The Ramanbhai Foundation 4th International Symposium on
Current Trends in Pharmaceutical Sciences

"Advances In Cardiometabolic Research - Basic Science And Clinical Aspects"

Feb 2-5, 2009, Zydus Research Centre, Ahmedabad, India

Scientific Abstracts

www.rbfsymposium.net

Advancing Cardiometabolic Research

INNOVATION Zydus Research Centre IN LIFE SCIENCE

ZRC MISSION

ZRC aims to be

the most admired

pharmaceutical research center

for innovation in life science

dedicated to alleviating

human sufferings.

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Advancing Cardiometabolic Research

Conference Venue :

Zydus Research Centre

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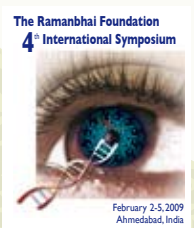

Zydus dedicated to life

Advancing Cardiometabolic Research

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Message from the Chief Patron

Dear Delegates,

I take great pleasure in welcoming you to the Ramanbhai Foundation 4th International Symposium. It's a journey that began in the year 2003 with an aim to create a knowledge sharing platform for exchanging scientific thoughts amongst the scientists engaged in pharmaceutical research. With your support and involvement, we have been able to step up the momentum through this biennial symposium.

The theme of the present symposium is "Advances in Cardiometabolic Research - Basic Science and Clinical Aspects" with a focus on research in the area of cardiovascular and metabolic diseases such as atherosclerosis, hypertension, dyslipidemia, thrombosis, heart failure, diabetes and obesity.

India, as you are aware, is battling with an increasing incidence of non-communicable diseases or lifestyle diseases, which poses a big challenge to all healthcare professionals. The epidemic of cardiovascular disease (CVD) is driven largely by hypercholesterolemia (elevated LDL-C), hypertension, diabetes and abdominal obesity. The increased cardiovascular risk in people with abdominal obesity relates in part to an associated insulin resistance, dyslipidemia, elevated plasma glucose and insulin levels, hypertension and proinflammatory state. Individually, each of these features contributes to an increased risk of CVD. The growing prevalence of metabolic syndromes has reached to such epidemic proportions that CVD remains a major cause of morbidity and mortality worldwide. This symposium aims to bring together experts from both the academia and industry to deliberate on the ways and means of fighting the cardiovascular and metabolic disorders epidemic through research and identifying new therapies and clinical interventions.

Over the past several years, the RBF symposium has been recognised as a premier event in this part of the world, and has drawn significant participation by the research community worldwide.

The Zydus Research Centre had first organized the international research symposium in 2003 on the theme 'Recent Trends in Pharmaceutical Sciences'. Since then, it has been held every two years. Scientists, academicians and experts from across the world converged once again in 2005 and then in 2007 to share their thoughts on the 'Role of Genomics and Proteomics' and 'Advances in Diabetes Therapy' respectively.

In this symposium we embark on a new knowledge sharing endeavour to look at the unmet medical needs in the areas of cardiovascular and metabolic disorders, share insights on new research explorations and discover new pathways to combat this mounting challenge.

I welcome you to the symposium and hope you find the sessions informative and interesting.

With warm regards,

Pankaj R. Patel
Chief Patron

Advancing Cardiometabolic Research

About Ramanbhai Foundation

The Ramanbhai Foundation is dedicated to encourage learning and knowledge sharing in the field of pharmaceutical research, education and healthcare. This mission is based on the philosophy of our late Founder Chairman, Mr. Ramanbhai B. Patel, who believed in the importance of research and enriching oneself through an ongoing quest for learning.

Under the aegis of the Foundation, the group organises The Ramanbhai Foundation International Symposium on the latest trends in Pharmaceutical Sciences, once every two years. The current Ramanbhai Foundation International Symposium is the fourth in the series of events devoted to 'Advances in Cardiometabolic Research - Basic Science and Clinical Aspects'. Through these symposia, the Foundation aims to bridge the research endeavours taking place across the world and create a platform for knowledge sharing.

As a part of the group's outreach programmes, annual healthcare camps are organised at Moraiya and Dabhasa, near Vadodara. Leading specialists from Ahmedabad and Zydus employees, volunteer their services in organising these camps. So far, the group has organised general healthcare camps, diagnostic, dental-care, eye-care and paediatric camps. The Ramanbhai Foundation is also committed to a number of special initiatives in the field of education. 'The Zydus School for Excellence' - a centre for learning where young minds are free to grow in relationship to his or her potential has been set up under the aegis of the Ramanbhai Foundation.

The Shri Ramanbhai B. Patel - AMA Centre for Excellence in Education which was inaugurated by His Excellency Dr. APJ Abdul Kalam in May 2002, provides a platform for parents, teachers and students to highlight the critical educational issues of the day. The centre conducts open house discussions, memorial lectures on excellence in education, progressive learning programmes for academicians and knowledge sharing forums, which study the successful learning models across the country.

Dedicated to the memory of the group's founder, Mr. Ramanbhai B. Patel, the IPA – Shri Ramanbhai B.Patel Foundation (IRF) has been set up jointly with the Indian Pharmaceutical Association. The IRF has been set up to recognise and award 'commitment and excellence' in the field of pharmacy.

Glimpses from Previous RBF Events

Zydus Cadila

- 5th largest player in the domestic pharma market and a global, integrated company with strengths all along the value chain
- A leader in the gastrointestinal and women's healthcare segments and a strong presence in the cardiovascular, respiratory, pain management, anti-infective and oncology segments
- 14 of our brands feature amongst the top 300 pharma brands in India (ORG, Oct 2008 MAT)
- Global operations in over 50 countries including USA, Europe, Japan and Latin America
- We have built world class manufacturing facilities comprising 8 state-of-the-art manufacturing plants for APIs and formulations, including novel dosage forms. Of these, 3 are USFDA approved
- 950 professionals spearhead our research programme. 6 INDs in the areas of dyslipidemia, diabetes, pain and obesity are in various stages of clinical trials
- A partner of choice for global pharma majors like Nycomed, Hospira, Bayer Schering Pharma, Madaus AG, Boehringer Ingelheim, Mallinckrodt to name a few, and these alliances are unlocking value for us
- Recipient of the Social and Corporate Governance Award 2008 for the innovative and measurable impact of our CSR programme, awarded by the BSE, NASSCOM and Times Foundation
- Over 9500 Zydans across the world unleashing value as an innovation research-driven global pharma company

Advancing Cardiometabolic Research

Zydus Research Centre (ZRC)

The Zydus Research Centre is the dedicated research arm of the Zydus Group. With its team of over 350 research professionals, ZRC spearheads the group's quest of creating healthier and happier communities globally. Spread over an area of over 3,60,000 sq ft, ZRC is working on cutting edge technologies in 14 different scientific disciplines.

ZRC is equipped to carry out research in the areas of new drug discovery, novel biologics and NDDS. The centre is recognised by the Department of Science and Industrial Research (DSIR), Government of India. The research scientists conduct seminal research in diverse disciplines including Medicinal Chemistry, Biotechnology, Bio-Informatics, Genomics, Molecular & Cellular Biology, Pharmacology & Toxicology, Microbiology, Analytical Research, CMC Research, Clinical Research, and Novel Drug Delivery Research.

Zydus Research Centre has also entered into collaborative research agreements with Prolong Pharmaceuticals Inc., a US-based, venture-backed drug delivery research and development company and Karo Bio of Sweden, a drug discovery and development company specialising in nuclear receptors. In collaboration with Prolong Pharmaceuticals Inc, ZRC is engaged in a drug discovery and development process for a next generation therapeutic protein, 'PEG-EPO', to treat severe anaemia. In a three-year strategic collaboration with Karo Bio, ZRC will address an unmet healthcare need by developing a novel, selective glucocorticoid receptor (GR) modulators for the treatment of inflammatory diseases.

ZRC's research pipeline since the commencement of IND filing in 2005:

- The NME - ZYH1, for treating dyslipidemia has recently completed the Phase II clinical trials successfully
- ZYI1, the novel anti-inflammatory and pain management compound is currently in Phase II clinical trials
- ZYH2, the novel agent for treating diabetes is undergoing Phase I trials
- ZYO1, a novel drug candidate for treating obesity and related disorders, has completed Phase I clinical trials
- ZYH7, a novel drug candidate for treating dyslipidemia and metabolic disorders is in Phase 1 clinical trials
- ZYT1, a novel drug candidate for treating dyslipidemia is in Phase 1 clinical trials

The Centre believes in teamwork and encouraging scientists to take up newer challenges and responsibilities. As a part of a growing organisation that continuously seeks to maintain a competitive edge through innovation, ZRC accords high value to diversity of thoughts, which is critical for arriving at the most innovative solutions to several problems and challenges confronting human healthcare

Co-organizers

Indiana University, USA

Indiana University has a rich tradition of scientific excellence in medicine, biology, chemistry and related disciplines. The interdisciplinary biotechnology programs are enhanced by a new multidisciplinary science research building which provides state-of-the art laboratories for research faculty from the fields of chemistry, biology and physics. The University science program is enriched by the presence of a set of companies active in peptide and protein sciences such as Cook Pharmica, Baxter Pharmaceutical Sciences, Roche Diagnostics, Lilly Research Laboratories and a community of start-up biotechs.

Center for Integrative Genomics, Switzerland

The Center for Integrative Genomics (CIG) is a new interdisciplinary research and training institute located in the Génopode building, situated on the spectacular Dorigny campus of the University of Lausanne (UNIL). It overlooks the nearby «Lac Léman» (Lake Geneva) and the Swiss and French Alps beyond.

The CIG forms the latest department of the newly established UNIL Faculty of Biology and Medecine, and has three main missions:

- The development of a first rate research program in the biological sciences
- The development of an outstanding teaching program
- The development of shared research technologies available to the Lémanic research community and beyond

The research at the CIG centers on genome structure and function in a number of different experimental systems, and a number of different techniques. It is performed by an international community of scientists. Yet the character of the CIG is one of a single, integrated research center, where interactions among groups are numerous both in informal and formal settings.

Day 1: February 2, 2009 (Pre-symposium Workshop)

10:00 – 10:10 hrs	Opening Remarks
Dr. Mukul R Jain	Vice-President, Zydus Reseach Center
10:10 – 11:30 hrs	"VH IVUS - intra vascular imaging and plaque characterization"
Dr. Angela Richter	Director Clinical Affairs and Education, Volcano Europe SA/NV, Belgium
	"Vulnerable plaque: the paradigm shift for treatment with new diagnostic modalties and live VP/ultrasound"
Dr. Ramtin Agah	Cardiologist, Interventional Cardiology, CA, USA
11:30 – 11:40 hrs	Tea Break
11:40 – 12:40 hrs	"Application of Molecular Biological Databases for Quality Research in Disease and Systems Pathology: Biobase Knowledge Library BioBase"
Dr. Olga Kel-Margoulis	BIOBASE GmbH, Vice President Database Curation, Germany
12:40 – 13:10 hrs	Presentation on Illumina platform
Dr. Ram Lakshman	Illumina, Singapore
13:10 – 14:00 hrs	Demonstration of Illumina microarray platform
14:00 – 14:30 hrs	LUNCH
14:30 – 15:15 hrs	"High resolution micro-CT in biological and biomedical applications"
Dr. Jeroen Hostens **Phil L. Salmon**	Biomedical Application Engineer, SkyScan N.V., Belgium
15:15 – 16:15 hrs	"Review of SPR technology: Focus on description of and theory behind binding analysis and kinetics"
Dr. Veena Rao	GE Healthcare - Lifesciences, Bangalore
16:15 – 16:25 hrs	Tea Break
16:25 – 17:25 hrs	"An Introduction of Concentration analysis and immuno-genecity testing on the platform & understanding of small molecules applications"
Mr. Lalith Jonnalgadda	GE Healthcare – Lifesciences, Bangalore
17:25 – 17:30 hrs	Closing remarks

Day 2: February 3, 2009 (Main Symposium)

Inauguration ceremony

09.00 – 09.10 hrs	Welcome Shri. Pankaj Patel, Chairman, Zydus Group
09.15 – 09.45 hrs	Inaugural Address by Chief-guest Padma Bhushan Dr. K. K. Talwar, Director PGIMER, Chandigarh
09.45 – 09.55 hrs	Vote of thanks

Session I

Chairpersons

- Dr. Jeffrey M. Friedman, Rockefeller University, USA
- Dr. Richard DiMarchi, Indiana University, USA

10.00 – 10.45 hrs	Keynote Address
Dr. Roger Newton	Co-founder of Esperion Therapeutics, USA [Co-Discoverer of Lipitor®]
10.45 to 11.15 hrs	Coffee Break
11.15 to 12.00 hrs	"Emerging therapeutic strategy for cardiovascular disease – adipocytokines"

Dr. Yuji Matsuzawa	Director, Sumitomo Hospital, Professor Emeritus, Osaka University, Japan
12.00 to 12.45 hrs	"Systemic Biomarkers in Atherosclerosis: New Horizons", Japan

Dr. John Chapman	President Elect, European Atherosclerosis Society Director, Dyslipidemia and Atherosclerosis Research Unit, INSERM, France
12.45 to 13.30 hrs	"Current understanding of the off-target activity of torcetrapib"

Dr. Eric Niesor	Metabolic & Vascular Disease Area, Roche AG, Switzerland
13.30 to 14.30 hrs	Lunch

Session II

Chairpersons

- Dr. Per-Olof Berggren, Karolinska Institutet, Sweden
- Prof. P. Rama Rao, Director, National Institute of Pharmaceutical Education and Research, India

14.30 – 15.15 hrs	"Inflammation as a marker and a target to reduce atherosclerosis related cardiovascular events"

Prof. François Mach	Head of Cardiology Geneva University Hospital, Switzerland
15.15 to 16.00 hrs	"Metabolic Approaches for treatment of ischaemia"

Dr. S. C. Manchanda	Senior consultant cardiologist,Sir Ganga Ram Hospital,Delhi Formaly Prof.and Head,dept.of cardiology,AIIMS
16.00 to 17.00 hrs	Poster presentation and networking
17.00 to 17.45 hrs	"Predictive metabolomic, lipomic and transcriptomic profiling of peripheral blood"

Dr. Charles Burant	Dr. Robert C. and Veronica Atkins Professor of Metabolism, University of Michigan, USA
17.45 to 18.30 hrs	Panel Discussion: (Chairperson: Dr. Richard DiMarchi USA)
19.30 to 20.30 hrs	Dinner 'Royal Taste of Gujarat' at Rajvadu

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Day 3: February 4, 2009

Session III

Chairpersons

- Dr. Y. K. Gupta, All India Institute of Medical Sciences (AIIMS), India
- Dr. John Chapman, Director, Dyslipidemia and Atherosclerosis Research Unit, INSERM, France

09.00 – 09.45 hrs "Energy Medicine-a new Vista"

Prof. B. M. Hegde Retd. Vice Chancellor, Manipal University, India, Visiting Prof. Cardiology, The Middlesex Hospital Medical School, University of London

09.45 – 10.30 hrs "Mipomersen: A Novel Lipid Lowering Drug, From the Bench to the Clinic"

Dr. Sanjay Bhanot Metabolic Franchise Leader, Vice President, Metabolic Diseases Research & Development,Isis Pharmaceuticals Inc., USA

10.30 to 11.00 hrs Coffee Break

11.00 to 11.45 hrs "Eprotirome: A novel and physiological approach to CVD risk reduction"

Dr. Jens Kristensen VP Clinical Development, Chief Medical Officer, Karo Bio AB, Sweden

11.45 to 12.30 hrs "Targeting Protein Kinase C to treat Ischemia-Reperfusion Damage in the Heart"

Dr. Steve Harrison Vice President, Research, KAI Pharmaceuticals

12.30 to 13.15 hrs PPARα and β/δ orchestrate hepatic and pancreatic functions

Dr. Walter Wahli Founder Director, Centre for Integrative Genomics, Switzerland

13.15 to 14.30 hrs Lunch

Session IV

Chairpersons

- Dr. N. K. Ganguly, Former Director General, Indian Council of Medical Research (ICMR)
- Dr. B. Sesikeran, Director, National Institute of Nutrition, Hyderabad, India

14.30 – 15.15 hrs "Leptin and the Homeostatic Control of Energy Balance"

Dr. Jeffrey M. Friedman Marilyn M. Simpson Professor; Investigator, HHMI, Rockefeller University, USA

15.15 to 16.00 hrs "Gut - Brain Communication in the Control of Metabolism"

Dr. Matthias H. Tschöp Associate Professor, Departments of Psychiatry and Medicine, Obesity Research Centre/Genome Research Institute, University of Cincinnati, College of Medicine, USA

16.00 to 17.30 hrs Coffee break, Poster presentation and networking

17.30 to 18.15 hrs "Stem cell therapy and diabetes"

Dr. Anil Bhansali Professor & Head, Endocrinology, Postgraduate Institute of Medical Education & Research, Chandigarh

18.15 to 19.00 hrs Panel Discussion: (Chairperson: Dr. Roger Newton, USA)

19.00 to 20.00 hrs Cultural Program

20.00 to 21.00 hrs Dinner

Day 4: February 5, 2009

Session V

Chairpersons

- Dr. Walter Wahli, Founder Director, Centre for Integrative Genomics, Switzerland
- Dr. Charles Burant, University of Michigan, USA

09.00 – 09.45 hrs "Molecular mechanisms of antidiabetic effects of estrogen"

Dr. Suad Efendic Professor, Karolinska Institutet, Sweden

09.45 – 10.30 hrs "SGLT2 Inhibition: A Novel Approach to the Treatment of Type 2 Diabetes"

Dr. Jean Whaley Director, Diabetes Drug Discovery, Bristol-Myers Squibb, USA

10.30 to 11.15 hrs Coffee Break

11.15 to 12.00 hrs "Cardio protection in diabetes mellitus: Some pharmacological considerations"

Dr. R. K. Goyal Vice Chancellor, MS University, Baroda, India

12.00 to 12.45 hrs "Signal-Transduction in the Endocrine Pancreas"

Dr. Per-Olof Berggren The Rolf Luft Research Center for Diabetes and Endocrinology, Karolinska Institutet, Sweden

12.45 to 13.30 hrs Lunch

Session VI

Chairpersons

- Dr. R. K. Goyal, Vice Chancellor, M. S. University, India
- Dr. Matthias H. Tschöp, University of Cincinnati, College of Medicine, USA

13.30 – 14.15 hrs "Engineering the pharmacology of proteins to treat vascular disease"

Dr. Ho Cho Vice President, Ambrx, USA

14.15 – 15.00 hrs "Beyond Small Molecules: The Use of Biologics in the Treatment of Metabolic Disorders"

Dr. Richard DiMarchi Linda & Jack Gill Chair in Biomolecular Sciences and Professor of Chemistry, Indiana University, Retired Group Vice President, Eli Lilly & Company, USA

15.00 to 15.30 hrs Oral poster presentation 1 (15 mins)
Oral poster presentation 2 (15 mins)

15.30 to 16.15 hrs Panel Discussion: (Chairperson: Dr. Charles Burant, USA)

16.15 to 16.30 hrs Closing Remarks
Pankaj Patel, Chairman & Managing Director, Zydus Cadila

Advancing Cardiometabolic Research

Chief-guest

Dr. K. K. Talwar
Director PGIMER, Chandigarh, India

Dr. Talwar, Director PGIMER, Chandigarh has immense contribution to the development of specialty of cardiology and to medical research in India. He initiated the technique of radiofrequency ablation to cure arrhythmic disorders in India and established state-of-the-art facility at the Department of Cardiology, AIIMS, New-Delhi. He is the first in India and South Asian region to introduce the therapy of automatic implantable cardioverter and defibrillator (ICD) in 1995 and this contribution is recorded in Limca Book of Records (1997). Another first to his credit is to implant the multisite pacing system (2000) as a therapy for heart failure in the country. Dr. Talwar is credited with initiating the technique of Endomyocardial Biopsy in 1986 and used this technique to evaluate patients with various tropical heart muscle diseases. For the first time in world literature, using this technique, he has documented the occurrence of inflammatory myocarditis in-patients with Takayasu arteritis resulting in heart failure. He has further demonstrated that myocardial dysfunction is reversible with the use of immunosuppressive therapy in these patients. Dr.Talwar's significant contribution in the field of tropical heart muscle diseases has earned him membership of Scientific Council of cardiomyopathies of World Health Federation and Asian region of Global Physician Network on myocarditis. Dr.Talwar has published more than 200 articles and 270 abstracts in both national and international journals of repute. He has contributed chapters in 15 national and international books. He is the recipient of various prestigious awards from the national and international Bodies including Basanti Devi Amir Chand Award (ICMR - 2003) Dr. B.C. Roy National Award (2000), and Amrut Mody Unichem Award (ICMR - I993), Ranbaxy Research Award (1997), Goyal Prize (2002), Norman Alpert Award by International Academy of Cardiovascular Sciences (2005), Prof. Sujoy B. Roy Memorial Investigator Award (CSI -1986), Shyam Lal Saksena Award (NAMS - 1988), Searle award (CSI -1987). He is on the Editorial Boards of prestigious international journals and is a member of Scientific Council on Cardiomyopathies of World Heart Federation (WHF). Dr. Talwar has been honored with Padma Bhushan the country's third highest civilian Award by Govt. of India (2006), for his contributions in the field of Medicine and Cardiology.

Session I:

Introduction to Chairpersons:

Prof. Jeffrey M. Friedman

Howard Hughes Medical Institute (HHMI), Rockefeller University, New York, USA

Dr. Jeffrey M. Friedman is a Marilyn M. Simpson Professor and Investigator at Howard Hughes Medical Institute (HHMI), Rockefeller University, New York (USA). He is Head of Laboratory of Molecular Genetics at the Rockefeller University, USA. Prof. Friedman also directs the Starr Center for Human Genetics, one of the country's largest centers for the study of diseases linked to heredity. He is a member of the National Academy of Sciences and its Institute of Medicine. Dr. Friedman's most recent honors include the 2007 Jessie Stevenson Kovalenko Medal, the sixth Danone International Prize for Nutrition, the 2004 Gairdner Foundation International Award and the 2004 Passano Foundation Award. Prof. Friedman's lab identified leptin, a hormonal signal made by the body's fat cells that regulates food intake and energy expenditure and has powerful effects on reproduction, metabolism, other endocrine systems and even immune function. Current research in the Friedman lab focuses on the genes and neural circuits that control food intake and body weight, and leptin's mechanism of action and its relevance to the development of obesity. Studies in Dr. Friedman's lab seek to elucidate the mechanism by which leptin, can modulate a complex behavior, feeding, and how leptin and other mechanisms control body weight and the pathogenesis of obesity. Dr. Friedman is also part of a collaboration to establish the genetic basis of human obesity on the Pacific Island of Kosrae.

Prof. Richard DiMarchi

Professor of Chemistry and Gill Chair in Biomolecular Sciences,Indiana University, Bloomington Indiana, USA

Dr. DiMarchi was formerly Group Vice President for Biotechnology and Product Development at Lilly Research Laboratories, where he made major contributions to Lilly in biotechnology and endocrinology. Dr. DiMarchi was directly involved in the discovery and development of several Lilly drugs, including Humulin®, Humatrope®, Evista®, Xigris® and Forteo®. He was a co-inventor of Humalog®, the first biosynthetic protein approved for human use. Additionally, at Lilly he championed the introduction and integration of cutting-edge biotechnologies, including genomics, proteomics, highthroughput screening, and combinatorial chemistry. Dr. DiMarchi is presently a Professor of Chemistry and the Jack and Linda Gill Distinguished Chair in Biomolecular Science at Indiana University (USA). He currently serves as a co-founder and Board Chairman of Ambrx, Inc. Prof. DiMarchi previously served as a board member to the biotechnology trade group BIO and the American Peptide Society, as well as companies such as Millennium Biotherapeutics and Inproteo. He currently serves as Board member to Isis Pharmaceuticals, and scientific advisor to Alba Inc., Epitome Biosciences, Kai Pharmaceuticals and Semafore Biotechnologies.

Speaker Profile

Dr. Roger Newton
Co-founder of Esperion Therapeutics Inc., USA

Dr. Roger Newton has worked for more than 27 years in the pharmaceutical and life sciences industries. He is currently founder, President & CEO and a director of Esperion Therapeutics, Inc. Prior to his current role, he was Senior Vice President, Pfizer Global R&D and Director, Esperion Therapeutics (a Pfizer, Inc. company). He was co-founder, President & CEO of the original Esperion founded in July 1998. Dr. Roger was with Warner Lambert / Parke-Davis (now Pfizer) from 1981-1998. As a Distinguished Scientist and Chairman of the Atherosclerosis Drug Discovery Team, he co-discovered and was the product champion of what is now the most prescribed cholesterol-reducing drug in the world, Atorvastatin (Lipitor®). Dr. Roger's research interests for the past thirty years have focused on the nutritional and pharmacological regulation of cholesterol and lipoprotein metabolism as they relate to atherosclerosis and vascular diseases. He is an adjunct Associate Professor in the Department of Pharmacology at the University of Michigan Medical School. He has co-authored nearly one hundred peer-reviewed articles and chapters during his research career. Dr. Roger is a member of the Board of Directors of Rubicon Genomics, Resverlogix, Inc., and Ann Arbor Spark. He is a member of the National Advisory Boards of the University of Michigan Cardiovascular Center and University of Michigan Life Sciences Institute. He is also a member of the Technology Advisory Boards of Arboretum Ventures and Metagenics, Inc.

Keynote Address

For Notes:

Speaker Profile

Dr. Yuji Matsuzawa
Director, Sumitomo Hospital, Osaka University, Japan

Currently, Dr. Yuji Matsuzawa is the Director of Sumitomo Hospital and Professor Emeritus, at Osaka University, Japan. Prior to these roles, Professor Matsuzawa was the Director of Osaka University Hospital, Osaka University Medical School, Japan. From 1988 to 1999, Prof. Matsuzawa has been Associate Professor and Professor at the 2nd Department of Internal Medicine, Osaka University and Professor at the Department of Internal Medicine and Molecular Science at the Graduate School of Medicine, Osaka University. Prof. Matsuzawa is the President of the Japan Atherosclerosis Society, the Japan Society for the Study of Obesity and the Japanese Society of Molecular Medicine. He is the former president of the XIII International Symposium on Atherosclerosis. Prof. Matsuzawa is an editorial board member of many journals including Arteriosclerosis, Thrombosis, and Vascular Biology, Journal of Lipid Research (Advisory Board), Diabetes Research and Clinical Practice, Clinical Medicine and Asia Pacific Journal of Clinical Nutrition. Prof. Matsuzawa is the winner of the 2006 IASO Willendorf Award for outstanding clinical contributions to the field of obesity.

Topic

Emerging therapeutic strategy for cardiovascular disease-Adipocytokines

Dr. Yuji Matsuzawa
Director, Sumitomo Hospital, Osaka University, Japan

Clustering of multiple risk factors such as impaired glucose metabolism, lipid disorders and hypertension has been shown to be major background of atherosclerotic diseases and disease entities such as metabolic syndrome become popular as highly atherogenic state. Although each common risk may generally co-exist by accident in one individual, multiple risk factors clustering in metabolic syndrome does not occur by accident and there should be a key player for the syndrome. Visceral fat accumulation has been shown to cause impaired glucose metabolism, lipid disorders and hypertension, therefore visceral fat accumulation is considered to be a key player in metabolic syndrome.

