INTERACTIVE MEET ON INSIGHTS IN TOXICOLOGY (IMIT- Sep 2019)

ToxGurukul
- Sōpānapatha

Theme: Pathology for Toxicologists

20th-21st September 2019

Course Director
Dr. P. Kalaiselvan, M.V.Sc., DICVP, DIBTP, DABT

Course Organizer
Dr. K.S. Rao, M.V.Sc., Ph.D., DABT

Organized by:
ToxGurukul Foundation

Co-Sponsored by:
Dr. Reddy's Laboratories

Venue:
Dr. Reddy's Laboratories Ltd.
Auditorium-Leadership Academy
Bachupally, Quthbullapur,
Hyderabad, Telangana 500072

Dr.Reddy's

INTRODUCTION

ToxGurukul Foundation

ToxGurukul Foundation is a registered non-profit organization for professionals in the field of toxicology who are in search of a platform to learn and share the vast knowledge in this area. This syndicate belongs to independent professionals from different backgrounds of toxicology who share their knowledge to un-puzzle the Rubik's cube that each face in their daily work routine.

Dr. Reddy's Laboratories Ltd.

Dr. Reddy's Laboratories Ltd. is an integrated pharmaceutical company, committed to providing affordable and innovative medicines for healthier lives. Through its three businesses - Pharmaceutical Services & Active Ingredients, Global Generics and Proprietary Products – Dr. Reddy's offers a portfolio of products and services including APIs, custom pharmaceutical services, generics, biosimilars and differentiated formulations. Our major therapeutic areas of focus are gastrointestinal, cardiovascular, diabetology, oncology, pain management and dermatology. Dr. Reddy's operates in markets across the globe. Thier major markets include – USA, India, Russia & CIS countries, and Europe.

Registration Details

Registration start date : 1st August 2019

Registration end date : 13th September 2019

Registration Fee: Rs. 1500/- only

Registration and Payment Procedure :

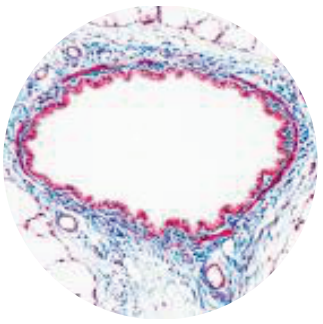
Registration is web based and all participants are requested to register and make payment through https://toxgurukul.org.in/registerimit-sep-19.

Kindly note invoice shall not be shared for any registration. An organization who sent minimum four participants will be enlisted in conference proceedings and in ToxGurukul Website as a "Token of Appreciation"

**No Spot registration available*

Who should attend?

All professionals in the in the field of toxicology, biomedical, non-clinical drug development, risk assessors and so on.



MESSAGE FROM PATRON

Dear Friends of Toxicology:

It is an honor bestowed on me by the ToxGurukul group of scientists to formally announce the workshop on **"Pathology for Toxicologists"** to be conducted on 20th and 21st September 2019 at the Campus of Dr. Reddy's Laboratories, Bachupally, Quthbullapur, Hyderabad.

This is the third in a series of training workshops that are conducted under the auspices of ToxGurukul Foundation in the last two years. The primary objectives of these workshops are to bring in new generation of toxicologists into the workforce who are ready to take up the challenge from the beginning and compete in the global scientific arena.

The topics covered at these workshops are primarily designed to sharpen the skills of younger toxicologists who can occupy higher positions over time in the Government, Academia and Industry at large.

The two-day workshop on Pathology for Toxicologists is spear headed by **Dr. Kalaiselvan** (Syngene International Ltd.) who has over 15-years of Industry experience and is a leading expert in Toxicopathology of laboratory animals in the country.

Everyone working in the field of toxicology must have a working knowledge of organ pathology as it pertains to normal and abnormal lesions in laboratory animals and their associated terminology for Integrated Interpretation of Toxicologic Data with Organ Pathology Lesions. An intelligent and credible determination of No Observed Adverse Effect Level (NOAEL) following treatment with the test agent (drug, pesticide, industrial chemical etc) to laboratory animals by the study director or toxicologic investigator can only be done if the investigator has a sound understanding of both toxicology and organ pathology. The proposed two-day workshop on Pathology for Toxicologists is designed to impart working knowledge of pathology to toxicologists which will make them an all rounded toxicologists, which is a real gap that exists in the country.

We urge all toxicologists working in the Government, Academic and Industrial sectors to take advantage of this maiden workshop which was never conducted so far in the country.

If any of the Sponsors wish to donate any amount **(no amount is too small)**, we welcome your contributions for the success of this maiden workshop which goes a long way to improve the cadre of toxicologists in the country.

Dr. K.S. Rao, M.V.Sc., Ph.D., DABT
Patron
ToxGurukul Foundation

FOREWORD BY COURSE DIRECTOR

Toxicologists play a key role in the discovery & development of new compounds and they work in diversified fields such as pharma, agrochemical, industrial chemical, medical devices and biopharmaceuticals, to name few and play a critical role in hazard identification and risk assessment. Although the field of *in-vitro* toxicology is evolving, *in-vivo* studies are critical for the discovery and product development wherein the toxicologist shoulder the responsibilities of conducting complex toxicology studies. In GLP terms, the toxicology study director is the key personnel responsible for the conduct of regulatory toxicology study. Toxicologists integrate contributing scientists reports such as from formulation analysis, toxicokinetic analysis and pathology report to prepare a comprehensive toxicology report for regulatory submission. Apart from in life data, the key parameters which decide the outcome of the study and determination of NOAEL lies with pathology part. Understanding of background findings, toxicant induced changes, species differences, adaptive changes and adverse outcomes will help the toxicologist to integrate the pathology data to the toxicology report and aid them to derive the defend-able NOAEL. The objective of this workshop is to discuss the anatomy, histology, physiology, background observations, induced changes, species differences, adverse vs adaptive changes, stress induced changes in various organ systems and correlation of pathology findings to *in-life* data, etc. This workshop is designed to provide basic knowledge in toxicologic pathology to the participants. For the general interest of toxicologists this workshop also covers the topics of impurity qualification and risk assessment.

