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**1<sup>ST</sup> INTERNATIONAL SYMPOSIUM ON INDUSTRY-ACADEMIA  
INTERACTIONS IN ADVANCED BIOTECHNOLOGY & DRUG  
DISCOVERY**

*Noida/New Delhi, India, Nov 22- 23, 2010*

*Venue*

*Conference Hall, Clongen Biotechnology Pvt Ltd*

*D-34, Sector 2, Noida, India*



## *From the Organizing Secretary's Pen*

*The past decade has witnessed significant changes in India with the emergence of several biotech companies and increased investments and focus on drug discovery by pharmaceutical companies. Activities of many multinational companies were seen to have their presence in India. The recent big acquisitions of Ranbaxy by Daiichi-Sankyo and Piramal Healthcare by Abbott Laboratories are good examples. The global pharmaceutical market is estimated at US\$ 427 billion and R & D cost is estimated at USD 60-65 billion annually. R & D Industry has opened up new vistas of employment for a large number of people. India has become one of the best destinations for Biotechnology industry due to good network of research laboratories, rich biodiversity, establishment of several state-of-the-art CRO's with GLP facilities, well developed base industries, rich agriculture sector and trained manpower that speaks English fluently.*

*While pharmaceutical industries in the USA, and to some extent in the Europe, are going through tough time resulting elimination of thousands of research jobs due to mergers and acquisitions, India has seen strong growth in this sector for the past few years, and job opportunities in R & D sector have increased. In addition, India also offers tax concessions on revenue to companies making R&D investments in India. These incentives are expected to substantially increase R&D activities of both multinational and domestic biopharmaceutical companies. An added advantage is that India's pharmaceutical market is the second largest in Asia, growing by more than 9% annually. We believe that at this time making efforts to bring industry and academia together to leverage the vast knowledge-base that India possess at academic institutions would help to adequately harness the expertise and translate into products.*

*The goal of this symposium is also to help reach the fruits of the developments to those underprivileged sections of the society who are cut-off from the main stream. These are the students in small towns and villages of India who have limited access to hear world-class scientists, educationists, entrepreneurs and technologists. The objective of the Society for Education, Research and Rehabilitation (S-LEARN) is to bring world experts in advanced biotechnology and drug discovery who have been successful and encourage students and budding scientists to listen to not only their success stories, but also the science and technology that they innovated in order to be successful. The objective is also to present to these young scientists the cutting edge science to arouse interest in the field of advanced biotechnology and drug discovery. To that end S-LEARN has teamed-up with Clonogen Biotechnology to train students in hands-on techniques and providing relevant knowledge to underprivileged students so that they become successful in pursuing a research career either in biotech industries or at academic institutions. This symposium was made free to all students.*

*Raj Ajit Srivastava, Ph.D., FAHA, MBA*

## *Organizing Committee*

Dr Rai Ajit Srivastava, Esperion Therapeutics, USA, *Organizing Secretary*, [ajitsriva@gmail.com](mailto:ajitsriva@gmail.com)

Dr Roger S Newton, President & CEO, Esperion Therapeutics, USA, *Advisor*

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Dr Charles L Bisgaier, President, Michigan Life Venture, USA, *Symposium Planning*

Dr. Neelam Srivastava, Bristol-Myers Squibb, USA, *Symposium organization and Planning*

Dr Salman Azhar, Stanford University, USA, *Abstract screening and selection*

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**The symposium was made possible through:**

1. Financial support and hosting from CloneGen Biotechnology, Noida, India
2. Generous contribution from Dr Kalyan Handique & Priyadarshini Gogoi, USA, to S-LEARN, India, a non-profit organization & co-organizer of this symposium
3. Generous gift from Dr Ajit Srivastava & Neelam Srivastava, PA, USA to S-LEARN
4. Generous contribution from Dr Roger S Newton & Coco Newton, Ann Arbor, MI, USA to S-LEARN

**These contributions helped all participating students participate in this symposium without paying any registration fee**



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**Naranjan S. Dhalla, CM, FRSC, PhD**  
*Distinguished Professor & Senior Fellow*  
*Centre for the Advancement of Medicine*

November 9, 2010

Dr. Rai Ajit Srivastava  
Executive Director  
Esperion Therapeutics

Dear Dr. Srivastava:

Thank you very much for your e-mail letter dated November 9, 2010 with scientific program for the International Symposium which you are organizing in Noida/Delhi, India during November 22-24, 2010. I wish to congratulate you for assembling an excellent team of invited speakers, who will talk on a wide variety of topics on metabolic diseases. I am sure it will promote the interaction of industry and academia as well as advance the drug discovery program for improving health. I am convinced that your conference will be a great success.

With my very best regards,

Naranjan S. Dhalla, MD (Hon), DSc (Hon)  
Director of Cardiovascular Developments, SBRC  
Editor-in-Chief, *Molecular and Cellular Biochemistry*  
Executive Director, International Academy of Cardiovascular Sciences

NSD/el



Division of Cardiothoracic Surgery

Doan Hall 8 North  
410 West 10th Avenue  
Columbus, OH 43210

November 15, 2010

Dear Ajit:

I am delighted to note the impressive list of speakers and topics for the 1st International Symposium on Industry-Academia Interaction in Advanced Biotechnology & Drug Discovery. The symposium covers several critical issues such as inflammation and dyslipidemia in diabetes and other forms of cardiovascular diseases. While improved life style and the availability of drugs, such as statins, have decreased cardiovascular death, the alarming increases in the incidence of diabetes and obesity around the world should caution us from being complacent. There is increased need for newer and better drugs and these could come only from better understanding of the disease process. The timing and topic of the symposium is quite appropriate and the hope and expectations are quite high.