In order to clarify the mechanism of metabolic syndrome, we studied on the molecular characteristic of adipose tissue and adipocytes by investigating expressed genes in visceral and subcutaneous adipocytes and revealed that adipocytes, especially visceral adipocytes are secreting a variety of bioactive substances which we called adipocytokines. We demonstrated that visceral fat accumulation causes abnormalities of adipocytokine secretion such as hypersecretion of PAI-1 which is related to thrombogenic vascular diseases. We also discovered an important benign adipocytokine named adiponectin which protects against the development of diabetes mellitus, hypertension, inflammation and atherosclerotic vascular diseases. We also demonstrated that plasma levels of adiponectin decreased in the subjects with visceral fat accumulation. In this lecture, I would like to show the molecular mechanism of metabolic syndrome with respect to visceral fat accumulation and the abnormality of adipocytokine secretion especially focusing on adiponectin. Also I would like to discuss about therapeutic strategy to increase plasma levels of adiponectin by life-style modification and drug treatment.

For Notes:

Speaker Profile

Dr. John Chapman

Director of the Dyslipidemia and Atherosclerosis Research Unit, at INSERM, France

Prof. M. John Chapman, is Director of the Dyslipidemia and Atherosclerosis Research Unit, at the National Institute for Health and Medical Research (INSERM), France. He was recently elected as President of the European Atherosclerosis Society (2008). Dr. Chapman is presently Associate European Editor of "Arteriosclerosis, Thrombosis and Vascular Biology" and "Pharmacology and Therapeutics". He is Editorial Board member of "Atherosclerosis", " Future Lipidology", and "Current Medical Research and Opinion" and has authored more than 400 peer-reviewed publications and book chapters. The focal points of his research interests have been (i) the structure, metabolism, and biological activities of atherogenic apo.B-containing particle subspecies (VLDL, LDL and Lp(a)), (ii) the relationship of HDL particle heterogeneity to atheroprotective activity in normolipidemia and in atherogenic dyslipidemia, (iii) the role of CETP in the regulation of intravascular lipoprotein metabolism, (iv) the pharmacological modulation of lipoprotein metabolism in atherogenic dyslipidemias and metabolic disease, and (v) the role of monocyte-macrophages and foam cells in the inflammatory fragilisation and thrombogenicity of the atherosclerotic plaque. Prof. Chapman is a Scientific Consultant to several international research organisations, including the Wellcome Trust, British Heart Foundation, NHMRC (Australia) and Medical Research Council (UK).

Topic

Systemic Biomarkers in Atherosclerosis : New Horizons

Dr. John Chapman
Director of the Dyslipidemia and Atherosclerosis Research Unit, at INSERM, France

Atherosclerosis, a chronic inflammatory disease which developes over several decades and is asymptomatic for much of its evolution, is clinically expressed as thromboembolic events primarily in the coronary, cerebrovascular and peripheral vasculatures. Despite, substantial progress in both invasive and non-invasive imaging modalities for assessment of atherosclerotic disease, our ability to predict a future cardiovascular (CV) event in a given patient remains inadequate. Several systemic biomarkers have however attracted attention in this regard, including CRP, IL-6, Lp-PLA2, PAI-1, Apo B, BNP and homocysteine. The predictive value and potential applications of these biomarkers are however the subject of debate.New approaches to the exploitation of biomarker data, such as that in the Framingham Heart Study suggest that combination into a multimarker score improves identification of individuals at elevated risk of CV morbi-mortality. Nonetheless, such an approach appears to add only moderately to the potential of classic CV risk factors to predict events in a given individual. Recently, it has been suggested that biomarker sensitivity can be improved by inclusion of biomarkers which provide information on pathophysiological features of atherosclerosis which are weakly-rather than strongly-correlated with each other. Several platforms are emerging which will facilitate the identification of new –and weakly related- CV biomarkers, among which are proteomics, lipidomics, metabolomics and transcriptomics. Application of such new findings to a biomarker strategy is highly feasible using new biochip array technologies.

For Notes:

Speaker Profile

Dr. Eric Niesor

Metabolic and Vascular Disease Area, Roche AG, Switzerland

Dr. Eric Niesor is Vice-Director at Metabolic and Vascular Disease Area, Hoffmann-La Roche, Switzerland. Earlier, he was Director and co-founder of Symphar SA. Dr. Eric did PhD from University of Geneva. He has published more than 100 research papers and has got 73 patents in his credit. Dr. Eric is a member of American Heart Association, American Association for Cancer Research and American Association for Bone and Mineral Research. His major activities and areas of interest include discovery of new drugs, identification and validation of new targets, studies of the mechanism of action, preclinical and clinical development of Antiatherosclerotic agents and drugs affecting lipid metabolism, HDL Cholesterol Inducers / mimetics, inhibitors of CETP, ACAT and of cholesterol synthesis, compounds which decrease specifically Apo(a) and ApoB/Lp(a) and LDL cholesterol in primates, Nuclear Hormone Receptor modulators (PPAR, LXR, FXR), in rodent and non-rodent animal models, Anti-angina and hypotensive drugs, New Calcium Entry Blockers, Anti-neoplastic compounds, antiproliferative and apoptosis inducers and compounds acting on bone metabolism and bone metastasis.

Topic

Current Understanding of the Off-target Toxicity of the CETP Inhibitor Torcetrapib

Dr. Eric Niesor
Metabolic and Vascular Disease Area, Roche AG, Switzerland

The clinical development of torcetrapib was suspended due to increased mortality and cardiovascular events in the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) study. An off-target effect evidenced by increases in blood pressure and in plasma aldosterone, indicating activation of the renin-angiotensin-aldosterone system (RAAS), may have contributed to the toxicity of torcetrapib. These effects have raised concerns over the class of drugs that act by inhibiting the activity of CETP, and questions were raised as to whether the off-target effects seen with torcetrapib are compound-specific or common to all drugs that act on CETP.

Investigations performed in vivo in normotensive and spontaneously hypertensive rats treated with torcetrapib and in vitro in the human adrenocarcinoma cell line H295R support the suggestion of RAAS activation by torcetrapib in an animal model not expressing CETP and demonstrate a potent direct steroidogenesis activity of torcetrapib measurable in vitro. Although other tissues cannot be excluded, the adrenal gland appears to be a major target organ of torcetrapib . None of these effects are observed with CETP inhibitors not derived from the torcetrapib chemical structure such as Dalcetrapib/JTT-705.

For Notes:

Session II:

Introduction to Chairpersons:

Dr. Per-Olof Berggren

The Rolf Luft Research Center for Diabetes and Endocrinology, Karolinska Institutet, Sweden

Dr. Per-Olof Berggren is Head of Cell Biology and Signal Tranduction and the Mary-Lou-Held Visiting Scientist at the Diabetes Research Institute (DRI) and Adjunct Professor of Surgery at University of Miami. He is also Professor and Head, Experimental Endocrinology at the Karolinksa Institute in Stockholm, Sweden. Dr. Berggren's work focuses on the detailed study and evaluation of beta cell function at various stages before and following transplantation. Through cell imaging techniques, his work aims to develop methods to prevent and reduce islet loss during the transplant process. He has joined the DRI to head up its new cellular biology lab. Dr. Berggren's has published more than 100 research papers and he is member of several associations.

Prof. P. Rama Rao

Director National Institute of Pharmaceutical Education and Research (NIPER), India

Prof. P. Rama Rao received his Ph.D. from the Banaras Hindu University (India) and did postdoctoral work at Department of Surgery, Harvard Medical School, Harvard University and the University of Illinois at Chicago, USA. After doing teaching & research for over two decades on various topics of pharmacology & pharmaceutics, he went on to become the Director of National Institute of Pharmaceutical Education & Research (NIPER). Prof. Rao is member of various professional bodies such as Advisory Board, IJPS, USP India Advisory Group, Editorial Board of CRIPS, Committee of 10th ISMAS Symposium and Advisory Committee of DIPSAR. Some of the awards received by him are P.P. Suryakumari Gold Medal, CDRI Oration Award, Dr. Sidhu Science lecture for the year 2005, Dr. I. C. Chopra Memorial Award for the year 2003 and UGC Career Development Award. His research interest includes pharmacological screening of NCEs, drug delivery, diabetic complications, opioids and nanotoxicology. He has more than 104 national / international publications and 9 patents to his credit.

Speaker Profile

Prof. François Mach

Prof. and Head of Cardiology, Geneva University Hospital, Switzerland

Dr. François Mach is Prof. and Head of Cardiology, Geneva University Hospital, Switzerland. He is affiliated to Swiss Society of Cardiology, Cardio-vascular biology working group of the Swiss Society of Cardiology, Fédération des Médecins Helvétiques, Groupe Suisse de Lipidologie et d'Athérosclérose, European Society of Cardiology, Councillor of the European Society for Clinical Investigation, American Heart Association Scientific Council, International Vascular Biology Organisation, Member of the European Vascular Genomic Network. Prof. Mach is reviewer for several scientific journals and also he is project reviewer at Swiss National Research Scientific Fund (SNF), ISERM/France, European Community Agence Nationale de la Recherche (ANR)/France and British Heart Foundation. He has more than 100 publications to his credit.

Topic

Inflammation as a Marker and a Target to Reduce Atherosclerosis Related Cardiovascular Events

Prof. François Mach
Prof. and Head of Cardiology, Geneva University Hospital, Switzerland

Atherosclerosis and its devastating clinical complications - arterial thrombosis, ischemia and infarction of the heart, brain and other vital organs, ruptured aortic aneurysms and peripheral vascular insufficiency - continue to account for the majority of the morbidity and mortality in the adult populations worldwide. Atherosclerosis is a progressive multifactorial process characterized initially by the subendothelial intimal accumulation of lipid-rich macrophages and T lymphocytes, followed by lesions composed of layers of foam cells and proliferating smooth muscle cells with deposition of extracellular matrix. Cardio-vascular risk factors include features related to life-style, such as cigarette smoking and obesity, as well as intrinsic factors such as hypertension, hypercholesterolemia and diabetes, which contribute to the pathological mechanisms that make the vascular endothelium dysfunctional, thereby inducing the early processes of atherosclerosis. Our concepts of atherogenesis have evolved from vague ideas of inevitable degeneration to a much better defined scenario of molecular and cellular events. As we enhance our understanding of its fundamental mechanism, we can begin to approach atherogenesis as a modifiable rather than ineluctable process. Recently, inflammatory and immunological mechanisms have been increasingly implicated in the pathogenesis of this disease. Postulates for the involvement of innate and adaptive immunity with cellular as well as humoral components have met with considerable experimental support. It is now well recognized that atherosclerotic lesions contain activated, immunocompetent cells, including T lymphocytes and macrophages. Inflammatory and immune mechanisms appear to be particularly active when plaques are activated and rupture and may therefore cause acute coronary syndromes or stroke. Insights derived from recent scientific advances should aid the discovery of new therapeutic targets that would stimulate development of novel treatment. Such new treatments could further reduce the considerable burden of morbidity and mortality due to this modern scourge, and reduce reliance on costly technologies that address the symptoms rather than the cause of atherosclerosis.

For Notes:

Speaker Profile

Dr. S.C. Manchanda

Senior Consultant Cardiologist, Sir Ganga Ram Hospital, Delhi, Formerly Prof. and Head, Dept. of Cardiology, AIIMS, India

Prof. Manchanda, after meritorious service at All India Institute of Medical Sciences (AIIMS) for 36 years, joined as Senior Consultant Cardiologist, at Sir Ganga Ram Hospital, New Delhi (2003). Prof. Manchanda has been a brilliant teacher, an excellent researcher and a human clinician. He has written over 300 original research articles including 4 books on Cardiology. Dr Manchanda's main contribution has been the original research on reversal of heart disease by meditation, diet and exercise. He conducts 'Heart Reversal Camps' regularly at Adhytma Sadhna Kendra, Chattarpur, Mehrauli. Dr Manchanda has been honoured with several awards and orations both nationally and internationally including padam shri award by the President of India in 2004.

Topic

Metabolic approaches for treatment of Ischaemia

Dr. S.C. Manchanda
Senior Consultant Cardiologist, Sir Ganga Ram Hospital, Delhi, Formerly Prof. and Head, Dept. of Cardiology, AIIMS, India

For Notes:

Speaker Profile

Dr. Charles Burant

Dr. Robert C. and Veronica Atkins Professor of Metabolism, University of Michigan, USA

Dr. Burant is Professor of internal medicine and of molecular and integrative physiology at the University of Michigan Health System in Ann Arbor, Michigan. Currently, he is Robert C. and Veronica Atkins Professor of Metabolism and directs the Michigan Metabolics and Obesity Center. Prof. Burant is board certified by the American Board of Internal Medicine with subspecialty certification in endocrinology, diabetes and metabolism. Dr. Burant earned both his medical degree, and doctorate of philosophy in molecular and cellular biology from Medical University of South Carolina (Charleston). Internship and residency both were served at the University of California (San Francisco), and Dr. Burant completed his fellowship in the Department of Medicine, Endocrinology Section at the University of Chicago. Dr. Burant has held several memberships and offices in professional societies, including the American Diabetes Association, Central Society for Clinical Investigation, the American College of Physicians, and the American Association of Clinical Endocrinology. He also is an associate editor for the Journal of Biological Chemistry, and the American Journal of Physiology. Dr. Burant is a recipient of many awards, including both the American Diabetes Association's and the American Medical Association's Award for Outstanding Research and the Medical Scientist Training Program Award. He also has been elected to the Central Society for Clinical Research, and serves on the Advisory Board for the National Diabetes Education Initiative. Current clinical interests include insulin resistance, novel therapies for diabetes, diabetic neuropathy, metabolic syndrome and thyroid disease. Dr. Burant's research interests include lipid and glucose metabolism, and molecular and cell biology of insulin resistance and the regulation of islet cell growth.

Topic

Predictive Metabolomic, Lipomic and Transcriptomic Profiling of Peripheral blood

Dr. Charles Burant
Dr. Robert C. and Veronica Atkins Professor of Metabolism, University of Michigan, USA

For Notes:

Session III:

Introduction to Chairpersons:

Dr. John Chapman

Director of the Dyslipidemia and Atherosclerosis Research Unit, at INSERM, France

Prof. M. John Chapman, is Director of the Dyslipidemia and Atherosclerosis Research Unit, at the National Institute for Health and Medical Research (INSERM), France. He was recently elected as President of the European Atherosclerosis Society (2008). Dr. Chapman is presently Associate European Editor of "Arteriosclerosis, Thrombosis and Vascular Biology" and "Pharmacology and Therapeutics". He is Editorial Board member of "Atherosclerosis", " Future Lipidology", and "Current Medical Research and Opinion" and has authored more than 400 peer-reviewed publications and book chapters. The focal points of his research interests have been (i) the structure, metabolism, and biological activities of atherogenic apo.B-containing particle subspecies (VLDL, LDL and Lp(a)), (ii) the relationship of HDL particle heterogeneity to atheroprotective activity in normolipidemia and in atherogenic dyslipidemia, (iii) the role of CETP in the regulation of intravascular lipoprotein metabolism, (iv) the pharmacological modulation of lipoprotein metabolism in atherogenic dyslipidemias and metabolic disease, and (v) the role of monocyte-macrophages and foam cells in the inflammatory fragilisation and thrombogenicity of the atherosclerotic plaque. Prof. Chapman is a Scientific Consultant to several international research organisations, including the Wellcome Trust, British Heart Foundation, NHMRC (Australia) and Medical Research Council (UK).

Dr. Y. K. Gupta

All India Institute of Medical Sciences (AIIMS) India.

Dr. Y.K. Gupta completed his M.B.B.S and his M.D pharmacology from King George Medical College, Lucknow in 1974 and 1979 respectively. He joined the All India Institute of Medical Sciences, New Delhi in 1983 as a faculty member and is presently the Professor and Head, Department of Pharmacology, All India Institute of Medical Sciences, New Delhi.

Dr. Gupta was the Director of the Industrial Toxicology Research Center (ITRC), Lucknow from 2003-2005. He has more than 150 publications in international and national journals and has been awarded several honors including the INSA young scientist medal, Shakuntala Amirchand Prize of ICMR, Chandrakanta Dandiya Prize, G. Achari Oration Award of IPS, Major General S. L. Bhatia Oration Award, Association of Physiologist and Pharmacologist of India (APPI), AEB honours award by the Academy of Environmental Biology, C. L. Malhotra Prize of APPI etc. Dr. Gupta was President of the Indian Pharmacological Society (2005-2006) and is the Editor of the Indian Journal of physiology and Pharmacology (Pharmacology Section). He is/ has been the member of Project Advisory Committee/ Project Review Committee/ Research Council/ and Scientific Advisory Committee of CDRI, ITRC, CFTRI, and CCMB. He is Chairman scientific Advisory Committee of NIOH. He is also chairman of National GLP Technical Committee of DST. Member Apex committee CSIR-Ayush coordinated partnership Golden triangle program. He has been the Governing body member of Indira Gandhi Postgraduate Institute of Medical Education and Research, Patna , Executive member of Navodaya Vidyalaya Samiti, and Governing body of CCRAS and CCRUM. He awarded Fellow of National Academy of Medical Sciences (FAMS). He is also in charge of the National Poison information Centre and Zonal Pharmacovigilance Centre at All India Institute of Medical Sciences, New Delhi. Dr. Gupta is Task Force Member in Ministry of Environment, ICMR, DBT and DST.

Speaker Profile

Prof. B. M. Hegde
Former Vice-Chancellor, Manipal University, India

Prof. Hegde did graduate and postgraduate medical education in India, He trained in cardiology at the Middlesex Hospital, Harefield, the National Heart Hospital, London and the Peter Brent Brigham Hospital, Harvard Medical School, Boston. Prof. Hegde has written 30 books and published more than 245 research articles. Health education of lay people is his passion. Prof. Hegde was former Vice Chancellor, Manipal University, Manipal (India). He was former Visiting Professor of Cardiology, University of London (UK), former Dean, Kasturba Medical College, Mangalore, Chairman, State Health Society's Expert Committee, Govt. of Bihar, Patna (India) and Chairman, Bharatiya Vidya Bhavan, Mangalore. Currently, he is Editor-in-Chief of the Journal of Science of Healing Outcomes (JSHO), He is affiliate Prof. to Human Health, University of Northern Colorado, Greeley (USA).

Topic

Energy Medicine-the Future of Modern Medicine (Electromagnetic indication of heat shock gene HSP70)

Prof. B. M. Hegde
Former Vice-Chancellor, Manipal University, India

Coronary artery disease induced myocardial damage seems to be one of the leading causes of death and disability in the world. There does not seem to be effective management strategy as of now, what with the multitude of drugs and invasive technique having done precious little at the end of the day, on retrospective objective audits. Many now feel that time has come for coronary revascularization procedures to get back to the medical museum, if not the majority of drugs in that arena.

People have been trying to protect myocardiocytes against ischaemic damage using thermal, chemical, and gene transfer methods without significant success although with much fanfare. The medical claptrap in this area seems not have dented disability and even mortality. Low energy electromagnetic field induction has been shown to up regulate the heat shock gene HSP70 and thereby induce elevated levels of the protein hsp 70 even in the absence of elevated temperature.

This has been shown in animal models to be very effective to protect the myocardium if done before ischaemia strikes. Theoretically, EMF could reinvigorate the stress protein even after ischaemia strikes. This also has been demonstrated in animals. Human studies are not found in the conventional medical literature as the device has not been licensed by the FDA.

Dr. Glen Gordon, a great researcher in this area, was struck down by massive myocardial infarction and has had revascualrisation procedures with little benefit and was waiting for a heart transplant with intractable left heart failure. It was then that he dared to make himself the guinea pig and tried his tool on himself with such great success that he is cycling round the US now. Heart transplant did not materialize as no one obliged him with a heart, thank God for that!

He donated this toy to me and this talk would give my experiences in my patients to date. Being a novel method of preserving and/or salvaging dying myocardiocytes this toy excels and needs the medical world to sit up and take note. I also want a good venture capitalist to come forward to fund large scale manufacture of this research tool which is very simple. In conclusion, it is wiser to believe that most complex problems of man must be having very simple solutions. Human body is but a bundle of jumping lepto-quarks. Disease is only an imbalance in their distribution. (Energy imbalance) Energy medicine looks like the future of modern medicine. Matter and energy are but the two faces of the same coin. My humble tributes and gratitude to my good friend Glen Gordon.

For Notes:

Speaker Profile

Dr. Sanjay Bhanot

Vice-President, Metabolic Diseases Research & Development Isis Pharmaceuticals Inc., USA

Dr. Sanjay Bhanot is Vice President, Metabolic Diseases Research & Development at Isis Pharmaceuticals, Carlsbad, CA. He currently oversees and provides strategic leadership in the area of metabolic disease drug discovery and development. Prior to joining Isis in 2000, Dr. Bhanot was Director, Diabetes Program at Kinetek Pharmaceuticals, Vancouver, Canada, where he developed a series of novel anti-diabetic compounds from benchtop through Phase I clinical trials. Dr. Bhanot received his M.D. in 1986 and his Ph.D. from the University of British Columbia in 1994. During his research career, he has won a number of awards that include: Heart and Stroke Foundation of Canada Pharmaceutical Roundtable Award (1995-1996), Medical Research Council of Canada Fellowship Award (1991-1997), Richard & Lewis Research Foundation Award (1996-1997) and Heart and Stroke Foundation of Canada Fellowship Award (1991-1995). Dr Bhanot also held a position of Adjunct Professor, Faculty of Pharmaceutical Sciences at The University of British Columbia, Vancouver, Canada (1999-2002) where his duties included research supervision of graduate students, collaborative research with Faculty members and participation in graduate teaching. His career has been focused on evaluating and developing small molecule and antisense drugs as therapeutics for metabolic disorders including diabetes and obesity.

Topic

Mipomersen: A novel lipid lowering drug, from the bench to the clinic.

Dr. Sanjay Bhanot
Vice-President, Metabolic Diseases Research & Development Isis Pharmaceuticals Inc., USA

Mipomersen (ISIS 301012)— Mipomersen is a novel, first-in-class apolipoprotein-B-100 antisense inhibitor currently in phase 3 development. Apolipoprotein B-100 (apoB-100) is a protein critical to the synthesis and transport of most atherogenic lipoproteins (LDL, VLDL and IDL) and is a target that is considered undrugable with small molecules. Mipomersen reduces the production of apoB-100, which is the protein that carries certain forms of cholesterol and triglyceride particles in the bloodstream. In preclinical studies, mipomersen or species-specific analogs reduced atherosclerosis in several animal models and the effects on atherosclerosis correlated with significant reductions in apoB-100 and atherogenic lipids, including LDL-cholesterol and triglycerides. In phase 2 studies, mipomersen, a weekly injectable therapeutic, was observed to reduce LDL-C >40% beyond reductions achieved with standard lipid-lowering drugs, enabling more patients to achieve LDL-C targets. It was also observed to reduce triglycerides, lipoprotein(a), and serum apo-B, all generally accepted risk factors for cardiovascular disease. The initial indication being sought for mipomersen is for patients with homozygous familial hypercholesterolemia (hoFH), a genetic disorder that causes extremely high cholesterol levels and results in the early onset of heart disease. The ongoing Phase 3 study will support the first U.S. filing for the indication in the second half of 2010. The presentation will discuss preclinical and clinical data highlights from this program.

For Notes:

Speaker Profile

Dr. Jens Kristensen
Vice-President, Clinical Development Chief Medical Officer, Karo Bio AB, Sweden

Dr. Jens Kristensen joined Karo Bio in November 2005. His latest position was at Astra-Zeneca as Senior Clinical Research Physician. Dr. Kristensen took his Medical education at Odense University, Denmark and achieved specialist competence in anaesthesiology and intensive care at Akademiska Sjukhuset in Uppsala. In 2001, Dr. Kristensen achieved specialist competence in pharmaceutical medicine at the University of Basel. During his 16 years of clinical practice, Dr. Kristensen held several positions, such as, Head of Cardiac Surgery Intensive Care Unit at Odense University Hospital. Dr. Kristensen also played an important role in the build-up of a private hospital for cardiac surgery in Denmark. Dr. Kristensen has served within the pharmaceutical industry where he has achieved a broad competence from early to late phases of pharmaceutical development, both strategically and operationally.

Topic

Eprotirome: A novel and physiological approach to CVD risk reduction

Dr. Jens Kristensen
Vice-President, Clinical Development Chief Medical Officer, Karo Bio AB, Sweden

Consequences of atherosclerotic cardiovascular disease such as coronary heart disease and stroke are major medical problems, and there is a need to develop improved means to treat these disorders and the risk factors that cause them, Thyroid hormones are known as key regulators of lipid metabolism through transcriptional regulation of a number of key enzymes involved in synthesis and degradation of cholesterol, and lipid transport. However, currently available thyroid agonists are non-selective, and cannot be use for the treatment of dyslipidemia due to extrahepatic consequences of hyperthyroidism, especially on heart, bone and muscle. Eprotirome is a first in class liver and receptor selective thyroid hormone receptor agonist, thus having beneficial effects on liver metabolism, without causing extra-hepatic thyroid hormone mediated effects.

Eprotirome has up to now been tested in 5 clinical studies; in monotheraphy as well as in combination with statins, and has proven to be clinically safe and well tolerated.Further, eprotirome has shown potent and clinically relevant reductions of LDL- cholesterol, triglycerides and Lipoprotein(a) levels, without disturbing extra-hepatic thyroid effects, such as cardiac function and bone turnover. The data will be discussed at the meeting.

We conclude that eprotirome, due to its unique efficacy profile, has the potential to be used as second-line therapy in patients inadequately controlled with or intolerant to statins. Patients with mixed dyslipidemia or diabetic dyslipidemia may also be suitable for treatment with eprotirome because they require simultaneous improvement in both LDL and triglyceride levels. Eprotirome may also become an alternative for those patients who have high levels of Lp(a).

For Notes:

Speaker Profile

Dr. Steve Harrison
Vice President, Research, KAI Pharmaceuticals

Dr. Harrison joined KAI in March 2005. Prior to KAI, he held senior research leadership positions at Chiron Corporation and Thios Pharmaceuticals. Dr. Harrison led multiple research programs at all stages from target identification to IND filing. Between 1994-2004, he held escalating positions at Chiron Corporation, most recently serving as Program Head of the kinase inhibitor program and member of the Research Management Team. At Chiron, Dr. Harrison was responsible for the evaluation of all new biological targets. As Chiron's Director of Lead Optimization Biology, he led all hit-to-lead projects and advanced many of these into full-scale lead optimization. Subsequently, as head of Chiron's kinase inhibitor program he oversaw kinase inhibitor research and personally led the identification of Advanced Pre-clinical Candidates (APCs) for cancer indications as well as heading the outlicensing of a pre-clinical program in diabetes and neurodegeneration. In 2004, Dr. Harrison joined Thios Pharmaceuticals as Vice President of Research, where he led efforts targeting biological sulfation, primarily for the treatment of inflammation. He directed the identification of the first lead series for inhibition of a sulfotransferase and his research group advanced two therapeutic antibodies to the point of humanization. In these roles Dr. Harrison also managed the identification and evaluation of pharmacogenomic technologies that can accelerate the research to development transition and support both indication and patient selection, as well as effective biomarker strategies. He is the author of numerous scientific publications and an inventor on thirteen issued U.S. patents.

Topic

Targeting Protein Kinase C to Treat Ischemia Reperfusion Damage in the Heart.