Dr. P. Kalaiselvan, M.V.Sc., DICVP, DIBTP, DABT
Course Director

Patron: Dr. K.S. Rao M.V.Sc., Ph.D., DABT

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Session Schedule

Day – 1 – Friday, 20-09-2019

Time	Topic	Speaker	Organisation
9:00 to 9:30	Inauguration & Course Overview	Dr. K.S Rao	Eurofins Advinus
		Mr. Sauri Gudlavalleti	Global Head-IPDO, Dr.Reddy's Laboratories Ltd
		Dr. Siddharth Chachad	Head - Global Clinical Management, Dr.Reddy's Laboratories Ltd
9:30 to 10:15	Role and Significance of Pathology in Preclinical Toxicology Studies	Dr. P. Kalaiselvan	Syngene International Ltd
10:15 to 11:15	Hepatobiliary System	Dr. Jayachandra K.C.	Eurofins Advinus
11:15 to 11:30	Tea break		
11:30 to 12:15	Urinary System	Dr. Pankaj Shelar	Lupin Pharmacueticals
12:15 to 13:00	Respiratory System	Dr. Madhusudan P.G.	Syngene International Ltd
13:00 to 13:30	Lunch		
13:30 to 14:30	Reproductive System	Dr. Shekar Chelur	Aurigene Discovery Technologies Limited
14:30 to 15:30	The Art of Impurity qualification: A scientific approach	Dr. Anirban Thakur	Cipla
15:30 to 15:45	Tea break and Photo Session		
15:45 to 16: 45	Risk Assessment	Dr. Sebastian Joseph	Pharmalex India
16:45 to 17:30	Case Discussions/Panel Discussion	Open for All	

Day 2 – Saturday, 21-09-2019

Time	Topic	Speaker	Organisation
9:00 to 10:00	Preclinical Development of Small Molecule Oncology Drugs	Dr. Shekar Chelur	Aurigene Discovery Technologies Limited
10:00 to 11:15	Toxic response of skin	Dr. P.C Prabu	Tamil Nadu Veterinary and Animal Sciences University
11:15 to 11:30	Tea break		
11:30 to 12:15	Nervous System	Dr. Selvam G	International Institute of Biotechnology and Toxicology (IIBAT)
12:15 to 13:00	Immune system	Dr. Sowmya Bharath	INTOX
13:00 to 13:30	Lunch		
13:30 to 14:30	Endocrine system	Dr. Jomy Jose	RCC India laboratories
14:30 to 15:30	Cardiovascular System	Dr. Pankaj Shelar	Lupin Pharmacueticals
15:30 to 15:45	Tea break		
15:45 to 16:30	Exploring 505 (b)(2) : An Abbreviated pathway for Repurposing of Existing Drugs with special reference to topical product development	Dr. Balaji, M R	Dr.Reddy's Laboratories Ltd
16:30 to 17:00	Sponsors Presentation		
17.00 to 17:30	Question and Answer Session	Open for All	

SPEAKERS

Dr. P. Kalaiselvan, M.V.Sc., DICVP, DABT, DIBTP

Dr. P. Kalaiselvan is a Veterinary Pathologist, currently working as Senior Principal Scientist in Safety Assessment department, Syngene International limited, Bangalore, India. In this role he is responsible for managing pathology group, involve as study pathologist and peer review pathologist for various repeat dose toxicology studies. Prior to Joining Syngene, Kalai has worked in Drug Safety Evaluation of Ranbaxy Research Laboratories, Gurgaon, India and IIBAT, Chennai. In these roles he served as study pathologist for toxicology studies involving NCE's, generic pharmaceuticals, biologics and agrochemicals. Kalai is a diplomate of Indian College of Veterinary Pathologists (DICVP), Indian Board of Toxicological Pathology (DIBTP) and American board of toxicology (DABT). He has obtained his bachelor's degree in Veterinary medicine from Madras Veterinary College, India and master's degree in Veterinary Pathology from College of Veterinary Sciences, Thrissur, Kerala. He is a recipient of ICAR's research fellowship for his master's degree. He has experience in toxicologic pathology for the past 15 years.

Session Topic: Role and Significance of pathology in preclinical toxicology studies

Toxicologic pathology is the study of molecular, cellular, tissue or organismal response to xenobiotics which play critical role in discovery and development of pharmaceuticals, biologics, vaccines, medical devices and agrochemicals. At the discovery stage, pathologists are involved in animal model development and efficacy studies in preclinical species. During development, pathology evaluation starts form early exploratory studies to pivotal GLP studies. Toxicologists and pathologists work together in the design and conduct of preclinical studies. Number of pathology parameters *viz,* hematology, coagulation, clinical chemistry, urinalysis, blood and bone marrow smear evaluation, gross pathology, organ weights and histopathological evaluation (about 40 tissues) are involved in the characterization of toxicity of a compound. Role of the pathologist is to identify the test compound related changes, describe using standard terminologies and interpretation of pathology findings (clinical pathology, gross pathology, organ weight and histopathology). Pathologist often needs to correlate the pathology findings with *in-life* and toxicokinetic data. At the end of pathology evaluations, the findings are classified as test item related or not, primary effect of test item administration or secondary to stress. If the findings are test item related, then the findings are further categorized as adaptive, adverse or non-adverse which is one of the critical aspects in defining NOAEL/NOEL for the compound under investigation. Hence, pathology is an essential component of hazard identification, dose response establishment, and risk characterization essential for risk assessment and risk management. Having knowledge in pathology helps the toxicologist to integrate the morphological, clinical pathological and functional changes in a logical manner with respect to their biological significance and help them in appropriate evaluation of toxicity and risk assessment of compounds under investigation.