I congratulate you on putting this symposium forward and having a wonderful list of experts presenting their findings and ideas that would benefit both the academic and pharmaceutical industries.

Sincerely,

Sampath Parthasarathy, Ph.D., M.B.A., F.A.H.A.

Klassen Chair and Professor of Surgery

Professor of Internal Medicine and Professor of Human Nutrition

The Ohio State University Medical Center

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Adult Cardiothoracic Surgery

Pediatric Cardiothoracic Surgery

Arrhythmia Surgery

Minimally Invasive  
Cardiothoracic Surgery

Robotic Surgery

Thoracic Oncology

Lung Volume Reduction

Heart Transplantation

Lung Transplantation

Mechanical Heart Devices

Cardiothoracic Research

International Medicine



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health  
National Eye Institute  
Bethesda, Maryland 20892

Nov 11, 2010

Dr. Raj Aji Srivastava  
Executive Director  
Esperion Therapeutics

Dear Aji:

Thank you very much for the invitation to participate in the International Symposium that you are organizing in Noida/Delhi, India from November 22-24, 2010. The scientific program and the list of invited speakers you have assembled are outstanding. The focus of the conference on drug discovery is timely and should promote interactions between academia and industry. Unfortunately, I have numerous prior commitments and will not be able to participate this time.

I congratulate you and your colleagues for organizing this impressive conference and wish you tremendous success in accomplishing your goals.

With best regards,

A handwritten signature in black ink that reads "Anand Swaroop". The signature is written in a cursive style with a horizontal line underneath.

Anand Swaroop, PhD  
Senior Investigator and Chief, N-NRL/NEI/NIH



## ***1st International Symposium on Industry-Academia Interaction in Advanced Biotechnology & Drug Discovery (Nov 22-23, 2010)***

### **Scientific Program**

10:00 AM-10:05 PM: *Welcome Address by the Organizing Secretary*

10:05 AM-10:15 PM: *Inauguration and Opening of the Symposium*

10:30AM – 11:30 AM: *Keynote Lecture*



Mahmood M Hussain (*Professor of Biology, State University of New York, USA*): *Role of Microsomal Triglyceride Transfer Protein in plasma and tissue lipid homeostasis*

**11:30 AM – 12:30 PM**



Rai Ajit Srivastava (*Executive Director, Esperion Therapeutics, USA*): *Beyond Statins: Targeting Reverse Cholesterol Transport to Treat Coronary Artery Disease*

**12:30 PM – 1:00 PM**

Oral Presentation by – *Mr. Arnab Datta, Clonegen Biotechnology, Noida, India* “*Influence of Ascorbic Acid on various Biochemical Constituents & rbcL gene expression in Soybean Seedlings*”

Oral Presentation by – *Ms. Hannah Hepsibah A., Clonegen Biotechnology, Noida, India* “*Amplification and Comparison of 16s – 23s rRNA Intergenic Spacer region in Shigella boydii and Shigella flexneri*”-

**1:00PM – 2:00 PM**

LUNCH

**2: 00 PM – 2:45PM**



*Rajiv Sharma (Vice President, Piramal Life Sciences, India, former Sr Principal Scientist, Amgen, USA): Impact of new technologies in industrial medicinal chemistry*

**3:00 PM- 3:30 PM**

Tea Break

**3:30 PM – 4:30 PM**



*\*Ravikumar Peri (Independent Pharmaceutical Professional/ former Group leader Wyeth/ Pfizer): Cardiovascular Safety Pharmacology in Pharmaceutical Development*

**4:30 PM-5:30 PM**



*\*Neelam Srivastava (Sr Research Scientist, Bristol-Myers Squibb, USA): G-Protein Coupled Receptors as Drug Targets*

### **Scientific Programs : Nov 23,2010**

**9:00AM – 10:00AM**



*\*Khosrow Adeli (Director & Professor, Clinical Biochemistry, University of Toronto, Canada): Molecular Mechanisms of Insulin Resistance and Diabetic Dyslipidemia: Lessons from the Fructose-Fed Hamster Model*

**10:00AM – 11:00 AM**

**Discussion**

**11:00 AM-12:00 PM**



Kailash N Pandey (*Professor and Vice-Chair of Medical Research, Tulane University School of Medicine, New Orleans, USA*): *Genomics and Molecular Determinants of Hypertension and Cardiovascular Regulation: Role of Nbr1 Gene*

**12:00PM –12:30PM**

Oral Presentation by – Ms. Varsha Sadashiv Naik “*Evaluation of Nootropic effect of Litchi chinensis on Alzheimer’s Disease*” Clonogen Biotechnology, Noida, India

**12:30 – 1:30PM**

LUNCH

**1:30PM – 2:00 PM**



Pramod Rath (*Professor, JNU, Delhi*): *Interferon Regulatory Factor-1 (IRF-1) Transcription Factor: Inflammation, Disease and Therapeutic Possibility*

**2:00PM-3:00PPM Discussion**

**3:00PM-3:30PPM TEA BREAK**

**3:30- 4:15 PM**



\*Kalyan Handique (*Vice President, BD, USA, Founder & Chief Technical Officer, HandyLab, USA*): *An Entrepreneurial Journey into Biotech: The HandyLab Experience*