Dr. Steve Harrison
Vice President, Research, KAI Pharmaceuticals

KAI Pharmaceuticals has developed unique technology to selectively modulate intracellular protein, protein interactions. The company has applied this approach to discover potent and selective inhibitors and activators for members of the protein kinase C (PKC) family of isozymes. In this presentation we will demonstrate the potential of such molecules to protect heart tissue during and after ischemia.

KAI's lead product candidate, KAI-9803, is an isozyme-selective delta protein kinase C (δPKC) inhibitor that has demonstrated efficacy in reducing damage to heart muscle and improving cardiac function in patients with myocardial infarction (MI) who undergo balloon angioplasty. KAI-9803 is partnered with Bristol-Myers Squibb and is currently enrolling patients in a phase 2b efficacy trial. KAI is also developing KAI-1455, an epsilon protein kinase C (εPKC) activator, which is designed to reduce ischemic injury during planned surgical procedures, such as coronary artery bypass grafting, vascular surgery and pediatric cardiac surgery. KAI-1455 has completed Phase 1 testing. We have shown that selective modulation of PKC isozymes is a powerful approach to minimize ischemic damage in the heart and we will illustrate how KAI's technology can be broadly applied to other cardiometabolic diseases.

For Notes:

Speaker Profile

Dr. Walter Wahli

Founder Director, Centre for Integrative Genomics, Switzerland

Dr. Wahli received his PhD in Bern in 1977. He carried out a postdoctoral research with Dr. Igor Dawid at the Department of Embryology, Carnegie Institution of Washington in Baltimore. He was at the Department of Biochemistry of the National Cancer Institute, NIH, in Bethesda, as visiting fellow and visiting associate. Dr. Wahli moved to Lausanne in 1980, where he was appointed as a Professor of biology and Director of the Institute of Animal Biology of the University. He was Vice-rector for Research and Postgraduate Education of the Lausanne University between 1999 and 2003 and Founding Director of the Center for Integrative Genomics. In 1996, he was elected member of the Research Council of the Swiss National Science Foundation and was President of its Biology and Medicine Division between 2004 and 2006. In 2008, Dr. Wahli became a member of the Swiss Science and Technology Council. One major research interest of Dr. Wahli is on understanding the role of nuclear hormone receptors. In recent years, he worked mainly on receptors that he co-discovered, the Peroxisome Proliferator-Activated Receptors (PPARs). Dr. Wahli's research mainly focuses on the genetic control of energy metabolism and tissue repair. He published more than 250 articles and Dr. Wahli received many career honors and awards include the prestigious Otto Naegeli Price and the Euro Fed Lipid Research Award.

Topic

PPARα and β/δ Orchestrate Hepatic and Pancreatic functions

Dr. Walter Wahli
Founder Director, Centre for Integrative Genomics, Switzerland

Gender-dependent responses to peroxisome proliferator-activated receptors (PPARs) are not well known. We found that PPARα has broad female-dependent repressive actions on hepatic genes involved in steroid metabolism and inflammation. In males, this effect is reproduced by the administration of synthetic PPARα ligands. Using the steroid hydroxylase gene Cyp7b1 as a model, we elucidated the molecular mechanism of this PPARα-dependent repression. Initial sumoylation of the ligand-binding domain of PPARα triggers the interaction of PPARα with the GA-binding protein α (GABPα) bound to the target promoter. Histone deacetylase is then recruited, and histones and adjacent Sp1-binding site are methylated. These events result in the loss of Sp1-stimulated expression, and thus the down-regulation of Cyp7b1. Physiologically, this repression confers protection against estrogen-induced intrahepatic cholestasis, paving the way for a novel therapy against the most common hepatic disease during pregnancy.

The activation PPARβ, also called PPARδ, by agonists induces a protection against diabetes and obesity, by reducing insulin resistance in various organs, such as muscle, adipose tissue, liver, heart and lowering lipid levels in the circulation. However, nothing is known about the function of PPARβ in pancreas, a major player of metabolic regulations. Ablation of the Pparβ gene was obtained with a Cre/Lox system using the Pdx1 promoter. During development, Pdx1 is expressed in pancreas, distal stomach and the epithelium of duodenum. We found that the knock-out mice develop a chronic hyperinsulinemia due to an increase of pancreatic β-cell mass and insulin secretion. Interestingly, electron microscopy analyses showed an alteration in the architecture of insulin vesicle in PPARβ mutant islets. Finally, deletion of Pparβ induces the dispersal of the cortical F-actin network in glucose-stimulated islets. Taken together, these results suggest that PPARβ has a repressive role of β-cell growth and insulin secretion, which is interesting in the context of its reported anti-diabetic action in in vivo models.

For Notes:

Session IV:

Introduction to Chairpersons:

Dr. N. K. Ganguly
Former Director General, Indian Council of Medical Research

Prof. N.K. Ganguly is Former Director of Indian Council of Medical Research, New Delhi. Prof.Ganguly is a distinguished academician who had specialized in Microbiology and Immunology. He is M.B.B.S., M.D. (Microbiology), FAMS, FNA, FNASC, FASC, FRCPATH, FRCTrop and held several important positions like Professor Microbiology (CGUS) All Indian Institute of Public Health and Hygiene, Calcutta, Professor, Immunology (CHUS) G.B.Pant Medical College Delhi, Professor, Microbiology, PGIMER, Chandigarh, Director, National Institute of Cholera and Enteric Diseases, Calcutta., Professor of International Health, University of Minnesota MINNEAPOLIS, Visiting Professor, Dr.B.R.Ambedkar Center for Biomedical Research, Delhi, and Honorary Professor, Jawaharlal Nehru Centre for Advanced Scientific Research , Bangalore.

During his distinguished career, Prof Ganguly won several National awards, honors and fellowships including Indian Council of Medical Research, National academy of Medical Sciences, Indian National Science Academy , Amrut Mody Research Foundation, Om Prakash Bhasin Foundation, Ranbaxy Research, Federation of Indian Chambers of Commerce and Industry, University Grants Commission, Indian Science Congress, West Bengal Academy of Science and Technology and awards instituted by Universities and National Institutes. He is a fellow and member of various National and International organizations like Royal School of Tropical Medicine, London, Fellow, Royal College of Pathologies, London, Fellow, Indian National Science Academy, New Delhi, Indian Academy of Sciences, Bangalore, National Academy of Medical Sciences, New Delhi, National Academy of Science, Allahabad, Indian School of Applied Immunology & Allergy, New Delhi.

Prof Ganguly has been an office bearer for international organizations such as International Society for Heart Research and Federation of Immunological Societies of Asia-Oceania (FIMSA). He is the past President of Indian Association of Medical Microbiologists. He was Chairperson for WHO Scientific Working Group on criteria for setting Health Research Priorities.

At the National level, Prof Ganguly has held the position of President , National Academy of Medical Sciences, New Delhi, President of Indian Immunology Society, President Indian Society of Parasitology and President, The Indian College of Allergy and Applied Immunology.

A prolific writer as he is Prof. Ganguly has to his credit several books, more than 600 International and National papers. He had guided more than 130 MD/MS Thesis and over 126 Ph.D thesis.

Dr. B.Sesikeran
Director, National Institute of Nutrition, Hyderabad, India

Dr Sesikeran's has completed his MBBS (1975) from Stanley Medical College Madras University, MD (1983), in Pathology, at Gandhi Medical College, Osmania University, Hyderabad. He has a distinguished Research Career at the National Institute of Nutrition (NIN), starting as Assistant Research Officer, in 1977 to taking charge as the Director in April 2006 where he has grown with the organization holding key positions during his tenure with NIN. Dr Sesikeran has been involved with major research areas of Nutritional Pathology, Toxicology, Oncology, Sub areas of Diet and Cancer, Nutrition and Apoptosis with forty eight publications and one chapter in text book of Dermatology. He has won five awards and has been a research guide for PhD, MD and MDS students.

Speaker Profile

Prof. Jeffrey M. Friedman

Howard Hughes Medical Institute (HHMI), Rockefeller University, New York, USA

Dr. Jeffrey M. Friedman is a Marilyn M. Simpson Professor and Investigator at Howard Hughes Medical Institute (HHMI), Rockefeller University, New York (USA). He is Head of Laboratory of Molecular Genetics at the Rockefeller University, USA. Prof. Friedman also directs the Starr Center for Human Genetics, one of the country's largest centers for the study of diseases linked to heredity. He is a member of the National Academy of Sciences and its Institute of Medicine. Dr. Friedman's most recent honors include the 2007 Jessie Stevenson Kovalenko Medal, the sixth Danone International Prize for Nutrition, the 2004 Gairdner Foundation International Award and the 2004 Passano Foundation Award. Prof. Friedman's lab identified leptin, a hormonal signal made by the body's fat cells that regulates food intake and energy expenditure and has powerful effects on reproduction, metabolism, other endocrine systems and even immune function. Current research in the Friedman lab focuses on the genes and neural circuits that control food intake and body weight, and leptin's mechanism of action and its relevance to the development of obesity. Studies in Dr. Friedman's lab seek to elucidate the mechanism by which leptin, can modulate a complex behavior, feeding, and how leptin and other mechanisms control body weight and the pathogenesis of obesity. Dr. Friedman is also part of a collaboration to establish the genetic basis of human obesity on the Pacific Island of Kosrae.

Topic

Leptin and the Homeostatic Control of Energy Balance

Prof. Jeffrey M. Friedman
Howard Hughes Medical Institute (HHMI), Rockefeller University, New York, USA

The discovery of leptin has led to the elucidation of a robust physiologic system that maintains fat stores at a relatively constant level. Leptin is a peptide hormone secreted by adipose tissue in proportion to its mass. This hormone circulates in blood and acts on the hypothalamus to regulate food intake and energy expenditure. When fat mass falls, plasma leptin levels fall stimulating appetite and suppressing energy expenditure until fat mass is restored. When fat mass increases, leptin levels increase, suppressing appetite until weight is lost. By such a mechanism total energy stores are stably maintained within a relatively narrow range. Recessive mutations in the leptin gene are associated with massive obesity in mice and some humans. Treatment with recombinant leptin markedly reduces food intake and body weight. The low leptin levels in patients with leptin mutations are also associated with multiple abnormalities including infertility, diabetes and immune abnormalities all of which are corrected by leptin treatment. These findings have established important links between energy stores and many other physiologic systems and led to the use of leptin as a treatment for an increasing number of other human conditions including a subset of obesity, some forms of diabetes including lipodystrophy and hypothalamic amennorhea, the cessation of menstruation seen in extremely thin women. Identification of a physiologic system that controls energy balance establishes a biologic basis for obesity and further establishes links between this endocrine system and numerous other physiologic responses.

For Notes:

Speaker Profile

Dr. Matthias H. Tschöp

Associate Professor, Departments of Psychiatry and Medicine, Obesity Research Centre/Genome Research Institute, University of Cincinnati, College of Medicine, USA

Dr. Tschöp is the Principal Investigator of the NEON laboratories. He is a neuroendocrinologist and physiologist by training, received M.D. from Munich Medical School, Germany in 1994. After 4 years as a resident and research fellow at the Munich University Hospital, he worked as a post-doctoral fellow at the Eli Lilly Discovery Research Laboratories in Indianapolis and then as a Senior Scientist at the Department of Pharmacology, German Institute of Human Nutrition in Potsdam, Germany. He is now an Associate Professor of Psychiatry and Medicine, at the University of Cincinnati's Obesity Research Centre and Genome Research Institute. He favors a translational approach including basic research tools, advanced animal models of disease and related clinical studies to study how neuroendocrine circuits link afferent with efferent signals in the control of lipid, glucose and energy metabolism.

Topic

Gut-Brain Communication in the Control of Metabolism

Dr. Matthias H. Tschöp
Associate Professor, Departments of Psychiatry and Medicine, Obesity Research Centre/Genome Research Institute, University of Cincinnati, College of Medicine, USA

For Notes:

Speaker Profile

Dr. Anil Bhansali
Professor & Head, Endocrinology, Postgraduate Institute of Medical Education & Research, Chandigarh, India

Dr. Bhansali is the Professor and Head of Endocrinology, Postgraduate Institute of Medical Education & Research, Chandigarh (India). His areas of interest are adrenals, gonads and T2DM. His current research is in childhood Cushing's: clinical profile and outcome, childhood Addison's: clinical profile and outcome, mortality data in T2DM, Hypogonadotropic -hypogonadism: Profile and outcome of 150 patients. His honors include visiting professorship to LKM University, Graz, Austria Vienna. He is a member of many professional bodies like: Endocrine Society of India, American Endocrine Society, American Diabetes Association, Association of Physicians of India, Research Society for Study of Diabetes in India, Indian Menopausal Society, Executive Member of Endocrine Society of India. He published more than 200 research articles, in various national and international journals.

Topic

"Stem cell therapy and diabetes".

Dr. Anil Bhansali
Professor & Head, Endocrinology, Postgraduate Institute of Medical Education & Research, Chandigarh, India

Diabetes mellitus is the most common endocrine disorder, with 90% of the patietns are bing of type 2 diabetes. It is characterized by insulin resistance and insulin deficiency, which eventually results into hyperglycemia with a prolonged duration of 8-10 yrs of impaired glucose regulation. Insulin resistance can be modulated by life style modification and insulin sensitizers while insulin deficiency is treated with sulphonylureas. However, currently Beta cell regenerative therapies are available including GLP-1 analogues, DPP IV inhibitors and stem cell therapy. This presentation will discuss our experience of autologous bone marrow derived stem cells in patients with T2DM.

For Notes:

Session V:

Introduction to Chairpersons:

Dr. Walter Wahli

Founder Director, Centre for Integrative Genomics, Switzerland

Dr. Wahli received his PhD in Bern in 1977. He carried out a postdoctoral research with Dr. Igor Dawid at the Department of Embryology, Carnegie Institution of Washington in Baltimore. He was at the Department of Biochemistry of the National Cancer Institute, NIH, in Bethesda, as visiting fellow and visiting associate. Dr. Wahli moved to Lausanne in 1980, where he was appointed as a Professor of biology and Director of the Institute of Animal Biology of the University. He was Vice-rector for Research and Postgraduate Education of the Lausanne University between 1999 and 2003 and Founding Director of the Center for Integrative Genomics. In 1996, he was elected member of the Research Council of the Swiss National Science Foundation and was President of its Biology and Medicine Division between 2004 and 2006. In 2008, Dr. Wahli became a member of the Swiss Science and Technology Council. One major research interest of Dr. Wahli is on understanding the role of nuclear hormone receptors. In recent years, he worked mainly on receptors that he co-discovered, the Peroxisome Proliferator-Activated Receptors (PPARs). Dr. Wahli's research mainly focuses on the genetic control of energy metabolism and tissue repair. He published more than 250 articles and Dr. Wahli received many career honors and awards include the prestigious Otto Naegeli Price and the Euro Fed Lipid Research Award.

Dr. Charles Burant

Dr. Robert C. and Veronica Atkins Professor of Metabolism, University of Michigan, USA

Dr. Burant is Professor of internal medicine and of molecular and integrative physiology at the University of Michigan Health System in Ann Arbor, Michigan. Currently, he is Robert C. and Veronica Atkins Professor of Metabolism and directs the Michigan Metabolics and Obesity Center. Prof. Burant is board certified by the American Board of Internal Medicine with subspecialty certification in endocrinology, diabetes and metabolism. Dr. Burant earned both his medical degree, and doctorate of philosophy in molecular and cellular biology from Medical University of South Carolina (Charleston). Internship and residency both were served at the University of California (San Francisco), and Dr. Burant completed his fellowship in the Department of Medicine, Endocrinology Section at the University of Chicago. Dr. Burant has held several memberships and offices in professional societies, including the American Diabetes Association, Central Society for Clinical Investigation, the American College of Physicians, and the American Association of Clinical Endocrinology. He also is an associate editor for the Journal of Biological Chemistry, and the American Journal of Physiology. Dr. Burant is a recipient of many awards, including both the American Diabetes Association's and the American Medical Association's Award for Outstanding Research and the Medical Scientist Training Program Award. He also has been elected to the Central Society for Clinical Research, and serves on the Advisory Board for the National Diabetes Education Initiative. Current clinical interests include insulin resistance, novel therapies for diabetes, diabetic neuropathy, metabolic syndrome and thyroid disease. Dr. Burant's research interests include lipid and glucose metabolism, and molecular and cell biology of insulin resistance and the regulation of islet cell growth.

Speaker Profile

Dr. Suad Efendic

Professor, Karolinska Institutet, Sweden

Dr. Suad Efendic was Head of Department of Endocrinology, Karolinska Hospital, Stockholm, Sweden (1988-1995), Chairman of the Department of Molecular Medicine, Karolinska Institutet, Stockholm, Sweden (1995-2000), Professor of Endocrinology, Department of Endocrinology, Karolinska Institutet, Stockholm, Sweden (1995-2004). He received several awards and honours such as Fellow of All Indian Institute for Diabetes Research, Vuk Vrhovec Award (Croatian Diabetes Association), Jacob Poulsen Award for Research in Endocrinology (Nordisk Insulin Foundation), Bertha Rosenstadt Lecture, University of Toronto, Toronto (Canada), Professor of Medicine, University of Zagreb, Yugoslavia, Adjunct Professor of Physiology, University of Toronto (Canada), Björn Sjögren's Lecture, University of Göteborg, Member of Nobel Assembly, Rolf Luft's Award (International Diabetes Federation), Novo Lecture (Indian Diabetes Federation), Laufberger Lecture (European Association for the Study of Diabetes), Banting and Best Diabetes Centre Lecture, Toronto (Canada), Member of the Royal Swedish Academy of Sciences, Member of the Croatian Academy of Sciences, Member of the Academia Europaea, Novo Lecture, Toronto (Canada), Thureus prize, The Swedish Society of Medicine, Marble Lecture, Harvard Medical School, Boston, Celal Öker Memorial Lecture (Turkish Diabetes Association), Hippocrates Award, Hellenic Society of Internal Medicine and Doctor Honoris Causa, Charles University, Prague.

Topic

Molecular Mechanisms of Antidiabetic Effects of Estrogen

Dr. Suad Efendic
Professor, Karolinska Institutet, Sweden

Lack of ERα, but not ERβ, caused glucose intolerance and insulin resistance in both female and male mice. Insulin resistance in ERKO mice is mainly due to profound hepatic insulin resistance, which results from the upregulation of lipogenic genes via the suppression of *Lepr* expression. E2 improves GT and insulin sensitivity in ob/ob mice. This effect may be mediated via stimulation of expression of *Stat3* and *Lepr* leading to decreased expression of hepatic lipogenic genes. Study with the ERα agonist PPT in ob/ob mice strongly confirmed that the antidiabetic effect of E2 is mediated via ERα signaling. Increases in the expression levels of *Stat3* and decreases in the expression levels of *G6pc* were identified as being involved in the potential mechanism behind the effects of E2 and PPT on glucose homeostasis. E2 treatment reduces obesity, improves GT and insulin sensitivity in HFD mice. These effects of E2 are mediated by downregulation of *Srebp1c* and its down-stream regulated lipogenetic genes, such as *Fas* and *Scd1* in WAT and *Scd1* in liver. Suppression of hepatic *G6pc* expression and decreased level of resistin upon E2 treatment could play a crucial role in this context.

For Notes:

Speaker Profile

Dr. Jean Whaley

Director, Diabetes Drug Discovery, Bristol-Myers Squibb, USA

Dr. Jean Whaley is currently working at Bristol-Myers Squibb (BMS) as Director in Diabetes Drug Discovery Program (2005 onward). She is with BMS since 1992 and earlier, she worked as Sr.Research Investigator. Dr. Whaley did her graduation and post doctoral studies at Harvard School of Public Health (1984-1989). Dr. Whaley's specialization is in the field of Biochemistry, Genetics and Molecular Biology Medicine, Pharmacology, Toxicology and Pharmaceutics. Dr. Whaley contributed significantly, in the field of diabetes, obesity and metabolic disorders, including discovery, preclinical and clinical development of a potent and renal selective Sodium-Dependent Glucose Cotransporter 2 (SGLT2) inhibitor (Dapagliflozin) for the treatment of type 2 diabetes and obesity. Earlier she worked on IGF 1R-inhibitors and dual Peroxisome Proliferator-Activated Receptor (PPAR α/γ) activator (Muraglitazar), as novel antidiabetic agents. During her 17 year's tenure at BMS, she published several research articles, in journal like JPET, Diabetes, JMC and BMCL and filed several patent applications.

Topic

SGLT2 Inhibition: A Novel Approach to the Treatment of Type 2 Diabetes

Dr. Jean Whaley
Director, Diabetes Drug Discovery, Bristol-Myers Squibb, USA

A new approach to treating hyperglycemia involves blocking glucose reabsorption in the kidney by selectively inhibiting SGLT2 and inducing glucose excretion in the urine. Relatively nonselective SGLT inhibitors such as phlorizin have demonstrated the potential to improve insulin sensitivity and reduce elevated endogenous glucose production in diabetic animals by correcting for glucotoxicity. Tissue expression profiling now suggests that SGLT2 is expressed almost exclusively in the renal cortex. Dapagliflozin, a novel SGLT2 inhibitor under clinical investigation, was identified in a drug discovery program which focused on the identification of stable, potent, and selective inhibitors of SGLT2. In preclinical studies, dapagliflozin produced robust glucosuria in rodents. In healthy human volunteers, dapagliflozin demonstrated dosedependent glucosuria over 24 hours, and suitability for once-daily dosing attributable in part to its C-glucoside chemical linkage that confers metabolic stability. In a 14-day Phase 2a trial in patients with type 2 diabetes mellitus (T2DM), dapagliflozin induced urinary glucose excretion rates of 35-40 g/24 hr (5 mg/d dose) and 66-82 g/24 hr (25 and 100 mg/d doses), reduced fasting serum glucose in a dose-dependent manner, and improved oral glucose tolerance. In a 12-week Phase 2b study in T2DM patients, dapagliflozin doses of 2.5–50 mg/d increased urinary glucose excretion by 46–76 g/24 hr, produced significant decreases in fasting plasma glucose (-16.2–30.5 mg/dL) and HbA1c levels (-0.6–0.9%), and led to greater weight loss vs placebo. Additional data will be presented on the preclinical and emerging clinical profile of dapagliflozin as a novel, insulin-independent treatment for hyperglycemia.

For Notes:

Speaker Profile

Dr. R. K. Goyal
Vice-Chancellor, MS University, Baroda, India

Dr. Ramesh K. Goyal, Vice-Chancellor, The Maharaja Sayajairao University of Baroda has been Professor of Pharmacology in L. M. College of Pharmacy, Ahmedabad having 31 years of experience in Teaching and Research in Cardiovascular Pharmacology & Diabetes. In between he was a post-doctoral scholar (1984) and visiting scientist (1995) at University of British Columbia, Vancouver, Canada and visiting Professor, Institute of Cardiovascular Sciences, University of Manitoba, Canada (1999, 2001 and 2003). He has three patents, 15 books, over 250 full papers, 300 abstracts and guided over 30 Ph.D and 150 M. Pharm students. He is the recipient of 58 awards including Best Pharmacy Teacher and Best Pharmaceutical Research Scientist (APTI) and Distinguished Service Award from International Academy of Cardiovascular Sciences, Canada. He is the Fellow of six professional bodies (FIPS, FIACS, FMS, FIC, FICN, FNASc.) and Member of different committees (ICMR, AICTE). He has attended number of Seminars, Workshops and Conferences as Resource Person and also chaired various sessions. Dr. Goyal has been invited to deliver about 100 lectures in India and 16 lectures abroad.

Topic

Cardio Protection in Diabetes Mellitus: Some Pharmacological Considerations

Dr. R. K. Goyal
Vice-Chancellor, MS University, Baroda, India

With the establishment of the fact that there occurs greater cardiac morbidity and mortality in diabetes, several humoral, cellular and sub- cellular targets have been identified, with a hope to get novel drug for the treatment of diabetic cardiomyopathy. Although, a number of molecules were developed to act on specific targets, one has to rely on the currently available antidiabetic, antihypertensives, anti-atherosclerotic and antithrombotic drugs for cardiovascular protection. In the early stages we carried out animal and clinical studies on proper selection of anti-diabetics and antihypertensives related to cardioprotection, justifying use of selective ACE inhibitors and calcium channel blockers in NYHA class-1 cardiac failure. Similarly metformin was reported to be relatively cardio-protective as compared to sulfonylureas, giving rise to a new era for insulin sensitizers. Further, clinical studies at a local hospital in patients undergoing coronary artery bypass surgery in NYHA class-2 and -3 heart failure, suggested suitability of perindopril and ramipril over other ACE inhibitors. Use of adenosine and sodium nitroprusside as intracoronary boluses administered sequentially were found to be effective modality to establish TIMI and TMP flow grade-3 in most of the patients. Monitoring of pulmonary artery pressure in NYHA class 3 and 4 heart failure patients showed that while metoprolol was effective in most of these patients, some patients did not show improvement possibly because of gene polymorphism. In conclusion, our studies on currently used drugs in different stages of heart failure suggest a need for extensive comparative evaluation of the currently available drugs for effective cardioprotection and getting novel leads for the development drugs for patients with heart failure.

For Notes:

Speaker Profile

Dr. Per-Olof Berggren

The Rolf Luft Research Center for Diabetes and Endocrinology, Karolinska Institutet, Sweden

Dr. Per-Olof Berggren is Head of Cell Biology and Signal Tranduction and the Mary-Lou-Held Visiting Scientist at the Diabetes Research Institute (DRI) and Adjunct Professor of Surgery at University of Miami. He is also Professor and Head, Experimental Endocrinology at the Karolinksa Institute in Stockholm, Sweden. Dr. Berggren's work focuses on the detailed study and evaluation of beta cell function at various stages before and following transplantation. Through cell imaging techniques, his work aims to develop methods to prevent and reduce islet loss during the transplant process. He has joined the DRI to head up its new cellular biology lab. Dr. Berggren's has published more than 100 research papers and he is member of several associations.

Topic

Signal-Transduction in the Endocrine Pancreas

Dr. Per-Olof Berggren
The Rolf Luft Research Center for Diabetes and Endocrinology, Karolinska Institutet, Sweden

Blood glucose homeostasis is controlled by a well-concerted secretion and action of pancreatic hormones from the various cell types in the endocrine pancreas, the islets of Langerhans. The secretion of insulin and glucagon from the pancreatic β-cells and α-cells, respectively, is regulated very precisely by nutrients as well as by autocrine, endocrine, paracrine and nervous signals. The islets of Langerhans have an important role in integrating these various signals. If hormone release is disturbed diabetes develops. The molecular mechanisms involved in the regulation of insulin secretion from the β-cell are relatively well understood and involve an exocytotic apparatus that in principle resembles the well studied presynaptic machinery mediating exocytosis from synaptic vesicles in neurons. Much less is known about exocytosis of glucagon from the α-cell. A pivotal question is how insulin and glucagon can be so effectively released subsequent to the relatively modest changes in blood glucose concentration prevailing in man under normal conditions. In this context, I will discuss how endogenously released ATP and glutamate serve as positive autocrine feedback loops for the human β-cell and α-cell, respectively. In addition, I will discuss a systems biology approach to study signal-transduction involved in the regulation of the multiple exocytotic processes prevailing in the islets of Langerhans.

