT meetings from 2004 to present. Prior to his current position at Amira Pharmaceuticals, he was the Director of Discovery Toxicology and Scientific Operations at Allergan and held positions starting in 2001 as Toxicology Study Director and Project Representative for Drug Discovery and Development teams at Allergan. Prior to Allergan, Drew was a scientist at Procter & Gamble where he participated as Toxicology Project Representative for global chemical registrations (1998-2001). Throughout his career, Drew has developed specific expertise in discovery and regulatory toxicology, and continues to develop a broad perspective of industrial toxicology having been employed by small, mid-size, and large companies spanning EPA and FDA-regulated arenas.

John Donello

John Donello, Senior Director of Biological Sciences at Allergan, Inc., is founder and leader of the Allergan Platform Discovery Team and is also a Global Team Leader of an early development team. The Platform Discovery Team is focused on identifying and validating new targets, new compounds and novel therapeutic strategies for ocular, neurodegenerative, and chronic pain conditions. He also oversees a discovery collaboration with a biotechnology company. Previously, he has been a key team member responsible for molecular pharmacology and compound optimization that resulted in development nomination of 5 compounds from late stage discovery programs. He earned his PhD in Biology from The University of California, San Diego in 1998, and performed his Ph.D work in the Infectious Disease Laboratory at The Salk Institute for Biological Studies. His doctoral work focused on viral RNA processing of HIV and Hepatitis B which led to the optimization of RNA export for current viral gene therapy strategies. John's experience in early discovery and shepherding compounds through phase II development has enabled a broad perspective about the challenges and value of interactions between discovery, discovery toxicology, regulatory toxicology, and clinicians.

Lois Lehman-McKeeman

Dr. Lois Lehman-McKeeman is currently a Distinguished Research Fellow in Discovery Toxicology at the Bristol-Myers Squibb Company in Princeton, NJ. She received a BS degree in Toxicology from the University of the Sciences in Philadelphia and holds a Ph.D. in Toxicology from the University of Kansas Medical Center. She was employed in the Human and Environmental Safety Division of the Procter and Gamble Company for 15 years prior to joining Bristol Myers Squibb in 2001. Lois has active research interests and programs broadly in biochemical mechanisms of toxicity, with emphasis on secondary mechanisms of carcinogenesis. She is also working to develop and apply metabolomic and transcriptomic technologies to mechanistic toxicology. She has published extensively in these fields. She has been active professionally in the Society of Toxicology (SOT) serving on numerous SOT committees, and she held elective office in the SOT as Councilor from 2000-2002. In 2003 she was appointed Editor of Toxicological Sciences, a position she currently holds, and she serves on a number of other editorial boards. She is presently a member of the Human Subjects Review Board of the USEPA and she has or is presently sitting on a variety of national and international advisory committees for EPA, NIH and IARC. She was named a Fellow of the American Association for the Advancement of Science in 2008. She is also a fellow in the Academy of Toxicological Sciences, the recipient of the Robert Scala Award in Toxicology for research excellence in an industrial laboratory in 1994, the Society of Toxicology Achievement Award in 2003 and the George H. Scott Award for scientific excellence from the Toxicology Forum in 2006.

Bill Foster

In 1993, Bill completed his Ph.D. research in the systems biology of nerve cell activity based on cross disciplinary work in the Chemical Engineering and Neuroscience Departments at the University of Pennsylvania. In 1996, Bill returned to the U. Penn in the Institute for Human Gene Therapy to learn molecular biology techniques and then joined DuPont as a Research Engineer performing bioinformatic analysis of EST libraries and cDNA arrays for microbes, agricultural plant species, and human immunology disease models. In 1999 Bill joined DuPont Pharmaceuticals as a Research Scientist analyzing microarray data from disease and toxicity models. In 2003 Bill joined Discovery Toxicology at Bristol-Myers Squibb Co. where he has led efforts to apply gene expression analysis to drug safety studies while also supporting drug discovery as a toxicologist.

Doug Lauffenburger

Douglas A. Lauffenburger is Uncas & Helen Whitaker Professor of Bioengineering and Head of the Department of Biological Engineering at MIT, and also holds appointments in the Department of Biology and the Department of Chemical Engineering. He is a member of the Biotechnology Process Engineering Center, Center for Biomedical Engineering, Center for Cancer Research, and Center for Environmental Health Sciences, and is Director of the Computational & Systems Biology Initiative.