**4:30PM- 5:30PM**



\*Roger S Newton (*President & CEO, Esperion Therapeutics, USA*): *Esperion Therapeutics: A Biotech Success and Rebirth in Michigan*

**Additional Speakers:**



*\*Robert Sigler (President & CEO, Research Essential Services, USA):  
"The Role of the Toxicologic Pathologist in Drug Discovery and  
Development"*



*\*Sriprakash Srivastava (President & CEO, Clintech, USA): Operational  
aspects of Clinical Research*

## **1<sup>st</sup> International Symposium on Industry-academia Interaction in Advanced Biotechnology & Drug Discovery, Noida, India, Nov 22-23, 2010**

Organized by S-LEARN & Clonogen Biotechnology

The society of learning, education, and rehabilitation for needy (S-LEARN) and Clonogen Biotechnology, Noida, organized the 1<sup>st</sup> International Symposium on Industry-academia interaction in advanced biotechnology and drug discovery at the premises of Clonogen Biotechnology during Nov 22-23, 2010. Dr Ajit Srivastava, Executive Director, Esperion Therapeutics, USA served as the organizing secretary. The incidence of diabetes in India is increasing at an alarming rate and the diabetic patients are at greater risks of developing cardiovascular disease. More than 75% of deaths in diabetic patients occur as a result of coronary artery disease. The focus of the symposium, therefore, was on diabetes and cardiovascular diseases, but students were allowed to present in any disease/technology area. Dr Ajit Srivastava's presentation focused on the ways to enhance the removal of arterial lipids by raising functional HDL. Many renowned and accomplished professors, scientists and successful entrepreneurs from the US, Canada, and India presented cutting edge science and ways to apply science and technology to help society through entrepreneurial efforts. Some of the notable presentations were keynote address by Dr Mahmood Hussain, Professor at State University of New York, USA who talked about how the main metabolic organ of our body, liver, regulates lipid metabolism. He described some of the studies from his recently published work in a renowned journal Cell Metabolism. Professor Pramod Rath from JNU, India, talked about how inflammation triggers and promotes lipid deposition in the arterial wall and causes coronary artery disease. Prof DK Srivastava from the North Dakota University, USA talked about novel ways for the targeted delivery of drug to treat cancer and other chronic diseases by selective modifications of isoenzymes. Prof Khosrow Adeli, from The University of Toronto, Canada gave an excellent presentation on how the consumption of fructose-rich drinks like coke has contributed to the increases in the incidence of insulin resistance, diabetes, and obesity. He discussed the dysregulation of the pathways that leads to metabolic derangement. Dr Kalyan Handique, founder of HandyLab, USA, and now Vice President BD Diagnostics, USA, gave an inspirational talk on "An Entrepreneurial Journey into Biotech: The HandyLab Experience". An excellent presentation was given by Dr Roger Newton, President and CEO, Esperion Therapeutics, USA. Dr Newton is a co-discoverer of Lipitor, a drug that lower cholesterol and has helped hundreds of millions of patients around the world and sells for \$12 billion a year. Dr Newton also started a new company that focused on a novel approach of regressing arterial lipids when a formulated HDL is infused into patients with preformed lipid-rich lesions in the arteries. Dr Newton's talk was very well received by the audience, and students participating in this symposium had great time interacting with those who were present to give their talk and also with those who presented through web-based video. The most notable presentation among students who presented was from the youngest presenter, Nishtha Srivastava, a high school student from the USA, who talked about the mechanism of apoptosis in cancer cells by natural products, curcumin, the main ingredient of turmeric, and quercetin, found in apple and onion skins. The 2<sup>nd</sup> Symposium will be held next year around same time and will be organized for a wider audience.

## **Symposium Abstracts**

### **Nuclear Hormone Receptor and other Novel Therapies for Cardiovascular-Metabolic Diseases**

Ranjan Mukherjee. Bristol-Myers Squibb Company, 311 Pennington Rocky Hill Road, Pennington, NJ. 08534, USA

#### **ABSTRACT**

The pandemic of obesity and diabetes is increasing at an astonishing rate. In India 50 million patients or nearly 6% of the adult population suffer from diabetes. Nearly 80% of diabetic patients die from cardiovascular complications and cardiovascular disease remains the leading cause of death in the developed world.

Diabetes is a progressive disease, and even though there are several therapies currently available, over time they become ineffective in enabling the patients to stay in control of the disease. Therefore, newer therapies are urgently needed. Importantly, effective means to arrest or slow the progression of the disease, in particular  $\beta$ -cell preservation and weight loss would be of great value.

This talk will discuss how to target cardiovascular and metabolic diseases via nuclear hormone receptors (e.g. PPARs) and other novel targets.

## **Beyond Statins: Targeting Reverse Cholesterol Transport to Treat Coronary Artery Disease**

Rai Ajit Srivastava, Executive Director, Biology & Pharmacology, Esperion Therapeutics, USA

With the discovery of statins, the management of hypercholesterolemia has greatly been improved, and has helped significant number of patients to manage their blood lipid levels to reduce the risk of cardiovascular disease (CVD). However, statins have been able to reduce the risk for vascular disease by approximately 20% to 24% in subjects of all ages and levels of risk for atherosclerosis. From the metanalysis of five separate clinical trials with statins, it is clear that an average of 75% of patients on statins still suffer the CV events when compared to the placebo treated groups. Therefore, residual risk still exists even in patients on statins. These patients are more likely have the characteristics of metabolic syndrome who are at risk of cardiometabolic diseases.