For Notes:

Session VI:

Introduction to Chairpersons:

Dr. R. K. Goyal

Vice-Chancellor, MS University, Baroda, India

Dr. Ramesh K. Goyal, Vice-Chancellor, The Maharaja Sayajairao University of Baroda has been Professor of Pharmacology in L. M. College of Pharmacy, Ahmedabad having 31 years of experience in Teaching and Research in Cardiovascular Pharmacology & Diabetes. In between he was a post-doctoral scholar (1984) and visiting scientist (1995) at University of British Columbia, Vancouver, Canada and visiting Professor, Institute of Cardiovascular Sciences, University of Manitoba, Canada (1999, 2001 and 2003). He has three patents, 15 books, over 250 full papers, 300 abstracts and guided over 30 Ph.D and 150 M. Pharm students. He is the recipient of 58 awards including Best Pharmacy Teacher and Best Pharmaceutical Research Scientist (APTI) and Distinguished Service Award from International Academy of Cardiovascular Sciences, Canada. He is the Fellow of six professional bodies (FIPS, FIACS, FMS, FIC, FICN, FNASc.) and Member of different committees (ICMR, AICTE). He has attended number of Seminars, Workshops and Conferences as Resource Person and also chaired various sessions. Dr. Goyal has been invited to deliver about 100 lectures in India and 16 lectures abroad.

Dr. Matthias H. Tschöp

Associate Professor, Departments of Psychiatry and Medicine, Obesity Research Centre/Genome Research Institute, University of Cincinnati, College of Medicine, USA

Dr. Tschöp is the Principal Investigator of the NEON laboratories. He is a neuroendocrinologist and physiologist by training, received M.D. from Munich Medical School, Germany in 1994. After 4 years as a resident and research fellow at the Munich University Hospital, he worked as a post-doctoral fellow at the Eli Lilly Discovery Research Laboratories in Indianapolis and then as a Senior Scientist at the Department of Pharmacology, German Institute of Human Nutrition in Potsdam, Germany. He is now an Associate Professor of Psychiatry and Medicine, at the University of Cincinnati's Obesity Research Centre and Genome Research Institute. He favors a translational approach including basic research tools, advanced animal models of disease and related clinical studies to study how neuroendocrine circuits link afferent with efferent signals in the control of lipid, glucose and energy metabolism.

Speaker Profile

Dr. Ho Sung Cho
Vice-President, Ambrx, USA

Dr. Cho is Vice-President (Technology & Process Development, Ambrx). He is a senior management team member that championed expanding the utility of Ambrx's core technology into Eukaryotic expression systems (CHO and Yeast) and enabling a new product platform, antibody conjugates of peptides and bioactive molecules. Dr. Cho is responsible for providing a clear scientific vision and plan that links protein lead optimization with process development of pre-clinical candidates and management of CMOs to deliver Drug Substance and Drug Product. Dr. Cho is also a leader of Ambrx's joint development team in Merck-Serono collaboration to advance ARX201 into Ph III and beyond. He is scientific leader and member of the Joint Steering Committee in Lilly collaboration to optimize and advance two proteins to achieve pre-set criteria for both pre-clinical efficacy and manufacturing feasibility. Earlier, Dr. Cho was Group leader, Associate Director and Director (Molecular Technology & Process Development, Ambrx). He contributed significantly to optimize Ambrx first therapeutic protein candidate toward an IND filing. Led scientific efforts in synthetic chemistry, molecular biology, bioprocess engineering, and protein chemistry. He did excellent work on protein expression, purification, modification and analysis. Dr. Cho developed strategy for GMP production of materials to support clinical studies (Phase I and II), implemented methodology for medium to high throughput protein expression, purification and characterization.

Topic

Engineering the Pharmacology of Proteins to Treat Vascular Disease

Dr. Ho Sung Cho,
Vice-President, Ambrx, USA

The last decade has seen the highly productive use of biology-based systems such as phage, yeast, ribosome, and mRNA display to create recombinant peptide and protein libraries of high molecular diversity and improved potency. Though valuable, these approaches are limited in their ability to optimize protein function because of the narrow range of chemical diversity present in the 20 amino acids used by nature for protein structure. The incorporation of chemically-specified novel amino acids, such as para-acetyl-phenylalanine (pAcF), promises to create new horizons in protein engineering by enabling "protein medicinal chemistry", leading to enhanced performance. The precise positioning of the site of PEG attachment into the primary protein sequence by the biosynthetic incorporation of pAcF into numerous proteins of interest has already enabled the invention of candidate molecules with preserved biological potency and enhanced pharmacology. Animal data obtained from rodents and primates, coupled with a large body of data from existing daily administered products, provide strong support for the hypothesis that engineering the pharmacology of proteins via protein medicinal chemistry can lead to better therapeutic agents. Examples to be discussed include PEGylated human growth hormone and Leptin.

For Notes:

Speaker Profile

Prof. Richard DiMarchi

Professor of Chemistry and Gill Chair in Biomolecular Sciences, Indiana University, Bloomington Indiana, USA

Dr. DiMarchi was Group Vice President for Biotechnology and Product Development at Lilly Research Laboratories, where he made major contributions to Lilly in biotechnology and endocrinology. Dr. DiMarchi was directly involved in the discovery and development of several Lilly drugs, including Humulin®, Humatrope®, Evista®, Xigris® and Forteo®. He was a co-inventor of Humalog®, the first biosynthetic protein approved for human use. Additionally, at Lilly he championed the introduction and integration of cutting-edge biotechnologies, including genomics, proteomics, highthroughput screening, and combinatorial chemistry. Dr. DiMarchi is presently a Professor of Chemistry and the Jack and Linda Gill Distinguished Chair in Biomolecular Science at Indiana University (USA). He currently serves as a co-founder and Board Chairman of Ambrx, Inc. Prof. DiMarchi previously served as a board member to the biotechnology trade group BIO and the American Peptide Society, as well as companies such as Millennium Biotherapeutics and Inproteo. He currently serves as Board member to Isis Pharmaceuticals, and scientific advisor to Alba Inc., Epitome Biosciences, KAI Pharmaceuticals and Semafore Biotechnologies.

Topic

Beyond Small Molecules: The Use of Macromolecules in the Treatment of Metabolic Diseases

Prof. Richard DiMarchi
Professor of Chemistry and Gill Chair in Biomolecular Sciences, Indiana University, Bloomington Indiana, USA

The recent emergence of new technologies in protein biosynthesis is dramatically enlarging the structural space that can be utilized by protein medicinal chemists. The simultaneous mutation of tRNAs and the tRNA-Synthetases has demonstrated that amino acids previously restricted to chemical synthetic approaches can now be successfully utilized in rDNA-based biosynthesis. Additionally, advances in fragment ligation peptide chemistries have proven that proteins of the synthetic complexity of erythropoietin can be readily prepared in quantity and quality sufficient to support a structure activity relationship. This period in protein chemistry is quite analogous to the advent of rDNA-based synthesis when the first natural sequenced proteins were produced and the foundation for the delivery of optimized proteins was established. The structure-activity relationships that delivered those first commercial hormone analogs, such as LisPro-human insulin were conducted by a combination of synthetic, semi-synthetic and biosynthetic methodologies. The integration of these new synthetic tools with more conventional methodologies is dramatically enhancing the academic and commercial opportunities for peptide and protein based medicines. The application of select methodologies to the optimization of peptides in the glucagon family will be presented.

For Notes:

Scientific Poster Presentations

PS-1: Neutralization of Heparin and Enoxaparin by Protamine in Plasma of Different Spesies: In-vitro Comparative Study

Akshyaya Chandan Rath, Hitesh Soni and Mukul R Jain
Zydus Research Centre, Ahmedabad, Gujarat (India).

Protamine is used routinely to reverse the anticoagulant action of heparin after cardiovascular surgeries. It is generally obtained from fish and consists of a group of heterogeneous peptides with an average molecular weight of 4500 dalton. Approximately 67% of amino acid composition in Protamine is Arginine. The polycationic protamine combines with polyanionic heparin through an electrostatic interaction there by neutralizing the anticoagulant function of heparin.

In this study we have demonstrated the sensitivity of protamine to neutralize Heparin and Enoxaparin (a Low Molecular Weight Heparin) by conducting *in-vitro* aPTT clotting assay in three different plasma i.e. rat, dog and human plasma. It was reported that clinically protamine showed neutralization of LMWH at much more higher dose as compared to unfractionated heparin. Our study demonstrated similar findings in invitro aPTT clotting assay-using plasma of various species. It was also concluded that the heparin neutralizing capacity of protamine showed a better profile in dog plasma as compared to other plasma samples. Enoxaparin is least sensitive in dog plasma therefore difficult to find the neutralizing capacity using protamine.

PS-2: LPS-Induced Suppression of Macrophage Cholesterol Effluxis Mediated by Adipocyte Enhancer-Binding Protein 1

Amin Majdalawieh* and Hyo-Sung Ro#
*Department of Biology and Chemistry, Faculty of Arts and Sciences, American University of Sharjah, Sharjah, United Arab Emirates.
#Department of Biochemistry and Molecular Biology, Faculty of Medicine, Dalhousie University, Halifax (Canada).

Macrophages facilitate clearance of cholesterol from the body via reverse cholesterol transport (RCT). The first event in RCT is internalization of modified low density lipoprotein by macrophages, upon which PPARγ1 and LXRα signaling pathways are turned on, leading to the transactivation of a cascade of genes (e.g. ABCA1 and ABCG1), whose products promote macrophage cholesterol efflux. Down-regulation of macrophage cholesterol efflux mediators leads to an imbalance in cholesterol homeostasis, promoting foam cell formation. Lipopolysaccharide (LPS) has been shown to suppress PPARγ1 and its downstream target genes in macrophages, inducing foam cell formation; a key mechanism proposed to underlie bacterial infection-induced atherosclerosis. Herein, we show that adipocyte enhancer-binding protein 1 (AEBP1) is up-regulated during monocyte differentiation. Moreover, we provide experimental evidence suggesting that AEBP1 expression is induced by LPS, and that LPS-induced down-regulation of pivotal macrophage cholesterol efflux mediators, leading to foam cell formation, is largely mediated by AEBP1. Although AEBP1-independent pathways seem to contribute to these LPS effects, such pathways can only mediate lesser and delayed effects of LPS on macrophage cholesterol efflux and development of foam cells. We speculate that AEBP1 may serve as a potential therapeutic target for the prevention/treatment of septic shock syndrome and bacterial infection-induced atherosclerosis.

PS-3: Design and Synthesis of Novel Thyroid Receptor β (TRβ) Ligands/Thyromimetics

Amitgiri Goswami, Archana Gite, Honey Modi, Amol A. Thorave, Pinkal N. Prajapati, Jeevan Kumar jamili, Kalpatapu V.V.M. Sairam, Debdutta Bandyopadhyay, Rajendra K. Kharul and Mukul R. Jain
Zydus Research Centre, Ahmedabad, Gujarat (India).

Hyperlipidemia, a directly contributing factor for development of coronary heart disease, the leading cause of morbidity and mortality in the developed world. Thyroid hormones are important endocrine signaling hormones that affect the metabolism of virtually every cell of the body. At normal levels, these hormones maintain body weight, metabolic rate, body temperature & mood, and influence blood levels of serum low density lipoprotein (LDL). Thyroid hormone receptors (TRs) are, like other nuclear receptors, single polypeptide chains. The $TR\alpha_1$, $TR\beta_1$ and $TR\beta_2$ isoforms bind thyroid hormone and act as ligand-regulated transcription factors. In adults, the $TR\beta_1$ isoform is the most prevalent form in most tissues, especially in the liver and muscle, where as $TR\alpha_1$ is mainly present in cardiac tissues. Recent studies suggest that thyroid hormone receptor subtypeβ (TRβ) selective agonists have a profile in which cholesterol can be reduced with minimal cardiac side effects such as tachycardia. In continuation of

our efforts in this direction, we have synthesized various novel 3′-substituted diaryl ether thyromimetics that possess good binding and functional activation of TRβ. Structure activity relationship studies on the 3'-positions provided compounds with enhanced TRβ affinity as well as selectivity. As shown in table-I compound **(14d)** had improved TRα/β selectivity as well as good TRβ activation EC_{50} = 5 nM.

Table 1: In Vitro EC_{50} for TRα, TRβ and selectivity ratio is expressed as TRα/β

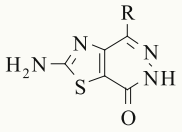
Comp	EC_{50} TRα (nM)	EC_{50} TRβ (nM)	TRα/β
14b	406	57	7.1
14d	37	5	7.4
19	32.5	10.1	3.2
22b	57.8	123.6	0.5
KB-141	4.5	1.12	4.0

The in vitro % TRα & TRβ activities of compounds 14b,d & 19, 22b were evaluated with respect to T_3 at three different concentrations viz. 0.001, 0.01, 0.1 μM and taking KB-141 as positive control.

PS-4: Convenient and General Strategy towards Synthesis of 4-substituted 2-aminothiazolo [4,5-*d*]pyridazinones

Amol A. Thorave, Pinkal N. Prajapati, Jignesh P. Pethani, Krunal C. Kothari, Darshan Joshi, Rajendra K. Kharul and Mukul R. Jain
Zydus Research Centre, Ahmedabad, Gujarat (India).

Sulfur containing fused pyridazinones has drawn much attention due to their potential biological and pharmacological activities. Recently, the heterocyclic fused pyridazinones have also been synthesized as potent phosphodiester (PDE) IV inhibitors for the treatment of asthma, inflammation, and several CNS pathologies. 2-Aminothiazolo [4,5-*d*] pyridazinones, which posses analgesic and anti-inflammatory activities were first synthesized by Takaya and co-workers. For our drug discovery program and in continuation of our interest, we have synthesized 4-substituted 2-aminothiazolo[4,5-*d*]pyridazin-7(6H)-ones (**13**) by using hybridization concept *i.e.* formation of thiazole ring subsequently followed by construction of [4,5-*d*] pyridazinone moiety. According to the notion, we first constructed substituted thiazole ring (**7**) followed by functional group transformations to have intermediate (**11**) and cyclization with hydrazine hydrate to furnish the desired heterocycle (**14**). We have demonstrated its generality by synthesizing differentially substituted derivatives. The developed methodology may prove suitable for alternative, rapid synthesis of thiazolopyridazinone libraries, which are of interest as promising structural analogs of biological active pyridazinones.



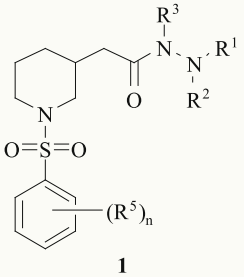
(14)

R = Ph, 2-CF_3-C_6H_4, *i*-C_3H_7

PS-5: Piperidines as Inhibitors of 11β-Hydroxysteroid Dehydrogenase Type-1 (11-β HSD1)

Arghya Dhar, Amol A. Thorave Archana S. Gite, Amitgiri Goswami, Pinkal N. Prajapati, Rajendra K. Kharul, Shital Shah, Prasenjit Mitra and Mukul R. Jain
Zydus Research Centre, Ahmedabad, Gujarat (India).

11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) is an enzyme which is involved in glucocorticoid regulation, and inhibition of 11β-HSD1 has been pursued by many pharmaceutical companies and academic laboratories as a treatment for metabolic syndrome including T2DM. Herein we disclose piperidine compounds as defined by the general formula (1) as potent inhibitor of 11β-HSD1. These piperidine derivatives were synthesized from commercially available nipecotic acid and various sulfonyl chlorides. Further one carbon homologation followed by coupling of the resulting acid with different amines furnished piperidines. These piperidine derivatives were screened for their in-vitro inhibitory activity against 11β-HSD1. The most of the derivatives showed excellent inhibition of 11β-HSD1. The compounds of this invention are therefore suitable for the prevention and treatment of disease states mediated by 11β-HSD1.



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PS-6: Assessment of Antidiabetic Potential of a Folklore Medicinal Plant from North East India.

Ansarullah*, Sahu S[ι], Laddha N.C[#], Dwivedi M.[#], Jadeja R. N.*, Thounajam M.*, Devkar.R.V.*, Hardikar A. A.[ι] and Ramachandran A.V.*
*Department of Zoology, [#]Department of Biochemistry, Faculty of Science, The M.S.University of Baroda, Vadodara-390002, Gujarat (India).
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Oreocnide integrifolia *(Gaud.)*Miq is a folklore medicinal plant commonly known as "ukhajing" is used as an

antidiabetic drug in north east India . The hypoglycemic effect of an aqueous extract of *Oreocnide integrifolia* (OI) leaves was tested in streptozotocin (STZ) diabetic rats. Significant glucoregulatory effect from the high diabetic status was recorded by a 30 day treatment schedule with a 500mg/kg body weight extract of OI leaves. Plasma insulin levels increased in diabetic rats treated with OI and immunoflourescence labelling of pancreatic sections further correlated with our present findings. Further, the ability of the extract to promote insulin release upon glucose challenge was tested in isolated pancreatic islets as well as in RINm5F cell line. Both these *in-vitro* systems showed potent insulin release in presence of OI extract. Further, we evaluated the effect of OI extract on type 2 diabetic model using high fat fed C57BL/6J mice. Insulin tolerance test, glucose tolerance test and enzyme markers were evaluated to assess the probable mechanism of action of plant extract. Overall, it can be concluded from the present observations the OI leaf extract affords significant protection against diabetes.

PS-7: PPARγ Agonist Attenuates the Angiotensin II mediated Enhanced Vascular Responses in High Fat Diet Fed Rats by Altering the L-Type Calcium Channels Functions

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Background/rationale:- Insulin resistance has emerged as a mechanism linking diabetes mellitus and hypertension. Insulin sensitizers such as pioglitazone and rosiglitazone [peroxisome proliferator activated receptor-γ (PPARγ) agonists] reduce blood pressure (BP) in some hypertensive and insulin resistance models but the mechanisms are not delineated.

Objective/Hypothesis: To determine the influences of PPARγ agonist and/or antagonist on AT_1 receptor mediated vascular responses and associated calcium channels in dietary model of insulin resistance.

Methods: Ang II-induced contractions were studied isometrically in thoracic aortic rings isolated from control [normal pellet diet (NPD) fed] and high fat diet (HFD) fed rats. To evaluate the involvement of L-type calcium channels in Ang II mediated contraction, cumulative concentration responses curves (CRC) to Ang II was constructed in the presence of various concentrations (0.01 nM -1μM) of nimodipine (dihydropyridine sensitive L-type Calcium channel blocker) and the -log IC_{50} of nimodipine was estimated. Receptor radioligand binding was carried out to study the characteristics (B_{max} and K_d values) of Ang II receptors and L-type calcium channels by [^{3}H]-Ang II and [^{3}H]-PN-200110, respectively. Radioactive calcium-45 ($^{45}Ca^{2+}$) influx studies were performed in vascular smooth muscle cells (VSMCs) isolated from insulin resistance rats

Results: The rats fed with HFD for four weeks exhibited the conglomeration of characteristic features of insulin resistance syndrome, such as obesity, hyperinsulinemia, mild hyperglycemia, hypertriglyceridemia, hypercholesterolemia, glucose intolerance and hypertension. Maximal contractile response (E_{max}) and $^{45}Ca^{2+}$ influx to Ang II were increased in HFD fed rats as compared to control rats. In addition, B_{max} values and affinity of Ang II receptors and L-type calcium channels were increased, respectively. Nimodipine dose-dependently blocked the Ang II induced contractions in a noncompetitive manner and its -log IC_{50} was significantly lower in aortic rings from HFD fed rats (8.87 ± 0.17) compared ($P<0.05$) to control (9.78 ± 0.18) rats. Pioglitazone treatment for 7 days restored -log IC_{50} values ($p<0.05$) nimodipine and $^{45}Ca^{2+}$ influx comparable to that of control and GW9662 (PPARγ antagonist) prevented the pioglitazone effect.

Conclusions: PPARγ agonist attenuates the development of hypertension and improves the vascular dysfunction of Ang II by altering the L-type calcium channel functions. Thus, PPARγ agonists may be useful in the prevention of hypertension particularly when it is associated with insulin resistance or diabetes mellitus.

PS-8: Role of Cannabis in Treating Cardiometabolic Disease

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Alard College of Pharmacy, Pune (57), Maharashtra (India).

Obesity, particularly visceral adiposity, and its related metabolic and cardiovascular disorders, is a worldwide pandemic. The biological properties of one of the most widespread illicit drugs of abuse, marijuana, have been recruited for obesity management. By uncovering the cellular interactions of the cannabinoid Δ^9-tetrahydrocannabinol (Δ^9-THC)—active component of marijuana—new molecular pathways for treating cardiometabolic disease have been identified. Modulation of the endocannabinoid system holds great therapeutic promise for the treatment of obesity, dyslipidemia, insulin resistance and atherosclerosis. Two G-protein-coupled cannabinoid receptors that bind Δ^9-THC with equal affinity have been identified: CB_1 and CB_2. The CB_1 receptor, believed to mediate the psychotropic effects of cannabis and participate in the modulation of food intake and adipogenesis.CB_2 receptors

were expressed in both human and mouse atherosclerotic lesions. Blockade of the CB_1 receptor appears to offer great promise in cardio metabolic risk reduction. Patients with a BMI of at least 30 kg/m^2,with dyslipidemia, and hypertension, received double-blind treatment with rimonabant—a selective CB_1 receptor blocker daily, 20 mg rimonabant, with a hypocaloric diet daily produced a weight-independent effect on lipid parameters and several other cardiovascular risk factors. To explain the observed weight-independent effect on lipid and glycemic variables, rimonabant-induced expression of adiponectin, a cytokine that has a role in the regulation of hyperglycemia, hyperinsulinemia and fatty acid oxidation and is reduced in obese individuals could be responsible. Waist-to-hip ratio is used recently as a marker of abdominal obesity in the INTERHEART study. Novel information from the endocannabinoid system biology continually arises, and this will surely lead to a better understanding of pathways, signaling, and targets for therapeutics.

PS-9: Comparative Hypolipidemic Study of Methanolic and Aqueous Extracts of *Phyllanthus reticulatus* Poir. using Intrinsic and Extrinsic Hyperlipidemia

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The comparative inhibitory effect of the Methanolic extract and aqueous extracts of *Phyllanthus reticulatus* Poir. ((Euphrobiaceae) were tested in hyperlipidemic rats using three animal models induced using poloxamer-407 and triton WR-1339 as intrinsic inducers and high fat diet as extrinsic inducer. It was found that after administration of both Methanolic extract and aqueous extracts the serum lipid profile, i.e. triglycerides, total cholesterol, LDL-cholesterol lowered significantly from the control while significant increase in cardioprotective lipid i.e. HDL-cholesterol and atherogenic index was observed. But after comparing the results of both the extracts it was concluded that Methanolic extract shows better results compared to aqueous extract. Moreover, these effects of Methanolic extract were comparable to atorvastatin, which was used as a positive control. Therefore, it was concluded that the *Phyllanthus reticulatus* have definite cardioprotective potentiality.

PS-10: Evaluation of Toxicological Effects of Torcetrapib in Diabetic Animal Model

Chitrang Trivedi, Lalabhai Patel, Jigarkumar Patel, Suresh Giri and Mukul R. Jain
Zydus Research Centre, Ahmedabad, Gujarat (India).

Torcetrapib is reported to cause marked increase in HDLc in humans. Recently, Pfizer has discontinued the development of torcetrapib due to increase in mortality in phase III trial. Torcetrapib was reported to cause an increase in blood pressure in some patients. However, no other major adverse reaction was reported. Since the trial consisted of aged diabetic patients with dyslipidemia, it will be interesting to investigate the toxicological effect of torcetrapib in an animal model of diabetes. 18-22 weeks old male db/db mice were treated with torcetrapib 30 mg and 100 mg/kg p.o. for 14 days. At the end of this period, all the animals were sacrificed. Plasma was collected for blood cell counting and hemoglobin. Various biochemical parameters such as ALT, AST, ALP, bilirubin, creatinine, urea, albumin, total proteins, glucose, triglycerides, total cholesterol, LDLc, HDLc were also estimated. As expected, torcetrapib treatment for 14 days did not cause any significant change in HDL cholesterol. Moreover, no statistically significant change in This was also accompanied by a marked reduction in LDL cholesterol. However, torcetrapib treatment did not produce any notable effect on serum triglycerides, total cholesterol and glucose. Furthermore, no significant changes were noted in serum ALT, AST, ALP, bilirubin suggesting that torcetrapib did not cause any hepatic damage at these dose levels. Similarly, there was no apparent renal toxicity as indicated by no change in serum creatinine and urea. On the other hand, torcetrapib (100 mg/kg) caused a marked decrease in serum albumin and there was a dose dependent decrease in total proteins. Since db/db mice develop albuminuria, a further reduction in serum albumin in these mice suggests an exacerbation of this phenotype by torcetrapib. Interestingly in torcetrapib treated animals, a trend towards decrease in RBCs, haemoglobin and haematocrit was noted although results are not statistically significant.

PS-11: The Reconstruction of Metabolism from Gene Expression Data

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Encyclopedia Genomica, A-4020, Linz (Austria).

Genome-wide transcript profiling allows systematic and unbiased characterization of variation in genes and RNA. Genetic variation, however, affects gene products that carry no defects, as biological systems are orchestrated by vast networks of interacting molecules that include metabolites. Deriving metabolic networks from transcriptomes may be useful to identify roles of metabolic interactions in disease. This has been enabled by Encyclopedia Genomica, see http://www.egenomica.com/background.php#reverse

We have connected about 6000 biochemical transformations to genes, expression data, proteins, enzymes & EC numbers, reactions, metabolites, prosthetic groups, co-factors, and compartments, one such pathway ID being

shown in http://www.egenomica.com/content/cyto.html. For healthy heart a demo is depicted in http://www.egenomica.com/Sources.html. The metabolic reconstructions made from transcriptomes can now address where and how reactions, enzymes, metabolites, co-factors and thus a pathway are affected. Pathway IDs can be connected to obtain metabolic overviews, as shown in http://www.egenomica.com/content/processes.html

Metabolic reconstructions made from gene expression data are presented in high resolution format, showing individual biochemical reactions. This high-resolution approach enables integration of additional data, for example protein-protein interaction or cDNA data, and it allows for association of biochemical reactions with patients, tissues, or pathologies to obtain connections between diseases associated with the same pathway and condition-specific outcomes useful as biomarkers. Indeed, most available cardiovascular biomarkers address known pathways, and measure what is already known or being measured. Genome-wide transcript profiling followed by metabolic reconstruction allows unbiased characterization of markers.

PS-12: Insulin Induced Changes in Multiple Histone Modification and Down Regulation of Gene Expression under Hyperglycemic Condition in L6 Skeletal Muscle Myoblast

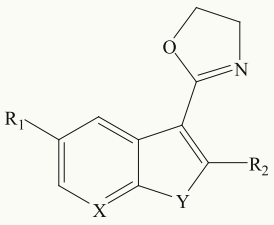
Dhiraj G. Kabra, Jeena Gupta and Kulbhushan Tikoo
Laboratory of Chromatin Biology Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research, Mohali (India).

Chromatin remodelling events especially the histone modifications are proposed to form the mainstay for most of the biological processes. However, role of histone modifications are still unknown in the progression of diabetes. Hyperglycemia plays a major role in diabetes and its associated complications. Present study was undertaken to check the effect of high glucose on alterations in post-translational modifications of histone H3. Our results shows insulin induces dephosphorylation and deacetylation of histone H3 in L6 skeletal muscle myoblasts under hyperglycemic condition. In addition, insulin treatment also leads to decrease in Lysine 4 methylation of histone H3 (H3-K4) with concurrent increase in Lysine 9 methylation (H3-K9). To see the effect of changes in these multiple histone modifications on gene expression, we performed gene expression profiling studies and have demonstrated global down regulation of gene expression of genes involved in different biological processes by insulin under high glucose condition. Our result provides first evidence that insulin under hyperglycaemic condition alters multiple histone modifications. Thus, these changes in epigenetic modifications can provide new insights in pathogenesis of diabetes.