Dr. Jayachandra K. C., M.V.Sc., DABT

Dr. Jayachandra is currently a Principal Scientist at Eurofins Advinus . In this role, at Eurofins Advinus, he provides GLP Pathology support for pharmaceutical, medical device and chemical industries. Dr. Jayachandra supports safety assessment department by providing scientific inputs in the design and conduct of toxicology experiments that focus on characterization and safety of novel test compounds and/or understanding potential mode of action for toxicity in preclinical studies.He obtained his Bachelor's degree in veterinary science and animal husbandry from UAS, Bangalore in 2004 and Master's degree in Veterinary Pathology from KVAFSU, Bidar in 2006. After finishing Master's degree he worked at Primate Research Lab, Dept of MRDG as Senior Research Fellow in Medhamurthy's Laboratory. Dr. Jayachandra has been engaged in the field of toxicologic pathology for 12 years at Eurofins Advinus and Syngene International. He is a diplomate of American Board of Toxicology (DABT) and member of Society of Toxicologic Pathology (STP) and Society of Toxicology (SOT) USA.

Session Topic: Hepatobiliary System

Drugs continue to be pulled out from the market with disturbing regularity because of late discovery of hepatotoxicity. Such unexpected toxicities appear to be the consequence of the unique vascular, secretory, synthetic, and metabolic features of the liver. About 75% of hepatic blood comes directly from the gastrointestinal viscera and spleen via the portal vein. Portal blood brings drugs and xenobiotics absorbed by the gut directly to the liver in concentrated form. Drug-metabolizing enzymes detoxify many xenobiotics but activate the toxicity of others. Hepatocytes are highly reliant on ATP for ureagenesis, gluconeogenesis, and fatty acid metabolism among many other metabolic processes. Hepatocytes with low hepatic glycogen content, hypoxia, mitochondrial inhibition and damage to mitochondrial DNA lead to hepatocellular necrosis.

The liver synthesizes, concentrates, and secretes bile acids and excretes other toxicants, such as bilirubin. Drug-induced injury to hepatocytes and bile duct cells can lead to cholestasis. Cholestasis, in turn, causes intrahepatic accumulation of toxic bile acids and excretion products, which promotes further hepatic injury. Fortunately, the liver has enormous regenerative capacity, but regeneration of hepatocytes lost by necrotic and apoptotic cell death may mask detection of drug-induced injury. Furthermore, the active proliferative response of hepatocytes makes the liver an important target of carcinogens. The goal of this presentation is to discuss how assessment of hepatobiliary toxicity is done based on clinical chemistry, gross pathology, organ weight and histopathology. This presentation will emphasize important injury mechanisms, which can be a consequence of metabolism and/or direct cell toxicity of chemicals.

Dr. Pankaj Shelar; B.V.Sc., M.V.Sc., DICVP, DIBTP

Dr. Pankaj Shelar graduated from Bombay Veterinary College and earned his master's in Veterinary Pathology from the same institute wherein he worked on Chromium toxicity in rats and dogs for which he is a recipient of 'Young Scientist Award' instituted by Society of Toxicologic Pathology-India (STPI). He is a dual board-certified toxicologic pathologist with experience spanning over more than a decade in non-clinical safety assessment of novel biopharmaceuticals. He was employed by Ranbaxy, Daiichi-Sankyo, Sun Pharma and currently affiliated with Lupin, and has shouldered responsibilities of increasing magnitude. He has authored more than 100 GLP-compliant pathology phase reports for non-clinical safety evaluation studies conducted on rodents and non-rodents, submitted to international regulatory agencies. Moreover, he has several publications in peer-reviewed journals of international repute including Toxicologic Pathology and lead authorship of an international patent. He has been an active member of Society of Toxicologic Pathology-India (STP-I) and Indian Association of Veterinary Pathology (IAVP) and is a certified diplomate of Indian Board of Toxicologic Pathology (IBTP) and Indian College of Veterinary Pathologists (ICVP). Also he holds an invited full-membership of Japanese Society of Toxicologic Pathology. He has been invited as lead speaker and session examiner for various workshops and conferences organized by IAVP/ICVP and Society of Toxicology-India (STOX). His routine responsibilities include supervising GLP-compliant histopathology and immunohistochemistry laboratories, performing histopathology evaluation, conducting formal and informal peer reviews and writing/reviewing pathology phase reports. His research interests include immunopathology and onco-immunopathology in particular.

Session Topic: Toxic Responses of the Urinary System: 'Keeping it Renal'

The mammalian urinary system consists of kidneys, ureters, urinary bladder and urethra. Kidney consists of numerous cell types organized into 'nephron' which is the basic structural and functional unit. Overall functional integrity of the kidney is pivotal to complete body homeostasis as it plays quintessential role in excretion of metabolic waste, regulation of electrolyte composition, maintaining acid-base balance and maintaining extracellular fluid volume. Additionally, it synthesizes, releases and metabolizes hormones and vitamins such as renin, erythropoietin and active vitamin D3 form. Kidney is especially poised to toxic insult as it receives a significant percentage of cardiac output and robust blood filtration regularly exposes it to drugs and drug metabolites. Acute Kidney Injury (AKI) is the foremost common manifestation of nephrotoxic damage induced by a variety of drugs classes, chemicals and biological toxins. Site-specific AKI may result into a spectrum of cellular and molecular responses manifested as functional and structural changes e.g. decline in glomerular filtration rate (GFR) and renal tubular epithelium (RTE) injury, histologically seen as degeneration/necrosis of RTE. Chronic Kidney Disease (CKD) may result from progressive deterioration of renal function with long term exposure to drugs/chemicals and culminate in end-stage renal disease. Therefore, timely assessment of renal function with the help of biomarkers coupled with precise pathological examination can prevent exacerbation of renal injury and its systemic adverse effects.