Dr. Lauffenburger's BS and PhD degrees are in chemical engineering from the University of Illinois and the University of Minnesota, in 1975 and 1979 respectively. His major research interests are in cell engineering: the fusion of engineering with molecular cell biology. A central focus of his research program is in receptor-mediated cell communication and intracellular signal transduction, with emphasis on development of predictive computational models derived from quantitative experimental studies, for cell cue/signal/response relationships important in pathophysiology with application to drug discovery and development. Lauffenburger has coauthored a monograph entitled Receptors: Models for Binding, Trafficking & Signaling,

published by Oxford University Press in 1993 and reprinted in 1996. More than 80 doctoral students and postdoctoral associates have completed their training under his supervision or co-supervision.

Prof. Lauffenburger has served as a consultant or scientific advisory board member for Astra-Zeneca, Beyond Genomics, CellPro, Eli Lilly, Entelos, Genstruct, Insert Therapeutics, Johnson & Johnson, Merrimack Pharmaceuticals, Pfizer, Precision Therapeutics, SyStemix, the Burroughs-Wellcome Fund, and the Whitaker Foundation. His awards include the Pierre Galletti Award from AIMBE, the A.P. Colburn Award, Bioengineering Division Award, and W.H. Walker Award from AIChE, the Distinguished Lecture Award from BMES, the C.W. McGraw Award from ASEE, the Amgen Award in Biochemical Engineering from the Engineering Foundation, and a J.S. Guggenheim Fellowship, along with a number of named lectures at academic institutions. He is a member of the National Academy of Engineering and of the American Academy of Arts & Sciences, and has served as President of the Biomedical Engineering Society, Chair of the College of Fellows of AIMBE, and on the Advisory Council for the National Institute for General Medical Sciences at NIH.

Vishal Vaidya

Dr. Vaidya received his PhD from University of Louisiana at Monroe in 2003 under the preceptorship of Dr. Hari Mehendale. His thesis work was to understand biochemical and molecular mechanisms of tissue repair after kidney toxicity. During his graduate studies, Vishal has received a number of awards for his research including the Society of Toxicology (SOT) graduate student fellowship award sponsored by Novartis in March 2001. Thereafter, he was awarded the National Kidney Foundation (NKF) grant to pursue postdoctoral fellowship with Dr. Joseph Bonventre in renal division of Brigham and Women's hospital, Harvard Medical School. He is currently an Instructor in Medicine at Harvard Medical School and an Associate Biologist at Brigham and Women's hospital. Dr. Vaidya directs the laboratory of kidney toxicology and regeneration and his primary research interests include identifying novel approaches for early detection of kidney injury. He has over 35 papers including original research articles, reviews and book chapters. Over the years Vishal's laboratory has been supported by funding from American Heart Association and National Institute of Environmental Health Sciences. He serves as an ad-hoc reviewer for several toxicology journals and recently served as a guest editor for a special issue on "Biomarkers of Toxicity" for the journal "Toxicology". He is a member of several scientific societies including Society of Toxicology and American Society of Nephrology.

Laura Andrews

Laura Andrews is Vice President of Pharmacology and Toxicology at Genzyme where she directs the nonclinical development programs for biotherapeutics. She is responsible for the nonclinical development programs for therapeutic biologics, gene therapy products, and cell based therapies. Laura oversees the design, implementation and interpretation of the in vivo GLP studies and the in vitro assays to support product development. Laura has authored the pharmacology and toxicology section for several Genzyme INDs and marketing applications in several different territories. Dr. Andrews received a BS (1983) in Biology and Chemistry from Dickinson College, and a Ph.D. (1987) in Pathology and Cell Biology from Thomas Jefferson University and Medical College in Philadelphia, PA. She was Board Certified in General Toxicology in 1998. She holds memberships in the Society of Toxicology (SOT), Society for Toxicologic Pathology (STP) and the American College for Toxicology (ACT). She is currently on the Board of Directors for the American Board of Toxicology.