PS-13: Synthesis and Glucose Dependent Insulinotropic Activity of Substituted-Hetero-Aryl Oxazolyl Derivatives

Dipam N. Patel, Pradip A. Jadav, Brijesh A Darji, Yernaidu Siriki, Mukul R. Jain, and Rajesh H. Bahekar
Zydus Research Centre, Ahmedabad, Gujarat (India).

Three series of hetero-aryl oxazolyl derivatives, mainly 3-(4,5-dihydro-oxazol-2-yl)-2,5-disubstituted-1*H*-indole (**2a-j**), 3-(4,5-dihydro-oxazol-2-yl)-2,5-disusbtituted-1*H*-pyrrolo[2,3-*b*]pyridine (**3a-j**) and 2-(2,5-disubstituted-benzo[*b*]thiophen-3-yl)-4,5-dihydro-oxazole (**4a-j**) were prepared as a new class of insulinotropic agents. All the test compounds **2a-j, 3a-j** and **4a-j** were screened in vitro, in RIN5F cell-based assay for glucose-dependent insulinotropic activity. A significant glucose and concentration-dependent insulin secretion effect was observed with compounds **2a-j** and **3a-j**, while compounds **4a-j** were found to be inactive. The insulinotropic activity of compounds **2f** and **3f** were found to be identical to that of BL 11282, while compounds **2d** and **3d** showed more insulin secretion than BL 11282. In I_1 and I_2-adrenoceptor binding assays, compounds **2d** and **3d** showed non-specificity towards I_1 and I_2 sites, indicating that these new class of compounds exhibit only glucose-dependent insulin secretion, without acting on I_1 and I_2 sites



X=CH, N; Y=NH, S

PS-14: Identification of Agonist for Fatty Acid Receptor GPR40 for Treatment of Type II Diabetes

Geetha Vani Rayasam, Vamshi Krishna Tulasi, Sindhuja Sundaram, Winny Singh, Rajiv Kant, Joseph Alex Davis, Kulvinder Singh Saini, Abhijit Ray and Pradip Kumar Bhatnagar
R&D III, Ranbaxy Research Labs, Plot No.20, Sector 18, Gurgaon, Haryana (India).

New family of fatty acid receptors (GPR40, 41, 43, GPR120, GPR119) have recently been identified which function in regulation of glucose metabolism. Of these GPR40 which is primarily expressed in βcells of pancreas functions

by stimulating glucose dependent insulin secretion and is a promising therapeutic target for type 2 diabetes. We have developed and validated an in house calcium mobilization assay using GPR40 over expression cell line. Several thousands of compounds have been screened and two agonists with EC50 <10uM have been identified and characterized. Further, these agonists have been demonstrated to stimulate insulin secretion in rat insulinoma cell line and efforts are on to further optimize the chemotypes.

PS-15: Evaluation of Anti-Obesity Activity of Duloxetine in Comparison with Sibutramine along with Its Anti-Depressant Activity - an Experimental Study in Obese Rats

H.P. Chudasama and P.A. Bhatt
L.M. College of Pharmacy, Gujarat University, Ahmedabad (India).

5-HT and NA are important neurotransmitters that control weight gain and are involved in the pathophysiology of obesity and depression. Sibutramine, an established anti-obesity agent and duloxetine, an anti-depressant agent are serotonin noradrenaline reuptake inhibitors. Objective of the present study was to compare the anti-obesity effect of duloxetine with sibutramine along with its effect on BP and depression in obese rats. Secondary objective was to determine if a relationship exists between obesity and depression. Obesity was induced by high fat diet (HFD) in healthy male Sprague-Dawley rats. After 5 weeks of feeding HFD, animals were over weight and had high food intake as compared to normal animals. These high fat fed obese animals were treated with duloxetine (30 mg/kg, p.o.) and sibutramine (5 mg/kg, p.o.) for 4 weeks. Our results depict that duloxetine was as effective as sibutramine in reducing food intake, body weight, relative adiposity and increasing rectal temperature with an added advantage of decreasing BP which sibutramine failed to do so. Duloxetine and sibutramine, both significantly improved serum glucose and lipid profile. Also duloxetine increased HDL-cholesterol which sibutramine failed to do so. Serum insulin was decreased by sibutramine where as duloxetine failed to do so. Besides reduction in body weight, duloxetine improved depressive state as evaluated by despair swimming test, tail suspension test and open field test, speculating its use as an anti-obesity agent in obese-depressive animals. Since obese control animals reflected a state of depression, a relationship exists between obesity and depression.

PS-16: To Study the Effects of Danazol on Cardiac Functions, Liver Functions Tests, Lipid Profile in Patients with Aplastic Anemia

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Department of Internal Medicine, Department of Cardiology, PGIMER, Chandigarh (India).

Background: Aplastic anemia is a rare and potentially life threatening disease. In India many patients can not afford bone marrow transplant or anti thymocyte globulin and are put on Danazol which is an anabolic steroid. The present study evaluated the effects of Danazol on lipid profile, liver functions and cardiac functions in a single set of patients with aplastic anemia.

Methods: It was a prospective clinical study. 36 patients with aplastic anemia on Danazol therapy (300mg/d) were enrolled at start and followed up for 6 months. There baseline blood tests including liver function tests, hemogram, lipid profile, and echocardiography using techniques of tissue Doppler were done and compared with the values at end of study at 6 months.

Results: Data from 36 patients were compared by wilcoxon signed rank test. Patients on Danazol were found to have significant higher platelets (p=0.006), urea (p=<0.001), creatinine (p=<0.001), alanine aminotransferase (p=0.004), aspartate aminotransferase (p=<0.001), LDL- cholesterol (p=0.002), and decreased HDL-cholesterol (p=<0.001). Echocardiographic data showed increased wall thicknesses of left ventricle at septal and posterior wall (p=<0.001 and 0.017 respectively), increased LV mass (p=<0.001), ejection fraction (p=<0.001), increased LA volumes (p=<0.001). Tissue Doppler and pulse wave Doppler at mitral inflow showed decrease in peak E-wave velocity (p=<0.001 and 0.035 respectively)

Conclusions: Danazol use was associated with deranged lipid profile, deranged LFT^{s} and cardiac hypertrophy with derangement in some of diastolic function parameters and improved systolic function due to cardiac hypertrophy.

PS-17: Cardioprotective Effect of Preconditioning with Exogenous Carbonmonoxide Releaser CORM-2 Against ischemia/reperfusion Injury in Isolated Rat Heart

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* Zydus Research Centre, Ahmedabad, Gujarat (India).
# L.M. College of Pharmacy, Ahmedabad, Gujarat (India).

Carbon monoxide (CO) has been known as toxic gas since decades. In the last few years' research on CO in the regulation of various physiological processes has been emerged. CO carriers, known as Carbon Monoxide Releasing Molecules (CORMs), have been developed as a pharmacological tool to simulate the effects of endogenously

generated CO via heme catalysis pathway. We studied the effect of CORM-2 on incidence of ischemia/reperfusion-induced myocardial injury in isolated rat hearts. Hearts were preconditioned with different doses of CORM-2 before the induction of 30 minutes of global ischemia followed by 120 minutes of reperfusion. Coronary effluent was analyzed for LDH and CPK release to assess the degree of cardiac injury. Coronary flow (CF) was measured by collection of coronary effluent in to measuring cylinder. Heart rate was calculated by means of two silver wire attached to the aorta and apex of the heart using ECG machine. Cardiodynamic parameters were measured with a fluid-filled latex balloon inserted in to the left ventricle using pressure transducer. Myocardial infarct size was estimated by TTC staining. Preconditioning with 30µM/L and 50µM/L of CORM-2 for 10 minutes markedly reduced LDH and CPK release and decreased myocardial infarct size. There was also improvement in the CF rate and heart rate. CORM-2 also prevented increase in LVEDP and decrease in LVDP, dp/dt_{max} and dp/dt_{min}. Cardioprotection was abolished on further increase in the concentration of CORM-2 to 100 µM/L. In conclusion, CORM-2 exerts cardioprotection against ischemia/reperfusion injury and cardioprotection is highly restricted to concentration used.

PS-18: Attenuation of Vascular Reactivity and Insulin Resistance by *Clerodendron glandulosum. coleb* in Fructose Fed Hypertensive Rats.

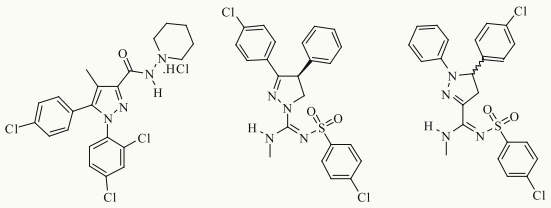
Jadeja R. N.*, Patel V. B.#, Thounaojam M.C.*, Ansarullah*, Devkar R.V.* and Ramachandran A.V.*
*Department of Zoology, Faculty of Science, #Department of Pharmacy, Faculty of Technology & Engineering, The M.S. University of Baroda, Vadodara-390002, Gujarat (India).

Syndrome X and insulin resistance syndrome induces a cluster of common pathologies like obesity, insulin resistance, dyslipidemia and hypertension that results mainly due to global changes in dietary habits and lifestyle. This study investigates effects of *Clerodendron glandulosum.coleb* (CG) extract on plasma lipid profile, insulin sensitivity and vascular reactivity in fructose fed hypersensitive rats. Plasma TL, TC, TG, FFA, VLDL and LDL was decreased with CG whereas HDL was significantly increased. CG extract treated rats showed increased insulin sensitivity as indicated by low AUC values in oral glucose tolerance test and intraperitoneal insulin tolerance test. Fasting levels of plasma glucose and plasma insulin titers showed decrement in CG treated groups. Hyposensitive activity of CG extract is indicated by decrease in systolic and diastolic blood pressure. Vascular reactivity showed an improved response in CG treated groups. Hence it can be concluded from present study that CG extract has therapeutic properties with multi faceted mode of action to control experimentally induced hypertension insulin resistance and dyslipidemia.

PS-19: Design and Synthesis of (±)-5-(4-Chlorophenyl)-N′-(4-Chlorophenylsulfonyl)-N-Methyl-1-Phenyl-4,5-Dihydro-1H-Pyrazole-3-Carboximidamide a Potent CB1 Receptor Antagonist as an Anti-Obesity Agent

Jayendra Z. Patel, Rina Soni, Amit Joharapurkar, Bhupendra Mishra, Nisha Sadhwani, Prasenjit Mitra, Mukul R. Jain, Pankaj R. Patel and Brijesh Kumar Srivastava
Zydus Research Centre, Ahmedabad, Gujarat (India).

Design, synthesis and pharmacological evaluation of (±)-5-(4-chlorophenyl)-N′-(4- chlorophenylsulfonyl)-N-methyl-1-phenyl-4,5-dihydro-1H-pyrazole-3-carboximidamide is reported. The primary pharmacological studies in rodent models gave interesting findings for the compound 4 as an anti-obesity agents, which is mediated through CB1 receptor.



SR 141716 A (Rimonabant) | 2 (SLV - 319) | 3 (Racemic) 4 (-) - isomer 5 (+) - isomer

PS-20: High Resolution Micro-CT in Biological and Biomedical Applications

Jeroen Hostens, Phil L. Salmon and SkyScan N.V.
Kartuizersweg 3B, 2550 Kontich (Belgium).

Micro computed tomography or “micro-CT” is x-ray imaging in 3D, but on a small scale with massively increased resolution. Over the past decade the improvement in x-ray micro-CT systems has led to an exponentional increase in biological and biomedical research applications.

Both ex-vivo as well as in-vivo scanners for imaging of small laboratory animals have been developed. We will

give an overview of some biological and biomedical applications using the micro-CT in the field of bone-, cancer-, COPD-, and cardiovascular-research. In addition the possibility to use the micro-CT as part of a multi-modality imaging system will be described.

PS-21: RoMitochip, a Rodent Mitochondrial Gene Chip to Study Functional Genomics of Cardiac Myocyte Mitochondria

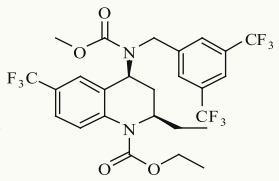
Jian B.*, Wang D.#, Chaudry I.* and Raju R.*
*Departments of Surgery and Microbiology, #Bioinformatics, Comprehensive Cancer Center, University of Alabama at Birmingham, AL 35294 (USA).

Mitochondria play an important role in cardiomyocyte energy metabolism, biogenesis and regulation of apoptosis. The alteration of cardiac myocyte mitochondrial function in cardiac physiology is not fully known, although mitochondrial dysfunction has been implicated in various cardiac pathologies. An integrated systems biological approach is being developed to understand the role of cardiac myocyte mitochondria in heart diseases. To complement an integrated approach, we developed a rodent mitochondrial gene chip, RoMitoChip using Affymetrix platform. The small number of genes on the mitochondrial genome is not represented in the Affymetrix rat or mouse GeneChip. The RoMITOchip includes genes from the nuclear genome that contribute to the mitochondrial structure and function as well as the genes on the mitochondrial DNA, together called as mitochondrial genes. We have incorporated mitochondrial genes of rat and mouse into the single gene chip; 37 probe sets representing mouse mtDNA genes, 45 probe sets representing rat mtDNA genes, 1041 probe sets representing mitochondrial genes from the nuclear DNA of the mouse and 371 from the rat. The RoMitoChip is being validated using a hypoxia model. Cardiomyocytes from C57BL/6 mice were subjected to 1% (7mmHg) or 2% (12 mmHg) hypoxia, RNA isolated and gene expression profile measured and compared to that in normoxia. The gene expression profile obtained using the RoMitoChip is further compared using the Affymetrix whole genome chips. The chip design and validation results will be presented. Mitohcondrial gene expression profile of $SOD2^{+/-}$ and $^{+/+}$ mice will also be presented. RoMitoChip will be a valuable tool in understanding mitochondrial structure and function in cardiovascular diseases.

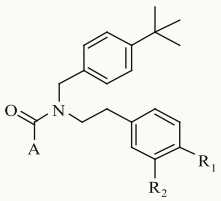
PS-22: N-(4-*Tert*-butyl benzyl)-N-phenylethyl amine, A Novel Class of CETP Inhibitors

Jigar Desai, Anil Argade, Kiran Shah, Sanjay Gite, Laxmikant Pavase, Pravin Thombare, Prasenjit Mitra, Mukul R. Jain and Pankaj R. Patel
Zydus Research Centre, Ahmedabad, Gujarat (India).

The anti-atherogenic role of high density lipoprotein (HDLc) in reverse cholesterol transport is now well established and elevation of HDLc has become a therapeutic target. Cholesteryl Ester transfer protein (CETP), a 72 kDa plasma glycoprotein, plays a critical role in both CE and TG transfer among lipoprotein. Thus inhibition of CETP would be an interesting target for raising HDLc level, lower LDLc and provide potential therapeutic benefit for patient with CAD. On December 2006, Pfizer suspended a large phase III clinical trial due to increase rate of mortality (death) in patient. In phase III Illuminate trial a patients treated with torcetrapib showed increase (~5.4 mm Hg) in systolic blood pressure, a decrease in serum K and increase in serum Na, bicarbonate and aldosteron level. Various studies has been performed to show that these side effect associate with torcetrapib is compound specific not the target specific. Hence there is a need to develop new scaffold which shows nanomolar potency against CETP and nontoxic.



Torcetrapib
IC_{50}= 50 nM



ZY-Series

Our efforts towards synthesis of new scaffold leads to N-(4-*tert*-butyl benzyl)-N-phenethyl amine derivatives, which is equipotent and structurally different than torcetrapib. Synthetic methodology, *Invitro* potency and pharmacokinetics of some selected compounds will be presentated.

PS-23: Evaluation of Pharmacological and Toxicological Effects of Torcetrapib in Dyslipidemic Hamsters

Jigarkumar Patel, Lalabhai Patel, Chitrang Trivedi, Praful Patel, Suresh Giri and Mukul R. Jain
Zydus Research Centre, Ahmedabad, Gujarat (India).

Torcetrapib is reported to cause more than 100 % increase in HDLc in humans. However, there are no reports of torcetrapib effects in preclinical animal models. Therefore, present study was designed to investigate the pharmacological effects of torcetrapib (30 mg/kg & 100 mg/kg) in hamsters. In recent clinical trials torcetrapib treatment was associated with increased mortality. Many of the patients treated with torcetrapib in Phase III trials may be severely dyslipdemic. Therefore, it will be interesting to investigate the toxicological effects of torcetrapib

in an animal model of dyslipdemia. Thus, hamsters were fed on high fat-high cholesterol diet for 14 days. At the end of this period, animals were divided into three groups. Group one received vehicle treatment for 14 days. Group two and three were treated with torcetrapib 30 mg and 100 mg/kg p.o. for 14 days. At the end of this period, all the animals were sacrificed. Citrated blood was collected for blood cell counting and hemoglobin. Various biochemical parameters such as SGOT, SGPT, creatinine, urea, glucose, triglycerides, total cholesterol, LDLc, HDLc were also estimated. Torcetrapib treatment for 14 days caused a significant increase in HDL cholesterol. This was also accompanied by a marked reduction in LDL cholesterol. However, torcetrapib treatment did not produce any notable effect on serum triglycerides, total cholesterol and glucose. Furthermore, no significant changes were noted in serum SGOT, SGPT, alkaline phosphatase and bilirubin suggesting that torcetrapib did not cause any hepatic damage at these dose levels. Similarly, there was no apparent renal toxicity as indicated by no change in serum creatinine and urea. On the other hand, torcetrapib (100 mg/kg) caused a marked decrease in RBCs, haemoglobin, haematocrit and mean corpuscular volume suggesting a bone marrow suppression.

PS-24: Effect of rimonabant on expression of adipokines in *ob/ob* mice:

Jogeswar Mohapatra, Umar Malik, Manoranjan Sharma, Gaurav Pandya, Abhijit Chatterjee, Balaraman R. and Mukul R Jain
Zydus Research Centre, Ahmedabad, Gujarat (India).

It has been recently reported that blockade of CB1 receptors function, by specific antagonist or genetic manipulation, alleviates dyslipidemia, hyperglycemia, and insulin resistance in animal models of obesity and type 2 diabetes. In order to determine whether the CB-1 antagonist, rimonabant has a direct effect on adipokine expression in visceral adipose tissue of obese mice, we examined the expression of TNF alpha, visfatin, adiponectin, and resistin mRNA in visceral adipose tissue of ob/ob mice treated with rimonabant (3 and 30 mg/kg/day, p.o) for two weeks. Body weight, oral glucose tolerance test (OGTT) and biochemical estimations were also conducted at the end of the experiment. Rimonabant at 30mg/kg significantly inhibited weight gain ($P<0.05$), and improved glucose tolerance significantly ($P<0.05$) after oral glucose challange. Treatment with rimonabant was accompanied by downregulated tumor necrosis factor alpha (TNF alpha) and visfatin mRNA expression in adipose tissues, however adiponectin and resistin expressions were significantly up-regulated. Results indicate that the alterations of adiponectin, TNF alpha, and visfatin may contribute to the amelioration of insulin resistance caused by rimonabant.

PS-25: Peripheral Blockade of CB1 Receptors Reduces LDLc By Stimulation of Thyroid Hormone Activity

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During the last decade, an important body of evidence has emerged showing the positive role of endocannabinoid system in the regulation of appetite, eating behaviour and body weight. Following this rationale and significant preclinical findings, clinical trials on the effects of the CB1 antagonist SR141716A (Rimonabant) on obesity have demonstrated the utility of cannabinoid receptor blockade as a therapy for obesity associated with cardiovascular risk factors such as hypertriglyceridemia, hypercholesterolemia and diabetes. Although the drug met utter failure in clinic owing to risks associated with its central nervous system effects, elucidation of the mechanism of its peripheral effects useful in the control of type 2 diabetes mellitus and dyslipidemia is an area of therapeutic research interest.

The purpose of this work was to evaluate the mechanism of acute hypolipidemic effect of a CB1 receptor antagonist, Rimonabant, in obese and hyperlipidemic Zucker fa/fa rats. single intraperitoneal dose of Rimonabant in Zucker fa/fa rats caused significant reduction in LDL and triglycerides. These results were in contrast to the absence of such effect when Rimonabant was administered via intracerebroventricular route. Both the peripheral and central treatments showed similar appetite suppressant action. A significant increase in serum T3 and T4 levels was also observed in these animals, while such effect could not be seen with central administration of Rimonabant. The combination of T3 with Rimonabant at sub-therapeutic doses showed an additive effect on LDL reduction.

These data indicate that acute peripheral blockade of CB1 receptors by Rimonabant causes significant LDL reduction. The mechanism of such effect could be attributed to the peripheral stimulation of thyroid hormone release.

PS-26: Sub-Therapeutic Dose of Thiazolidinediones Reduce Expression of Inflammatory Cytokines in White Adipose of Zucker Fatty Rats

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Peroxisome proliferator activated receptor-gamma (PPAR-γ) agonists such as pioglitazone & rosiglitazone are

known to enhance insulin sensitivity by influencing expression of various adipokines. Some of these adipokines are also known to be involved in inflammatory processes. In order to investigate if the anti-inflammatory and antihyperglycemic effects of thiazolidinediones (TZDs) are distinct and are exerted at different dose levels in Zucker fa/fa rats, animals were dosed with pioglitazone(3 and 30mg/kg/day) and rosiglitazone (0.3 and 10 mg/kg/day) for 28 days and expression of inflammatory markers (COX-2, TNF-α, IL-6, MCP-1, IL-11, IL-1beta, MMP-3, MMP-9) in white adipose tissue (WAT) were monitored. At similar dose levels, metabolic parameters (serum glucose, triglyceride, total cholesterol) were also measured. Repeated dose treatment of Zucker fa/fa rats with sub-therapeutic doses of pioglitazone (3 mg/kg) and rosiglitazone (0.3 mg/kg) although did not affect metabolic parameters such as serum TG, glucose levels, OGTT or WAT adiponectin expression, there was significant suppression in the levels of TNF alpha (75.9%, 54.3%), IL-6 (64.5%, 60.2%), MCP-1 (39.3%, 32.3%) and COX-2 (42.2%, 60.2%) respectively when compared with the control fa/fa rats. In contrast to the above findings, treatment with a therapeutic dose of pioglitazone (30mg/kg) and rosiglitazone (10 mg/kg) improved insulin sensitivity, reduced serum glucose, triglyceride levels and increased adiponectin expression in WAT along with suppression of inflammatory markers.

Our results indicate that sub-therapeutic dose of TZD class of PPARγ activators exhibit potent anti-inflammatory effects whereas metabolic effects are only seen at therapeutic doses.

PS-27: Evaluation of Adverse Effect of Arsenic Trioxide, a Potent Anti-APL Drug on Myocardium.

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Arsenic trioxide (ATO) is a new promising regimen for patient with a relapse of acute promyelocytic leukemia (APL), but causes frequently life threatening arrhythmias. This study aims to investigate various cellular and molecular mechanisms of cardiac adverse effects employing various techniques. The result of the present study using electrophysiological method showed the dose dependent effect of ATO (0.2, 0.4, 0.8, 1.6, 3.2, 6.4 μM) on electrically driven cardiac action potential from papillary muscle of guinea pig. It caused significant prolongation of action potential duration at various levels of repolarization, conduction delay and increased triangulation, which is a novel marker for proarrhythmic potential of a compound. To evaluate cytotoxic effect of ATO on cardiac myocytes, primary culture of myocytes was treated with different doses (30, 60 and 90μM) of ATO for various periods (24, 48 and 72 hours). Cardiac toxicity was evaluated by monitoring cell viability, mitochondrial and deoxyribonucleic acid (DNA) integrity, reactive oxygen species (ROS) generation, calcium overload and apoptosis. Studies on cardiac myocytes showed that ATO exposure caused alteration in mitochondrial integrity, generation of ROS, calcium overload, and apoptosis in cardiac cells in dose and duration dependent manner. In *in vivo* experiments, administration of ATO (10mg/kg) for 10 days caused myocardial disorganization, interstitial edema and infiltration of inflammatory cells in heart. Besides, ATO also caused significant increase in serum creatine kinase isoenzyme, lactate dehydrogenase, glutathione peroxidase and reduced glutathione. We conclude that ATO causes significant adverse cardiac effect and suggest that cardiac function should be monitored during treatment with ATO.

PS-28: Antihypertensive and Anti-Ischemic Effects of the Combination of the Aliskiren and Enalapril in Rat

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Aliskiren is a novel antihypertensive agent that acts via inhibition of plasma renin activity, whereas Enalapril is an inhibitor of angiotensin converting enzyme (ACE). We have evaluated the combined effect of renin & ACE inhibition on Hypertension & ischemia reperfusion injury. Antihypertensive effect was evaluated using acute (bilateral renal artery ligation and reperfusion) and chronic (2K1C Goldblatt) rat model. Anti-ischemic activity was evaluated using anesthetized rat model of LAD ligation and reperfusion induced injury. Rats were divided in 4 groups consisting of 3 mg/kg Aliskiren, 0.3 mg/kg Enalapril, combination of Aliskiren and Enalapril and vehicle. In acute model, Aliskiren & enalapril caused 66, 63 % restoration of elevated MBP that was significantly better than vehicle treated control. The combination of Aliskiren & Enalapril caused 100 % restoration of elevated MBP. In chronic model of hypertension, 5 week of clipping caused 35-40 mmHg rise in SBP in 2K1C rats in comparison with sham control. In these rats, SBP was lowered by 19.2 mmHg with Aliskiren (3mg/kg, ip), 19.6 mmHg with Enalapril (0.3 mg/kg, ip) whereas vehicle control showed 3 mmHg reduction. The combination of Aliskiren (3mg/kg, ip) and enalapril (0.3 mg/kg, ip) lowered SBP by 34.4 mmHg. In LAD ligation model, 1-week combination treatment showed smaller infarct area (16.2 ± 1.7 vs. 27.4 ± 2.1 of vehicle control). Combination of Aliskiren with Enalapril provided synergistic antihypertensive effect in the animal models of hypertension and also showed reduction in the infarct size after one week of chronic treatment.

PS-29: Energetic Changes in Heart Cells of White Rats in Conditions Stress Induced by Violated Diurnal Cycle

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Tbilisi Iv. Javakhishvili State University, Tbilisi (Georgia).

We have studied dynamic of activity changes of some enzyme systems, taking place in cell energetic metabolism under 30-day long stress induced by isolation and violated diurnal cycle. It was seen that there is an obvious change in the functionality of systems, such as creatine/creatinphosphokinase/phosphocreatine. It was observed that creatinephosphokinase responds to stressing conditions induced by isolation and violation of diurnal cycle; particularly with declining activity of two enzyme isoforms (CK-BB and μMtCK). Reduction in enzyme activity is especially evident after 30 days of stress. Similar result was shown in creatine researches.

We also studied Krebs cycle properties in white rat heart cells, focusing on trend of activity changes in a Krebs cycle enzyme - succinatedehydrogenase under 30 days of stress induced by isolation and violation of diurnal cycle. It turned out that the enzyme activity started decreasing after 10 days of stress.