Session Topic: Toxic Responses of the Cardiovascular System: 'Pathology beyond Rhythm'

The components of cardiovascular system (CVS) are susceptible to a wide spectrum of insults from natural disease and xenobiotics including drugs. Accurate and precise histopathological description coupled with elaborate functional assessment are important for comprehensively understanding the pathogenesis and mechanisms involved in CVS toxicity. Responses of CVS to the injury may reflect functionally as decreased cardiac output and peripheral tissue hypoperfusion resulting from perturbations in biochemical, energy metabolism, electrophysiology pathways and contractility of the heart. The functional and morphological alterations induced by a toxic insult are collectively referred as toxicological cardiomyopathy. Although responses to injury by the CVS are similar in nature to those of other organs, it is noteworthy that minimal and/or insufficient regenerative capacity of cardiomyocytes to replace significant loss of cardiac tissue marks it as an exception.Pathogenesis of xenobiotic-induced vascular injury may be due to immunologic, biochemical or direct cellular cytotoxicity. Direct cytotoxicity and biochemical mechanisms are predominantly seen in laboratory rodents while immune-mediated vasculitis are more common on clinical side. Spontaneous or non-drug induced vascular lesions may pose interpretive challenge, however differentiation by considering incidence, dose-response and historical experience with spontaneous disease can be made.

Dr. Madhusudan P.G. M.V.Sc, PhD, DACVP, DABT

Madhusudan P. G is currently working as a senior principal scientist in the Department of Safety Assessment at Syngene International Limited, Bengaluru. He has approximately 10 years of combined experience in diagnostic and toxicologic pathology. He is the only American College of Veterinary Pathologists (ACVP) certified pathologist working in India. Prior to joining Syngene, he worked in one of the top CROs in US (Covance Laboratories) for approximately 4 years as a veterinary pathologist in preclinical safety assessment. He did anatomic pathology residency training at College of Veterinary Medicine, Kansas State University in US, followed by passing ACVP certification exam in 2013. He has two years of postdoctoral training in respiratory toxicologic pathology at National Institute for Occupational Safety and Health (NIOSH) in US, where he worked on elucidating the mechanisms of respiratory toxicity induced by artificial butter flavorings. He has bachelor's degree in Veterinary Science from Bengaluru and master's degree in Animal Biochemistry from National Dairy Research Institute (NDRI), Karnal. He obtained PhD degree in reproductive physiology from West Virginia University in 2009, where he researched on cellular mechanisms of differential sensitivity of bovine corpus luteum to prostaglandin F2 alpha. He has presented his research findings in many international conferences and published several research articles. He has extensive diagnostic pathology experience in diseases of various domestic and pet animals and pharmaceutical industry experience in histopathology evaluation of several subacute, chronic and carcinogenicity studies involving multiple laboratory animal species including rats, mice, primates, rodents and rabbits.

Session Topic:Respiratory System

Respiratory system is in direct interface with the environment and therefore constantly exposed to contents in the air through inhalation. Respiratory toxicity can result from either exposure through inhalation or blood. Some understanding regarding gross and microscopic anatomy with subtle differences among species are essential to understand and interpret toxic response of respiratory system. Respiratory system has an inherent defensive and repair mechanisms to prevent and protect against exposure to injurious agents, which when overwhelmed can to lead to pathologic changes in the respiratory changes. This pathologic response of respiratory system to toxins can be assessed by gross and microscopic pathology, which can provide information on mechanism, severity, and reversibility of toxic responses. Assessment of pathology endpoints by specialized techniques can provide insight into mechanisms of toxicity, which can be effectively utilized in experimental toxicology pathology. Animal models of human respiratory diseases provide relevant information on safety and efficacy of new therapies. Knowledge of common diseases of respiratory system in laboratory animals is essential to undertake preventive animal husbandry practices in the vivarium. Importantly, an appropriate use of diagnosis and terminologies by pathologist in toxicology studies and effective communication with the toxicologist or study director is essential to make a clear distinction between adaptive versus adverse findings in the respiratory system.

Dr. G. Selvam, M.V.Sc., PhD, DICVP, DIBTP, DABT, PGDRM, FASc (AW)

Dr. G. Selvam received his B.V.Sc. degree from Madras Veterinary College followed by his post-graduation (M.V.Sc. & A.H.) degree from Jabalpur Veterinary College, Madhya Pradesh and Doctoral degree from University of Madras, Chennai. Besides, he holds related specialty board certifications in Veterinary Pathology (Diplomate, ICVP), Toxicologic Pathology (Diplomate, IBTP) and Toxicology (Diplomate ABT). To fill his penchant towards stem cell research and tissue engineering, he completed a Post Graduate Diploma course in Regenerative Medicine (PGDRM) from Madras Veterinary College, Chennai.As a Toxicologic Pathologist, he has 12 years of experience in risk of assessment of chemicals and has been presently working as Senior Scientist / Head In-charge of Pathology division at International Institute of Biotechnology and Toxicology (IIBAT), Padappai, Tamil Nadu. He has worked in several regulatory toxicity studies and has actively participated in various basic science / academic researches concerned with engineered nanoparticles like MWCNTs, amorphous silica and various metal oxide nanoparticles. By virtue of these research endeavors he has published research articles in various, well-acclaimed, peer reviewed journals. His expertise and interest lies in inhalation toxicology, nanotoxicology, neurotoxicology and regenerative medicine.