Rafael Ponce

Dr. Ponce is a Scientific Director in the Comparative Biology and Safety Assessment group at Amgen (Seattle, WA). Prior to this position he was Director of Preclinical Safety Assessment at ZymoGenetics, Inc. (Seattle, Washington). He has previously worked as a research toxicologist at SNBL USA and the University of Washington, and as a toxicologist for the Alaska Department of Health and Social Services. Dr. Ponce is an Affiliate Associate Professor in the Department of Environmental and Occupational Health Sciences, University of Washington and is a Diplomate of the American Board of Toxicology.

Alison Easter

Alison received a B.Sc degree in Pharmacology from the University of Bristol (including one year full-time employment at Merck Sharp and Dohme, UK) followed by a Ph.D. degree in Molecular Pharmacology at The University of Birmingham. Since 2002, Alison has worked in Safety Pharmacology within the Safety Assessment Division at AstraZeneca Pharmaceuticals, both in the UK and Wilmington, Delaware. During this time, her work has been focused on early stage in vitro screening, particularly using electrophysiological techniques to detect potential cardiovascular and CNS adverse effects.

Bob Chapin

Bob Chapin received his PhD from UNC-CH in Pharmacology in 1980, post-doc'd at the Chemical Industry Institute of Toxicology, and spent 18 years working on male reproductive toxicology at the National Toxicology Program in the RTP before moving to Pfizer in 2002. At Pfizer, Bob leads a lab of gifted developmental toxicologists in the Developmental and Reproductive Tox group who perform screening and investigative activities, as well as continuing to improve the predictivity of alternative or low-bulk-requiring assays. Bob collaborates tirelessly with colleagues inside and outside of Pfizer to explore new approaches to testing and to share those results widely

Dmitri Mikhailov

Dmitri Mikhailov holds M.S. in Chemical Physics/Applied Math and Ph.D. in Structural Biology. After a postdoc at Harvard in 1998-99, Dmitri joined SGI Life Sciences as Bioinformatics Application Scientist responsible for major academic, biotechnology and pharmaceutical client collaborations.

In 2003 Dmitri joined Novartis in Cambridge, US to establish Advanced Scientific Computing Lab. Since 2004 Dmitri headed Cheminformatics team responsible for developing global scientific web tools. More recently Dmitri's focus has been on early safety assessment and establishing best practices for using informatics approaches to manage early drug safety risks.

Steven Whitebread

Senior Scientist at the Novartis Institutes for Biochemical Research (NIBR) in Cambridge, MA, heading the In Vitro Safety Pharmacology Lab. Studied Analytical Biochemistry at Bromley, UK, followed by more than 30 years experience in Drug Discovery Research with Novartis.

Bruce Car

Bruce D. Car received his Veterinary Medicine and Masters (B.V.Sc., 1983; M.V.S., 1985) degrees at The University of Melbourne, Victoria, Australia, and Ph.D. from Cornell University, NY in 1989 in the field of pulmonary inflammatory disease and its interactions with coagulation and fibrinolysis. Dr. Car obtained specialty certifications with the American College of Veterinary Pathology in Anatomic Pathology (1987) and Clinical Pathology (1990), and with the American Board of Toxicology (1995) by examination. He undertook postdoctoral work at the Theodor Kocher Institute, University of Berne, and Institute for Toxicology of the University of Zurich/ETH in Switzerland (1989-1994) in the areas of chemokine research, hematopoiesis and immunology. Since 1994, Dr. Car worked at DuPont Pharmaceuticals/DuPont-Merck as a Safety Assessment pathologist and led that organization's Discovery support effort. After DPC's acquisition by Bristol-Myers Squibb in 2001, Bruce continued as the leader, now Vice President, of Discovery Toxicology. His group of approximately 70 researchers is charged with pharmaceutical target validation, and identifying and placing compound liabilities in perspective prior to their entry into formal preclinical development, in addition to conducting focused risk-assessment work for compounds with toxicology issues at all stages of development. Discovery Toxicology leads the application of toxicogenomic, proteomic and metabonomic technologies to the risk assessment of compound liabilities at BMS. Bruce presents extensively within the toxicology and pathology communities and has authored over 70 scientific manuscripts.