Along with the enzyme activity we studied quantitative changes in signal molecules, such as nitric oxide (NO) and Ras proteins. It was shown that along with declining enzyme activity in white rat kardiomyocytes, NO as a signal molecule also increases. This proves that the latter is related to he structural changes in signal molecules such as H-Ras proteins.

Similar studies were related to certain white rat brain enzymes. In accordance with experimental data we supposed heart cells to be most sensitive towards stress factors that can cause various heart disorders.

PS-30: Inhibition of VLDL Secretion Improves the Hyperlipidemia and Insulin Resistance in Genetically Obese Zucker fa/fa Rats

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The secretion of VLDL by liver and chylomicrons by intestine is mediated by microsomal triglyceride transfer proteins. These secreted triglyceride (TG)-rich molecules are taken up by various peripheral tissues. The decrease in secretion of VLDL and chylomicrons has profound effect on hyperlipidemia and obesity, which has been utilized in the design and profiling of small molecule MTP inhibitors. Though the development of these antagonists have concerns like steatohepatosis, additional studies are necessary for elucidation of mechanism of the safety and efficacy of these agents.

The purpose of current work is to evaluate the effect of decreased secretion of TG rich molecules on various metabolic parameters in Zucker fatty rats by repeated dose treatment with Compound-9 (BMS-201038) for 14 days. Zucker fatty rats are hyperlipidemic, insulin resistant and show all the symptoms of diabetic dyslipidemia, and thus could be useful for assaying the effect of MTP inhibitors on normalization of deranged lipid metabolism in insulin resistance.

The treatment doses were selected based on the acute efficacy seen with Triton WR 1339-induced elevation in serum TG levels in Zucker fa/fa rats. The repeated dose administration resulted in significant decrease in plasma TG and LDL cholesterol levels. The body weight was significantly reduced without any change in food intake, and there is decrease in circulating free fatty acid levels. The decrease in body weight was mainly attributed to reduction in subcutaneous and epididymal adipose depots. A mild increase in liver triglycerides and hepatic enzyme levels was observed, though it was not dose-dependent.

Interestingly, there was significant improvement in insulin resistance owing to reduced lipogenesis and greater insulin sensitivity in Zucker fatty rats after inhibition of MTP mediated secretion of TG rich lipoproteins. We conclude that small molecule inhibitor of microsomal triglyceride transfer protein improves the symptoms of diabetic dyslipidemia. The improved insulin sensitivity could be attributed to the reduced uptake of lipids and reduced lipogenesis, which was confirmed by decreased adiposity.

PS-31:Discovery of Selective Hydroxamic Acid Inhibitors of Tumor Necrosis Alfa Converting Enzyme

Kiran Shah, Jigar Desai, Bhavesh Dave, Anil Argade, Sanjay Gite, Archana Gite, Laxmikant Pavase, Mukesh Chunara, Gaurang Trivedi, Bhaumin Patel, Jogeshwar Mahapatra, Mukul R. Jain and Pravin Thombare
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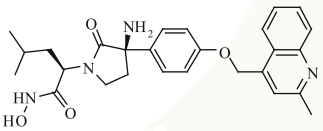
Tumor Necrosis Factor-α (TNF-α) converting enzyme (TACE) is an 85kD a membrane bound metalloprotease disintegrin that processes the membrane bound 26 kD TNF-α to a biologically active soluble form of 17 kD TNF-α via proteolysis of Ala 76-Val 77 peptide bond. More than 90% of soluble TNF-α is catalytically produced by TACE indicating that TACE may be one of the attractive targets in the anti-TNF-α therapy.

The Hydroxamic acid of cyclic urea derivatives (I) were synthesized starting from corresponding amine and isocyanate in 5 different synthetic steps. Hydroxamic acid based inhibitors showed better activity profile studied from SAR. Synthesized compounds showed good in vitro TNF-α inhibition.



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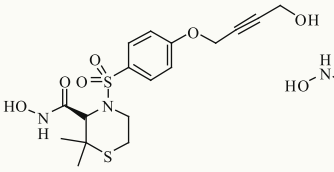

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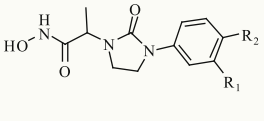

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PS-32: Design And Synthesis of Squaric Acid Derivatives as Thyroid Hormone Receptor β (TR β) Selective Ligands

Krunal Soni, Preeti Raval, Saurin Raval, Debdutta Bandyopadhyay, Amit Joharapurkar, Digambar Yevale, Digvijay Jogiya, Jaymin Barot, Krishna Jadeja and Mukul R. Jain
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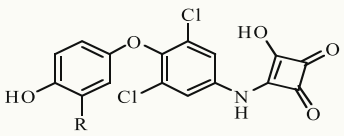
Design and synthesis of a few novel 3-Hydroxy-cyclobut-3-ene-1,2-dione derivatives are reported and their in vitro thyroid hormone receptor selectivity TRα/TRβ has been evaluated in a thyroid luciferase receptor assay. 3-[3,5-Dichloro-4-(4-hydroxy-3-isopropyl-phenoxy)-phenylamino]-4-hydroxy-cyclobut-3-ene-1,2-dione has shown significant thyroid hormone receptor β selectivity.



PS-33: HDL-C Elevation by Peroxisome Proliferator-Activated Receptor Delta Agonist is Dependent on Cholesteryl Ester Transfer Protein Pathway

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PPARα and PPARγ agonists have shown therapeutic benefits in the treatment of diabetes and dyslipidemia. PPARγ has been identified as a key regulator for insulin sensitivity. PPARδ agonists have been reported to induce the elevation of plasma HDL-C levels in obese mice, rhesus monkeys as well as humans, indicating their potentials as a new class of HDL-C raising agent. In addition, anti-atherosclerotic effects of PPAR agonists were reported in LDLR-KO and ApoE-KO mice. In these mice, however, the lipoprotein profiles are greatly different from those in humans in terms of the deficiency in CETP. It has been reported that human CETP transgenic (hCETP-Tg) mice have similar lipoprotein profiles with humans. In this study, we used hCETP-Tg mice and wild type (C57) mice for evaluation of HDL-C elevation by using PPARα agonist Fenofibrate) PPARγ agonist (Pioglitazone) and one of the most potent and selective PPARδ agonist GW501516. For evaluation of plasma HDL-C levels, the hCETP-Tg mice and its wild type (C57) mice were orally treated with all three agonist at their sub maximal pharmacological doses for 15 days. Treatment with GW501516 resulted in significant elevation of plasma HDL-C levels. The HDL-C elevating effect of GW501516 was better than one seen with fenofibrate or pioglitazone (57 % vs. 17 % and 16% respectively). A different trend was seen for serum triglyceride lowering effect of these three different PPAR Agonists. Fenofibrate & pioglitazone caused greater decrease in serum TG than GW501516 (57 % and 56 % vs 32 % respectively). The triglyceride lowering activity of PPAR agonists was markedly blunted in wild type (C57) mice as compared to CETP-Tg mice. Whereas, the HDL-elevating effect was seen only in CETP-Tg mice and not in wild-type C57 mice. Our study confirms that Peroxisome Proliferator-Activated Receptor Delta Agonist causes potent HDL-C elevation amongst three PPAR agonists and is mediated through mechanisms related to cholesteryl ester transfer protein.

PS-34: PPAR-γ-Inducing Property of Telmisartan in Cardiometabolic Research.

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Alard College of Pharmacy, Pune (57), Maharashtra (India).

The metabolic syndrome is strongly associated with insulin resistance and consists of a constellation of factors such as hypertension and hyperlipidemia that raise the risk for cardiovascular diseases and diabetes mellitus. Conversely, hypertensive patients are more likely than normotensive persons to develop diabetes. In addition, up to 75% of

CVD in diabetic patients can be attributed to hypertension. Therefore, the primary goals of treating hypertensive patients with insulin resistance are prevention of type 2 diabetes and cardiovascular events. Several clinical trials suggest that the renin-angiotensin system (RAS) plays a pivotal role in the pathogenesis of insulin resistance and CVD in diabetes. Interruption of the RAS with angiotensin-coverting enzyme inhibitors (ACEIs) or angiotensin II type 1 receptor blockers (ARBs) has been shown to prevent the onset of diabetes in hypertensive patients and to reduce cardiovascular and renal disease progression in diabetic patients with hypertension. However, whether we should recommend ARBs for insulin resistant-hypertensive patients or type 2 diabetic patients without nephropathy due to its insulinsensitizing property remains to be clarified. Recently, telmisartan, an ARB, was found to act as a partial agonist of peroxisome proliferator-activated receptor-γ (PPAR-γ). PPAR-γ influences the gene expression involved in carbohydrate metabolism, and pioglitazone and rosiglitazone, ligands for PPAR-γ, improve insulin resistance in diabetic patients. Furthermore, there is a growing body of evidence that activators of PPAR-γ exert anti-inflammatory, anti-oxidative and anti-proliferative effects on vascular wall cells, thus decreasing the risks for atherosclerosis. Due to its unique PPAR-γ-modulating activity, telmisartan will become a promising 'cardiometabolic sartan', that targets both diabetes and CVD in hypertensive patients. This review on clinical studies will provide further information whether the beneficial cardiometabolic actions of telmisartan could be ascribed to its PPAR-γ-inducing property.

PS-35: A comparative study of marketed GR modulators on their effects versus side effects

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Several glucocorticoid receptor (GR) modulators are available in market as potent anti-inflammatory agents. However, their clinical benefits are accompanied by metabolic side effects particularly on chronic usage. It is now well known that the GR mediated beneficial effect are produced via transrepression of genes responsible for cytokine production; whereas the side effects are mediated via transactivation of certain genes. Although several steroidal GR modulators are available in market for long time, there are no comparative clear-cut data available to explain their benefit versus side effect profile in *in vivo* pre-clinical studies. Therefore in our present study we profiled several marketed steroidal GR modulators for dissociation between their transactivation versus transrepression related effects. The acute ant-inflammatory effects were mesured in rat paw edema (RPE) model as percentage inhibition in paw swelling at 3 h. The same drugs were profiled for the side effects after acute (6h) and sub-acute (7 days) treatments. All the steroids produced significant anti-inflammatory effect in RPE model. As expected treatment with GR agonist caused metabolic side effects also. Although in the acute situation there were effects on glucose levels, the effects on other parameters as TG, TC, LDL, HDL and body weight were significantly altered after sub acute exposure. There was also reduction in body weight. All the steroids showed different degrees of side effects that did not correlate with their potency for anti-inflammatory effects. Beclomethasone and betamethasone appear to be relatively safe steroids which might be prescribed for chronic treatments.

PS-36: Protein Modeling Guided Molecular Docking Studies of Muscarinic Receptor Antagonists

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Muscarinic receptor belongs to the rhodopsin-like family Class A of G protein coupled receptors (GPCRs) and controls a wide variety of multiple intracellular signal transduction pathways. Bovine rhodopsin, crystallized by Palczewsky *et al.,* provided the first direct visualization of the seven-transmembrane helices of a G-protein-coupled receptor in the inactive state. Knowledge of the 3D structure of Muscarinic receptors could be of great help in understanding their function and would help in rational design of specific ligands. Experimental site-directed mutagenesis has revealed that the Asp 272 is important for antagonist affinity in M3. Apart from this, Asp148, Tyr149, Tyr271, Tyr293, Cys297 and Tyr298 are particularly important residues for M3 antagonists. Similarly Asp103, Tyr104, Ser107, Asn108, Tyr177, Leu197 are important residues for M2 receptor and Asp105, Tyr106, Tyr381, Asn382, Tyr404, Cys407, Ty408 are important residues for M1 receptor. In this present study, we report a homology model of M1, M2 and M3 protein models in inactive form based on human rhodopsin protein. We validated our model by docking M1, M2 and M3 selective antagonist molecules from open literature with the aim of finding the reasons for antagonist selectivity towards the Muscarinic receptor sub-types. These studies confirmed that the developed protein models show selectivity towards M1, M2 and M3 antagonist molecules in terms of both H-bond interactions and docking score. These studies are further reconfirmed by *in silico* mutagenesis experiments.

PS-37: Qtc Dispersion- A Non Invasive Indicator of Cardiac Autonomic Neuropathy.

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Background: The determination of the presence of Cardiac Autonomic Neuropathy (CAN) is usually based on a battery of autonomic function tests rather than just one test.

Objectives: The present study was conducted to detect CAN in type 2 diabetic patients using QTcd as a single, non- invasive indicator.

Design: Diabetic patients (100 males and 100 females) with regular treatment and follow-up were tested for the presence of autonomic neuropathy using Ewing's tests. Based on this, they were grouped into normal, early, definite and severe autonomic neuropathy changes. 12 lead ECG was recorded, analyzed and the percentage of CAN was determined using QTcd.

Results: 'Definite' autonomic neuropathy changes were detected in 27.5% (55/200) diabetic patients. Among them 36.3% (20/55) showed abnormal QTcd, in that males were 55% (11/20) and females 45% (9/20). All were more than 60 years of age. Based on the duration of diabetes, 71.5% males and 100% females more than 5 years duration of diabetes showed abnormal QTc dispersion.

Conclusion: All patients with abnormal QTcd showed 'definite' CAN changes. CAN was found to be more common in males, increased with the age of the patient and duration of diabetes. As QTcd is easy to assess, it can be used as a single, non- invasive indicator to detect CAN in daily clinical practice.

PS-38: Sumoylated PPARα Mediates Gender-Specific Gene Repression and Protects the Liver from Estrogen-Induced Toxicity

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The molecular mechanism behind gender-specific responses to peroxisome proliferator-activated receptors (PPARs) is not known. Here, we show that PPARα has a broad female-dependent repressive action on hepatic genes involved in steroid metabolism and inflammation. In male, this effect is reproduced by administration of a synthetic PPARα ligand. Using Cyp7b1 steroid hydroxylase gene as a model, we elucidated the molecular mechanism of this PPARα dependent repression. First, sumoylation of the ligand binding domain of PPARα promotes the interaction of PPARα with the GA binding protein alpha (GABPα) bound to the target promoter. Then, via the recruitment of HDAC, methylation of an adjacent binding site for Sp1 is triggered. This results in the release of Sp1 from the promoter and, consequently, reduces gene expression. We show that physiologically this repression mechanism confers protection against experimental estrogen-induced intrahepatic cholestasis, paving the way for the development of a novel therapy against the most common hepatic disease during pregnancy.

PS-39: Pharmacological Inhibition of 11-Beta Hydroxysteroid Dehydrogenase Type 1 Activity Improves Diabetic Phenotype of db/db Mice

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The obese and diabetic C57BL/Ks db/db mice show phenotype resembling to human type 2 diabetes mellitus. These animals are hyperglycemic and hyperinsulinemic and also show significant hypersensitivity to stress. Though central nervous system involvement could not be ruled out in these stress responses, evidences indicate that phenotype of type 2 diabetes in C57BL/Ks db/db mice is associated with the increased expression of glucocorticoid receptor and 11beta –hydroxysteroid dehydrogenase type 1 (11β- HSD1) activity in the liver.

The current work was planned to evaluate the effects of pharmacological manipulation of 11β -HSD1 activity by carbenoxolone in adult and frankly diabetic C57BL/Ks db/db mice. Daily twice treatment of carbenoxolone improves glycemic control, reduces body weight and mesenteric fat mass, lowers serum triglycerides, and increases serum HDL level in these animals. The treatment regimen was decided using the PK-PD modeling in acute dosing regimen. These beneficial effects of carbenoxolone were attributed to 11 β-HSD1 inhibition in adipose and liver, when tested after termination of the treatment. The evaluations further confirmed that the inhibition of 11β -HSD1 activation resulted in increased glucose utilization and glycogenesis in liver.

We conclude that inhibition of hepatic and adipose 11β -HSD1 contributes to the normalization of obese and diabetic phenotype of C57BL/Ks db/db mice. The increased liver glucokinase activity along with increased glycogenesis partially mediate this beneficial effect. However, further studies are needed to elucidate the role of such beneficial effect in pancreas.

PS-40: Saxatilin, A Snake Venom Disintegrin, Suppresses Platelet Activation Associated with Human Vascular Endothelial Cell Migration and Invasion.

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National Research Laboratory for Protein Biochemistry, Department of Biochemistry, College of Life Science and Biotechnology, Yonsei University, Seoul (Republic of Korea).

Objectives: Platelet activation, essential in hemostasis and thrombosis, is also actively involved in inflammatory reactions, immune responses and atherosclerosis. The activation of platelets leads to the release of microparticles that are capable of activating endothelium and inducing chemotaxis of monocytes. Saxatilin, a snake venom disintegrin, is known to inhibit fibrinogen dependent platelet aggregation, tumor growth, metastasis and bFGF-induced angiogenesis of endothelial cells. Here, we have investigated the effect of saxatilin on collagen-induced platelet activation and also on the consequences of platelet activation by estimating the migration and invasion of human umbilical vein endothelial cell (HUVEC).

Methodology: HUVEC migration/invasion induced by PDS, derived from collagen-activated platelets, was accessed using Boyden chamber system. Cytokine levels in PDS and the various integrins ($\alpha_v\beta_3$,$\alpha_3\beta_1$,$\alpha_5\beta_1$,α_1,α_4,α_6 or β_3) levels in HUVEC were measured by ELISA using respective antibodies.

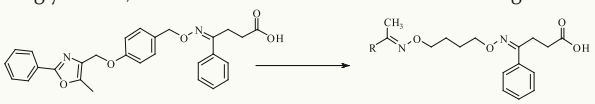
Results: PDS, derived from collagen induced platelet, stimulated the migration/invasion and upregulation of integrin $\alpha_v\beta_3$ in HUVEC. Antibody against platelet-derived growth factor (PDGF)-B abolished HUVEC migration/invasion and integrin $\alpha_v\beta_3$ upregulation, indicating PDGF-AB as a key mediator for the pro-angiogenic effects of collagen-activated PDS. Saxatilin inhibited the collagen-induced platelet activation and the angiogenic properties of PDS. Saxatilin also abolished the collagen-induced phosphorylation of Syk, which mediates inside-out signaling in platelet activation.

Conclusion: Saxatilin inhibits platelet activation, platelet PDGF-AB release as well as endothelial cell migration and invasion. [This work was supported by the Korea Science and Engineering Foundation (KOSEF) grant funded by the Korea government(MOST) (No. ROA-2004-000-10297-0)].

PS-41: Design, Synthesis and Evaluation of Novel Bisoximinoalkanoic Acids as PPARα Activators

Pandurang Zaware, Pankaj Makadia, Suresh Pola, Baban Thube, Darshit Patel, Pravin Patil, Priyanka Priyadarshini, Dinesh Suthar, Manan Shah, Harikishore Pingali and Mukul R. Jain
Zydus Research Centre, Ahmedabad, Gujarat (India).

In view of unsuccessful intensive efforts within the pharmaceutical industry to develop PPAR α/γ dual agonists based on the hypothesis that PPARα/γ dual agonism provides an additive, and possibly synergistic, pharmacology and recent finding that activation of PPARα is known to lower triglycerides, elevate HDL and exert insulin-sensitizing effects which suggests that even chronic administration of selective PPARα agonist will serve as a better remedy for the treatment of metabolic disorder we intended to develop selective and potent PPARα agonist. A series of Bisoximinoalkanoic acids were prepared by chemical modifications in lipohlilic tail and middle spacer regions of Imiglitazar, a PPARα/γ dual agonist without modifying pharmacophore. Selected compounds exhibited good degree of selectivity towards PPARα over PPARγ.

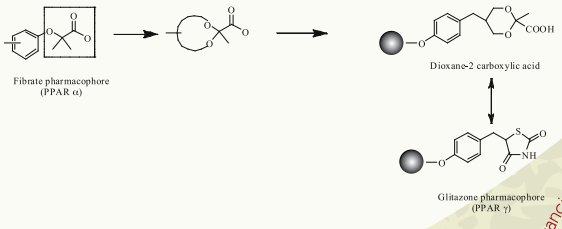


Imiglitazar

PS-42: Design and Synthesis of Novel PPAR α/γ Dual Agonists Containing 5-benzyl-2-methyl-[1,3]dioxane-2-carboxylic acid as Potent Hypoglycemic and Hypolipidemic Agents

Pankaj Makadia, Pandurang Zaware, Dinesh Suthar, Suresh Giri, Harilal Patel, Harikishore Pingali and Mukul R. Jain
Zydus Research Centre, Ahmedabad, Gujarat (India).

A novel pharmacophore containing 1,3-dioxane carboxylic acid was designed by incorporating structural features of glitazones in fibric acid chemotype and developed as a pharmacophore of PPAR α/γ dual agonists. Compounds were synthesized using this phamacophore and a variety of lipophilic heterocyclic tails and evaluated their transactivation potentials towards PPARα and γ. The hypoglycemic and hypolipidemic activities of a selected compounds were evaluated in *Swiss Albino mice* and *db/db* mice. The pharmacokinetic parameters of the lead compound were measured in *Sprauge-Dauley rats*.



PS-43: The Low CYP3A Activity in Diabetic Rats Further Decreased by Bioflavonoids Resulting into Higher Bioavailability of Nateglinide: A Safety Concern

Pankaj Vinod Dixit and Sudhir Niranjan Umathe
University Department of Pharmaceutical Sciences, Mahatma Jyotiba Fuely Shaikshanik Parisar, Amravati Road, Nagpur – 440033 (India).

Nateglinide is a commonly used antidiabetic agent that is metabolized via cytochrome P450 (CYP) 3A4 isoenzyme. Recent studies indicate that diabetic subjects exhibit polymorphism of cytochrome P450 (CYP) 3A4 that reflects on its content and activity. Secondly, the bioflavonoids present in herbal preparations, which are used as an add-on therapy in diabetes are the inhibitors of CYP3A4. In view of these facts, the bioavailability of nateglinide is assessed in diabetic rats that are also treated with bioflavonoids such as berberin or quercetin.

The studies were carried out in rats after the induction of diabetes by alloxan. The bioavailability of nateglinide (50 mg/kg, p.o.) was determined in diabetic rats treated for two weeks with berberin (100 mg/kg, p.o.) or quercetin (10 mg/kg, p.o.), in terms of its plasma levels at various time points (0.25, 0.5, 1, 1.5, and 2 h) by HPLC. Another group of diabetic animals received similar bioflavonoid treatment for two weeks, and CYP3A activity was assessed in intestinal and hepatic microsomes by using erythromycin-N-demethylase assay.

These results indicated that the vehicle treated diabetic rats and bioflavonoid treated non-diabetic and diabetic rats exhibited significant reduction in CYP3A activity. Further, it is seen that the bioavailability of nateglinide is higher in diabetic rats as compared to non-diabetic group. Moreover, bioflavonoid treated diabetic as well as non-diabetic rats exhibited similar higher bioavailability of nateglinide.

The present findings raise a safety concern of using bioflavonoid containing herbal preparatios along with nateglinide.

PS-44: Neuroprotective Effect of Embelin *(Embelia ribes)* in Middle Cerebral Artery Occlusion Induced Focal Cerebral Ischemia in Rats

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*Shri B. M. Shah College of Pharmaceutical Education & Research, Modasa, Gujarat (India).
#S. K. Patel College of Pharmaceutical Education & Research, Kherva, Gujarat (India).

In the present study, we investigated the neuroprotective effect of Embelin in Middle cerebral artery occlusion induced focal cerebral ischemia in rat. Adult male wistar rats were used and treated with Embelin at a dose of 50 mg/kg, 75 mg/kg and 100 mg/kg. Control rats were received 2% tween 80. After 20 days treatment, all animals were anesthetized with chloral hydrate and subjected to focal ischaemia by occlusion of the middle cerebral artery using an intraluminal suture. After 2 h middle cerebral artery occlusion, reperfusion was allowed by retracting the thread. After 24hr of ischemia, Animals were sacrificed and brains were removed for triphenyltetrazolium chloride staining. A subgroup of animal was used for the lipid peroxidation and antioxidant parameters. Treatment with Embelin at a dose of 100 mg/kg causes significant reduction in the volume of infarction in the cerebral cortex but no significant effect at the dose of 50 mg/kg and 75 mg/kg. In control animals there was a significant increase in lipid peroxidation and decrease in superoxide dismutase (SOD) and Catalase (CAT) activity. Embelin at a dose of 100 mg/kg produces significantly reduced lipid peroxidation and enhanced SOD and CAT activities but no effect in lower doses. So, it was concluded that neuroprotective effect of Embelin in focal ischemic brain may be due to its anti-oxidant effect.

PS-45: Analgesic Activity of a Triterpenoid Isolated from Fruits of *Barringtonia racemosa*

Patil K. R.*, Patil C. R.*, Jadhav R. B.*, Surana S. J.* and Fursule R. A.#
*R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur, Maharastra (India).
#H. R. Patel Women's College of Pharmacy, Shirpur, Maharastra (India).

Introduction: Barringtonia racemosa has been reported to have promising biological activities such as anti-tumor, anti-asthmatic, anti-inflammatory, analgesic, cytotoxic and anti-bacterial. The isolation of active components of this plant in a bioassay guided manner is proposed to yield druggable phytoconstituents.

Isolation of triterpenoid: The targeted triterpenoid was isolated from Barringtonia racemosa by cold maceration of the powdered fruits of this plant in petroleum ether followed by extraction with methanol. The methanolic extract was fractionated with ethyl acetate and was subjected to separation on a silica gel column with varying compositions of ethyl acetate and chloroform. The isolation was monitored on TLC by comparing the isolated fractions with the Bartogenic acid as a marker.

Characterization: The isolated triterpenoid was characterized for its chemical structure through HPTLC, IR, LC-MS and NMR analysis.

Biological activity: The isolated compound was screened for its analgesic activity through following assays;

- Acetic acid induced writhing in mice
- Hot plat test in mice
- Tail immersion test in mice

Results & conclusion: The isolated compound was found to match with Bartogenic acid in analytical tests. This compound exerts very potent analgesic activity in animal models of pain and inflammation at doses as small as 2 mg/kg/p.o. which is a rarity for phytochemicals.

Hence, it is proposed that the Bartogenic acid is a very potent biologically active constituent of this plant and possesses potent analgesic activity worth of further explorations.

PS-46: Restoration of Impaired Acetylcholine-mediated Relaxation by ET_A Antagonist BMS182874 in Thoracic Aortic Rings Isolated from High Fat Diet Fed Rats

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*Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER), Mohali, SAS Nagar, Punjab–160 062 (India).
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Background: Incidence of type 2 diabetes and cardiovascular complications are an increasing concern all over the world. Insulin resistance (IR) generally precedes type II diabetes. ET-1 activity is known to alter in IR which is characterized by endothelial dysfunction.

Aim: To test the hypothesis that ET-1 plays an important role in endothelial dysfunction associated with IR.

Research Design and Methods: IR was induced in male Sprague-Dawley rats (170 ± 10 g) by feeding high-fat diet (HFD) for 4 weeks. IR was characterized by estimating different biochemical parameters and oral glucose tolerance test. ET-1-induced contraction and ACh-mediated relaxation in the presence and absence of selective ET_A blocker (BMS182874) were recorded isometrically in thoracic aortic ring preparations from HFD-fed and normal pellet diet (NPD)-fed rats.