Session Topic: Nervous System

Risk assessment for the neurotoxicity potential of a chemical or drug, demands an integrated, multidisciplinary approach where the entire assessing unit is expected to be thorough with the basic principles, concepts and technical procedures in designing the experiment with appropriate endpoints, obtaining the intended information as accurate as possible and in evaluating the data.This approach involves specific aspects on behavior, neurochemistry, neurophysiology and neuropathology. Several factors, like superlative degree of complexity in the wiring pattern of the near and distant neurons that act in a coordinated fashion, high lipid content and energy demand, restricted regenerative capability, to name a few, predispose the nervous system to be extremely vulnerable to certain chemical insult. Further, the manifestation of the nervous system to the toxic insult is highly unpredictable where, in certain circumstances, the erratically triggered communication mechanism leads to overt clinical signs and even sudden death. In contrast, in other situations, the toxicity is exhibited in a very subtle manner that could be detectable only in the advanced stages, for example, in case of altered cognitive functions. Thus, the understanding of the animal behavior and cognition, neurochemistry, neurophysiology, neuroanatomy, and principal techniques used for evaluating the selected endpoints are considered as a paramount prerequisite in the risk assessment of neurotoxicity in a preclinical set-up.

Dr.Shekar Chelur, M. V. Sc., DABT, DIBTP

Dr. Shekar Chelur graduated in 1996 and completed his Master's in Veterinary Pathology from Bangalore Veterinary College in 1999. He has worked at Jai Research Foundation, Torrent Research Centre and Zydus Research Centre before joining Aurigene Discovery Technologies Ltd in 2004. He is a Diplomate of American Board of Toxicology (DABT) and Indian Board of Toxicologic Pathology (IBTP). He is currently Vice President of Society of Toxicologic Pathology- India (STP-I), Registrar of Indian Board of Toxicologic Pathology (IBTP) and actively involved in various professional activities of STP-I and IBTP.

Shekar has been extensively involved in safety evaluation of NCE's in the area of Metabolic Disorders (Diabetes and Obesity), Oncology (Kinase inhibitors, protease inhibitors, hormone receptor modulators, epigenetic targets, TLR pathway inhibitors, PROTAC's), Pain & Inflammation, Immunomodulators, Musculoskeletal disorders and anti- Apoptotic therapy. He is recipient of several merit scholarships including senior research fellowship from Indian Council of Agricultural Research. He is co-inventor of 3 international patents. He is author of 15 publications and co-author of three chapters in 2019 reference book "The Illustrated Dictionary of Toxicologic Pathology and Safety Science".

Session Topic: Preclinical Drug Discovery and Development of Small Molecule Oncology Drugs

Abstract: Cancer is the second leading cause of death, and was responsible for 8.8 million deaths globally in 2015 (WHO Cancer Fact sheet, February 2017). There are more than 200 anticancer drugs currently in the global market and still there is unmet medical need for treatment of several cancer types. The pharmaceutical companies and regulators worldwide follow different approach for oncology drug development vs development of drugs for non-life-threatening diseases. Phase 1 clinical trials are conducted in patients with non-responsive late stage disease with mean life expectancy of three to five months. Phase 2 trials are conducted in late stage disease with mean life expectancy of only one to two years excluding few cancer types such as, hormone-dependent metastatic prostate cancer, breast cancer. US Food and Drug Administration (FDA) terms oncology drug development as a "Permissive Process" and advocates fast-track mechanisms, including accelerated approval with phase 2 data, priority review, and orphan drug status, more recently breakthrough therapy for approval of new anticancer molecules.

Newly identified targets in tumors and cancer cell lines holds great promise for oncology therapy. Molecules directed at a novel target has only about an 11% chance of success after entering first in human trials and the probability for novel oncology drug success is even less (less than 5%). Risk lies with the fact that novel targets, by definition lack validation through proof of efficacy in the clinic and they rapidly move through drug candidate selection and enter development well before the function of the target in normal tissues and physiology is fully understood.

Outcome of preclinical toxicology studies are both subjective and context-dependent. Several factors must be considered sufficiently to halt progression of an anticancer compound to human subjects based on a toxicology finding.

- Are toxicities consistent with mechanism of target inhibition?

- Are PK-PD-Toxicity inter-relationship well established?
- What is the severity and reversibility of the finding?
- What is the margin between the concentrations of the compound at which toxicity is observed compared with the concentration needed to show beneficial effects (also known as the therapeutic index)?
- What is the risk–benefit ratio in the intended disease setting?
- What is the likelihood of such an effect translating to humans?
- the ability to monitor and treat any subsequent consequences?

Decision to stop an oncology drug candidate for toxicological reasons is both a complex and nuanced judgement. Mechanism based toxicities in preclinical species are now shown to have considerable correlation to modulation of pharmacodynamic biomarkers and clinical efficacy of Oncology molecularly targeted therapies.

Success of Drug Discovery and Development of Small Molecule Oncology Drugs at the preclinical stage depends on a. understanding of adequate target/s knowledge through "target safety assessment profile" which helps to understand potential liabilities of inhibition of a certain target and to understand the risk tolerance for liabilities based on the intended therapeutic use, b. validation of target to help define the physiological function of a target, as well as potential adverse effects resulting from inhibition of the target, characterization of candidate's molecular properties to help target validation and eventually influencing compound developability. and more importantly, understanding and managing toxicities than trying to reduce or eliminate toxicities which are more commonly futile in cancer therapeutics.