Framingham, Helsinki, BIP, and VA-HIT clinical trials have identified that raising HDL-C and reducing triglycerides (TG) reduced the cardiovascular events in patients with low HDL and high triglycerides. Thus, additional benefit can be obtained by raising HDL-C and reducing triglycerides, a feature of individuals with metabolic syndrome. Both animal studies as well as human clinical trials have shown that HDL-C regress arterial lipid deposition. An increase of 11% increase in HDL-C has been shown to decrease the mortality by 34%. Therefore, small increase in HDL-C has large benefits in protecting from future CV events.

This presentation discusses various ways to raise HDL-C, how to quantitate the functionality of HDL, the animals models to screen HDL-raising compounds and data to support how the HDL functionality assays translate into human disease models, especially LDL receptor-deficient and hamster models.

## **Role of Microsomal Triglyceride Transfer Protein in plasma and tissue lipid homeostasis**

Mahmood M Hussain, Professor of Biology, State University of New York, USA

Microsomal triglyceride transfer protein (MTP) is required for the intracellular assembly of apoB and fatty acids during the process of assembly and secretion of VLDL particles by the liver. MTP is also involved in the chylomicron assembly in the gut. While inhibition of gut MTP has clear advantage of impeding dietary lipid absorption, inhibition of hepatic MTP was anticipated to cause cellular triglyceride buildup, which impeded the progress on developing MTP inhibitors for the treatment of liver steatosis. Therefore, by understanding the mechanism of regulation of MTP it is possible to design and develop therapies to reduce proatherogenic particles as well as to treat patients with fatty liver.. Triglyceride synthesis involves fatty acid uptake, intracellular transport to microsomes by fatty acid-binding proteins, and acylation with glycerol by several monoacylglycerol and diacylglycerol acyltransferases. Inhibition of these steps will likely reduce cellular triglyceride levels. In this respect, repression of liver fatty acid-binding protein along with MTP inhibition has been shown to lessen steatosis. To have further understanding of how MTP is regulated, we have examined the role of clock genes in the diurnal regulation of plasma triglyceride-rich apolipoprotein B-lipoproteins and their biosynthetic chaperone, microsomal triglyceride transfer protein (MTP) using CLOCK (mt/mt) mice, CLOCK knockdown, and Shp KO mice. We showed that SHP suppressed MTP expression by binding to the HNF4alpha/LRH-1 at the MTP promoter. Plasma triglyceride and MTP showed reduced diurnal variations in Shp(-/-) mice. Expression of Shp abrogated hypertriglyceridemia in Clock(mt/mt) mice. Together, these studies describe a role of Clock/Shp in the diurnal regulation of MTP and plasma triglyceride and indicate that disruptions in circadian regulation might cause hyperlipidemia.

## **Molecular Mechanisms of Insulin Resistance and Diabetic Dyslipidemia: Lessons from the Fructose-Fed Hamster Model**

Khosrow Adeli PhD, FCACB, DABCC, Head and Professor of Clinical Biochemistry, Program on Molecular Structure and Function; Research Institute, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, CANADA

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The incidence of insulin resistant states such as obesity and type 2 diabetes have been increasing at an alarming rate in recent years in both pediatric and adult populations. Metabolic dyslipidemia associated with insulin resistant states such as type 2 diabetes is a key factor contributing to a significantly higher rate of cardiovascular complications in these patients.

Our laboratory is currently investigating the underlying cellular and molecular mechanisms of the development of metabolic dyslipidemia in insulin-resistant states. Using diet-induced animal models of insulin resistance and obesity, we are investigating the link between perturbations in insulin signaling pathway and dysregulation of hepatic and intestinal lipoprotein metabolism.

Over the past decade, a number of diet induced animal models of insulin resistance were developed in our laboratory including the fructose-fed Syrian golden hamster. We have employed these model systems to investigate the mechanisms of action of a number of pharmaceutical drugs used as hypolipidemic agents in patients with high plasma cholesterol and/or triglyceride levels. Up to the present time we have studied the mechanisms of action of a number of HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin, rosuvastatin), fibrates (fenofibrate), insulin sensitizers agents (rosiglitazone), DPP-IV inhibitors (sitagliptin), and cholesterol absorption inhibitors (ezetimibe). The fructose fed hamster model has thus proved to be an excellent in vivo model system for testing new and existing pharmaceutical drugs to examine metabolic effects and their mechanisms of action.

In this presentation, I will review our current understanding of the molecular mechanisms underlying metabolic/diabetic dyslipidemia in insulin resistance states, and then discuss the mechanisms of action of a number of new pharmaceutical agents tested in the fructose-fed hamster model.

## **Design and Evaluation of Isozyme-Selective “Two-Prong” Inhibitors against Pathogenic Enzymes as Potential Drugs**

D. K. Srivastava, James A. Meir Professor, Department of Chemistry and Biochemistry, North Dakota State University, Fargo, ND 58105, USA.

### **ABSTRACT**

We have developed an approach of designing highly potent and isozyme selective inhibitors against pathogenic enzymes as potential drugs. This approach involves attaching a tether group to an active site directed inhibitor such that the former moiety loops around and interacts with the surface exposed amino acid residues of the enzyme. Due to the “two-prong” attachment, our inhibitors exhibit much higher binding affinities for their target enzymes as compared to their active site directed counterparts. In addition, since the surface exposed amino acid residues are not conserved during the course of evolution, our overall “two-prong” methodology has potentials to generate isozyme selective inhibitors. We have successfully employed our methodology in selectively inhibiting a tumorigenic carbonic anhydrase and a matrix metalloproteinase. The level of selectivity in case of matrix metalloproteinases is further enhanced via developing the liposome based novel drug delivery system.