Results: The HFD-fed rats exhibited characteristic features of IR viz., obesity, hyperinsulinaemia, mild hyperglycemia, hypertriglyceridemia, hypercholesterolemia and glucose intolerance. Significant ($P < 0.01$) increase in the ET-1 induced contraction (E_{max}) was observed in aortic ring preparations obtained from HFD-fed rats as compared to that of NPD-fed rats. In IR rats, significant impairment in the ACh mediated relaxation was observed as compared to that of control. Incubation of aortic ring with BMS182874 (10^{-6} µM), in-vitro, significantly restored ACh mediated relaxation ($P < 0.001$). In addition, marginal relaxation (15-20%) was observed in PE pre-contracted aorta with BMS182874.

Conclusion: Our results show enhanced E_{max} of ET-1 in IR. Further, ET-1 plays crucial role in the endothelial dysfunction via ET_A receptor. ET_A receptor blockade can be of vital importance in preventing the IR associated endothelial dysfunction.

PS-47: Facile Synthesis and in-vitro Activity of 2,1-Benzisothiazolin-3-one Derivatives as Novel Inhibitors of Human 11β-Hydroxysteroid Dehydrogenase Type 1

Pinkal N. Prajapati, Amol A. Thorave, Hardik Shah, Arghya Dhar, Rajendra K. Kharul, Shital Shah, Prasenjit Mitra, Leena Sharma, Kalpatapu V.V.M. Sairam and Mukul R. Jain
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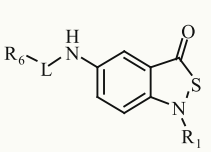
Glucocorticoids (GCs) play an important role in a variety of physiological functions including immune & inflammatory responses, stress responses, aspects of development & metabolism. Being so important, obviously, secretion of these glucocorticoids is tightly regulated by negative feedback loop controlled by hypothalamus-pituitary-adrenal (HPA) axis. While intracellular glucocorticoid levels are regulated by 11β-hydroxysteroid dehydrogenases (11β-HSDs). In continuation of our interest, we have designed and synthesized various novel 2,1-benzisothiazolin-3-one derivatives (1). By taking into consideration indazole derivatives 2 & 3 known in the literature as a starting point for design, -NH at 1-position from these inhibitors was replaced with sulfur to obtain a series of novel 2,1-benzisothiazolin-3-one derivatives (1), which was screened by using suitable in-silico model. The derivatives showing desired in-silico correlation were synthesized from commercially available isatoic anhydride



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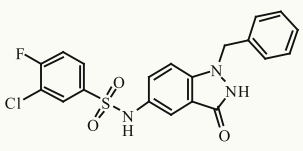


2
h 11b-HSD1
IC 50 = 0.007 nM

(Scheme 1). Isatoic anhydride, 6 was nitrated by standard nitrating procedure to obtain 5-Nitro Isatoic anhydride 7, which was converted into benzoisothiazolinone derivative 8. It was reduced to its corresponding amine group and then coupled with differentially substituted arylsulfonyl chlorides. Thus, the obtained derivatives were screened for in-vitro inhibitory activity against 11β-HSD1. Two derivatives 1h & 1i showed either comparable or superior enzyme inhibition than the reference compound 2.

PS-48: Preclinical Pharmacokinetics of P1738-05, a Novel Non-PPAR Activating, Glucose Lowering Agent in Rats and Mice

Prabhu S., Damre A., Hariharan S., Singh K., Patil V., Iyer S., Varghese A., Srivastava A. and Sharma S.
Drug Metabolism and Pharmacokinetics, Piramal Life Sciences Limited, Goregaon (E), Mumbai (India).

P1738-05 is a non-PPAR activating glucose-lowering agent whose activity is not associated with weight gain. The objective of this investigation was to study the pharmacokinetics and distribution of P1738-05 to liver and brain in mice and rats, respectively.

Pharmacokinetic profile of P1738-05 was investigated in rats and mice following 100 mg/kg, p.o. dose. After a 3-day repeat oral dosing, the plasma and liver exposure of P1738-05 was studied in db/db mice at 50, 100 and 200 mg/kg doses. The in vivo brain uptake of P1738-05 was studied in rats at 5 mg/kg, i.v. dose. Further in vitro protein binding of P1738-05 was studied in mouse, rat and human plasma. Concentrations of P1738-05 were analyzed by HPLC and pharmacokinetic parameters were calculated using WinNonlin®.

P1738-05 (100 mg/kg, p.o.) showed a Cmax of 16.42 µg/mL at 2.25 h, half-life of 6.19 h and an exposure of 175.79 h*µg/mL in rats, and a Cmax of 95.31 µg/mL at 2.00 h, half life of 9.35 h and an exposure of 1453.15 h*µg/mL in mice. A dose-dependent increase in P1738-05 concentrations was seen in plasma and liver at 2 h post-dose in db/db mice. In rats, P1738-05 showed a hundred-fold lower concentration in the brain as compared to plasma. Extensive plasma protein binding (~99-100 %) was observed.

P1738-05 thus showed a good Cmax, long half-life and a dose-dependent increase in exposure in mice and rats. It showed a very low brain uptake, a property desirable for non-CNS acting drugs. Extensive protein binding of P1738-05 may contribute to the long half-life and low blood-brain- barrier permeability associated with this compound in vivo.

PS-49: Gene Expression Analysis of Rat (Zucker fa/fa) Brains Treated with Rimonabant

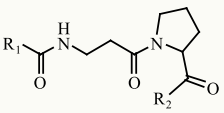
Prabodha Swain, Gaurav Pandya, Priyanka Priyadarsiny, Abhijit Chatterjee, Rajesh Sundar, Avisheka Acharya, Pankaj R. Patel and Mukul R. Jain
Zydus Research Centre, Ahmedabad, Gujarat (India).

Rimonabant, a CB-1 receptor antagonist has been implicated in inducing depression and other neurological abnormalities in human. Although, CB-1 receptor antagonism has been exploited to reduce feed intake to tackle obesity, the associated neurological complications have been a major drawback in adopting as prescription drug in clinics. To understand the effect of rimonabant in brain tissues, Zucker fa/fa rats were treated with 30 mg/kg rimonabant and were sacrificed after 3 hrs to collect the whole brain tissues for gene expression studies. A rat bead chip array was used to study the gene expression profile in an Illumina Microarray system. Differential expression of gene was analyzed by Bead studio analysis software. Further validation was done by SYBR green real time RT-PCR. Out off 12000 genes, 130 genes showed differential changes in expression in rimonabant treated brain compare to the control. Genes showing >1.5 fold altered- expression was categorized into different functional groups designated as lipid metabolism, vesicular trafficking, neurotransmitter synthesis, transport and neurogenesis. Four representative genes among the altered genes were further verified for the fold changes by RT-PCR analysis. Current studies indicate that several genes associated with neurogenesis, synthesis and transport of neurotransmitter are altered in brains treated with rimonabant. Such altered expression could affect neural function and induce different neurological complications observed in experimental animal models as well as the humans in clinical trial.

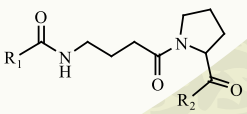
PS-50: Design, Synthesis and Pharmacological Evaluation of Dipeptide Based DPP IV Inhibitors as New Class of Antidiabetic Drugs

Pradip A. Jadav[#], Dipam N. Patel[*], Bony R. Shah[#], D. J. Sen[#], Brijesh A. Darji[*], Yernaidu Siriki[*], Mukul R. Jain[*] Debdutta Bandyopadhyay[*], Amit Joharapurkar[*] and Rajesh H. Bahekar[*]
[*] Zydus Research Centre, Ahmedabad, Gujarat (India).
[#]Shri Sarvajanik Pharmacy College, Mehsana, Gujarat (India).

Dipeptidyl peptidase-IV (DPP IV) is a serine protease enzyme. It selectively cleaves first two amino acids (His-Ala) of 29 amino acid GLP-1 peptide and thereby makes it inactive. Thus, inhibition of DPP IV enzyme activity, using suitable DPP IV enzyme inhibitor likely to increase the levels of endogenous intact and bioactive GLP-1 peptides, thereby, it acts as antidiabetic agents.



Compound I (a-f): R_2 : NH_2
Compound II (a-f): R_2 :OH



Compound III (a-f): R_2 :NH_2
Compound IV (a-f): R_2 :OH

In this project, based upon SAR study of NVP-DPP728, we have designed new series of dipeptide based DPP IV inhibitors, which mainly consist of five member proline ring system, attached to sterically hindered aromatic acid, with suitable linker. Total 24 new DPP IV inhibitors were prepared, using solid phase peptide synthesis approach and all the compounds were purified using Prep-HPLC. All the test compounds were subjected for DPP IV inhibitory activity and also selectivity of test compounds was assessed against DPP8, DPP9 and QPP enzymes (in vitro). Most potent compounds from each series were subjected for in vivo antidiabetic activity.

PS-51: A Reverse Phase HPLC Method for the Separation of Diastereomers of 2-(4-(Methylsulfonyl)phenyl)-3-(3*(R)*-oxocyclopentyl)propanoic acid

Prakash M. Davadra, Timir Patel, Jignesh Chauhan, Jignesh Pethani, Darshan Joshi and Ravindra Chambhare
Zydus Research Centre, Ahmedabad, Gujarat (India).

The present study describes a RP-HPLC method for the separation of diastereomers on achiral column. C-alkylation of ethyl 2-(4-(methylthio)phenyl)acetate with 2*(S)*-(iodomethyl)-8,8-dimethyl-6,10-dioxaspiro[4.5] decane and consecutive hydrolysis and oxidation yielded two diastereomers of 2-(4-(methylsulfonyl)phenyl)-3-(3*(R)*-oxocyclopentyl)propanoic acid. Baseline resolution was achieved on a J'Sphere, C18 (150 * 4.6 mm, 4 µm) column using mobile phase consisting of 0.05% Triflouroacetic acid in water:Acetonitrile (85:15, v/v) at a flow rate 1.0 ml/min. The detection was carried out at 228 nm. The developed method was partially validated. Specificity and homogeneity of the peaks were conformed by PDA and MS detector. The limit of detection and limit of quantification were found to be 150 and 450 ng/ml, respectively, for both the diastereomers. The method precision at limit of quantification level was within 2 % R.S.D. for both the diastereomers. Detector response for both diastereomers was linear over the studied ranges (500-200000 ng/ml) with correlation coefficient greater than 0.999. The proposed method was found to be suitable and precise for the monitoring of epimerization of one diastereomer to the another.

PS-52: Separation of Enatiomers of 4-phenyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine on Cellulose Based Stationary Phase

Prakash M. Davadra, Jignesh Dhanani, Vivek Mepal, Shidhartha Kar and Ravindra Chambhare
Zydus Research Centre, Ahmedabad, Gujarat (India).

A chiral HPLC method is developed for the separation of enatiomers of 4-phenyl-4,5,6,7-tetrahydrothieno[3,2-c] pyridine on cellulose based stationary phase. 4-phenyl-4,5,6,7-tetrahydrothieno [3,2-c] pyridine is an intermediate, used versatilely for many drugs. Baseline resolution is achieved on Chiralcel OJ-H (250 mm x 4.6 mm) column using mobile phase consisting of n-Hexane:Ethanol containing 0.1 % diethyl amine (95:05, v/v) at a flow rate 0.8 ml/min. The resolution between two enatiomers was found to be not less than 3.9. The developed method is validated for some important parameters, such as system suitability, limit of detection, limit of quantification, precision and linearity for both the enatiomers. The peak homogeneity was conformed by photo diode array detector. The proposed method is found to be suitable and precise for the monitoring of enatiomeric separation of racemic, 4-phenyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

PS-53: Development of Innovative & Efficient Method for the Purification & Salt Preparation of Short Chain Class-3 Peptides using Reverse Phase Preparative High Performance Liquid Chromatography (RP-HPLC)

Pranav N. Bhatt, Ashok M.Chaudhari, Batuk D. Dabhi, Hiren R. Patel, Kalpesh Shah, Rajesh H. Bahekar and Ravindra Chambhare
Zydus Research Centre, Ahmedabad, Gujarat (India).

In the present investigation, we have developed novel method for the one step purification and acetate salt formation of short-chain class-3 peptides using RP-HPLC. Two different types of highly hydrophilic 8 amino acids peptides were synthesised, which are zwitterionic in nature. In general, highly water soluble peptides with zwitterionic nature are difficult to purify and convert into non-TFA salt in a single step at large scale. However, by adopting suitable chromatographic conditions such as time programme, gradient, pH and flow rate, using different stationary phases, such as Kromasil C-4 & C-8 (100A,10um), phenomenox Luna C18(100A,5um), Diasogel C18 (100A,10um) and YMC-ODS-AQ(100A,10um), best resolution, purity and yield was selectively obtained on YMC-ODS-AQ(100A,10um) media. In general, we achived 3gm crude sample loading per injection and obtained 55% recovery (on the basis of crude assay) with purity above 95% within 2 hrs run-time per injection. Added advantage of our method is that we got direct acetate salt of peptide.

PS-54: Gene Expression Profiling of PPAR Dual Agonist ZYH1 in Rodent Liver and Kidney Using Illumina Microarrays

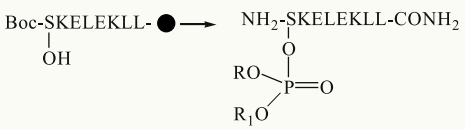
Priyanka Priyadarsiny, Prabodha Swain, Maanan shah, Dinesh Suthar, Abhijit Chatterjee, Rajesh Sundar, Vijay Kale, Pankaj R. Patel and Mukul R. Jain
Zydus Research Centre, Ahmedabad, Gujarat (India).

Over the last decade PPAR activators are used to treat metabolic abnormalities such as dyslipidemias and Type 2 diabetes. The regulation of gene expression via the peroxisome proliferator-activated receptor (PPAR) leads to a cascade of events that result in the pharmacological (hypolipidemic) and adverse (carcinogenic) effects in rodents. To identify a panel of genes/proteins as markers that can ultimately be used to predict carcinogenesis in different organ tissues, we performed gene expression studies on liver and kidney samples of wistar rat treated with 100 ppm ZYH1 for one year. The expression analysis was performed using bead based Illumina oligonucleotide microarray platform. Bead studio analysis software was used to identify the differentially expressed genes in the samples. Genes showing a difference of ~1.5 fold and above compare to the control were filtered separately and grouped to identify potential association with carcinogenesis from published literature. Analysis of the genes indicated that several known PPAR-target genes are upregulated in both liver and kidney. In contrast, several pro-oncogenes identified in control samples were significantly repressed in liver and kidney treated with ZYH1. Several of the short listed genes can be identified to have role in lipid metabolism, growth factors, cell adhesion and angiogenesis. This gene expression analysis studies support the preclinical evidence of a safe profile of ZYH1 with respect to hepatotoxicity, renal toxicity and development of urinary bladder tumor.

PS-55: Preparation of Alkyl Protected Phosphoramidites and their application in Solid-Phase Synthesis of Phosphopeptides

Rajendra S. Chopade, Vijay M. Prajapati, Vibhuti A. Raval, Mukul R. Jain and Rajesh H. Bahekar
Zydus Research Centre, Ahmedabad, Gujarat (India).

Novel method for the synthesis of symmetrically and asymmetrically protected (octyl and decyl) phosphoramidites was developed. Furthermore, using these new global phosphorylation reagents (phosphoramidites), the side chain of resin bound serine residue of a linear peptide was phosphorylated. Surprisingly, after the final cleavage and deprotection of resin bound phosphopeptides, the alkyl side chains (octyl and decyl) on phosphate ester of phosphopeptides were found to be stable to the TFA cleavage.



12a (R& R_1=C_8H_{17}-)
12b (R& R_1=$C_{10}H_{21}$-)
12c (R=C_8H_{17}-; R_1=$C_{10}H_{21}$-)

PS-56: Comparison of Serum Apo B, Lp(A) And Oxidized LDL Among Normal Subjects Consuming Two Different Types of Cooking Oil in Kerala

Sabitha P.*, Prakash Kamath# and Vasudevan D. M.*
*Department of Biochemistry, Amrita School of Medicine, #Department of Cardiology, Amrita Institute of Medical Sciences, Kochi, Kerala (India).

Kerala has a high incidence of CAD among Indian states. The prevalence of risk factors for CAD such as hypertension, type 2 diabetes etc. among this population is also high. Dietary fats affect lipid metabolism and has been considered as a major factor influencing CAD risk. It is generally believed that coconut oil, rich in medium chain saturated fats, contribute to high incidence of CAD in this region. Recently, a tendency has been observed among people of this region to shift to cooking oils rich in PUFA, especially sunflower oil. Numerous studied have recognized apo B, Lp(a) and oxidized LDL as predictors of CAD risk. There are not many studies that have evaluated these parameters in Kerala population. In our study, we compared lipid profile, apo B, Lp(a) and oxidized LDL among normal subjects consuming coconut oil and sunflower oil. Male subjects between 40 to 60 years of age without any known morbidities were recruited and grouped according to the cooking oil they used. Serum total cholesterol, triacylglycerol, HDL-cholesterol and LDL-cholesterol were determined in Hitachi 912 auto analyzer. Lp(a) and oxidized LDL were determined by ELISA and apo B was estimated immunoturbidimetrically. Student's 't' test was used to compare mean values of the parameters. Our results indicate that the parameters considered did not vary significantly between the two groups.

PS-57: Differential effects of Exendin-4 in correction of diabetic phenotype in genetic versus experimentally-induced type 2 diabetes in mice

Samadhan Kshirsagar, Nirav Dhanesha, Vipin Dhote, Amit Joharapurkar, Rajesh H. Bahekar and Mukul R. Jain
Zydus Research Centre, Ahmedabad, Gujarat (India).

The glucoregulatory actions of Exendin-4 are exerted through array of mechanisms imparting glucose sensitive insulinotrophic action, suppression of glucose dependent glucagon secretion, neogenesis of ß-cells and improvement in pancreatic functions. Exendin-4 also exerts effect on body weight through peripheral as well as central actions. However, these effects may differ according to the glycemic status of the animals exposed to the GLP-1 agonism.

The current study was designed to ascertain the effect of acute and chronic treatment of the efficacious dose of Exendin-4 on hyperglycemic animals. The acute treatment of obese and hyperglycemic phenotype of mice (db/db, ob/ob) showed significant reduction in glucose, which was accompanied by significant increase in circulating insulin after IPGTT (glucose load 1.5 gm/kg). However, in nonobese and mild hyperglycemic mice (C57 BL/6J, db+) Exendin-4 reduced glucose levels without increasing circulating insulin levels. This effect can be visualized as the increased insulin sensitivity imparted by the GLP-1 agonism caused by the Exendin-4.

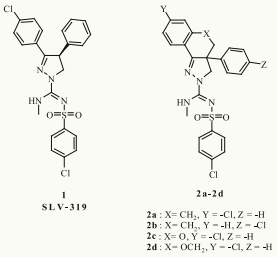
The chronic administration of Exendin-4 in obese and diabetic mice reproduced the similar effects on insulin and glucose as observed in acute treatments, along with reduction in glycated hemoglobin levels. The body weight in these animals was significantly decreased after chronic treatment, which could be attributed to the sustained reduction in feed intake. However, The decreased food intake by Exendin-4 is contributed by nausea like effect which was confirmed by LiCl induced CTA test in all these animal models. Significantly enough, in C57 BL/6J mice rendered diabetic by high fat diet and low dose STZ could not show such increase in insulin, though it has significantly improved the insulin sensitivity after chronic Exendin-4 treatment.

We conclude that exendin-4 induces persistent hyperinsulinemia in the context of chronic hyperglycemia and hyperlipidemia as seen in genetically diabetic and obese mice. On the other hand, in the experimentally induced diabetes, additional action in liver and periphery may attribute the improved insulin sensitivity.

PS-58: Conformation Constraints of 4*S*-(-)-3-(4-chlorophenyl)-*N*-methyl-*N*′-[(4-chlorophenyl)-sulfonyl]-4-phenyl-4,5-dihydro-1H-pyrazole-1-caboxamidine: Design, Synthesis and Pharmacological Evaluation as Cannabinoid Modulators.

Sandeep Shedage, Rina Soni, Jayendra Z. Patel, Amit Joharapurkar, Mukul R. Jain, Pankaj R. Patel and Brijesh Kumar Srivastava
Zydus Research Centre, Ahmedabad, Gujarat (India).

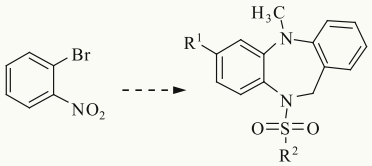
Design, synthesis and pharmacological evaluation of conformationally constraints of 4*S*-(-)-3-(4-chlorophenyl)-*N*-methyl-*N*′-[(4-chlorophenyl)-sulfonyl]-4-phenyl-4,5-dihydro-1H-pyrazole-1-caboxamidine (SLV-319) 1 as cannabinoid modulators is reported.



PS-59: Design and Synthesis of Novel Dibenzo[*b,e*][1,4]Diazepine -Sulfonamide Derivatives as Potential Anti-Inflammatory Agents

Sanjay Ghosh, Jayendra Z. Patel, Amitgiri Goswami, Mayur S. Mukim, Prashant B. Deshmukh, Pravin Thombare, Mukul R. Jain and Sameer Agarwal
Zydus Research Centre, Ahmedabad, Gujarat (India).

Dibenzo[*b,e*][1,4]diazepine derivatives offers a wide range of useful biological activities and the sulfonamide derivatives are known to exhibit anti-inflammatory properties. In pursuit of our ongoing efforts to discover pharmacophores possessing anti-inflammatory properties, we sought to identify new scaffold having sulfonamides that could be combined with dibenzo[*b,e*][1,4]-diazepine. Towards this end, we herein describe the synthesis of novel 7-substituted-10-(aryl-sulfonyl)-5-Methyl-10,11-dihydro-5*H*-dibenzo-[*b,e*][1,4]-diazepine as potential anti-inflammatory agents. The synthesized compounds contain a wide range of substitution pattern for establishing structure-activity relationship. Functional biological activity studies of these compounds are currently in progress and will be reported in due course.



PS-60: In Vivo and In Vitro Effects of Atorvastatin on Angiotensin II and Acetylcholine Signaling Pathways in Vascular Tissues of Diabetic Rats

Sanjay A. Parmar#, Viswanad Bhoomi* and Ramarao P.*
*Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER), Mohali, SAS Nagar, Punjab–160 062 (India).
#Dept. of Pharmacology, L. M. College of Pharmacy, Gujarat University, Ahmedabad (India).

Altered vascular signaling pathways in diabetes are responsible for vascular complications. Among various pathways, angiotensin II and acetylcholine mediated vascular signaling play critical role. In the present study, in vitro and *in vivo* effects of atorvastatin treatment on these pathways in type 2 diabetes rat model were studied. In vitro atorvastatin (10^{-6} M) causes rightward shift in angiotensin II mediated vasocontractile response and was surmountable with high dose of angiotensin II. But higher concentration (10^{-5}M) causes non surmountable antagonism. Atorvastatin (10mg/kg per oral, p. o.) after 2 week of treatment shows attenuation of diabetes associated hypercontractility to angiotensin II. Atorvastatin reduces E_{max} ($p<0.001$) of angiotensin II response in diabetic rats to a level comparable to control rats without change in pD_2 value. In diabetes, acetylcholine mediated vasorelaxation is impaired due to endothelial dysfunction. Atorvastatin (10mg/kg p. o.) shows significant improvement in acetylcholine mediated vasorelaxation ($p < 0.001$). Further the effect of atorvastatin on angiotensin II induced vascular oxidative stress with the help of fluorescent microscopy was studied. Atorvastatin (10^{-6} M) shows inhibition of oxidative stress in diabetic rat thoracic aorta. These findings indicate the beneficial role of atrovastatin in diabetic vasculopathy, which are mediated through angiotensin II.

PS-61: Pre Column Derivatisation Technique Established for Determination of Amino Acid from Biological Sample-ZYBIO by High Performance Liquid Chromatography using Fluorescence Detection

Shailesh Buha, Ashwin Panchal, Haresh Panchal and Ravindra Chambhare
Zydus Research Centre, Ahmedabad, Gujarat (India).

A rapid, sensitive and reproducible pre column derivatisation high performance liquid chromatography with fluorescence detection is developed for simultaneous identification of twenty amino acid in 19 minutes in biological media-ZYBIO. The automated pre-column derivatisation with OPA and FMOC at room temperature was carried out. The derivatised samples were analyzed by C18 stationary phase using sodium acetate buffer and acetonitrile in gradient mode, an analytes were detected at excitation wavelength 340nm and emission wavelength 450nm. The results were reproducible with high level of accuracy in highly complex biological media-ZYBIO. The methodology was successfully applied to the identification and quantification of amino acid in ZYBIO.

PS-62: A Sensitive Liquid Chromatography Method Developed for Peptide ZY09 Component Amino Acids using Hydrolysis by Automated Pre Column Derivatisation

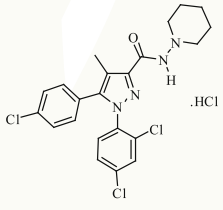
Shailesh Buha, Ashwin Panchal, Haresh Panchal and Ravindra Chambhare
Zydus Research Centre, Ahmedabad, Gujarat (India).

In order to evaluate and extend the applicability of analytical methodology that enables the qualitative and quantitative high performance liquid chromatography determination of amino acid by automated pre column derivatisation with O-phthalaldehyde together with 9-fluorenylmethyl chloroformate by fluorescence detection. Peptide ZY09 was hydrolyzing with 6M hydrochloric acid, the hydrolysis solution was kept at 110°C for 24 hours. Glutamic acid, Serine, Histidine, Arginine, Tyrosine, Trptophan, Leucine and proline were separated on C18 column using binary mixture of sodium acetate buffer, tetrahydrofuran and sodium acetate buffer, acetonitrile, methanol under gradient elution conditions. The derivatives were eluted within 19 minutes with good resolution and reproducibility. The RSD of retention time and result were within acceptance criteria.

PS-63: Design and Synthesis of Novel 2-aryloxy-2-methyl-*N*-(3-morpholin-4-ylmethyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-propanamide Derivatives as Cannabinoid Modulators

Shivaji Gugale, Rina Soni, Rahul Salunke, Sandeep Shedage, Nisha Sadhwani, Amit Joharapurkar, Prasenjit Mitra, Mukul R. Jain, Pankaj R. Patel and Brijesh Kumar Srivastava
Zydus Research Centre, Ahmedabad, Gujarat (India).

A Series of novel hybrid 2-aryloxy-2-methyl-*N*-(3-morpholin-4-ylmethyl-2, 3-dihydro-benzo [1, 4]oxazin-4-yl)-propanamide derivatives were rationally designed, synthesized and investigated as cannabinoid modulators using in vitro hCB1, cAMP assay.



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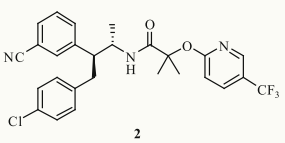

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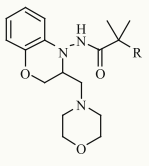
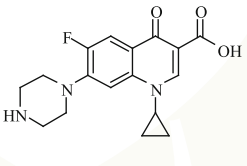


3 -13

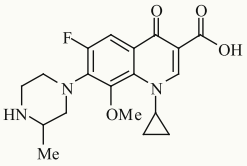
PS-64: Synthesis and Antibacterial Activity of Novel Mannich Quinolones

Sidhartha Kar, Darshan Valani, Rina Soni, Sandeep Shedage, Pravin Kadam, Jayendra Z. Patel, Mukul R. Jain, Pankaj R. Patel and Brijesh Kumar Srivastava
Zydus Research Centre, Ahmedabad, Gujarat (India).