Session Topic: Reproductive system

Xenobiotic induced effects on the reproductive system can be pivotal in development of drugs and chemicals as human fertility is considered too fragile to compromise. Reproductive tissues in both males and females are assessed by several evaluations including weights of testes, epididymis, and accessory glands; ovaries and uterus, sperm morphology, motility, and concentration; estimation of hormone hormones and impact on fertility, but histopathology evaluation is essential for safety assessment and for elucidation of mechanism of action. Background pathology, knowledge of reproductive endocrinology, development, and comparative biology and species differences are also important for evaluation. The reproductive system also has several unique features that require special attention, including regulation by hormones from the hypothalamus, pituitary, and other endocrine organs; stress related changes, age-related dynamic changes at puberty and senescence and stage-aware evaluation of spermatogenesis in the males. Use of mature animals in studies is prerequisite for effective risk assessment of reproductive toxicants. This is a greater problem in dogs and non-human primates than in rodents, which mature at about 8-10 weeks of age. Organ weights (particularly of the testes and epididymis), sperm analysis, endocrine hormone estimation and fertility assessment can be more sensitive than histopathological evaluation. Prostate and seminal vesicle weights can be more useful to evaluate xenobiotic induced effects on hormone levels than histopathological examination.

Dr. Jomy Jose M.V.Sc., DIBTP, DABT

Dr. Jomy Jose is currently heading the Pathology group at RCC Laboratories India Ltd, Hyderabad. In this role she supports evaluation of toxicity of environmentalchemicals and safety assesssment of pharmaceutical compounds. She is a toxicopathologist with 16 years of experience and prior to this she was associated with Vimta Labs and Advinus Therapeutics . She is a Diplomate of Indian Board of Toxicologic Pathologists and an American Board Certified Toxicologist. Being a member of national and international professional societies for pathology and laboratory animals she had served as executive committee member and treasurer for the Society of Toxicologic Pathology-India. Currently she is one of the board of directors for Indian Board of Toxicopathology

Session Topic: Pathology of Endocrine system

A vast number of critical biological processes are regulated by the endocrine system and hence regulation of hormonal activity is critical to all biological systems in their quest for biological homoeostasis. Because of the structural similarity to certain hormones, some toxic substances interfere directly with the glands that synthesize and secrete hormones. The chemical vulnerability of the endocrine system are exacerbated by the tier and feedback systems of many hormones. In effect, the glands producing the regulatory hormones are also target organs of the primary hormone; hence every cell in the endocrine system is chemically linked to every other cell within the sphere of influence. The effects can be widespread and can be life threatening if they do not function in synchrony. Interestingly, chemically induced changes in the endocrine system are not always considered undesirable. The lecture on endocrine system focuses on some effects of pharmaceutical compounds and environmental chemicals on various aspects of the system's function. Mechanistic information is included whenever possible to aid in the interpretation of findings and to assess their potential for human risk.

Dr. P.C.Prabu, M.V.Sc., Ph.D., DICVP, DIBTP

Dr. P.C.Prabu, hailing from a small town of Erode, is a Dual Board Certified Veterinary Pathologist (Diplomate ICVP (Indian College of Veterinary Pathology)& Board certified Toxicologic Pathologist - Diplomate IBTP (Indian College of Toxicologic Pathology), currently working as Assistant Professor at the Madras Veterinary College, TANUVAS Chennai. He is one of the Directors of the prestigious Indian Board of Toxicologic Pathology. He has more than 10 years of experience in preclinical research at various levels as Lab Animal Veterinarian, study pathologist, study director and deputy technical manager. He has served as Research Scientist under DST Animal Facility Project and was involved in the establishment of the Laboratory Animal Facility including the Transgenic facility as a Lab Animal Veterinarian at the Central Animal Facility, SASTRA University. He has also established the Histopathology and Clinical Pathology Laboratories. In 2014, all these laboratories were accredited by NABL (ISO: IEC 17025) for Biological Testing. He has been primarily, a study pathologist and have done slide reading for 200 + studies including both toxicology and pharmacology studies as per the regulatory guidelines (OECD, Schedule Y, WHO and ISO). He has served as the Member Secretary of the IAEC, SASTRA for 11 years involving more than 350 animal projects. The drugs / compounds evaluated were herbal medicines, biofilms, and nano-drugs / nano-materials. He has been the Principal Investigator / Co-investigator of several projects funded by MHRD, ICMR, SASTRA University, etc., to the tune of 1 Crore. He has to his credit more than 23 international papers in peer reviewed journals of repute with a cumulative impact factor above 65 and h index of 10. He is a recipient of several National and International Awards including the coveted IFSTP (International Federation of Society of toxicologic pathologists) Student Travel Grant Award (2012) for best Ph.D work in Toxicologic Pathology and Charles Capen Trainee Award (2014) for demonstrated achievements in the field of toxicologic pathology awarded by the International Academy of Toxicologic Pathology, .

Session's Topic: Toxic responses of skin

Skin guards the internal organs against external injuries and plays vital role in the maintenance of internal homeostasis. Itsbiological sophistication allows it to perform a myriad of functionsabove and beyond that of a suit of armor. However, its large volume and high accessibility to different chemicals makes it the most affected organ particularly through topical route. The National Institute of Occupational Safety and Health (NIOSH) considers disorders of skin as the most pervasive occupationalhealth problems and has been placedin the top 10 leading work-related diseases. The major mechanisms by which skin is injured by chemicals include systemictoxicity via skin absorption, direct effects that damage the skin and immune-mediated responses to chemicals that contact theskin.In this brief presentation, normal anatomy / physiology of skin, mechanisms of dermal toxicity, types of dermatitis, phototoxicology, pigmentary disturbances, neoplasms, etc., are discussed.