Dale Morris

Dale received his Ph.D. in Pharmacology & Toxicology from the Medical College of Virginia in 1991, specializing in the areas of Immunology & Immunotoxicology. After completing his postdoctoral training at the Boston University Medical Center in 1993, he joined the legacy Pfizer company, G.D. Searle. Currently, Dale is the Drug Safety Research Site Lead for the Pfizer St. Louis Research Site. The St. Louis DSRD organization is focused on providing an integrated toxicology & pathology approach to the discovery and development of novel targets and drug candidates for the treatment of auto-immune and chronic inflammatory diseases. Dale is an author of 30+ peer reviewed journal articles, one book chapter and two patents, and is a full member of the Society of Toxicology and the American Association of Immunologists.

Paul Levesque

Paul Levesque received a B.S. in Pharmacy from the University of Rhode Island in 1984, and a Ph.D. in Neurotoxicology from the Department of Pharmacology and Toxicology at Michigan State University in 1990. After postdoctoral training focused on cardiovascular electrophysiology at the University of Nevada, School of Medicine in Reno, he joined the Department of Physiology faculty where he received NIH funding to study the molecular physiology of cardiac ion channels, with emphasis on the role of chloride channels and sodium-calcium exchange in cardiac pathophysiology. He joined the Cardiovascular Drug Discovery Department at Bristol-Myers Squibb in Princeton in 1995 where he served as biology leader on a number of cardiovascular drug discovery programs targeting arrhythmia and hypertension. He joined the Discovery Toxicology Department within Pharmaceutical Candidate Optimization in 2003. He is currently a Senior Research fellow and heads the Cardiovascular Safety Pharmacology Group in Discovery Toxicology. In addition to conducting core ICHS7B assays to support regulatory requirements, this group is responsible for the early detection and resolution of potential cardiovascular issues during drug discovery and the mechanistic evaluation of cardiovascular toxicities identified pre-clinically or during clinical development. In addition to his role in Discovery Toxicology, he continues to serve as biology leader for a cardiovascular drug discovery program and a core member on early development teams.

Husam Younis

Husam Younis is a toxicologist at Pfizer Inc. La Jolla Laboratories, Drug Safety Research and Development, San Diego, CA. Husam has assumed roles of increased responsibility at Pfizer since 2002, and currently holds the position of Director and Head of the General Toxicology group within the Drug Safety Department. He manages a group of study directors/toxicology team representatives and study scientists in the conduct of non-GLP in vivo toxicology studies. Husam also serves as a toxicology team representative on project teams in discovery and development in the areas of ophthalmology, diabetes and

Derek Leishman

Dr Derek Leishman is Research Fellow and Global Head of Safety Pharmacology with Eli Lilly and Company. Dr Leishman is a pharmacologist and electrophysiologist by training. His long-standing field of interest is in safety pharmacology and in particular cardiovascular safety. He studied for his degree and PhD at the University of Aberdeen. Dr Leishman worked for Marion Merrell Dow in France before joining Pfizer in the UK. After 12 years with Pfizer Dr Leishman joined Lilly in 2005 as Research Fellow to lead the Safety Pharmacology discipline

Art Levin

Arthur Levin is Chief Development Officer at Santaris Pharma, Hørsholm Denmark. He has more than 25 years of experience in the pharmaceutical industry with the last 15 in the field of RNA-based drug research and development. Dr. Levin is responsible for the drug development programs at Santaris Pharma and for the management of Cureon, its wholly-owned US subsidiary. Before joining Santaris, Dr. Levin consulted for leading biotechnology and pharmaceutical companies conducting research and development in RNA-based therapies such as mRNA, microRNA, and siRNA. Prior to consulting, Dr. Levin was Senior Vice President of Development at Isis Pharmaceuticals where he was responsible for the drug development of Isis' products across a range of therapeutic areas. He was instrumental in advancing more than a dozen antisense drugs from basic research to clinical development. Dr. Levin also held broad corporate responsibilities with investors and corporate partners. He joined Isis from Hoffmann-La Roche Inc. where he was Research Leader. Dr. Levin holds a Ph.D. in Toxicology from the University of Rochester School of Medicine and Dentistry, Rochester, New York and a B.S. in Biology from Muhlenberg College. He completed his post-doctoral work at the Chemical Industry Institute of Toxicology in Research Triangle, North Carolina. Dr. Levin is the author of more than 50 papers and book chapters.