## **Impact of New Technologies in Industrial Medicinal Chemistry**

Rajiv Sharma, Vice President, Piramal Life Sciences Ltd, Mumbai, India

### **ABSTRACT**

Drug discovery is a very time-consuming and resource-intensive process. Pharmaceutical industry is intensely interested in methods which can increase productivity at all stages of the drug discovery and development process. Over the last decades, several new technologies have been introduced in the arsenal of drug hunters. This talk will detail the impact of molecular modeling, combinatorial chemistry and fragment based drug design in medicinal chemistry.

# **Genomics and Molecular Determinants of Hypertension and Cardiovascular Regulation: Role of Npr1 Gene**

Kailash N. Pandey

Department of Physiology, Tulane University Health Sciences Center, School of Medicine, New Orleans, LA 70112-USA

## **ABSTRACT**

Cardiac hormones atrial and brain natriuretic peptides (ANP and BNP) activate guanylyl cyclase-A/natriuretic peptide receptor-A (GC-A/NPRA) and produce the second messenger cGMP, which have advanced our knowledge towards understanding the control of high blood pressure, hypertension, and cardiovascular disorders to a great extent. The progress in this field of research has significantly strengthened and advanced our knowledge about the critical roles of Npr1 gene (coding for GC-A/NPRA) in regulation of physiological functions and pathological disease states. Biochemical and molecular studies have delineated the receptor function and signaling mechanisms and the role of second messenger cGMP in pathophysiology of hypertension, renal hemodynamics, and cardiovascular functions. The development of gene-knockout and gene-duplication Npr1 mouse models along with transgenic mice have provided a framework for understanding the importance of the antagonistic actions of natriuretic peptides receptor in anti-inflammatory, antimitogenic, and anti-hypertrophic renal and cardiovascular events at the molecular level. Now, natriuretic peptides are considered as circulating markers of congestive heart failure, however, their therapeutic potentials for the treatment of cardiovascular diseases such as hypertension, renal insufficiency, cardiac hypertrophy, congestive heart failure, stroke, and inflammatory responses have just begun to unfold. Indeed, the alternative avenues of investigations in this important field are need to be undertaken, as we are at the initial stage of the molecular therapeutic and pharmacogenomic implications to treat the hypertension and cardiovascular diseases.

## **Cardiovascular Safety Pharmacology in Pharmaceutical Development**

Ravikumar Peri, Ex Principal Scientist, Pfizer/Wyeth, NJ, USA

### **ABSTRACT**

Ion channels play an important role in mediating myocardial contractility and maintaining the normal physiology of the cardiovascular system. Cardiac action potentials are triggered by activation of Nav<sub>1.5</sub> channels followed by subsequent voltage-gated flux of Ca<sup>2+</sup> through Cav<sub>1.2</sub> during the plateau phase to facilitate contractility and are terminated by activation of Kv<sub>11.1</sub> (hERG) and Kv<sub>7.1</sub> (KVLQT1) potassium channels to repolarize the myocardial cells. Nonspecific inhibition of Kv<sub>11.1</sub> channels by pharmaceuticals, subsequent prolongation of the QT interval on cardiac electrocardiogram and precipitation of fatal polymorphic ventricular tachycardia, Torsades de pointe has lead to withdrawal of several marketed drugs and delayed the development of several others. Regulatory guidance document ICH S7B discusses pre-clinical strategies for testing the pro-arrhythmic potential of human pharmaceuticals and strongly recommends in-vitro Kv<sub>11.1</sub> assays, in-vivo QT assessment.

This seminar will focus on an introduction to ionic basis of cardiac electrophysiology and pharmaceutical strategies for mitigating proarrhythmic risk during drug development

## **G-Protein Coupled Receptors in Drug Discovery with Focus on Cancer Therapy**

Neelam Srivastava, Senior Research Scientist, Bristol-Myers Squibb, Lawrenceville, NJ, USA

### **ABSTRACT**

G protein-coupled receptors (GPCRs) are seven-transmembrane domain and comprise a large protein family of transmembrane receptors that sense molecules outside the cell and activate inside signal transduction pathways and, ultimately, cellular responses. Upon activation of distinct G-proteins by agonist, a cascade of intracellular signaling events is initiated through a number of downstream effector molecules including adenylyl cyclase, cGMP phosphodiesterase, phospholipase C and several ion channels. The ligands that bind and activate these receptors include light-sensitive compounds, odors, pheromones, hormones, and neurotransmitters, and vary in size from small molecules to peptides to large proteins.

G protein-coupled receptors are involved in many diseases, and are also the target of approximately 30% of all modern medicinal drugs. GPCRs represent the most successful small-molecule drug targets. Drugs that target GPCRs accounted for \$ 60 billion in sales in 2000 with 31 of the top 100 drugs currently on the market acting on GPCRs. Thus, GPCRs present an attractive target for drug discovery.

Despite tremendous successes in the discovery of GPCR agonists/antagonists for the treatment of diseases, there has not been proportional success in the area of cancer therapy. This presentation will primarily focus on the Endothelial Differentiation Gene (EDG) Receptors, a GPCR subfamily. Data will be presented and discussed to show validation of EDG receptors as a druggable target for cancer therapy.