Dr. Soumya Bharath M.V.Sc., DABT, DIBTP

Sowmya Bharath received veterinary degree from University of Agricultural sciences, Veterinary College, Bangalore, then she also completed Masters in Veterinary Pathology with gold medal. In 1993 she joined Rallis Research Center (Advinus) as Research Officer- Pathology in Histopathology department where she was responsible for evaluation of molecules in GLP setup. In 1998 she moved to AstraZeneca Bengaluru and served for 16 years where she was responsible for efficacy studies initially and safety support in drug discovery for Tuberculosis and Malaria later on. A Diplomate of American Board of Toxicology , she established the safety criteria for TB and Malaria along with Global safety assessment of AstraZeneca. Currently Dr. S. Bharath is working in a CRO "INTOX Pvt. Ltd" as Head of Section-Histopathology and Clinical pathology. She is responsible for evaluation of molecules in 28-day/90-day repeat dose toxicity studies under the principles of Good Laboratory Practice (GLP) following OECD guidelines. She recently got certified as Diplomate Indian Board of Toxicologic Pathology. She has coauthored more than 15 papers in reputed international journals. She has also authored a chapter in a colour atlas.

Session Topic: Immune system

Thymus, spleen, lymph node, bone marrow and mucosa -associated lymphoid tissue (MALT), and other lymphoid tissues like serosa -associated lymphoid clusters (SALC) and tertiary lymphoid structures (TLSs) form haematolymphoid system. These haematolymphoid organs produce and maintain the cells of acquired and innate immunity and immune responses (lymphocytes, monocytes, macrophages, dendritic cells and granulocytes) and they also produce the cells that carry blood gases (erythrocytes) and maintain vascular integrity (megakaryocytes). The hematolymphoid organs are the organs of the immune system and they collectively produce the lymphocyte repertoire, conduct immune surveillance and mount immunologic reactions. The classic primary or central organs are the bone marrow and thymus where lymphocyte proliferation and maturation take place independent of stimulation by exogenous antigens. The spleen, lymph nodes, MALT and SALC are secondary lymphoid organs where exogenous antigen-dependent lymphocyte development and proliferation take place. TLS are tertiary lymphoid tissues that are induced in non-lymphoid organs.

A key feature of the hematolymphoid organs is that blood cells can move from one organ to another using the blood and lymph for transportation. Mature naïve lymphocytes are particularly mobile and constantly cycle through secondary lymphoid organs in their continual search for cognate antigens. Erythrocytes, monocytes and platelets are also stored in the red pulp for ready release. The level of background activity for each strain and group of animals is influenced by nutritional status, antigen load, age, genetics, spontaneous lesions, steroid hormone status and infectious agents (opportunistic, incidental or concurrent). Data from standard toxicity studies should be evaluated for signs of immunotoxic potential. Histomorphologic assessment of the immune system is a recognised cornerstone in identification of immunotoxicity. Drug or drug-protein adducts might also be recognized as foreign and stimulate an anti-drug response. Subsequent exposures to the drug can lead to hypersensitivity (allergic) reactions.

The purpose of this presentation is to provide standardized nomenclature for classifying changes observed in hematolymphoid. This will also introduce to conventional terms which were used earlier. Differentiation and identification of background, individual, local or systemic effects requires accurate description and interpretation of histologic findings in conjunction with ancillary data such as clinical history, clinical pathology, organ weights and gross observations.

Dr. Sebastian M.V.Sc., DABT

Dr. Sebastian is a Veterinarian and Certified Toxicologist (Diplomat of American Board of Toxicology/European Registered Toxicologist), and currently working as Director and Principal Consultant-Development Consulting and Scientific Affairs at PharmaLex India Private Limited. Dr. Sebastian has close to 14 years of industrial experience that includes drug discovery, non-clinical development, experimental toxicology and pharmacology, Good Laboratory Practices (GLP), computational toxicology, human health risk assessment, environmental risk assessment, and medical writing. In his past assignment at Dr. Reddy's Laboratories Ltd., and Aurigene Discovery Technologies Ltd., he gained hands-on experience in design, conduct, review, analysis, interpretation, and reporting of *in-vitro* and *in-vivo* (rodent and non-rodent) toxicology and pharmacology experiments. He established and validated number of *in-vitro* and *in-vivo* safety pharmacology models and contributed significantly in establishing an integrated safety pharmacology facility. He has extensive knowledge of OECD principles of GLP, its implementation and application in a regulatory environment for the safety evaluation of pharmaceuticals. He functioned as study director for toxicology and safety pharmacology studies and also as study monitor for outsourcing key investigational new drug (IND) application enabling studies.

Dr. Sebastian is currently involved in strategic development and consulting services in pharmaceutical product development with special reference to non-clinical and toxicological requirements; non-clinical evaluation strategy in support of IND and NDA; risk assessment of pharmaceutical active ingredients and excipients; impurity qualification of API's and drug products; risk assessment and derivation of permitted daily exposure (PDE) and occupational exposure limit in support of GMP manufacturing; environmental risk assessment of pharmaceuticals; provide expert review of investigator's brochure, non-clinical and clinical overview of CTD modules; author/review briefing book for regulatory consultation; respond to regulatory queries as appropriate; and toxicological risk assessment and safety evaluation of cosmetic ingredients/products, medical devices, and consumer products.

Session Topic:Toxicological risk assessment

Fundamental principle of toxicology assumes that every chemical is a poison; there is none that is not a poison. However, all chemicals won't result in harm in all situations; adverse effects occur only under certain specific situations. The risk assessment attempts to find out the possibility of occurrence of harmful effects under certain specific conditions. An adverse effect to a chemical is likely to occur when the chemical is inherently toxic (hazard) and when the exposure is sufficiently high to cause an adverse effect. Irrespective of type of chemical for which the assessment is done, the human health risk assessment comprises of hazard assessment, dose-response, exposure assessment, and risk characterization. The hazard data required for a risk assessment comes principally from the experimental study reports. The most critical information the risk assessor looks at in the study reports is the NOAEL and LOAEL values. An incorrectly defined NOAEL/LOAEL can dramatically alter the course of the risk assessment. Therefore, it is important that Study Directors critically evaluate the study findings and draw conclusion based on the expert judgement. In a typical risk assessment, potential adverse effects on all health end points are considered. Broadly, they can be categorized in to effects which show a 'threshold' and those which does not show a typical threshold, accordingly the risk assessment methodology also varies. This concept is applicable to all areas of risk assessment– pharmaceutical, medical device, industrial chemicals, environmental pollutants, food contaminants, cosmetics, consumer products, etc. This presentation covers the application of basic concepts of toxicological risk assessment to address chemical safety related issues that affect these industries, but with special focus on pharmaceuticals. It also deals with the most common challenges in the risk assessment such as data gaps and route-to-route extrapolation using illustrations that include case studies.