Page Bouchard

Dr. Page Bouchard joined Archemix Corp. in November 2004 and currently heads non-clinical R&D. Dr. Bouchard has extensive experience in the area of preclinical drug discovery and development. Prior to joining Archemix he was Vice President of Drug Safety Evaluation at Millennium Pharmaceuticals. In this position, Dr. Bouchard led the preclinical Drug Safety and Pathology organization, leading development projects to critical clinical and regulatory milestones. Prior to joining Millennium, Dr. Bouchard was Assistant Vice President of Pathology at Wyeth, heading the discovery support pathology, toxicologic pathology, clinical pathology and toxicogenomics efforts. Dr. Bouchard has over 14 years of Pharma/Biotech experience working on a diverse range of product types including recombinant human proteins and antibodies, small molecules and medical devices. He has been intimately involved in the successful filing of dozens of INDs and several NDAs for products in a wide range of therapeutic applications, and has published over 28 articles, book chapters and abstracts. He received a bachelor's degree from Wesleyan University and a D.V.M. from Tufts University Veterinary School. He trained in veterinary pathology at Cornell Veterinary School and is Board certified in veterinary pathology by the American College of Veterinary Pathologists and he currently serves on the executive committee of the Society of Toxicologic Pathologists.

Scott Henry

Received a Ph.D. in Biochemistry from North Dakota State University in 1991, studying the phosphorylation and regulation of the glycogen synthesis pathway in heart. Following his Ph.D., he was a post-doctoral fellow at Parke Davis in Ann Arbor Michigan in the department of toxicology until 1993. He then joined Isis Pharmaceuticals, Inc. as a Senior Scientist in the department of toxicology. Along with a team of dedicated colleagues, he has characterized and studied the mechanisms of various toxicities that include the effects of oligonucleotide treatment on clotting time prolongation, alternative complement pathway activation, proinflammatory effects in rodents, and the effects related to the accumulation of oligonucleotide in kidney. Now as Vice President of Non-Clinical Development at Isis he has participated in the development of approximately 8 different phosphorothioate oligodeoxynucleotides and 10 different 2'-MOE modified phosphorothioate oligonucleotides.

Oliver Flint

Education: Cambridge University and Glasgow University (PhD - Developmental Biology) Occupation: Development of in vitro safety assays and investigation of toxic mechanisms as applied to drug discovery and development. Areas of specific expertise related to drug safety include HIV drug-induced lipodystrophy, teratogenicity, hepatotoxicity, neuropathy, and nephrotoxicity.

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Parking

For your convenience we have included details on the public parking garages within walking distance to the facility. These rates are subject to change. Updated 1/1/08

Standard Parking

(Located at Harvard COOP, 2 blocks)

333 Longwood Ave.

Boston, MA 02115

3hrs. - \$13

4-5hrs. - \$25 5hrs.+ - \$30

Daily Maximum - \$30

Pilgrim Parking, Inc.

Longwood Galleria Parking Garage

(3 blocks)

350 Longwood Ave.

Boston, MA 02115 3hrs. - \$15

4hrs. - \$18 5hrs. - \$20

6hrs. - \$23 Over 6hrs. - \$30

Trilogy

180 Brookline Ave

(10 min. walk, 7 blocks)

Boston, MA 02115 Early Bird Special

(In by 8am out by 7pm) - \$15

Hourly Rate - \$5 per hour

Daily Maximum - \$20

Taxi Cabs

Taxicab Company	Phone Number	Protocol	Payment Method
Boston Cab	617-262-2227	Call with 1/2 to 1 hour notice	Cash or *Credit
City Cab	617-536-5100	Call with 1/2 to 1 hour notice	Cash or *Credit
MetroCab (John Ward)	617-242-8000	Call with 20 min to 1/2 hour notice	Cash or *Credit
Town Taxi	617-536-5000	Call with 20 min to 1/2 hour notice	Cash or *Credit

*If paying by credit card please inform when calling.