## **Update on the role of dietary fats in CHD**

Pramod Khosla Dept. of Nutrition and Food Science,  
Wayne State University, Detroit, MI, USA

### **ABSTRACT**

For almost fifty years health agencies have been focusing on restricting dietary fat, saturated fat and cholesterol for the management of plasma lipids. As the science evolved, attention shifted from fat quantity to fat quality with an emphasis on the types of fatty acids. Saturated fatty acids (SFA) were to be avoided and monounsaturated (MUFA) and polyunsaturated fatty acids (PUFA) were encouraged. However, starting in 1990 with the discovery that trans MUFA were the most detrimental in terms of CHD risk, SFA began to be re-evaluated. A spate of studies in the last five years has begun to provide evidence that our assessment of SFA may not be as clear-cut as once thought. In this regards, Wayne State University hosted a Symposium on October 14, 2010 on the “Health Effects of Dietary Saturated Fatty Acids’ where nine speakers from the USA and overseas provided some updates on this new evidence. The current talk will a) provide an update on our current thinking regarding the role of dietary fat (specifically saturated fat) in CHD management and b) provide a summary of some of the key findings presented at the recently concluded Symposium. This is important in countries like India where economic reforms have led to dramatic shifts in diet and lifestyle with a corresponding impact on chronic disease risk.

## **Role of Drug Metabolism and Pharmacokinetics in Drug Discovery**

Rangaraj Narayanan, Sr Research Investigator, Bristol-Myers Squibb, USA

### **ABSTRACT**

Drug metabolism and pharmacokinetics (DMPK) is the study of absorption, distribution, metabolism and elimination properties of new chemical entities (NCE) in pre-clinical species and in man. DMPK serves a very critical role in help identifying NCEs which can be progressed into the clinic for human testing. The presentation will cover role of DMPK in various stages of drug discovery, critical assays that are employed along with their interpretation and future direction for this science. Examples from published studies along with in-house data will be used to illustrate above thoughts.

## **Interferon Regulatory Factor-1 (IRF-1) Transcription Factor: Inflammation, Disease and Therapeutic Possibility**

Jyothi Ramanathan, Artatrana Pal and Pramod C. Rath

Molecular Biology Laboratory, School of Life Sciences, Jawaharlal Nehru University, New Delhi-110067, India

Interferon Regulatory Factor-1 (IRF-1) and IRF-2 are twins, which belong to the IRF-family (IRF-1 to IRF-10) of mammalian transcription factors and are involved in host cell immune response against pathogens, regulation of cytokines, chemokines, cell adhesion molecules and enzymes, cell growth control and apoptosis during various cellular processes. IRF-1 functions as a tumor suppressor while IRF-2 has oncogenic potential. Both IRF-1 and IRF-2 have been implicated in several diseases, e.g., cancer, autoimmunity and metabolic disorders. We have investigated involvement of IRF-1, IRF-2 in mouse tissues during experimental inflammatory and disease conditions and explored the possibility of therapeutic intervention of the pathological situation by small molecular natural product.

We have studied mRNA and protein expression, DNA binding activity of IRF-1 and IRF-2 and expression of some of their target genes in the mouse liver during inflammatory response caused by lipopolysaccharide (LPS) as well as in the aorta during atherosclerosis caused by high fat diet. Both the experimental approaches showed involvement of IRF-1 and IRF-2 during inflammatory response as well as pathological situation in the mouse liver and aorta as shown by the elevated expression level and activity of IRF-1 and IRF-2. A number of IRF-regulated genes were also involved in these processes as shown by RNA expression. Reduction of the atherosclerotic condition was observed by a small molecular natural product, which also caused alterations in expression of IRF-1, IRF-2 and their target genes. We propose that regulating IRF-1, IRF-2 transcription factors and their target genes by small molecular natural product in the mouse tissues, e.g., liver and aorta may help controlling pathological as well as disease conditions. This study shows an example of regulation of transcription factors by small molecular natural products in experimental mouse model, which may be further extended to clinical situations in human patients.

## **Clinical Trial Operation – Things To Consider**

Sri P Srivastava, PhD, Founder & CEO, ClinTech Research LLC, NJ, USA

### **ABSTRACT**

More and more pharmaceutical and biotechnology companies in the USA and Europe are outsourcing their Research & Development (R&D), including clinical trial operations to offshore locations in Asia such as India and China. India is considered to be particularly important because of long standing historical awareness of FDA regulatory requirements, reasonable cost and the wide range of contract research and business process organizations in that country. This presentation will discuss key components of clinical trial operations focusing on the recent trends and challenges of clinical operations outsourcing. Furthermore, the importance of 21 CFR Part 11 validation and Quality Assurance including real examples of non-compliance and ways to mitigate such noncompliance will be discussed...

# **Curcumin and Quercetin Synergistically Inhibit Cancer Cell Growth via Caspase3/7 mediated Pathway**

Nishtha Srivastava, Council Rock South High School, PA, USA

## **ABSTRACT**

The aim of this project was to find out if natural compounds such as Curcumin, Quercetin, Berberine, and Epicatechin alone or in combination have an effect on the proliferation of Colon, Breast, Melanoma and Lung cancer. I tested following hypotheses: a) natural products alone will have varying efficacy on proliferation in different cancer cells; b) Curcumin will have greater efficacy; and c) a combination of Curcumin and Quercetin will have a greater efficacy and will show synergistic effect on inhibition of cancer cell proliferation.