Dr. Anirban Mallik Thakur, B.V.Sc & A.H.; M.V.Sc.

Anirban is currently working as Functional Head for Toxicology and Preclinical Research for Cipla Ltd. and has over 15 years of experience in different Pharmacology and Toxicology Labs as a researcher, study director and monitoring scientist. He has hands in experience of more than seven years in OECD GLP certified toxicology laboratories. He has more than 10 years of experience calculating and deriving different toxicological values and health based exposure limit calculation. He also has experience handling pharmacology, pharmacodynamics and toxicity study of small to large molecules, biotechnology derived products, biosimilar, stem cells, medical devices, veterinary products etc. He also has rich experience in in-vitro biowaiver studies. He has the experience of working on the global development of Veterinary pharmaceuticals. He has the experience of attending many interaction with regulatory agencies.

Sesssion Topic: The Art of Impurity qualification: A scientific approach

In pharmaceutical industry impurity/ extractable/ leachable poses a great challenge in timely approval. There are many guidelines available which helps in mitigating the challenge. However, because of diverse nature of the impurities, extractable and leachable it's many time poses great challenge. Many time late stage identification of impurities at three-month stability data makes the things more complicated. There are many unknown territories like peptides, fermented products, biosimilar posed additional challenge where the guidelines are scant.

Impurity qualification itself is a great art, with umpteen number of approaches with last resort of conducting a toxicity study. There are many in-silico tools, smart data mining, taking help from analytical colleagues can lead to successful time efficient paper based justification.

Last but not the least, toxicity study gives assurance about impurity qualification. However, there are many approaches needed to considered like selection of species, umber of groups, inclusion or exclusion of toxicokinetic groups etc. Proper strategy is the need of the hour to smooth approval.

In short it's an art of drawing a collage to sail through the approval process without compromising the quality of product and as a toxicologist assuring patient safety.

Dr. Balaji M R, M.V.Sc

Dr. Balaji M R, is currently working as Senior Director and Head of Toxicology at Dr. Reddy's and has over 22 years of experience as a drug discovery and regulatory toxicology and development of new chemical entities in pharmaceutical industries. Vast experience in the development of preclinical strategy, development of target product profile, drug target assessment, risk assessment, study design, conduct, reporting and evaluating safety data for new chemical entities, impurities in drug substance/products and bridging toxicology studies; extensive experience in regulatory filing of repurposed products 505 (b)(2); in training and managing staff; in dealing with regulatory bodies, contract research organizations; in writing investigational new drug application toxicology summaries; Author , review and approve nonclinical sections for regulatory submissions including IBs, INDs, annual reports, CTAs, MAAs & NDAs. Analyse & integrate toxicology reports & other documentation in support of regulatory submissions. Non clinical strategy, execution and filing of 6 NDA's 505 (b)(2)for repurposed products at Dr.Reddy's Laboratories in the last 8 years. All the 6 NDA's were approved by FDA in the first cycle review.

Session Topic: Exploring 505 (b)(2) : An Abbreviated pathway for Repurposing of Existing Drugs with special reference to topical product development

Drugs are approved by the FDA by three main regulatory pathways: (I) 505(b)(1) new drug applications (NDAs); (ii) 505(b)(2) NDAs; and (iii) 505(j) abbreviated NDAs (ANDAs). Various aspects governs the drug development through 505(b)(2) pathway. The appropriate pathway depends on the active ingredient, already approved drug products, drug formulation, clinical indication, route of exposure, among other factors. A 505(b)(2) application is one for which one or more of the investigations relied upon by the applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained aright of reference or use from the person by or for whom the investigations were conducted" .The 505(b)(2) NDA pathway is a regulatory approval pathway that allows sponsors to use existing public data in lieu of conducting studies; thus, potentially offering significant drug development and marketing advantages. Nonclinical testing programs for 505(b)(2) submissions are often reduced and, in some cases, are not even required. For 505(b)(2) NDA drug development, the nonclinical program typically focuses on: (i) filling any nonclinical data gaps (ii) justifying the safety of any differences between the new drug product and the Listed drug (e.g., justifying the local safety of a new route of administration); (iii) justifying the safety of the excipients; and (iv) qualifying impurities and degradants. The nonclinical development program for a 505(b)(2) NDA drug product is highly drug-product-dependent and many factors enter into whether nonclinical testing is required and the number and types of studies that might be needed. The FDA has issued a guidance document that provides general information on the types of nonclinical studies that might be required for reformulated drug products and drug products administered by an alternate route. Nonclinical development of a topical (dermal) product for 505(b)(2) application is highly complex and needs careful assessment of dermal toxicity and may require extensive evaluation including carcinogenicity in some instances.

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4. Display of Company details(Name and/or Logo) and One page of advertisement
5. Display of company logo in Toxicology newsletters (3 Months)
6. Company Logo will be displayed on promotional materials related to the event (conditions apply)
7. 30% discount on the registration fee for one participant, or a 15% discount in the registration fee for two participants

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Learning gives creativity, creativity leads to thinking, thinking provides knowledge, knowledge makes you great.
Dr. A P J Abdul Kalam