Limousine Services

Hello Limo

24 Hour Service to airport

617-953-7969

ABC Shuttle & Limo Service

24 Hour Service to airport

Call 1 hour in advance

781-244-8998

Restaurants

Restaurants in Boston with varying cuisines are listed below. For more information and reviews visit one of the following links: <http://calendar.boston.com/restaurants> or <http://www.phantomgourmet.com/>

Al Dente

Snuggled in the heart of the world famous North End, Al Dente Restaurant lets you feast on a bountiful array of Italian specialties. The outstanding menu, featuring pasta, chicken, veal and seafood, highlights a spectrum of lavish Italian specialties that are sure to please discriminating palates. The open kitchen lets you in on the action behind the superb dishes, and you'll enjoy their lavish fare amid a cozy, casual setting. | Italian | 109 Salem St., Boston, MA, 02113 (617) 523-0990

La Galleria 33

The hot top spot for swank Italian dining in Boston. Tucked away on Salem Street in the heart of the North End – well off the boisterous, beaten track of Hanover Street – this cozy, warm and romantic restaurant serves some of the best, reasonably priced Italian food found anywhere. | Italian | 125 Salem St., Boston, MA, 02113 (617) 723-7233

Boston Public

Located in the Louis Boston building, this used to be Restaurant L. Chef Pino Maffeo, now an owner, is still at the helm, and the place has been revamped as Boston Public. | Steak House | 234 Berkeley St., Boston MA, (617) 266-4680

Bouchee Boston

The menu at this lively place spans classic brasserie to lighter, updated fish dishes. Open early till late all week long, it's a great addition to Boston's favorite shopping street. | French | 159 Newbury St., Boston MA, (617) 450-4343

Ko Prime Nine Zero Hotel

Ken Oringer's steakhouse does what you'd expect a Ken Oringer steakhouse to do: serve high-quality meat prepared in ways you won't see at Outback. Filet mignon goes to Argentina with a topping of chimichurri; thin slices of skirt steak are edged in North African spices. | Steak House | 90 Tremont St., Boston MA, (617) 772-0202

Skipjack's Boston

The staff is cool. The food is cool, as in "rad." The decor is perfectly upscale "mod." And the chef knows how to cook fish. We've never gone wrong here with the likes of Atlantic salmon and juicy broiled scallops. | Seafood | 199 Clarendon St., Boston MA, (617) 536-3500

Mantra Restaurant

Stunning architecture and a glittery crowd almost overshadow chef Thomas John's French and Indian cuisine. But his subtle and sure way with spices prevails. | American/Indian/French/Fusion/Eclectic | 52 Temple Pl., Boston MA, (617) 542-8111

Northend Pomodoro

The food and personal service far outweigh the decor at this small but inviting spot specializing in creative veal, fresh seafood, and pasta dishes. There's no bar, but during long waits you get sidewalk delivery of the best fried calamari in Boston. | Italian | 319 Hanover St., Boston MA, (617) 367-4348

No. 9 Park

Taking a slightly different approach to the bar menu idea, the cafe at No. 9 Park has an extensive menu of very ambitious dishes, only slightly scaled down in portion size and changing with the season, making it a good way to sample chef-owner Barbara Lynch's cuisine. (Boston Globe) | Mediterranean, French, Italian / Pasta | 9 Park St., Boston MA, (617) 742-9991

Pho Thien Thien

This new Vietnamese restaurant has a gracious owner who learned cooking in her mother's kitchen and later in native restaurants. The fresh vegetables taste as if they've come from a garden out back. | Vietnamese / Southeast Asian | 8 Kneeland St., Boston MA, (617) 357-5536

The Capital Grille

Dry aged steaks have earned high praise from the nation's toughest food critics, and their seafood is flown in daily. Award-winning collection of over 400 wines is an experience in itself. | Steak/Seafood | 359 Newbury Street, Boston, MA 02115, (617) 262-8900

Chart House Restaurant

An incredible landmark location on Boston's Long Wharf. The Chart House is situated in the Gardiner Building - the restored 18th-century offices of American Patriot John Hancock. Combine the extraordinary setting with outstanding cuisine & it's not hard to see why the restaurant is a longtime favorite. | Steak/Seafood | 60 Long Wharf, Boston, MA, 02110, (617) 227-1576

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