To test these hypotheses, MTT assay was used to measure the cancer cell proliferation, and Caspase Glo 3/7 was used to measure apoptosis. The natural compounds mentioned above were tested either alone in varying concentrations or used in combinations, and the inhibition of proliferation was recorded. Analysis of the results showed that Epicatechins, up to 100  $\mu\text{M}$  concentration, did not inhibit cancer cell proliferation, while Curcumin showed a concentration-dependent inhibition of proliferation with an  $\text{IC}_{50}$  of 5 to 15  $\mu\text{M}$  in various cancer cell lines. Quercetin and Berberin also showed concentration-dependent inhibition of cell proliferation with an  $\text{IC}_{50}$  of  $\sim 15$   $\mu\text{M}$  for Quercetin and  $\sim 25$   $\mu\text{M}$  for Berberin, respectively.

Since Curcumin and Quercetin showed the highest efficacy in the 4 cancer lines tested, the combination of Curcumin and Quercetin was examined for synergistic effects. The combination of Curcumin and Quercetin had a synergistic effect on the cancer cell proliferation. Lung cancer had the most synergistic effect, where  $\text{IC}_{50}$  lowered from 5  $\mu\text{M}$  to 2  $\mu\text{M}$  for Curcumin and from 10  $\mu\text{M}$  to 2  $\mu\text{M}$  for Quercetin. Similarly, synergistic effects were noted in melanoma, breast and colon cancer cell lines with a 2-5 fold reduction in  $\text{IC}_{50}$ . Further studies were done to find out if Curcumin and Quercetin alone and in combination induced apoptosis in lung cancer cells. For this, Caspase 3/7 activity, a measure of apoptosis, was quantitated. Results showed that, indeed, Curcumin and Quercetin induced apoptosis in lung cancer cells synergistically.

In conclusion: these studies suggest that curcumin and quercetin inhibit cancer cell growth synergistically by activating apoptosis via caspase3/7 pathway. Thus, natural products can effectively be used for the prevention and therapy of cancer without any adverse side effects as seen with synthetic small molecules.

## **Regulation of ATP-binding cassette transporter A1 (ABCA1) by cyclic AMP in stably transfected 293 cells occurs via cAMP dependent protein kinase-mediated pathway**

Neelam Srivastava, Angelo B Cefalu, Maurizio Averna, Rai Ajit Srivastava  
University of Palermo, Italy, CloneGen Biotechnology, USA, Esperion Therapeutics, USA

### **ABSTRACT**

ATP-binding cassette transporter A1 (ABCA1) is a key player in the cholesterol efflux pathway that prevents excess cholesterol accumulation in the cells. In this study, we examined the mechanism of cAMP-mediated regulation of the ABCA1 gene in a stably transfected 293 cells expressing ABCA1 under the control of CMV promoter harboring cAMP response element. The wild-type 293 cells showed undetectable levels of ABCA1, but transfected 293 cells expressed high levels of ABCA1. Treatments of transfected cells with cAMP without serum, or with 1% and 10% serum, induced the expression of ABCA1 by 2-fold, 3-fold, and 8-fold, respectively. cAMP treatments of transfected cells increased ABCA1 protein by 10-fold and mRNA by 20-fold. Cholesterol efflux also increased in parallel. cAMP withdrawal caused time-dependent rapid diminution of ABCA1 protein and mRNA, suggesting that cAMP regulates ABCA1 gene expression by transcriptional mechanism, and continued transcription of ABCA1 gene is required to maintain cellular level of ABCA1. To examine the mechanism of cAMP-mediated transcriptional up-regulation of the ABCA1 gene, the transfected cells were treated with protein kinase (PK) inhibitors in the presence and absence of cAMP. PK inhibitors abolished the cAMP-mediated induction of the ABCA1 gene expression as well as ABCA1-dependent cholesterol efflux. These results demonstrate that transfected cell line mimics similar cAMP response as with cells having natural ABCA1 promoter, and cAMP-induced ABCA1 regulation occurs via PK-mediated pathway.

## **Evaluation of Nootropic effect of Litchi chinensis on Alzheimer's disease**

Varsha Sadashiv Naik, C. C. Govimath  
Clonegen Biotechnology, Noida, India

### **ABSTRACT**

Dementia is an age related mental disability and Alzheimer's disease is its most common form. Alzheimer's disease (AD) is a chronic, progressive organic brain disorder characterized by disturbance of multiple cortical functions, including memory, judgment, orientation, comprehension, learning capacity and language. Standard drugs like Donepezil and Piracetam have side effects making their use limited. Hence the utility of herbal medicine is important. Litchi chinensis is known for its antioxidant properties, thus making it a potential drug. Scopolamine hydrobromide(0.4 mg/kg,i.p.) and Piracetam (200 mg/kg) were used in the experiment. Elevated plus maze and Morris water maze were employed as the experimental models to evaluate learning and memory. Litchi chinensis (Lychee) fruit pericarp ethanolic extract (25, 50 and 100 mg/kg, p.o./day) was used as the drug and was administered for a sufficient number of days. The dose of 50 mg/kg/day of Litchi chinensis extract significantly improved learning and memory in young and aged mice and also reversed scopolamine induced amnesia in young mice. Litchi chinensis also significantly decreased the whole brain acetylcholinesterase(AChE) activity as per the results obtained from AChE estimation. Hence, Litchi chinensis may be used in the future in the treatment of dementia, particularly AD, in the elderly after successfully moving through different stages of Clinical trials.