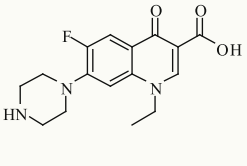
Synthesis and antibacterial activities of a few Mannich quinolones are reported. The antibacterial activities were evaluated in standard in vitro MIC assay method. Some of the compounds showed in vitro (MIC) antibacterial activity superior to Gatifloxacin, Norfloxacin and Ciprofloxacin and more interestingly far superior pharmacokinetics.



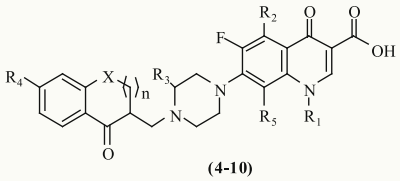
1
Ciprofloxacin



2
Gatifloxacin



3
Norfloxacin



(4-10)

PS-65: Effect of Biocompatible Gold Nanoparticles on Experimentally Induced Inflammatory Bowel Disease in Rats.

Suraj Tubachi*, N.A. Khatib*, Thippeswamy B.S.#, Ajit Zambre and Veeresh B*.
* Department of Pharmacology & Pharmacotherapeutics, J. N Medical College, Nehrunagar, Belgaum, Karnataka (India).
# Department of Pharmacology, S.E.T's College of Pharmacy, S.R Nagar, Dharwad, Karnataka (India).
 NanoBio Chemicals India Private Ltd., Hindwadi, Belgaum, Karnataka (India).

Inflammatory bowel disease (IBD) is a chronic condition of the intestine with unknown etiology involving multiple immune, genetic and environmental factors. Gold, a potent anti-inflammatory agent could be expected as an alternative in patients suffering from IBD. In the present study, to minimize the deleterious side-effects while retaining the efficacy of gold, nano-sized gold (AuNP) - 3 nm was evaluated on Acetic acid induced Colitis & Indomethacin induced Entro-colitis in rats. Sulfasalazine was used as the standard drug for comparison. Clinical activity score, macroscopic & microscopic evaluation, & colonic contractility studies was performed. Biochemical evaluation of the inflamed ileum/colon was carried out using assays of myeloperoxidase (MPO) activity and lactate dehydrogenase (LDH) levels as the indicator of intestinal damage.

Results indicated that the activity of MPO and LDH was increased in acetic acid treated groups, while reduced by pretreatment with AuNP (150 µg/kg b.w.; p.o) and Sulfasalazine. Furthermore, pretreatment with AuNP and Sulfasalazine treated groups showed significant lower score values of macroscopic and microscopic characters when compared to the acetic acid-treated group. In addition, we observed reduced colonic contractile response to carbachol in acetic acid treated group; while AuNP treated group significantly restored reduced colonic contractile response. The beneficial effect of AuNP was comparable to that of Sulfasalazine in colitis model, while AuNP (150 µg/kg b.w.; p.o) was ineffective in Indomethacin induced Entro-colitis in rats

It is concluded that AuNP inhibits acetic acid induced inflammatory changes in the rat bowel by the virtue of its anti-inflammatory properties. Further study is required to explore the different possible mechanism of action.

PS-66: Off target Effect of Torcetrapib in Sprague-Dawley Rats- Acute or Subacute?

Suresh Giri, Lalabhai Patel, Jigarkumar Patel, Chitrang Trivedi, Gaurav Pandya, Prabodha Swain and Mukul R. Jain
Zydus Research Centre, Ahmedabad, Gujarat (India).

Inhibition of cholesteryl ester transfer protein (CETP) with torcetrapib in humans increases plasma high-density lipoprotein (HDL) cholesterol levels but is associated with increased blood pressure. In a phase 3 clinical study, evaluating the effects of torcetrapib in atherosclerosis, there was an excess of deaths and adverse cardiovascular events in patients taking torcetrapib and it was postulated to have associated with increase in blood pressure and

plasma aldostrone levels. Michael Forrest has reported that torcetrapib evoked the acute increase in blood pressure and an acute increase in plasma aldosterone, but there was no in-vivo repost regarding the subacute exposure of torcetrapib. The studies reported herein sought to evaluate off-target effects of torcetrapib after 2-3 weeks treatment in Sprague-Dawley rats. Acute administration of torcetrapib (20 mg/kg) has shown increase in blood pressure as reported by Michael Forrest along with increase in plasma aldodstrone levels. The subacute treatment for 2-3 weeks does not have any effect on blood pressure and liver and kidney fuction tests enzymes. The RAS- related gene, angiotensinogen and CYP11B2 was dose dependently increased after 5 days treatment. This shows that torcetrapib induced presser effect is short lived (acute) and after sub-acute (2-3 weeks) treatment there is no effect on blood pressure, and toxicity markers of liver and kidney in Sprague-Dawley rats.

PS-67: Plasma Volume Expansion Potential of Marketed and Failed PPAR Agonist

Suresh Giri, Lalabhai Patel, Jigarkumar Patel, Chitrang Trivedi and Mukul R. Jain
Zydus Research Centre, Ahmedabad, Gujarat (India).

Peroxisome Proliferator-Activated Receptor (PPAR) agonists have shown therapeutic benefits in the treatment of diabetes and dyslipidemia. TZD's, PPAR γ ligands, have demonstrated a great potential in treatment of Type 2 diabetes. This had led to the development of a number of dual α/γ agonists such as muraglitazar, farglitazar and several others but most of these were having side effects like body weight gain, edema and fluid retention. Body weight gain can be due to adipogenesis in the subcutaneous adipose tissue or due to plasma volume expansion. In this study we characterized the plasma volume expansion potential of two currently marketed TZDs, pioglitazone and rosiglitazone along with failed dual PPAR agonist farglitazar and muraglitazar in Sprague-dawley rats at doses 10 times than those required to improve glycemic control in rodent models to T2DM. Evan's blue dye dilution technique was used for estimation of plasma volume. Among the marketed TZD's Rosiglitazone causes 31% plasma volume expansion, which is 2 times than the pioglitazone, which has 16.4% plasma volume expansion. When we compare the dual PPAR agonist which failed in clinical development farglitazar causes 33.8% and muraglitazar causes 20.4% plasma volume expansion as compare to vehicle treated group and this is negatively correlated with change in hematocrit having the coefficient of regression 0.97. The body weight gain caused by pioglitazone and muraglitazar was 54% and 90% whereas rosiglitazone and farglitazar causes 33% and 35% body weight gain. The contribution of plasma volume expansion in body weight gain is 30%, 23%, 93% and 97% for pioglitazone, muraglitazar, rosiglitazone and farglitazar respectively and rest of body weigh gain might be due to adipogenesis. The change in plasma electrolytes and plasma volumes were accompanied by an increase in renal m-RNA levels of ENaC alpha and Na^+K^+ATPase gene confirming the greater contribution of plasma volume expansion in body weight gain for rosiglitazone and farglitazar which is also correlating to their PPAR γ specificity. Our data suggest that amongst TZDs used for treatment of Type 2 diabetes, pioglitazone is safest for plasma volume expansion potential.

PS-68: Attenuation of High Fat Diet Induced Visceral Adiposity and Insulin Resistance by *Sida rhomboidea.roxb* Extract.

Thounaojam M. C., Jadeja R. N., Ansarullah, Devkar R. V. and Ramachandran A. V.
Division of Phytotherapeutics and Metabolic Endocrinology, Department of Zoology, Faculty of Science, The M.S. University of Baroda, Vadodara-390002, Gujarat (India).

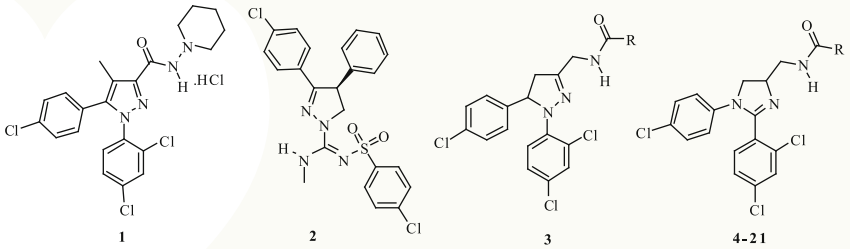
C57BL/6J mouse develops visceral adiposity and insulin resistance when fed on high fat diet (60% fat). This experimental model is used to study human type II diabetes and is widely used for screening of various synthetic or herbal drugs. Present study investigates protective role of SR extract against high fat diet induced visceral adiposity and insulin resistance. Animals were fed on high fat diet with or without plant extract for 6 months and result were compare with ***Rosiglitazone*** (oral anti-diabetic agent). Results clearly indicate decrease in body weight gain, feed efficiency and Lee index. Decrease in perirenal, abdominal and epididymal fat weight in SR treated groups indicates improvement of visceral adiposity. SR treated groups also showed improved intraperitoneal glucose and insulin tolerance indicted by low AUC values. Plasma glucose and insulin was decreased in SR treated groups. Plasma biochemical parameters like TL, TG, TC, VLDL and LDL recorded significant decrement whereas HDL recorded significant increment. Histological analyses of adipose showed decrease in adipocyte diameter. It can be concluded from present study by extract treatment SR extract feeding improves adiposity and insulin resistance by decreasing plasma and tissue lipid load.

PS-69: Design and Synthesis of Novel 1,2-Diaryldihydro imidazole 4-methyl amide Derivatives as Cannabinoid Modulators

Umesh Mali, Rina Soni, Rahul Salunke, Shivaji Gugale, Jayendra Z. Patel, Nisha Sadhwani, Purvi Vyas, Prasenjit Mitra, Amit Joharapurkar, Mukul R. Jain, Pankaj R. Patel and Brijesh Kumar Srivastava
Zydus Research Centre, Ahmedabad, Gujarat (India).

A few novel 1,2-diaryldihydro imidazole 4-methyl amide derivatives as cannabinoid modulators have been designed

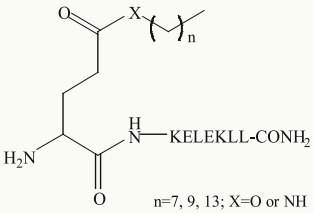
and synthesized. Among them, compounds with an alkyl chain at the amidic linkage of the 1,2-diaryldihydro imidazole system exhibited CB1 antagonism and selectivity, thus might serve as candidates for antiobesity agents.



PS-70: Synthesis of Novel Peptide Amphiphiles (Lipopeptides)

Vibhuti A. Raval, Rajendra S. Chopade, Vijay M. Prajapati, Mukul R. Jain and Rajesh H. Bahekar
Zydus Research Centre, Ahmedabad, Gujarat (India).

The acylated or amidated Glu linkers attached to different alkyl chains were synthesised using classical solution phase chemistry. Furthermore, six different lipopeptides were synthesised by attaching acylated or amidated Glu linker to a linear peptide chain, demonstrating facile synthetic scheme, suitable for obtaining peptide amphiphiles.



PS-71: Oxidative Stress in Pancreas Succeeds Hypersensitivity to Adrenergic Stimulus in Establishment of NIDDM in Genetically Diabetic Mouse Animal Model

Vipin Dhote, Nirav Dhanesha, Avnish Patel, Amit Joharapurkar and Mukul R. Jain
Zydus Research Centre, Ahmedabad, Gujarat (India).

The expression of NIDDM is closely associated with hypersensitivity to stress-induced hyperinsulinemia, which terminates into pancreatic beta cell dysfunction. On the other hand, increased oxidative stress precedes the onset of high fat diet-induced insulin resistance and obesity. The purpose of the current study is to evaluate the contribution of these pathways in establishment of NIDDM in mice models of type 2 diabetes.

The adult and mild hyperglycemic C57BL/6J mice were subjected to acute behavioral stress, which has resulted into significant hyperglycemia. Prophylactic treatment with resveratrol, an antioxidant could not attenuate the stress or epinephrine-induced hyperglycemia in these animals, whereas it was blunted with adrenergic blocker. When the C57BL/6J mice were made hyperthyroid for inducing hypersensitivity to adrenergic stimulus, four day's treatment with resveratrol can rescue the oxidative stress in blood, liver, and pancreas, and partially prevents the increase in epinephrine-induced hyperglycemia.

To further confirm these findings, young and normoglycemic C57BL/Ks db/db mice were chronically treated with resveratrol for 28 days. Significant attenuation of hyperglycemia and normalization of circulating insulin values was observed as the result of this treatment, though no significant differences in body weight or feed intake were observed. The treatment has also prevented triglyceride accumulation in islets and liver, and reduced the free fatty acid in circulation. The epinephrine-induced hyperglycemia was also significantly blunted in these animals. Significantly enough, such normalization of diabetic phenotype was not observed when the animals were treated after establishment of frank diabetes in C57BL/Ks db/db mice.

We conclude that both hypersensitivity to sympathetic stimulus and oxidative stress associated with chronic elevation of free fatty acid contribute to the expression of NIDDM.

PS-72: Bioisosteric Replacement of Dihydropyrazole with Oxazole Compromises the Interaction with Proximal Groove of CB1 Receptor thus Converting an Inverse Agonist to a Neutral Antagonist

Vishal Unadkat, Sunil Metiya, Hitesh Bhayani, Nisha Sadhwani, Rina Soni, Jayendra Patel, Kalapatapu V. V. M. Sairam, Mubeen Shaikh, Jeevan Kumar Jamili, Shital Doshi, Purvi Vyas, Dipesh Kanani, Brijesh Kumar Srivastava, Mukul R. Jain, Pankaj R. Patel and Prasenjit Mitra
Zydus Research Centre, Ahmedabad, Gujarat (India).

The cannabinoid receptor type1 (CB1R) is one of the most abundant G-protein-coupled receptor in the brain regulating diverse physiological functions involving orexigenic response, cognition and habit formation. An essential feature of CB1R is its constitutive activity which empowers it to transduce a biological signal in the absence of ligand. Majority of CB1R antagonists which are attractive targets for appetite suppression are inverse agonists that compromise with the constitutive activity of the receptor eventually precipitating in serious side effects. Malaise generated on treatment with any of the known CB1R inverse agonists points to the necessity of development of a neutral antagonist which would hinder ligand binding without fixing the receptor in an inactive state. For biaryl pyrazole class of CB1R antagonist like rimonabant, the interaction with Lys 192 in 3rd transmembrane helix of CB1R was reported to be crucial for evoking inverse agonistic response. Loss of this interaction has been reported to convert a biaryl pyrazole inverse agonist to neutral antagonist. In our present study we tested inverse agonistic activity of rimonabant, SLV319 and 5-(4-Chlorophenyl)-1-(2,4 dichlorophenyl)-4-methyl-3- [(E)-piperidinoiminomethyl]-1H-pyrazole (PIMSR), a biaryl pyrazole antagonist which, unlike rimonabant and SLV319, does not interact with lysine 192 of CB1R. We also synthesized and evaluated 4-Chloro-*N*-{[4-(4-chlorophenyl)-5-phenyl-oxazol-2-yl]-methylamino-methylene}-benzene sulfonamide whose docking studies and end results are discussed. Our study reveals that while attenuation of interaction with Lys 192 reduces inverse agonistic prowess, complete loss of interaction with Lys 192, Ser 383 and with proximal groove of CB1R is essential to impart neutral antagonism to biaryl pyrazole CB1R antagonist.

PS-73: Induced-fit or Preexisting Equilibrium Dynamics? Lessons from Protein Crystallography and MD Simulations on Acetylcholinesterase and Implications for Structure-Based Drug Design

Yechun Xu*,#, Jacques Ph. Colletier@, Hualiang Jiang†,‡,Israel Silman#, Joel L. Sussman* and Martin Weik@
*Department of Structural Biology Weizmann Institute of Science, Rehovot (Israel).
#Department of Neurobiology, Weizmann Institute of Science, Rehovot (Israel).
@Laboratoire de Biophysique Mole´culaire, Institut de Biologie Structurale, Jean Pierre Ebel, CEA-CNRS, Universite´ Joseph Fourier, F-38027 Grenoble (France).
†Center for Drug Discovery and Design, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai (China).
‡School of Pharmacy, East China University of Science and Technology, Shanghai (China).

Crystal structures of acetylcholinesterase complexed with ligands are compared with side-chain conformations accessed by native acetylcholinesterase in molecular dynamics (MD) simulations. Several crystallographic conformations of a key residue in a specific binding site are accessed in a simulation of native acetylcholinesterase, although not seen in rotomer plots. Conformational changes upon ligand binding thus involve preexisting equilibrium dynamics. Consequently, rational drug design could benefit significantly from conformations monitored by MD simulations of native targets.

PS-74: Flexibility of Aromatic Residues in the Active-Site Gorge of Acetylcholinesterase: X-ray versus Molecular Dynamics

Yechun Xu*#, Jacques-Philippe Colletier¶**, Martin Weik**, Hualiang Jiang@†, John Moult‡, Israel Silman# and Joel L. Sussman*
*Department of Structural Biology and #Department of Neurobiology, Weizmann Institute of Science, Rehovot 76100 (Israel).
¶University of California, Los Angeles-Department of Energy Institute of Genomics and Proteomics, University of California, Los Angeles, California (USA).
**Laboratoire de Biophysique Moleculaire, Institute de Biologie Structurale, 38027 Grenoble (France).
@Center for Drug Discovery and Design, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203 (China).
†School of Pharmacy, East China University of Science and Technology, Shanghai 200237 (China).
‡Center for Advanced Research in Biotechnology, University of Maryland Biotechnology Institute, Rockville, Maryland (USA).

The high aromatic content of the deep and narrow active-site gorge of acetylcholinesterase (AChE) is a remarkable feature of this enzyme. Here, we analyze conformational flexibility of the side chains of the 14 conserved aromatic residues in the active-site gorge of Torpedo californica AChE based on the 47 three-dimensional crystal structures available for the native enzyme, and for its complexes and conjugates, and on a 20-ns molecular dynamics (MD) trajectory of the native enzyme. The degree of flexibility of these 14 aromatic side chains is diverse. Although the side-chain conformations of F330 and W279 are both very flexible, the side-chain conformations of F120, W233, W432, Y70, Y121, F288, F290 and F331 appear to be fixed. Residues located on, or adjacent to, the V-loop (C67–C94), namely W84, Y130, Y442, and Y334, display different flexibilities in the MD simulations and in the crystal structures. An important outcome of our study is that the majority of the sidechain conformations observed in the 47 Torpedo californica AChE crystal structures are faithfully reproduced by the MD simulation on the native enzyme. Thus, the protein can assume these conformations even in the absence of the ligand that permitted their experimental detection. These observations are pertinent to structure-based drug design.

PS-75: Antidiabetic Study of Alcoholic Tuber Extract of *Kyllinga nemoralis* in Streptozotocin-Nicotinamide Induced Type-2 Diabetes Rats

Yogesh Kamariya*, Bharat Patel*, Meril Varghese# and Annie Shirwaikar#
*Zydus Research Centre, Ahmedabad, Gujarat (India).
#Manipal College of Pharmaceutical Sciences, Manipal University, Karnataka (India).

The plant *Kyllinga nemoralis* (Foster) Dandy ex Hutch belonging to family Cyperaceae, is an erect glabrous sledge with creeping rhizomes, 7.5-30 cm in height, distributed throughout India as well as SriLanka. *K. nemoralis* tubers are reported as stomachic, astringent, expectorant, antidiarrhoeal, diuretic and anthelmintic. The plant has been documented earlier as therapeutic agent for diabetes, hence the present study was undertaken to evaluate the possible antidiabetic effect of the alcoholic extract of the tuber of *K. nemoralis* in STZ-nicotinamide induced type-2 diabetic model. Acute toxicity study of alcoholic extract was performed according to OECD guidelines, which showed no toxicity signs up to 4000 mg/kg body weight. Alcoholic extract when given to the rats for Oral Glucose Tolerance test showed significant reduction in fasting blood glucose levels compared with normal rats. Two doses of the alcoholic tuber extract i.e. 200 and 400 mg/kg were administered to experimental diabetic rats for 21 days. Significant ($p<0.05$) reduction in fasting blood glucose levels were observed in the normal as well as in the treated diabetic animals. In addition, changes in body weight, serum cholesterol, serum triglyceride, HDL cholesterol, glycated haemoglobin, liver glycogen levels were assessed in the extract treated diabetic rats and compared with diabetic control, standard glibenclamide and normal animals. Significant results were observed in the estimated parameters with minimal toxicity, thereby justifying the use of the plant in the indigenous system of medicine.

PS-76: Isolation of Nickel Resistant Bacteria and its Role in Bioremediation

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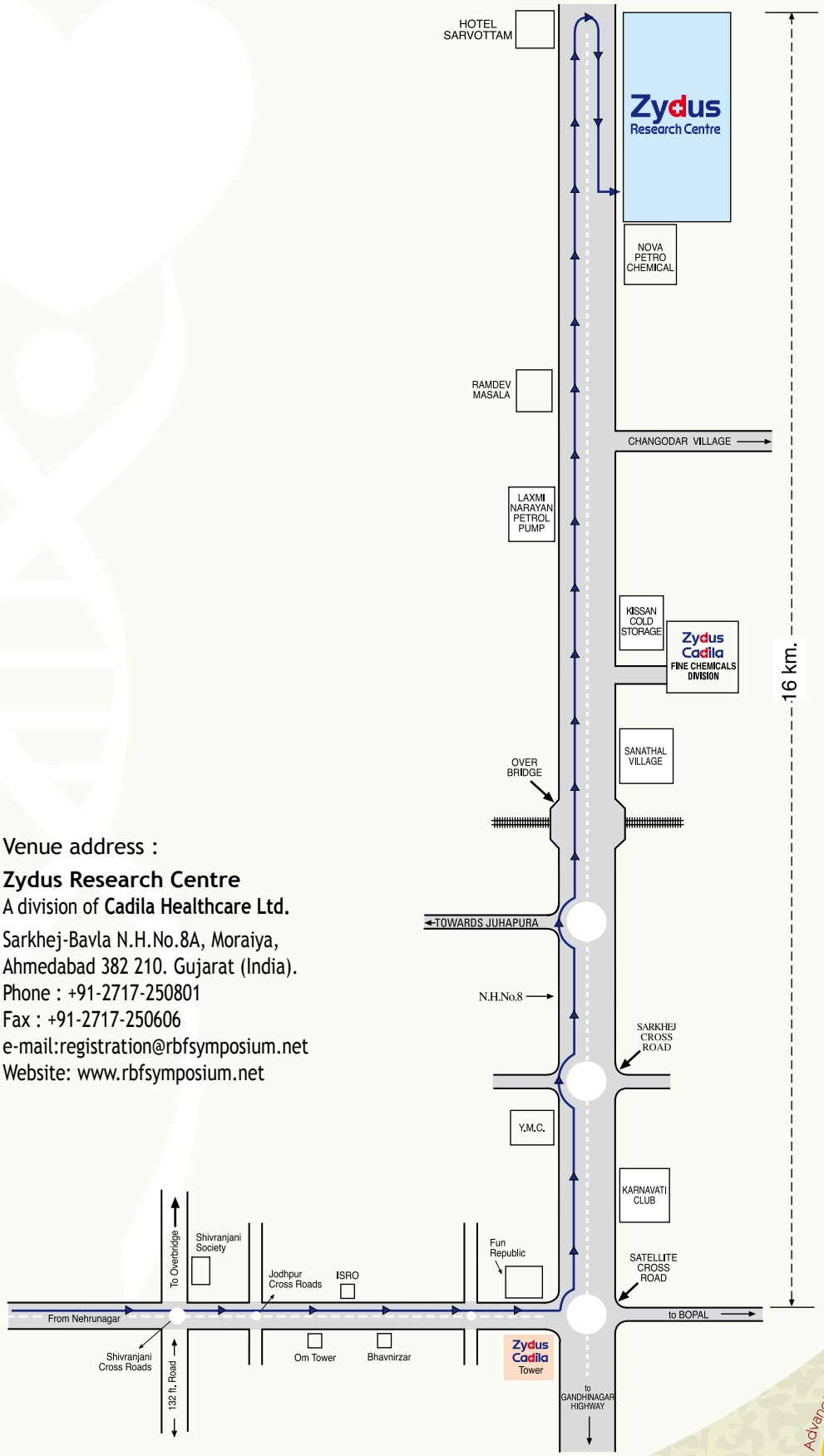
*Zydus Research Centre, Ahmedabad, Gujarat (India).
Department of Environmental Microbiology and Biotechnology, Gujarat University, Ahmedabad (India).

Nickel is a naturally occurring metal existing in various mineral forms and is found throughout the environment. Nickel is released into the atmosphere from burning fossil fuels, mining and refining operations, cigarettes and incineration of municipal waste. It is also found in soil treated with sewage sludge. Nickel is of high toxicity to humans. The most toxic of nickel compounds is nickel carbonyl, a very volatile liquid at room temperature, which is known to be a lung carcinogen when inhaled. It is highly irritating to the skin, and is toxic to the cardiovascular system and is carcinogenic. Nickel has been implicated as an embryotoxin and teratogen. Here bioremediation of nickel using bacteria has been shown as an effective tool for removal of nickel. Five nickel resistant bacterial strains that can tolerate heavy nickel concentration have been isolated and characterized from nickel contaminated sites and they have been optimized to give maximum bioremoval. Both Freundlich and Langmuir's absorption isotherms fitted well with the experimental data. The entire process has been scaled up through biomass immobilization in columns with efficient breakthrough curves and showing high level of nickel bioremoval. This work serves as a good platform for heavy metal decontamination using microbial bioremediation.

How to reach the venue



Venue address :

Zydus Research Centre
A division of **Cadila Healthcare Ltd.**
Sarkhej-Bavla N.H.No.8A, Moraiya,
Ahmedabad 382 210. Gujarat (India).
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Advancing Cardiometabolic Research

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"Advances In Cardiometabolic Research- Basic Science And Clinical Aspects"

Feb 2-5, 2009, Zydus Research Centre, Ahmedabad, India

Thank you for attending The Ramanbhai Foundation 4th International Symposium.

Your participation helped make this event yet another success! We hope that you developed fruitful relationships, gained insight from the presentations and expert speakers, learned more about the latest in the therapy area of Cardio-metabolic research. Please take a moment to provide any feedback and suggestions that you may have for our next Symposium

Please use the following scale to evaluate your experience for the sessions:

1 - Met Expectations

2 - Exceeded Expectations

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Rate your satisfaction with the Symposium agenda:

1 ____ 2 _____ 3 _____

Additional comments: Were all the scientific sessions valuable? Did you find value in the format of the presentation and the topics selected for these sessions?

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Additional comments: Was there any particular session that you enjoyed the most , and why? Which are the sessions that you found compelling? Did you gain any insights from the workshop and the Scientific Sessions of the symposium ? Which speaker did you enjoy the most

Rate your satisfaction with the Hospitality offered during the Symposium :

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Additional comments: Any specific feedback on the arrangements regarding travel, accommodation cuisine or cultural event

Share your feedback on the knowledge application of the sessions:

Which of the session attended by you matched your current queries and found most valuable?

Describe the elements and the sessions of the Symposium that were least valuable

How can we make the Symposium even better next time?

General comments or observations: Would you like to come again next year?

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Your brief profile: _____

Question Card

Name: _____

Affiliation _____ Session _____

Question Addressed to _____

Question

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