Key words: Litchi chinensis, Amnesia, Learning, Memory

## **AMPLIFICATION AND COMPARISON OF 16s-23s rRNA INTERGENIC SPACER REGION IN *Shigella flexneri* AND *Shigella boydii***

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Present affiliation: Clonogen Biotechnology, Noida, India

### **ABSTRACT**

The intergenic transcribed spacers (ITS) between the 16s and 23s rRNA genetic loci are frequently used in PCR fingerprinting to discriminate bacterial strains at the species and intra species levels. PCR amplification of 16s-23s intergenic spacer regions was attempted on 3 strains of *Shigella flexneri* and *Shigella boydii* each. Primers were obtained from previous experiment done to differentiate common septicemia bacteria which included *Shigella flexneri* and *Shigella dysenteriae*. *Shigella flexneri* was amplified and showed a single band in contrast to two bands observed in the previous experiment; hence further studies should be conducted using more strains. *Shigella boydii* could not be amplified using the primer; this could have been due to non availability of the conserved sequence in *S.boydii*. The study shows possibility of differences in the 16s-23s ITS regions in *Shigella flexneri* strains. Designing of a primer specific to the *Shigella* sp. for differentiation would be more appropriate.

## **Advertisement**

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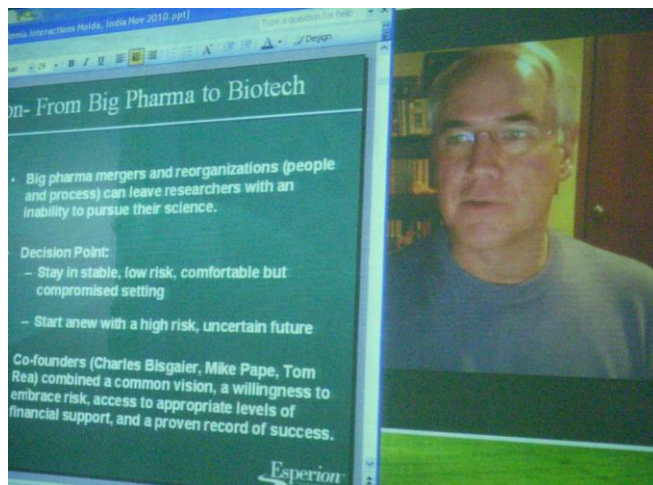
*The field of science and technology has been developing at a rapid pace, and at times it becomes extremely impractical to capture all information that becomes available through research journals and online resources. The professional course was developed with a view to encompass rapid changes in science. The course materials are, therefore, updated every 6 months to add new information. The course is designed such that it covers most of the advanced laboratory techniques to study and analyze proteins/enzymes, DNA, RNA and apply recombinant DNA technology for specific needs. In addition, this course also consists of some of the most advanced technologies like transgenesis, gene knockout, RNAi, SAGE, microarray, real-time PCR and monoclonal antibody production.*

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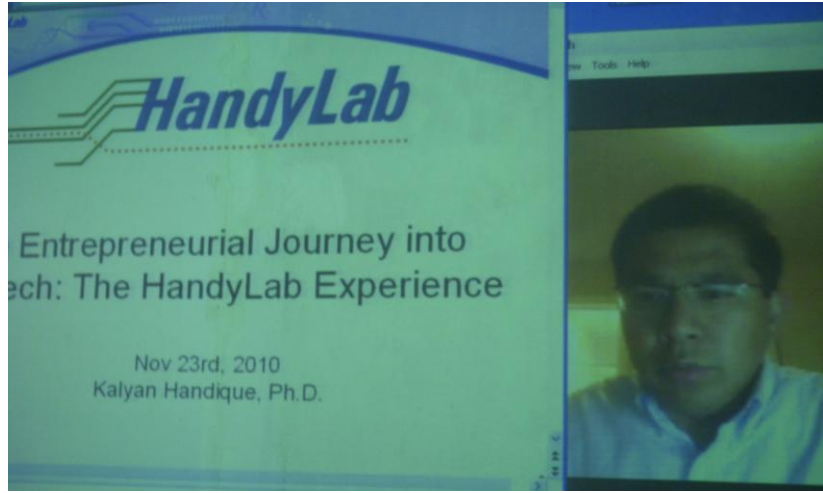


*Dr Ajit Srivastava*

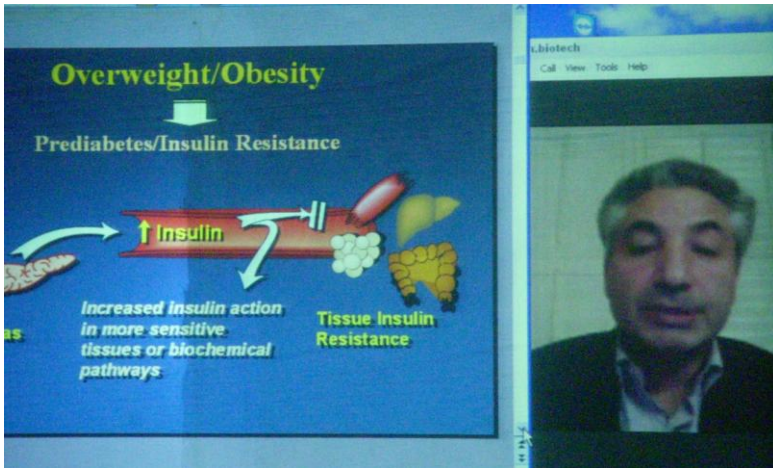
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